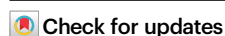


Structural origin of fracture-induced surface charges in piezoelectric pharmaceutical crystals for engineering bulk properties

Received: 2 July 2024

Accepted: 11 March 2025

Published online: 25 July 2025



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Altering surface chemistry of functional materials is an attractive route to enable large property enhancements without sacrificing overall structural order, appealing to diverse fields of application sciences; however, the same remains unexplored for organic crystalline materials. Herein, piezoelectricity in pharmaceutical crystals is reported to show colossal surface charges driven by mechanical fracture – where a collection of dipoles arranged in polar head-to-tail fashion generates opposite surface charges on freshly fractured faces – causing them to actuate large distances over 75 μm in milliseconds. Kelvin probe force microscopy is leveraged to show many-fold surface potential enhancement in fractured surfaces relative to the pristine crystals. Further, complementarity of the surface potentials in a pair of fractured crystal shards and asymptotic decay behaviour with time are observed. Newly formed surfaces of the pharmaceutical crystals show long-lasting charges despite their relatively lower piezo-response confirmed by bulk piezometry. To establish the generality of surface phenomena, statistical analyses (≈ 50 samples) of post-fracture-attraction behaviour of crystals are performed. Finally, the application of fracture-driven surface charges in industrial processes is achieved by investigating flow-property and tablet-strength of bulk pharmaceutical materials. This multiscale approach unveils the symmetry-dependency of surface charges in fractured materials, and probes the same for utilisation in bulk-property engineering.

Surface electronic properties of solid materials greatly differ from the bulk because of dangling bonds and complex surface reconstruction phenomenon¹, and understanding it remains one of the unmet challenges in materials science². Peculiar surface characteristics are exploited in diverse applications like heterogeneous catalysis³,

biosensors⁴, smart electronics⁵, drug development⁶ and so on⁷. In particular, the surface chemistry of anisotropic solids like molecular crystals has gained extensive attention for regulating physicochemical attributes like surface energy⁸, surface charges⁹ and adhesion behaviour¹⁰. Moreover, it is widely known that mechanical stress can

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perturb local structure and energetics of crystals^{11–15}. On the other hand, processing of bulk solid APIs, agrochemicals, nutraceuticals and fine chemicals involves complex operations which tend to modify their surface energetics^{16,17}. In industrial processes, bulk solids routinely develop surface charges, affecting the flow, wettability, and compaction properties of the material¹⁸. Generally, charged particles can result in multiple obstructions including agglomeration, segregation during flow or adhesion to process equipment^{19,20}. On the other hand, surface charges can often help in homogeneous powder blending²⁰ and pulmonary drug delivery²¹. However, the mechanisms and atomistic structural basis for different surface phenomena are yet to be established in molecular crystals. Pharmaceutical crystals stand out as suitable materials for the investigation of surface charges due to their molecular diversity and immense industrial importance. Pharmaceutical materials are generally regarded as single-component or multi-component crystalline or amorphous forms of an active pharmaceutical ingredient (API). Solid APIs include neutral solid forms, salts, co-crystals, solvates and their polymorphs^{22–25}. The frequently observed electrostatic surface charge accumulation in pharmaceutical

crystals during handling processes is typically attributed to triboelectricity¹⁹. Triboelectricity or contact electrification, i.e., generation of static surface electricity due to collision or rubbing of dissimilar particles with differences in work functions, is known to occur randomly in APIs and remains unpredictable. The generation of surface charges, although almost always attributed to the triboelectric effect in pharmaceuticals, may also be observed in acentric crystals under uniform mechanical stress, which is known as the piezoelectric effect²⁶. Piezoelectric crystals, investigated from the 19th century, have various applications in sensors²⁷, transducers²⁸, energy harvesters²⁹ and biomedical devices³⁰. Accumulation of surface potentials on fractured surfaces has been shown recently to prompt actuation followed by self-healing in piezoelectric organic crystals^{2,31}. Herein we delve into the intricacies of such surface charge generation in piezoelectric solids of essential active pharmaceutical ingredients (APIs).

In this multiscale exhaustive study (Fig. 1a–e), we examined the structural origin of one of the significant yet unexplored surface charge phenomenon in some model pharmaceutical materials. Further, our systematic analysis of the crystal structures, and the absence/

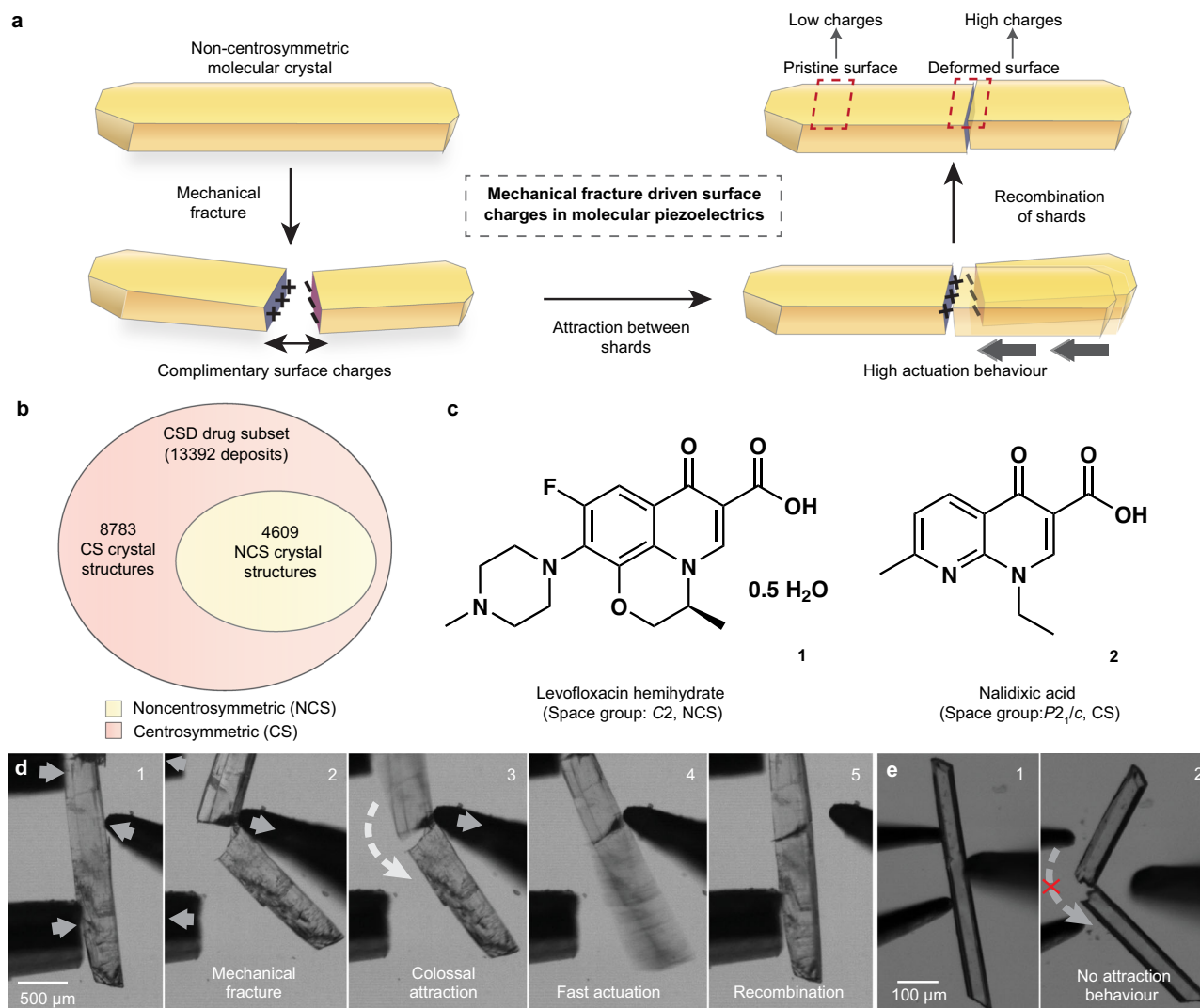


Fig. 1 | Mechanistic insights into the fracture-driven surface charges in pharmaceutical crystals. **a** Schematic elucidation of fracture-induced surface charge generation in piezoelectric crystals. **b** Cambridge structural database (CSD) drug subset (version 5.43) search results showing the abundance of NCS hits. **c** Molecular structure of levofloxacin hemihydrate (NCS) and nalidixic acid (CS). **d** Video grabs showing mechanical fracture (images 1–2) of crystals, leading to generation of

