

Saccharin as a salt former. Enhanced solubilities of saccharinates of active pharmaceutical ingredients†

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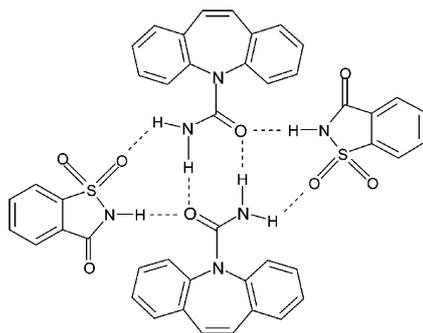
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Saccharin, acting as a weak acid, forms salts with basic APIs and these salts have the desirable property of enhanced water solubility.

The solid state chemistry of active pharmaceutical ingredients (APIs) is a subject of fundamental, practical and legal interest.¹ Polymorphs, solvates (pseudopolymorphs), salts, molecular complexes and co-crystals of APIs represent extensions of chemical space wherein enhanced or new chemical and physical properties may lead to extended patent coverage and consequent legal protection of products.² These matters are of great concern to innovator and generic pharmaceutical companies alike, even as some of the underlying chemical principles are only now being understood.

Almarsson and Zaworotko have proposed the use of synthon theory³ to design pharmaceutical co-crystals.⁴ According to them, a co-crystal is “a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion”. This definition is used in the present paper without any other implication.⁵ The co-crystals that they have designed and/or claim comprise what they refer to as a “co-crystal former” hydrogen bonded to an API. The structure of the co-crystal former is derived retrosynthetically from that of the API by invoking appropriate hydrogen bonded supramolecular synthons. For example, in the carbamazepine–saccharin co-crystal (Scheme 1), multipoint N–H⋯O hydrogen bonding is the interaction of choice.⁶ Saccharin is the co-crystal former in this example and



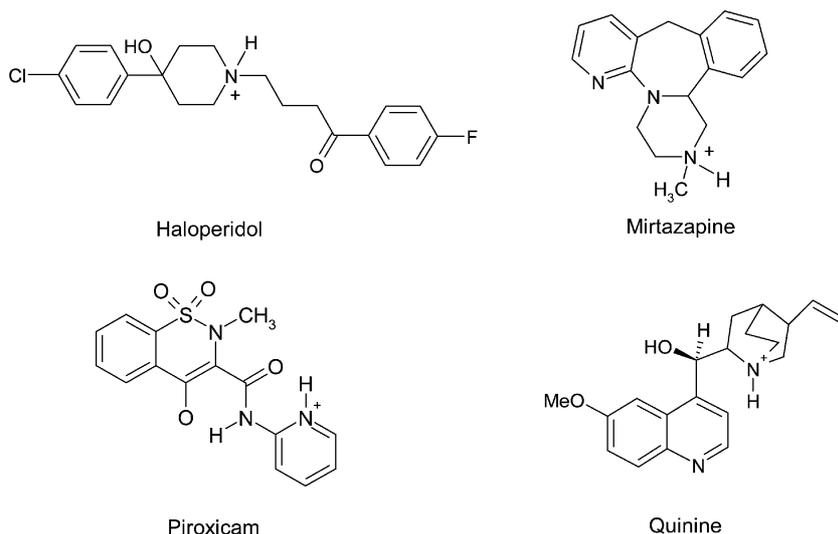
Scheme 1 Supramolecular synthon in the carbamazepine–saccharin co-crystal. See ref. 6.

† Electronic supplementary information (ESI) available: ORTEP diagrams for haloperidol, mirtazapine, piroxicam and quinine saccharinates. See <http://www.rsc.org/suppdata/cc/b4/b416137h/>
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behaves both like a hydrogen bond donor (N–H) and acceptor (S=O).

However, we have found that rather than behave as co-crystal former, saccharin acts as a weak acid when it is co-crystallized with APIs that contain an adequately basic centre. In these cases, protonation of the API by saccharin is facile and what are obtained are not co-crystals, as defined above, but salts, that is API saccharinates. We co-crystallized haloperidol, mirtazapine, piroxicam and quinine (Scheme 2) with saccharin and Table 1 gives salient properties of the resulting API saccharinates.‡ In three cases a crystalline salt was isolated and characterized satisfactorily with IR, NMR, DSC and single crystal X-ray diffraction. In each of these cases, it was shown (difference Fourier maps) that proton transfer occurs from the saccharin to the API tertiary amine N-atom. For piroxicam, however, what is obtained is not a salt but a co-crystal in which the API exists as a zwitterion. Quantitative conversion to the saccharinate or co-crystal was also achieved after 15 minutes of grinding in each case. Fig. 1 shows the crystal structures of the saccharin adducts of the four APIs in this study.§ In haloperidol saccharinate the N⁽⁺⁾–H group of the API cation and the N⁽⁻⁾ group in the saccharin anion are not hydrogen bonded. For mirtazapine and quinine such hydrogen bonds are observed along with other hydrogen bonds.

