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An Investigation into the Influence of Counterion on the Properties of Some Amorphous Organic Salts

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Abstract: Amorphous solids and crystalline salts are both of interest as a means of improving the dissolution characteristics and apparent solubility of poorly water soluble active pharmaceutical ingredients which have low bioavailability in humans. The theory and selection of both crystalline drug substance salt forms and amorphous products have been extensively studied. However, less is known about the impact of different counterions on the properties of amorphous drug substance salts. In this study, several salts of either nicardipine or propranolol were prepared and characterized with respect to glass transition temperature, crystallization tendency and moisture sorption behavior. Although the moisture sorption behavior and crystallization tendency varied depending on the counterion used, no trends were readily apparent. The glass transition temperature was found to be dependent on the counterion used to form the salt, and was higher in all instances for the salts than for the neutral compound. Several molecular descriptors were calculated for the various counterions, and multivariate analysis was used to build a model that successfully correlated T_g with a number of these parameters. Important parameters which influenced T_g included counterion pK_a and electrophilicity index. In conclusion, it is apparent that, as for crystalline salts, the counterion has an effect on the properties of amorphous materials.

Keywords: Amorphous; salts; glass transition; pK_a; counterion

Introduction

The thermodynamically stable crystalline solid is generally the preferred form for pharmaceuticals; however, due to modern trends of using high throughput screening for drug discovery, many compounds have extremely poor aqueous solubility[1] and dissolution characteristics. This low solubility can result in low bioavailability and lead to many challenges in the development of such compounds. Hence, solubility is one of the earliest properties measured for new molecules and is often used as a criterion to rank them in terms of developability.[2] Solubility and dissolution rate may be improved by affecting a bulk property such as particle size[3] or addressed on a molecular level for ionizable molecules by salt formation.[4] For nonionizable molecules improvements

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may be gained through the use of metastable polymorphs,[5] amorphous materials[6] and cocrystals.[7]

Of the solid state approaches mentioned, amorphous materials often show substantial improvements in solubility and dissolution.[8] However, in general, the commonly held view is that amorphous materials are undesirable forms, except in the case of parenteral products where a stable amorphous product is often developed to aid rapid dissolution. Amorphous forms tend to be hygroscopic and have low bulk powder densities giving rise to less than optimal mechanical properties[9] and poor chemical and physical stability,[10] potentially leading to short and unpredictable storage lives. As the amorphous phase is metastable with respect to the crystalline, there is the possibility it may crystallize over time, negating any dissolution improvement. Furthermore, as a metastable form, amorphous forms are more kinetically soluble than the crystalline counterpart and any "wet" processes, such as wet granulation, may be problematic because any dissolution creates supersaturation relative to crystalline form and hence the labile solution may spontaneously crystallize.

A thorough understanding of the amorphous state of a compound is also important because a small amount of amorphous material in a crystalline sample may have a large effect on the bulk properties of the sample.[11] Unwanted amorphous material may be unintentionally produced as byproduct of some unit operations such as lyophilization, milling and spray drying or from suboptimal crystallization procedures.

Despite the aforementioned problems, interest in amorphous compounds is increasing with the recognition that using the amorphous form of a drug can be a useful approach to improve the dissolution behavior, apparent solubility via superstaturation and ultimately bioavailability of poorly water-soluble drugs,[12] particularly when stabilized by a polymer in a solid dispersion.[13–16] Because of the issues discussed, many studies of amorphous materials have appeared in the pharmaceutical literature in recent years. However, very few studies have probed a potentially important group of amorphous materials, namely, pharmaceutical salts.

It is well-known that the properties of crystalline materials with ionizable groups can be changed by forming salts, and although this strategy is commonly employed for crystalline phases,[17,18] little attention has been paid to the role of the counterion on amorphous properties. To our knowledge, only a limited number of studies have been conducted in this area. Tong and Zografi compared the properties of amorphous indomethacin and its sodium salt.[19] They found the amorphous salt has a much higher glass transition temperature (T_g) compared to that of the amorphous free compound. In an extension of this work, the effect of several other metallic cations on the T_g of amorphous indomethacin salts was investigated.[20] It was found that T_g depended on the cation and decreased systematically down the series lithium to cesium and that the T_g of the neutral amorphous phase was lower than any of the salts. This change in T_g was attributed to an increased electrostatic interaction of smaller ions with the carboxylate group of indomethacin leading to a decrease in the molecular mobility and an increase in T_g. Comparable phenomena have been noted previously for inorganic salts.[21,22] Salt formation between the ionized amine of loperamide and carboxylate group of poly(acrylic acid) was cited as a cause of increased T_g in solid dispersion of loperamide and