colossal surface charge, followed by ultra-fast actuation and recombination (images 3–5) in a crystal of **1**. Images 1–5 are captured at 0, 247, 249, 251 and 254 ms respectively. **e** No attraction behaviour (images 1–2) is observed in crystal **2** after fracture, as it belongs to CS. Images 1–2 are captured at 0 and 352 ms respectively. See also Supplementary Movies 1–6. Source data are provided as a Source Data file.

presence of attraction and repulsion behaviour of the materials at the single particle level, reveal that pharmaceutical crystals lacking centre of symmetry, i.e., levofloxacin hemihydrate (non-centrosymmetric, NCS) show colossal surface charges upon mechanical fracture, whereas crystals having inversion centre, i.e., nalidixic acid (centrosymmetric, CS) do not. Piezometric measurements confirmed the piezoelectric nature of levofloxacin crystals ($d_{33} = 1.29 \text{ pC N}^{-1}$) while Kelvin probe force microscopy (KPFM) experiments revealed the nature, type and time dependency of surface potentials. Here for the first time, we demonstrate a direct link between the inherent electro-mechanical coupling and surface charge in non-centrosymmetric pharmaceutical crystals using single crystal structures which allowed us to rationalise the bulk behaviour of particles, like flowability, compactibility and tabletability. The generality of our approach is further confirmed by studying additional systems, including a polymorphic drug system.

Results

Piezoelectricity requires inherent non-centrosymmetry in dielectric materials³². Hence, to explore surface charges in mechanically impacted pharmaceutical crystals (Fig. 1a), we investigated the Cambridge Crystallographic Data Centre (CCDC Conquest) by restraining to “non-centrosymmetric” and “organic” crystal structures in CSD drug subset of more than 13,000 pharmaceutical crystals, which resulted in a set of 4609 hits³³ (Fig. 1b, Supplementary Note 1). Interestingly, the overall occurrence of NCS structures is 34.4% in the CSD drug subset which is higher than the overall percentage of acentric crystals (22%) in the entire CSD database, perhaps due to the abundance of chiral centres in drug molecules. Further, we investigated a select API pair to identify crystals that may generate surface charges upon fracture. As currently there are no clear guidelines to find such crystals, we picked some readily available APIs which contain hydrogen bonding functionalities, may it be strong or weak and dispersive groups².

The list includes three pairs of unrelated API crystals. Each pair consists of one non-centrosymmetric and one centrosymmetric counterpart (Supplementary Table 1). The first pair includes quinolone drugs levofloxacin (**1**, NCS hemihydrate form, space group $C2$) and nalidixic acid (**2**, CS anhydrous form, space group $P2_1/c$) (Fig. 1c); the second pair consists of two popular analgesic drugs, metacetamol (**3**, NCS form, space group $Pna2_1$) and paracetamol (**4**, CS form, space group $P2_1/n$); while the third pair consists of polymorphic forms of the API, tolbutamide (**5**, NCS polymorph, space group $Pna2_1$ and **6**, CS polymorph, space group $P2_1/n$) (Supplementary Table 1). Our molecular pairs are diverse but the molecules in each pair show a good similarity; in the first pair, the quinolone backbone is common, in the second pair there is only a change in the position of amide functionality (meta to para) and in the third, the molecule is identical as they are polymorphs.

Three-point mechanical bending test is a simple yet very useful technique to examine the mechanical properties of crystals^{34–36}. Here, we performed the tests under a stereo microscope equipped with a high-speed camera and analysed the fracture behaviour as well as actuation motion of the fractured shards, frame by frame in ambient conditions. When crystal **1** (NCS) is subjected to three-point bending, it fractures in a brittle manner, breaking into two shards, followed by a remarkable attraction between them, leading to autonomous recombination within milliseconds (Fig. 1d, Supplementary Fig. 1, Supplementary Movies 1–3). Interestingly, the oppositely fractured shards actuate from distances as far as $75 \mu\text{m}$ confirming the presence of a large force of attraction between them (Supplementary Fig. 2; Supplementary Movie 3). On the other hand, similar tests performed on crystal **2** (CS) did not exhibit any attraction behaviour between the fractured shards even when they were brought in close contact (Fig. 1, Supplementary Movie 4). In the case of the second pair, mechanically broken pieces of crystal **3** (NCS) did show a high attraction behaviour

while crystal **4** (CS) did not (Supplementary Figs. 3 and 4, Supplementary Movie 5). The same trend is observed in polymorphic systems **5** (NCS)/**6** (CS) where the non-centrosymmetric polymorph exhibited post-fracture recombination whereas the centrosymmetric polymorph was devoid of such affinity to recombine after mechanical fracture (Supplementary Figs. 5 and 6, Supplementary Movie 6). Here it is noteworthy that the ultra-fast actuation and high affinity to recombine after mechanical fracture are observed in the case of all three piezoelectric pharmaceutical crystals (Supplementary Note 2, Supplementary Tables 2 and 3) but not in the non-piezoelectric systems, demonstrating the positive correlation of piezoelectricity with coulombic attraction between the fractured shards in these systems.

To gain mechanistic insights into the origin of the colossal surface charges, we chose to focus on a specific pair of NCS/CS systems, levofloxacin hemihydrate (**1**) and nalidixic acid (**2**) crystals. They grow in comparable acicular (needle) shaped morphologies and are easily availed in good quantities for bulk-property studies. Hence, we proceeded with this specific pair first with all the exhaustive characterisation methods. Levofloxacin (**1**) crystallises as a hemihydrate³⁷ in polar space group $C2$ (Fig. 2a). The asymmetric unit contains two independent levofloxacin molecules each interacting with water molecules via O–H...N hydrogen bonds. The two independent levofloxacin molecules stack along the short axis ($b = 6.88 \text{ \AA}$) by strong π -stacking interactions in a columnar fashion, which are connected with neighbouring molecules via C–H...O and C–H...F interactions (Supplementary Figs. 7 and 8). Our semiempirical level calculations³⁸ indicate that each levofloxacin molecule acts as a dipole (Fig. 2b); eight such molecules, combined with four water moieties, form a unit cell having a permanent net dipole moment along the b -axis. Hence, the unit cells can be considered as micro-dipoles in the crystal, each with a dipole moment of 3.8 D (Fig. 2c). The summation of such micro-dipoles, arranged in a head-to-tail fashion, generates a macro-dipole moment along the crystal's growth axis, i.e., b -axis (Fig. 2d–f). The mechanical fracture perpendicular to the growth axis, shall expose the opposite dipoles (head and tail) on the opposite faces of the fractured shards (Fig. 2g). This can be considered as the reason for the appearance of opposite polarities and hence, opposite charges on the fractured shards. Notably, the charges on the fractured surfaces are retained over a period (a few hours to days) which might be due to the slow relaxation of accumulated permanent local strain (fatigue) on the broken pieces upon the fracture event, probably facilitated by the mechanical softness of the crystals². However, crystal shards fractured parallel to the growth axis $[010]$, show minimal attraction behaviour which demonstrates the direction dependency of the surface charge generation in the polar crystal **1** (Supplementary Fig. 9, Supplementary Note 3, Supplementary Movie 7). Crystals of nalidixic acid (crystal **2**), which adapt centrosymmetric space group $P2_1/c$ (Fig. 2h), have molecules in herringbone arrangement where neighbouring molecules form C–H...O hydrogen bonds (Supplementary Fig. 10). Though nalidixic acid molecule has a permanent net dipole moment, due to the presence of inversion centre between dimers in its unit cell, the molecular dipoles are cancelled, making the net micro-dipole moment of the unit cell zero (Fig. 2i, j). As a result, the crystal is inherently non-piezoelectric. Even after deformation, due to the coincidence of the centre of positive and negative charges in CS crystal systems, it results in no change in overall polarisation. Hence it can be inferred that the inversion symmetry in the structure impedes any change in overall polarisation upon fracture, rendering no charge generation in nalidixic acid crystals.