Almarsson and Zaworotko have emphasised that enhanced water solubility is a desirable property of API co-crystals.⁷ However, we have found that the enhancements in solubility are greater in our API saccharinates than in cases where saccharin acts merely as a hydrogen bonded co-crystal former. For example, carbamazepine is insoluble in water and so is its co-crystal with saccharin. However saccharinates of haloperidol, mirtazapine and quinine are freely soluble in water. From Table 1 the reader will appreciate that the device of saccharinate formation of an API is a convenient and readily applicable method to give soluble drug formulations. The example of piroxicam confirms that co-crystals are less soluble than salts. This API forms a zwitterionic co-crystal with saccharin (pure piroxicam exists as a neutral molecule in the solid state)⁸ which is much less soluble than the saccharinates of haloperidol, mirtazapine and quinine. The literature on saccharin salts is scanty. There are claims of API saccharinates being less soluble than the corresponding hydrochlorides,⁹ and there is also a solitary example of an alkaloid (vincamine) that is rendered more soluble by salt formation with saccharin.¹⁰ The CSD also contains some examples of deprotonated saccharin.¹¹ However, we believe that our results are the first demonstration of the general use of saccharin as a weak acid in pharmaceutical chemistry, and the results show the variety of APIs that may thus form highly soluble saccharinates.



Scheme 2 APIs in this study represented as found in their saccharin adduct (cation or neutral).

Table 1 Solubility and other properties of API–saccharin adducts in this study

API	Use as a drug	Nature of adduct	mp/°C	R-factor (100 K)	Hydrogen bond(s) present	Water solubility/mg mL ^{-1a}			pH of saturated solution
						API	Marketed product	Saccharinate	
Haloperidol	Antipsychotic	Salt	140.6	0.046	N–H···O O–H···O	<0.01	<0.01	6.08	5.44
Mirtazapine	Antidepressant	Salt hydrate	106.5	0.045	N–H···N O–H···O O–H···N	<0.05	<0.05	2.08	5.85
Piroxicam	NSAID	Co-crystal	222.2	0.042	N–H···O	<0.10	<0.10	<0.10	3.27
Quinine	Antimalarial	Salt	185.9	0.064	O–H···N N–H···N	<0.10	1.96	5.40	5.55

^a The solubilities were determined with UV spectroscopy.

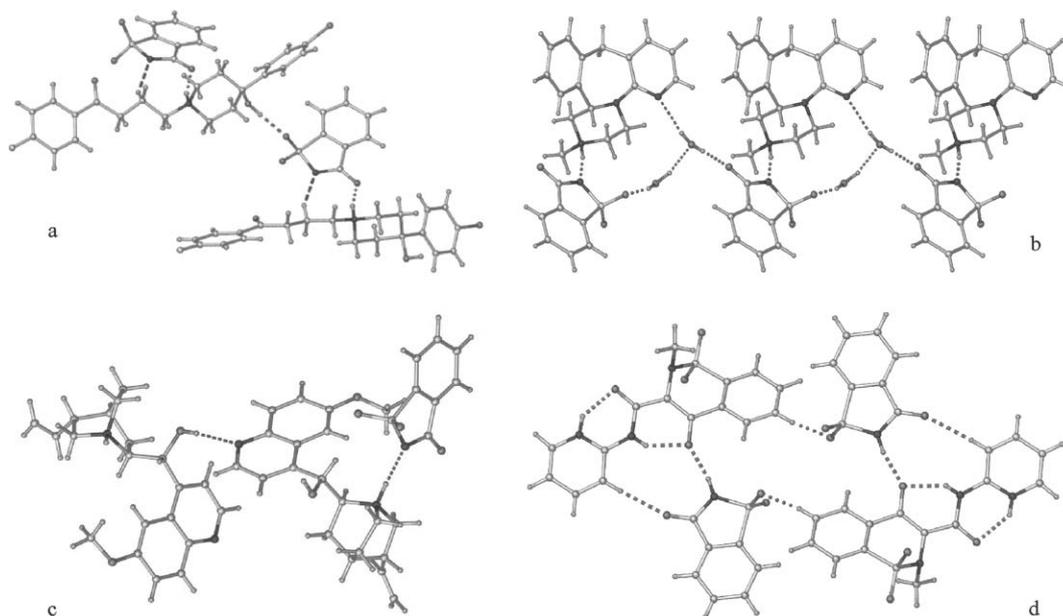


Fig. 1 API–saccharin adducts in this study: (a) salt formation with haloperidol showing N⁽⁺⁾–H···O, C–H···N⁽⁻⁾ and O–H···O hydrogen bonds; (b) salt formation with mirtazapine showing N⁽⁺⁾–H···N⁽⁻⁾, O–H···O and O–H···N hydrogen bonds; (c) salt formation with quinine showing N⁽⁺⁾–H···N⁽⁻⁾ and O–H···N hydrogen bonds; (d) co-crystal formation in piroxicam–saccharin showing N⁽⁺⁾–H···O, N–H···O⁽⁻⁾ and C–H···O hydrogen bonds. The API exists as a zwitterion.

There are several advantages to using saccharin in this manner. Firstly it is a GRAS (generally recognized as safe) compound and therefore the API saccharinates do not need exhaustive and separate clinical trials, barring perhaps toxicological studies. The high water solubilities of the saccharinates mean that they can be used in injectible and drop formulations. Because saccharin is a potent sweetener, it masks the bitter taste of many drugs and the saccharinates may be used in pediatric medication. Finally, the pH of the saccharinate solutions are higher (pH 5–6) than the corresponding hydrochlorides and other usual salt formulations (pH 2–3). This means that injectible forms of the drug are less likely to cause irritation and other undesirable side effects on the skin.

Chemically and legally, the saccharinates of the type that we report are fundamentally different from the co-crystals claimed in recent patent applications.^{4,7,12} Most significantly a co-crystal as defined in these applications consists of two components each of which is capable of a unique existence. API saccharinates consist of cations and anions, which are not capable of unique existence. In the co-crystals, the constituents are held by hydrogen bonds in multipoint assemblies and all the molecules are neutral (except where a co-crystal former is crystallized with a salt¹²). Hydrogen bonding is also important in our saccharinates but there is no necessity for the formation of an $N^{(+)}-H\cdots N^{(-)}$ hydrogen bond. Our salts contain $N^{(+)}-H\cdots O$ and $O-H\cdots N^{(-)}$ hydrogen bonds and proton transfer has occurred in solution prior to crystallization. While the strategy outlined by Almarsson and Zaworotko is an elegant route to co-crystals based on specified supramolecular synthons, our results show that one of the most desirable properties of APIs, namely enhanced water solubility, may be achieved much more satisfactorily with acid–base chemistry thus constituting a further extension of chemical and pharmaceutical space.

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Notes and references

‡ The free base API was used as such, or generated from the hydrochloride. Co-crystallization was carried out from 1 : 1 MeOH–EtOAc.

§ X-Ray data were collected on a Bruker SMART 4K-CCD area detector at 100(2) K. *Crystal Data*: haloperidol saccharinate: (C₂₁H₂₄ClFNO₂).(C₇H₄NO₃S), *M* = 559.04, monoclinic, *a* = 19.0609(10),

b = 7.2197(4), *c* = 21.5624(12) Å, β = 113.961(2)°, *V* = 2711.6(3) Å³, space group *P*2₁/*m*, *Z*' = 2, μ (Mo–K α) = 0.266 mm⁻¹, size 0.38 × 0.14 × 0.11 mm. 11182 total reflections of which 4610 were independent, 3746 observed [*I* > 2 σ (*I*)]. Refinement against *F*² with 455 parameters, *R*₁ [*I* > 2 σ (*I*)] = 0.0468. Mirtazapine saccharinate: (C₁₇H₂₀N₃).(C₇H₄NO₃S).(H₂O)_{1.34}, *M* = 473.84, monoclinic, *a* = 9.5791(12), *b* = 26.733(3), *c* = 9.4055(12) Å, β = 109.511(2)°, *V* = 2270.2(5) Å³, space group *P*2₁/*c*, *Z*' = 4, μ (Mo–K α) = 0.184 mm⁻¹, size 0.50 × 0.40 × 0.16 mm. 12697 total reflections of which 4002 were independent, 3485 observed [*I* > 2 σ (*I*)]. Refinement against *F*² with 319 parameters, *R*₁ [*I* > 2 σ (*I*)] = 0.0392. Piroxicam–saccharin: (C₁₅H₁₃N₃O₄S)(C₇H₅NO₃S), *M* = 514.52, triclinic, *a* = 9.5117(8), *b* = 10.3862(9), *c* = 12.6635(11) Å, α = 66.983(2), β = 71.011(2), γ = 89.380(2)°, *V* = 1078.99(16) Å³, space group *P*1, *Z*' = 2, μ (Mo–K α) = 0.303 mm⁻¹, size 0.14 × 0.12 × 0.11 mm. 7625 total reflections of which 4011 were independent, 3208 observed [*I* > 2 σ (*I*)]. Refinement against *F*² with 388 parameters, *R*₁ [*I* > 2 σ (*I*)] = 0.0423. Quinine saccharinate: (C₂₀H₂₅N₂O₂).(C₇H₄NO₃S), *M* = 507.60, orthorhombic, *a* = 9.607(3), *b* = 8.634(3), *c* = 30.371(9) Å, *V* = 2519.2(13) Å³, space group *P*2₁2₁2₁, *Z*' = 2, μ (Mo–K α) = 0.172 mm⁻¹, size 0.26 × 0.20 × 0.16 mm. 8453 total reflections of which 4368 were independent, 2953 observed [*I* > 2 σ (*I*)]. Refinement against *F*² with 338 parameters, *R*₁ [*I* > 2 σ (*I*)] = 0.0647. CCDC 253201–253204. See <http://www.rsc.org/suppdata/cc/b4/b416137h/> for crystallographic data in .cif or other electronic format

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