Since non-centrosymmetry and piezoelectricity are largely congruent, with a few exceptions³⁹, we set out to characterise the piezoelectric properties of molecular crystal **1**. The d_{33} piezometry measurements of a polycrystalline pellet sample of **1** reveal a piezoelectric coefficient of 1.29 pC N^{-1} at the bulk level (Supplementary Fig. 11) which is comparable to different organic and biological

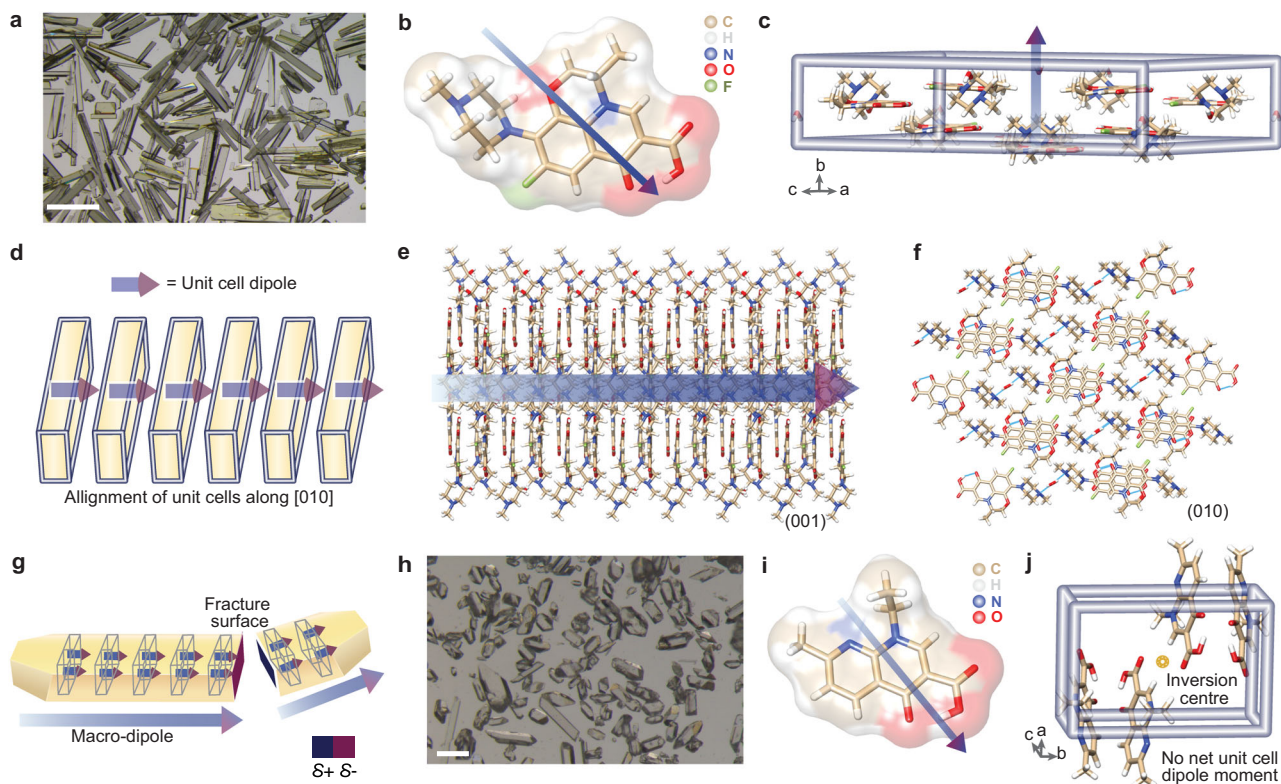


Fig. 2 | Analysis of dipolar arrangement in the structures of crystals 1 and 2. **a** Polarised optical microscopy image of bulk levofloxacin hemihydrate crystals (scale bar: 2 mm). **b** Molecular net dipole moment of levofloxacin. **c** Unit cell net dipole moment of crystal 1. **d** Arrangement of unit cell net dipoles (micro-dipoles) and **e** overall macro-dipole along needle axis in crystal 1. **f** Crystal packing viewed $\perp$

(010) in crystal 1. **g** Schematic representation of the arrangement of macro-dipoles and generation of surface charges after fracture in crystal 1. **h** Optical image of bulk nalidixic acid crystals (scale bar: 0.5 mm). **i** Molecular net dipole moment of nalidixic acid. **j** Unit cell of crystal 2 having net zero dipole moment, due to the presence of inversion symmetry.

materials, although some organic single crystals show very high d_{33} coefficients⁴⁰ (Supplementary Table 4). Piezo-response force microscopy (PFM) technique was also employed on pristine single crystals to further characterise the piezo-response at the nanoscale. The piezo-response in the vertical direction (VPFM) of crystal 1 (NCS) and crystal 2 (CS) was estimated in an amplitude vs frequency plot (Fig. 3a) when the excitation frequency sweeps around the contact resonance frequency in dual-ac resonance tracking mode (DART-PFM)^{41–44}. An ac bias of 2 V was applied on both the samples; we could observe a prominent peak in the case of NCS crystal 1 (red in colour) while CS crystal 2 (blue in colour) did not show any significant peak in the whole frequency range (Supplementary Note 4). VPFM imaging was performed on the pristine crystal of 1 showing the topography, amplitude and phase responses (Fig. 3b–d) on the accessible major face (10-1). The amplitude channel depicts the nanoscale mechanical response experienced due to applied electrical bias (Fig. 3c). Whereas, in the phase channel (Fig. 3d), we can observe the presence of non-180° strip-like domains which elucidates the relative orientation of spontaneous polarisations. Such non-180° domains are not uncommon in molecular crystals as reported elsewhere⁴⁵.

We examined the surface electrical potentials on the fractured crystals of systems, 1 and 2, using KPFM experiments. KPFM is a powerful scanning-based tool, a variant of atomic force microscopy (AFM) where conducting probes are used to quantify the electrical potential distribution of surfaces⁴⁶. In spite of its extensive use to reliably measure surface potentials in perovskites⁴⁷, its use in organic single crystals is limited^{9,48,49}. KPFM experiments were performed on both pristine and freshly fractured crystal faces of 1 calibrated with reference sample (Supplementary Fig. 12). Multiple measurements on different crystals of 1 showed an average of 152 to –228 mV for the pristine (undeformed) crystal faces (Fig. 4a). Fracturing a crystal

perpendicular to its growth axis on the other hand, showed many-fold rise of residual potential, up to 8.89 V, on the freshly created surfaces, as denoted in Fig. 4b. More importantly, we could confirm for the first time in pharmaceutical crystals that, the net residual potential on the freshly created surfaces of opposite shards was either completely positive or negative (Fig. 4b, Supplementary Note 5). To investigate the complementary nature of the surface potentials in opposite faces, we further performed another set of KPFM experiments on a pair of fracture planes of shards taken from the same crystal. A mm-sized single crystal of 1 was fractured into two pieces and each shard was mounted separately on a base so as to access the freshly cleaved (010/0-10) surfaces by the cantilever tip (Fig. 4b). The average values of the potentials obtained on the complementary faces were 7.19 V and –3.32 V. This experiment showed that the surface potentials of opposite planes indeed have opposite sign. We further performed the KPFM tests across a crack line on the (10-1) face of crystal 1. The change in potential from positive to zero to negative on moving over the crack junction was observed, which reaffirms the presence of opposite polarity on opposite faces (010/0-10) (Fig. 4c, Supplementary Fig. 13). Additionally, surface potential on one side of the fractured face mapped at different locations showed the same nature (Supplementary Fig. 14). This again confirms that one shard has one type of sign of effective charge, and it is opposite to that of its counterpart. We observed that the fractured crystals when kept in contact through the complementary faces, retain the surface charges for prolonged periods (from days to weeks) (Supplementary Figs. 15 and 16, Supplementary Note 6, Supplementary Movie 8). However, when the broken shards are stored separately, at ambient conditions, they lose the surface charges, probably due to relaxation or surface reconstruction¹. It is noteworthy that there is a gradual decrease in surface potential with time as the scan progresses (indicated by arrows in Fig. 4a, b) in

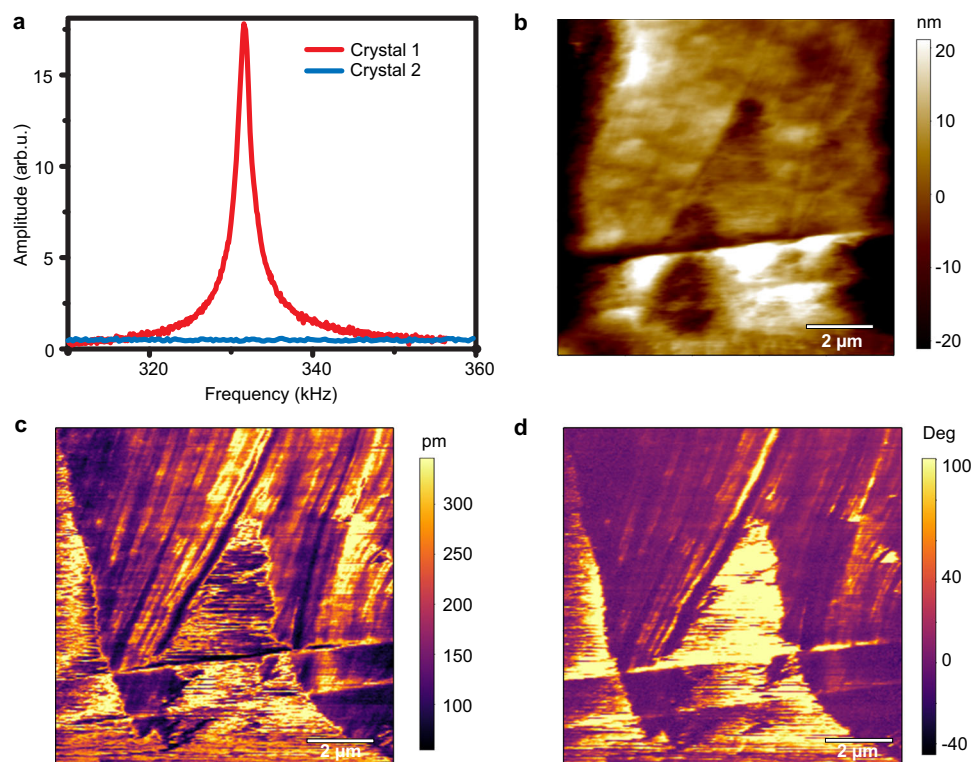


Fig. 3 | Characterisation of piezoelectric properties. **a** Comparison of piezo-response of crystal **1** (NCS, red in colour) and **2** (CS, blue in colour) versus excitation frequency measured with DART-PFM. Vertical mode PFM on (10–1) face of pristine

crystal of **1** showing **b** topography, **c** amplitude, and **d** phase image, showing non-180° domains.

the case of fractured surfaces of NCS crystals, such as **1**, which can be attributed to the decay of surface charges during a scan which typically takes about 15–17 min. To accurately establish any time dependency, KPFM experiments were performed at periodic time intervals. It was observed that in the fractured crystals the surface potential decays with time in an asymptotic manner (Fig. 4d, Supplementary Fig. 17) and reaches approximately a constant value after several hours. This indicates that piezoelectric pharmaceutical crystals may acquire high surface charges when subjected to mechanical impact which decays slowly with time when exposed to air. Further, KPFM was also performed on a pristine crystal and at a crack junction of centrosymmetric crystal **2** (Supplementary Figs. 18 and 19). Both the magnitude and polarity of surface potential remained unchanged across the crack region (Supplementary Fig. 21). This proves the absence of fracture-induced surface charges in the CS crystals. Surface charges can be affected by environmental conditions like humidity. To understand the effect of moisture, we performed KPFM experiments on mechanically fractured crystal **1** at two different relative humidities of 60% and 91% (Supplementary Fig. 20). Note that the surface potential at RH 91% remains low from the beginning indicating a quick decay of the charges. The higher water content on the fractured surface in high humidity seems to be neutralising the surface charges faster due to its polar nature and high dielectric constant. These results are further supported by the absence of any attraction behaviour when crystal **1** was fractured in water as a medium (Supplementary Fig. 21, Supplementary Movie 9). Also, during mechanical manipulations, we used a metal pin as well as wooden needles and did not observe any differences in attraction behaviour (Supplementary Fig. 22, Supplementary Movie 9).

To gain deeper insights into the mechanics led by surface attractive forces in NCS crystals, we performed multiple types of fracture tests on about 50 samples of **1** and analysed their behaviour (Fig. 5). From the experiments on crystals gathered from three

different crystallisation batches, we observed that in almost all the cases, brittle fracture of crystals shows self-attraction behaviour followed by recombination of the opposite shards. This suggests that fracture-induced surface charge generation is an intrinsic property of crystal **1**. Next, we induced fracture at two different locations of crystal **1** to analyse the affinity between the complementary vs non-complementary pieces (Fig. 5a, b, Supplementary Movie 10). For example, the fractures at positions i and ii led to the generation of complementary pairs of faces Aⁱ/Bⁱ and Aⁱⁱ/Bⁱⁱ. As expected, both the A/B pairs showed mutual attraction. For instance, when faces Aⁱ and Bⁱⁱ were brought closer to each other, they also showed high attraction leading to actuation followed by recombination (Fig. 5b). In contrast, no affinity was found between face Aⁱ and Aⁱⁱ or Bⁱ and Bⁱⁱ as these pairs are expected to possess a same polarity (as exemplified from the bar chart in Fig. 5e). Next, we took two separate samples (named as sample I and II) to check the behaviour of fractured shards originating from two different crystals of **1** (Fig. 5c, d, Supplementary Movie 11). As expected, we observed attraction between the fractured shards, IA and IIB, as well as IIA and IB. No attraction was observed between pairs IA/IIA or IB/IIB (as exemplified by the bar chart in Fig. 5f). It is clear that, due to the generation of opposite polarity during fracture in these crystals, a fractured shard attracts any other fractured shard of opposite polarity, irrespective of whether it is originated from a same crystal or another. This can have a significant effect on the powder properties of pharmaceutical solids as their bulk processing and manufacturing involve various types of mechanical impact.

In the pharmaceutical industry, particle size reduction by means of mechanical grinding or jet milling^{50,51}, inputs very high energy into the materials, severely impacting the surface energetics of bulk powders⁵². Here, surface charge generation by electromechanical coupling can be a plausible outcome in piezoelectric crystals. In this context, we performed standard ball-milling experiments (Supplementary Note 7) on both crystals **1** and **2**. The batch purity of the

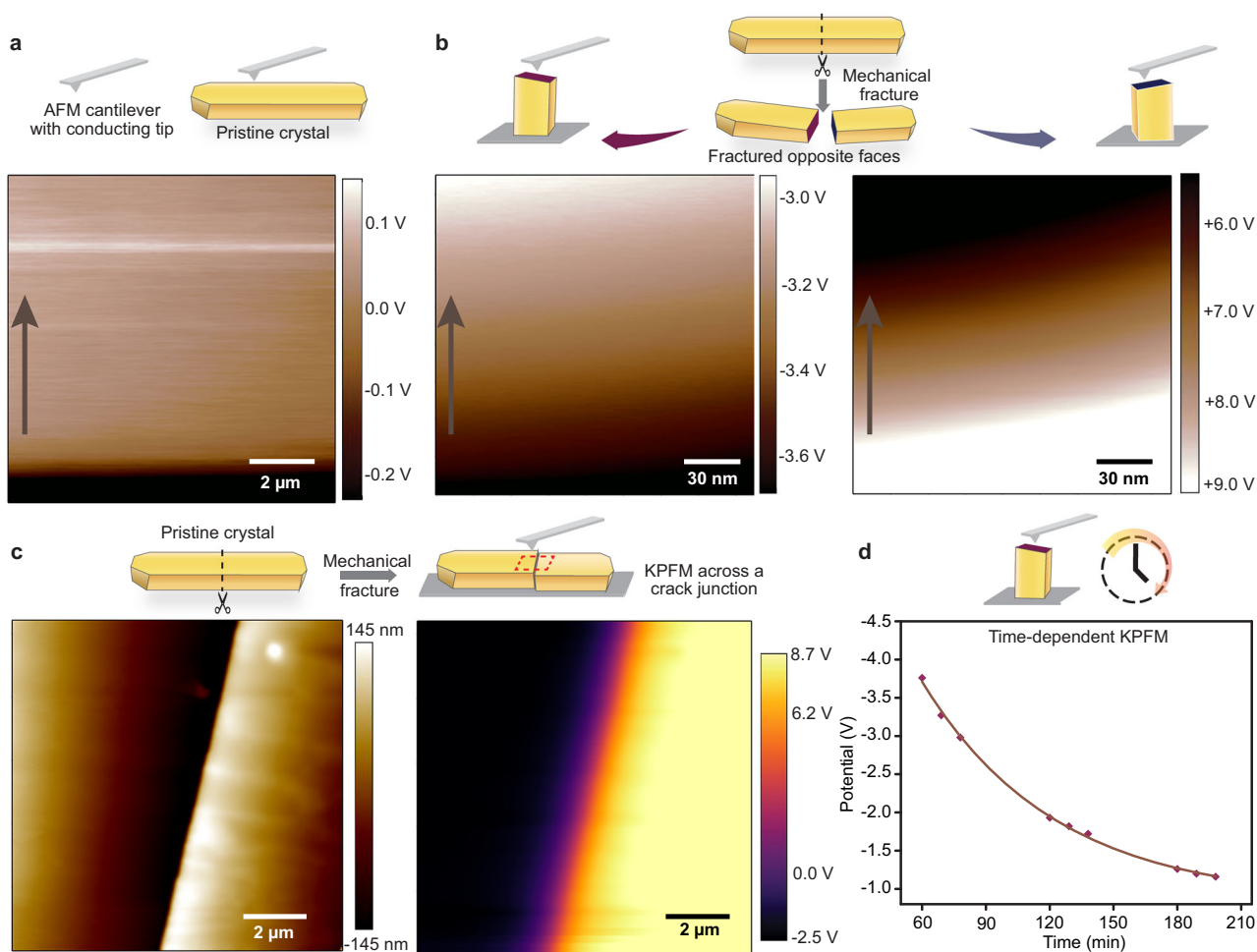


Fig. 4 | Quantitative assessment of surface potentials on crystal 1. **a** Kelvin Probe Force Microscopy on a pristine major (10-1) face, and **b** freshly fractured complementary (010/0-10) faces. The arrows indicate the direction of the scan (frame up) during potential mapping. **c** Topography and potential mapping across

a crack line on (10-1). **d** Time-dependent decay of surface potential on a freshly fractured face perpendicular to the needle axis. Source data are provided as a Source Data file.

samples was confirmed by powder X-ray diffraction (PXRD) before milling experiments (Supplementary Figs. 23 and 24). For crystal **1**, large spherical agglomerates (diameter up to 1 mm) were found in the ball-mill jar after 5 mins of milling (Fig. 6a, b) whereas relatively much smaller aggregates with mostly fine powders were spotted in the case of crystal **2** (Fig. 6c). These results suggest that in case of samples of **1**, attractive forces among particles lead to agglomeration. This can be attributed to the surface charge generated upon fracture of the piezoelectric crystals during milling which is consistent with our observation in single crystals. Abramov et al. previously demonstrated that favourable dipole-dipole interactions can lead to microcrystal aggregation of polar pharmaceutical crystals during crystal growth³⁸. Next, we performed flowability studies before and after milling of both crystals **1** and **2** (Supplementary Note 8). Although milling of pharmaceutical crystals generally results in poor flow due to the cohesive nature of microparticles, a significant decrease in angle of repose was observed in the case of crystal **1** which indicates a contrary behaviour, i.e., an increase in flowability after milling (Fig. 6d). This may be attributed to the formation of spherical agglomerates which can enhance flow properties as reported previously⁵³ (Fig. 6b). Fracture of the needle-shaped crystals perpendicular to their needle axis can also contribute toward the increase in flowability due to decrease in the aspect ratio. Flowability of crystal **2** was also increased but to a lesser extent, which can be attributed to the decrease in aspect ratio of the crystals alone.

Tablet is one of the widely used oral dosage forms in medication⁵⁴. The strength of a tablet primarily depends on the deformation behaviour of the powder and the inter-particle interaction under compressive stress⁵⁵. Since mechanical energy transfer is involved in multiple stages during the manufacturing of a tablet, the piezoelectric surface charges might have a significant contribution to the same. Hence, we performed compactibility and tableability studies for both piezoelectric crystal **1** and non-piezoelectric crystal **2** (Fig. 6e–g, Supplementary Fig. 25). The mechanical impact was acted on bulk crystals in two steps: they were milled at first using planetary ball-mill (Supplementary Note 8) and then tablets were made through direct compression using controlled force. Compactibility is a measure of particle-particle interaction within a tablet and is represented by a plot of tablet tensile strength vs porosity⁵⁶. Fig. 6e indicates the higher tensile strength of crystal **1** compared to crystal **2** at a comparable porosity range. For example, calculated tensile strength at zero porosity (τ_0) was relatively higher in crystal **1** (6.04 MPa) in comparison with crystal **2** (4.61 MPa) (Fig. 6e). As, τ_0 is an indicator of inter-particulate bonding strength, the higher value of τ_0 in crystal **1** is in good agreement with the fracture-induced charges in piezoelectric crystal **1** which contributes to the bonding strength of particles in tablets. Moreover, some previous studies have demonstrated a positive correlation between true density and inter-particulate bonding strength⁵⁷. In the present investigation, the true density of crystal **1** and crystal **2** was similar (Supplementary Table 5). Despite the similar true

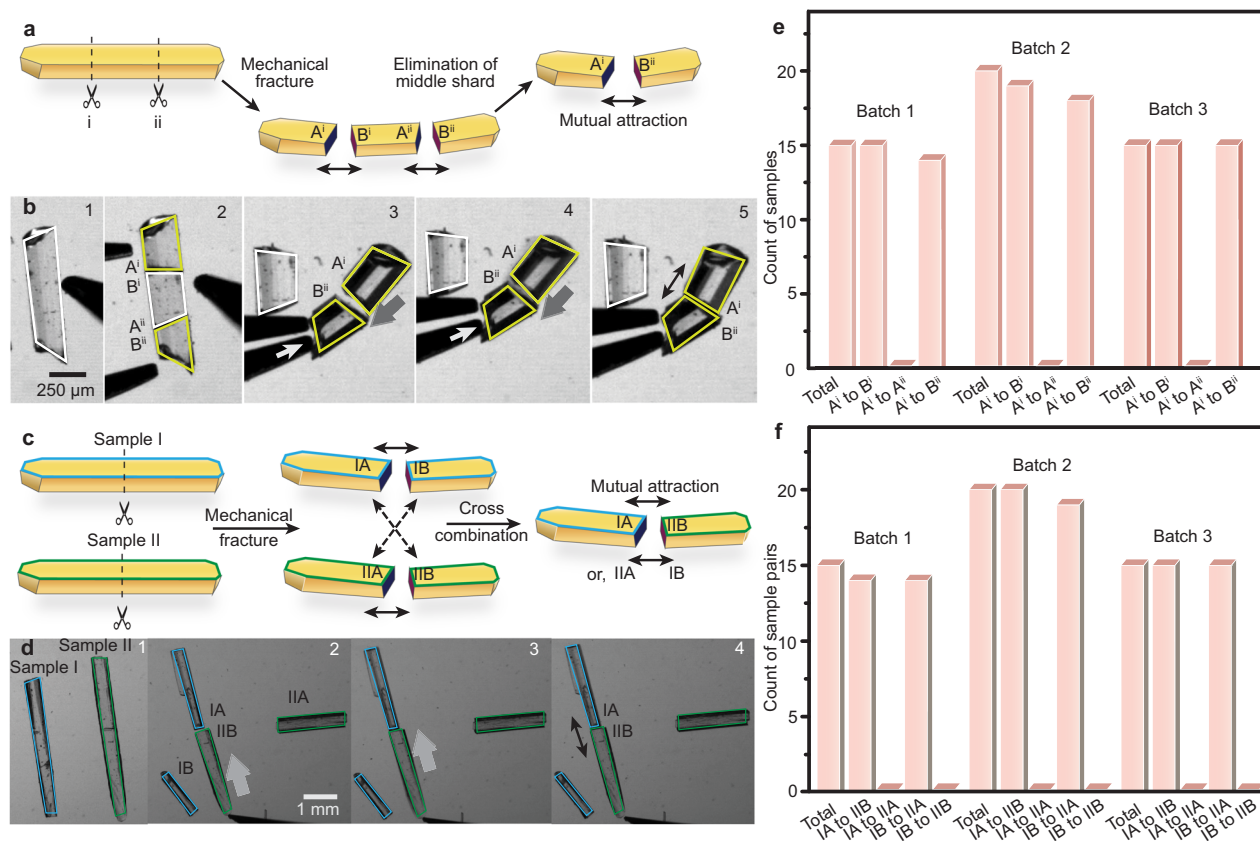


Fig. 5 | Multiscale analyses of mutual attraction behaviour between fractured shards of crystal 1. a Schematic representation of initiation of fracture at two locations (i and ii) in a single crystal, generating freshly cleaved surfaces A'/B' and A''/B''. **b** Video grabs (images 1–5) showing substantial mutual attraction between A'/B''. **c** Schematic showing mechanical fracture of two separate crystals (sample I and

II) generating freshly cleaved surfaces (IA/IB and IIA/IIB). **d** Video grabs (images 1–5) showing substantial mutual attraction between IA/IIB. **e, f** 3D bar chart showing assessment of mutual attraction behaviour among the fractured shards for cases (a) and (c) respectively. The fracture tests were performed on more than 50 crystals, harvested from three different batches. See also Supplementary Movies 10 and 11.

density, the higher inter-particle bonding strength of crystal 1, further points toward the contribution of fracture-induced charge in piezoelectric crystal 1, resulting in higher compactibility.

Mechanical properties of particulates and inter-particle interaction together contribute to the tabletability of a material^{57–59}. Thus, nanoindentation was performed on pristine crystals prior to the tabletability experiment which reveals comparable mechanical properties of these two API crystals under compressive indentation stress (Supplementary Figs. 26 and 27, Supplementary Table 6). Higher tensile strength of tablets from crystal 1 compared to crystal 2, at all compaction pressures, indicates better tabletability of the former (Fig. 6f). Further, to understand the time dependency of surface charges in tablet strength, we performed compactibility studies of crystal 1 at different time intervals. The relatively higher τ_0 (6.64 MPa) of crystal 1 just after compaction (0 h) compared to 24 h (6.04 MPa) further supports the role of surface charges (Fig. 6g) and is consistent with the decay of charge with time in single crystals as shown by KPFM experiments (Fig. 4d).

To evaluate the generality, we studied the compactibility behaviour of the pair of crystal 3 (NCS) and crystal 4 (CS). We observed better compactibility in the case of crystal 3 when compared to crystal 4 powders (Supplementary Fig. 28, Supplementary Note 9) which is consistent with our analysis. Hence, it can be stated further that, surface charge generated during mechanical deformation can contribute to the increased bonding strength which may enhance the compactibility as well as tabletability of a piezoelectric pharmaceutical powder, as compared to non-piezoelectric crystals, provided all other attributes are comparable.

Discussion

We demonstrate the electromechanical coupling as a source of surface charges in mechanically impacted piezoelectric pharmaceutical crystals, using a multiscale approach. In the levofloxacin hemihydrate (crystal 1), a model piezoelectric system, we observed the generation of colossal long-lasting surface charges on mechanically fractured single crystals, which drive an attraction-based ultra-fast actuation among the deformed shards and large spherical agglomeration in bulk powders. In contrast, no such observation was found in the non-piezoelectric crystals of nalidixic acid (crystal 2), despite having comparable mechanical properties. The underlying mechanism for the generation of long-lasting surface charges can be attributed to the mechanical fracture-driven reorientation of the linearly arranged unit cell dipoles (micro-dipoles) along the polar axis, resulting in opposite polarity on the counter faces of fractured NCS crystals, whereas the presence of inversion symmetry nullifies overall polarisation in CS crystals. Nano-level piezo-response of levofloxacin hemihydrate was confirmed from vertical PFM experiments revealing the existence of piezoelectric domains. KPFM experiments reveal substantial surface potential on the fracture surfaces of the single crystals, which are oriented nearly perpendicular to the polar axis and decay with time in an asymptotic manner. Extensive KPFM experiments indicate the existence of one type of charge on one side of the fracture surface. In other words, the opposite faces of a fractured crystal possess complementary charges. In addition, an examination of the actuation behaviour of shards generated by inducing multiple fractures on crystals confirms that the inter-particle attraction behaviour depends on the nature of the charge (polarity) but not on whether the shards

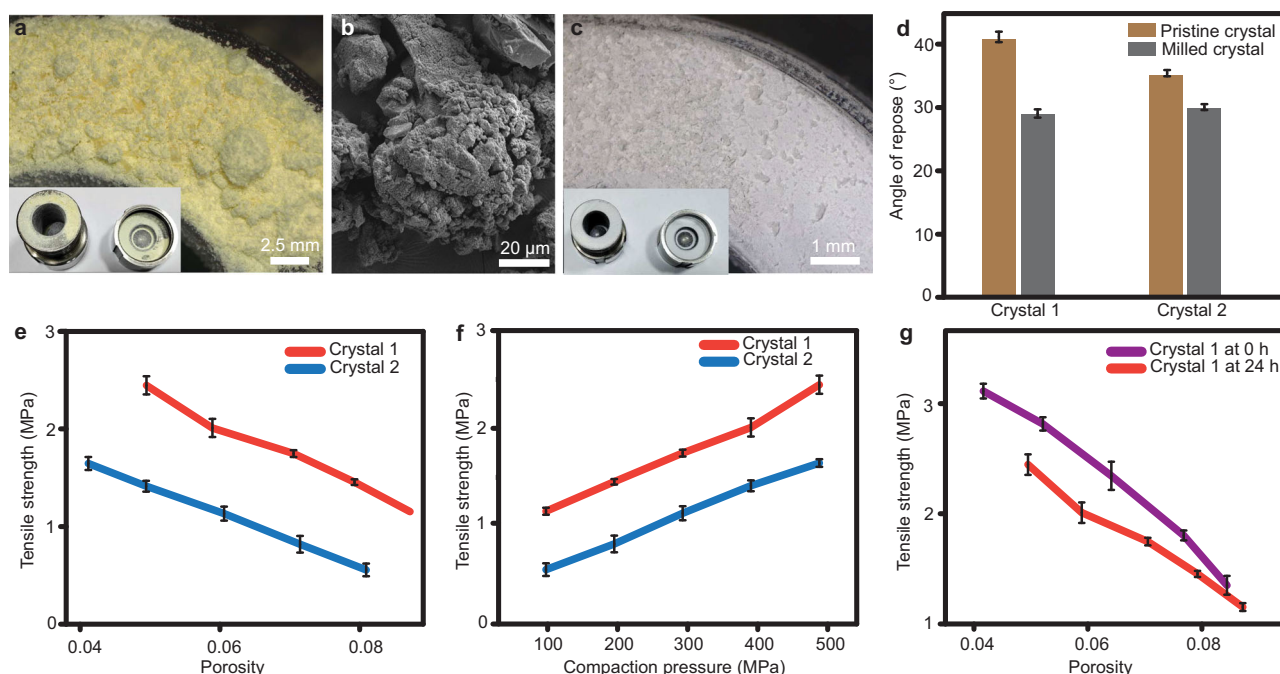


Fig. 6 | Effect of surface charges on bulk powder properties relevant to the chemical industry. **a** Optical microscopy image of milled crystal **1** showing the formation of spherical agglomerates. **b** Scanning electron microscopy image of such an agglomerate of crystal **1**. **c** Optical microscopy image of milled crystal **2** showing few small aggregates with mostly fine powders. **d** Comparison of the angle

of repose for both pristine and milled crystals **1** and **2**. **e** Comparison of compactibility and **f** tabletability of crystals **1** and **2**. **g** Compactibility of crystal **1** measured at 0 h and 24 h after milling showing the time-dependent effect of charge. Experiments were performed on five samples (independent measurements) at each compaction pressure for (**e–g**). Source data are provided as a Source Data file.

come from the same crystal or not. Finally, the enhancement of flowability (due to spherical agglomeration) and compactibility (due to higher particle-particle attraction) of milled bulk piezoelectric crystals show a good correlation with the fracture-induced surface charges established at the single particle level. Extreme modification of surface properties observed on piezoelectric crystals, post-mechanical impact, also suggests that the mechanical properties and crystal structure information together have to be considered for predicting bulk properties of organic crystalline materials. The lower extent of surface charges observed in highly humid conditions suggests that the problems that arise due to surface charges could be mitigated by carrying out the unit operations in humid conditions if this option is viable. Alternatively, the negligible attraction observed upon fracturing crystals parallel to the polar axis indicates that the crystal morphology control could also be another means to mitigate the charge-related issues in bulk powders. Since the NCS crystal forms are abundant among APIs, nutraceuticals, agrochemicals, etc., they can potentially develop surface charges, hence our study has broad implications for a range of molecular materials.

Methods

Crystallisation

All starting materials were purchased from TCI. All other reagents and solvents were purchased from commercial sources and used without further purification. Crystals of the APIs were grown by the slow evaporation method from suitable solvents as follows: acetonitrile (crystal **1**), chloroform (crystal **2**), ethanol (crystals **3**, **4**, and **6**) and hexane/benzene mixture (crystal **5**) respectively. Crystals suitable for testing mechanical properties and single crystal data were obtained in 4–5 days in all the cases.

Single crystal X-ray diffraction

Single crystal X-ray diffraction (SCXRD) data on a pristine single crystal was collected on Rigaku Cu Synergy-i at room temperature with a Cu-

K_{α} source. Data reduction was performed using CrysAlis Pro and structure solution and refinement was done in Olex 2-1.5⁶⁰. Images of crystal structures were constructed using Mercury (version 2022.3.0) and Chimera software (version 1.17.1).

Powder X-ray diffraction

Powder X-ray diffraction (PXRD) patterns were obtained on a Rigaku SmartLab benchtop with Cu- K_{α} radiation at RT. The tube voltage and current were ramped up to 40 kV and 15 mA respectively. Samples were scanned between 5° and 50° of 2θ with a step size of 0.02°. Calibration of the instrument was done with a silicon standard.

Scanning electron microscopy

Scanning electron microscopy (SEM) was performed using Zeiss DSM 950 operating at 10 kV where tungsten filament was used as the electron S4 source. The samples were sputtered with gold (nano-sized film) using an SCD 040 Balzers Union sputterer before acquiring SEM images to avoid charging during the experiment.

Piezoelectric constant measurements

The piezoelectric constant d_{33} measurements were carried out using the “quasi-static” or so-called “Berlincourt” method using the Piezo-Meter System (PIEZOTEST, PM300). The system works by subjecting the sample in the form of a pellet (un-poled) to a low-frequency force and processing the electrical signals to show a direct reading of piezoelectric constant d_{33} .

Piezo-response force microscopy

The PFM measurements were performed using a commercial atomic force microscope (Oxford instrument, Asylum Research Cypher ES). Conductive Pt/Ir-coated silicon probes (NANOSensors, ATEC-EFM-10, resonance frequency: 75 kHz) were employed for the experiments. The PFM technique works under the principle of converse piezoelectric effect to induce mechanical deformations when a low

amplitude sinusoidal AC voltage signal is applied with a conducting AFM tip to any piezoelectric sample surface. For our system, we performed all PFM measurements on the pristine surfaces. To achieve a good signal-to-noise ratio, we performed the measurements using Dual AC Resonance Tracking (DART) PFM mode⁴¹. The spring constant of the probe for detecting the piezoelectric performance is 2–3 Nm⁻¹. An ac bias of 2 V was applied on both crystal **1** and **2** pristine surfaces for comparing their piezo-response (surface tuning) when the excitation frequency sweeps around the contact resonance frequency in DART mode. For PFM imaging of the pristine surface of crystal **1**, a 2 V ac drive voltage was applied to the probes (NANOSensors, ATEC-EFM-10, resonance frequency: 75 kHz) in a commercial Asylum Research MFP 3D system.

Kelvin probe force microscopy

KPFM is a noncontact technique that measures the local nanoscale surface potential and topography, directly correlating the two. Measurements were performed by commercial atomic force microscopy system Asylum Research Cypher ES with Ti/Ir-coated tip [ASYLEC-01-R2] with tip radius of 25 nm, resonant frequency of 75 kHz and force constant k of 2.8 Nm⁻¹. All KPFM scans were performed in dual-pass mode with a topographic scan in tapping mode and a lift height of 50 nm at RT. For measuring the fracture-induced surface potential, crystal **1** was mounted on a conductive substrate (FTO) and the mechanical fracture was performed using a tweezer to expose the freshly fractured surface. During the mechanical fracture, no direct contact occurred between the fractured surface and the metal tweezer. To measure surface potential across a crack junction, a fractured single crystal of **1** was mounted on an AFM stub over conducting carbon tape where complimentary surfaces were in contact. All the experiments were carried out at an RH of 60% except the humidity-dependent experiments where KPFM was performed immediately after mechanical fracture at two different relative humidities of 60% and 91%.

Nanoindentation

Nanoindentation experiments were performed on the major faces of single crystals **1** and **2** using the TI Premier from Hysitron, Minneapolis, USA. The indenter is equipped with a scanning probe microscope (SPM) for capturing post-indent impressions in-situ. The load-controlled experiments were performed using a Berkovich tip (three-sided pyramidal tip with a total included plane-edge angle of 142.3°) of radius ≈150 nm. The hardness (H) and elastic modulus (E) were extracted using the standard Oliver–Pharr method⁶¹.

Optical microscopy equipped with a high-speed camera

All the fracture experiments were carried out under a Leica (M205 FCA) optical microscope equipped with a high-speed camera (Fastcam Mini) using a pair of tweezers and a needle. The videos were recorded in the range of 6–12× magnification and at 500–5000 fps. Frame-by-frame analysis of the captured videos was done using Fastcam software (PFV) to visualise the mechanical actuation in slow motion and real time and to identify charge-induced inter-particle attraction behaviour.

Dipole moment calculation

The nonperiodic molecular cluster was created from a single unit cell with atoms from available X-ray crystal structures. It was used to calculate the unit cell dipole moment at the PM6 semiempirical level of theory in Gaussian.

Statistical analysis

50 crystals of **1**, harvested from three different batches were used for the analysis of the attraction behaviour of fractured shards. Two fractures were generated in a single crystal to analyse the affinity

between the complementary vs non-complementary pieces. Next, 50 pairs of crystal **1** were used for the analysis of the mutual attraction behaviour of fractured shards.

Flowability studies

Angle of repose. The simplest method for the determination of the angle of repose is the “poured” angle. A funnel with a wide outlet was affixed at a distance of 10 cm above the bench, where a piece of paper was placed directly beneath the funnel. A crystalline sample (5 g) was added while the funnel was closed. The contents were flown through and collected on the paper. The diameter of the cone (D) and the height of the pile were measured by ruler (h).

The angle of repose (θ) is calculated by $\tan^{-1}(2h/D)$

Compressibility-tabletability-compactability (CTC) profile

Particle size distribution (PSD). PSD measurement of crystals **1** and **2** was performed microscopically. Mounting of samples was done using silicone oil and was observed at 500× magnification using an optical microscope (Leica DMLP, Leica Microsystems, Wetzlar, Germany). Photomicrographs were captured with a JVS colour video camera and analysed using Linksys software. The length of the longest axis of around 300 individual particles was counted for each sample and D_{10} , D_{50} and D_{90} were calculated.

True density. Helium gas pycnometry was utilised to measure true density (Smart Pycno30, Smart Instruments, Mumbai, India). Sample powder was poured into the sample cell up to 3/4th of its volume. Initially, a known reference volume of pressurised helium gas was allowed to pass into the reference cell and the first pressure reading (P_1) was recorded. Then, the same gas was transferred from the reference to the sample cell and a second pressure reading (P_2) was recorded. These values of P_1 and P_2 were incorporated into Eq. (1) to calculate the true volume V_p .

$$V_p = V_c - V_r \left(\frac{P_1}{P_2} - 1 \right) \quad (1)$$

Where V_c and V_r are the cell volume and reference volume having values of 18.9522 and 11.9587 cm³ g⁻¹ respectively. To obtain the true density, the sample mass was divided by true volume (V_p).

Preparation of compacts at different compaction pressure. Compacts of powder samples (≈200 mg) were prepared by applying different compaction pressures (97.5–487.9 MPa) in a hydraulic press (Type KP, Sr. No. 1125, Kimaya Engineers, Maharashtra, India) using a round and flat-faced punch-die set with 8 mm diameter. 1 min dwell time was applied for each compaction. Compaction pressure was calculated by using Eq. (2).

$$P = \frac{F}{A} \quad (2)$$

Where, F is the applied force in N, and A is the surface area of the flat punch-die set in mm². Compacts were analysed for different post-compaction parameters, including weight, thickness, and breaking force.

Calculation of tensile strength and porosity. The breaking force and dimensions of the compacts were measured 24 h after preparation, using a tablet hardness tester (Tablet hardness tester, Erweka, USA) and a digital vernier calliper (Digimatic Mitutoyo Corporation, Japan), respectively. Tensile strength (τ) was calculated using Eq. (3)⁶²

$$\tau = \frac{2F}{\pi dt} \quad (3)$$

Where F is the breaking force, d is the diameter, and t is the thickness of the compact.

The porosity (ε) of the compacts was calculated by the Eq. (4)

$$\varepsilon = 1 - \frac{\rho_c}{\rho_t} \quad (4)$$

Where ρ_c is the density of the compact, and ρ_t is the true density of the powder.

In a separate set of experiments, to understand the time dependency of surface charges in tablet strength, measurement of tensile strength and porosity of the crystal **1** and crystal **3** compacts were performed immediately after preparation (0 h).

Further, tensile strength at zero porosity (τ_0) was calculated by applying Ryshkewitch analysis (see Eq. (5)) to the tensile strength and porosity value of the compacts.

$$\tau = \tau_0 e^{-k\varepsilon} \quad (5)$$

Where k is a constant.

τ_0 represents the bonding area-normalised inter-particulate bonding strength of the material undergoing compaction. A higher value of τ_0 indicates higher bonding strength.

Data availability

The data that support the findings of this study are available from the corresponding author upon request. Source data are provided with this paper.

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Acknowledgements

C.M.R. thanks SERB (CRG/2021/004992) and the Swarnajayanti Fellowship (DST/ SJF/CSA-02/2014-15) for funding and IISER Kolkata for facilities. K.D. thanks CSIR for SRF. I.G. thanks PMRF for the fellowship. The authors wish to acknowledge Dr Surojit Bhunia for his help with the initial experiments and analysis of results. The authors thank Dr S. Basavaraja from Toshniwal Brothers Pvt. Ltd., Bangalore for help with PFM experiments.

Author contributions

Mechanical manipulation of crystals and quantification of performance parameters were done by K.D.; Crystallisation, nanoindentation and SEM were performed by K.D.; I.G. performed KPFM and PFM experiments; I.G. and K.D. analysed KPFM and PFM results. S.C. performed and analysed tabletability measurements under the supervision of A.K.B.; A.G.N. performed flowability measurements under the supervision of D.K.; S.K.K. performed piezometry measurement; S.M. and K.D. performed multi-fracture experiments; K.D. and C.M.R. planned all the experiments, analysed the results and co-wrote the manuscript with inputs from all co-authors and C.M.R. coordinated the whole project.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41467-025-58138-1>.

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Peer review information *Nature Communications* thanks the anonymous reviewers for their contribution to the peer review of this work. A peer review file is available.

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