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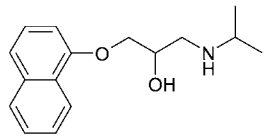
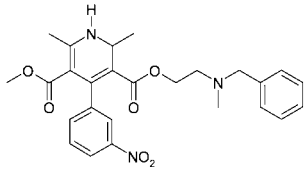
Table 1. Model Compounds Used in This Study

	pKa[57]	MW
Propranolol	9.5	259.3
		
Nicardipine	8.6	479.5
		

poly(acrylic acid).[23] Thus it appears that salt formation will increase T_g relative to the neutral form of the compound.

In order to address further the hypothesis that amorphous salt forms will have higher T_g than the amorphous free compound, we have studied the properties of a number of amorphous salts of two basic compounds, propranolol and nicardipine (Table 1). Propranolol is a highly lipophilic, nonselective beta blocker. Nicardipine is a dihydropyridine calcium-channel blocking agent used for the treatment of vascular disorders. These compounds were chosen as they are basic and both have reasonably high pK_a values: a secondary amine with a pK_a of 9.5 for propranolol and a tertiary amine with pK_a of 8.6 for nicardipine, suggesting that salt formation may be likely with a wide range of acidic counterions. The main objective of the study was to establish if the solid state properties of these amorphous materials, in particular their T_gs, could be manipulated by changing the counterion. A secondary objective was to probe the relationship between the properties of the counterion used to form the salt and the resultant T_g. Partial least-squares projection to latent structures (PLS)[24,25] has been used to find quantitative structure−activity relationships (QSAR) between molecular descriptors and a property of interest,[26–28] and a similar approach was used in this study.

Experimental Details

Nicardipine hydrochloride, citric, benzenesulfonic, oxalic, benzoic, methanesulfonic, phosphoric, sulfuric and *p*-toluenesulfonic acids were purchased from Sigma-Aldrich (St Louis, MO). Propranolol hydrochloride was purchased from Spectrum Chemicals (Gardena, CA). Acetic and hydrochloric acids were obtained from Mallinckrodt Chemicals (Phillipsburg, NJ). Tartaric acid was bought from Merck & Co. (Rahway, NJ).

Nicardipine hydrochloride and propranolol hydrochloride were dissolved in water at concentrations of 10 mg/mL. 5 M sodium hydroxide solution was then added dropwise in order to cause precipitation of the free compound. Nicardipine was obtained as a yellow colored amorphous residue and propranolol as white crystalline powder. Because the solubility of both propranolol and nicardipine is low in water, further water was added to dissolve any sodium chloride and the remaining solid was filtered by vacuum and dried at ambient conditions.

As the aqueous solubility of the base material was poor, other organic solvents were used for the acid−base reactions: ethanol for propranolol, and acetone for nicardipine at concentrations of 20 mg/mL. Counterion was then added as aqueous solution to give the required base to counterion molar ratio. Sulfuric acid was diluted to give a 10% w/v solution and then added to the base solution. Volatile solvent was then removed from the salt solutions using a rotary evaporator. Solvent was reduced until only a small volume (less than 1 mL) remained. Often an amorphous residue was observed around the inside of the round bottomed flask. Six mL of distilled water was then added, and the remaining volatile solvent was removed. As well as removing solvent, the rotary evaporator was used to facilitate dissolution of any amorphous residue and reduce the total volume of the solution to 5 mL.

Salt solutions were dispensed into 10 mL vials and freeze-dried using a FTS Lyostar I tray drier (FTS Systems, Stone Ridge, New York). The solutions were frozen at −45 °C for 12 h before a vacuum was applied. At a residual pressure of 100 mT, the temperature of the freeze drier was programmed to −30 °C (24 h) and −10 °C (24 h). Following this procedure the freeze-dried cake was dried under vacuum at 5 °C for 12 h to remove any residual water. The freeze-dried material was then stored in a desiccator over P_2O_5 at 0% RH. Salt formation was confirmed by Raman spectroscopy. It was not possible to prepare all salts for each compound due to the poor response of some salts to the freeze-drying procedure.

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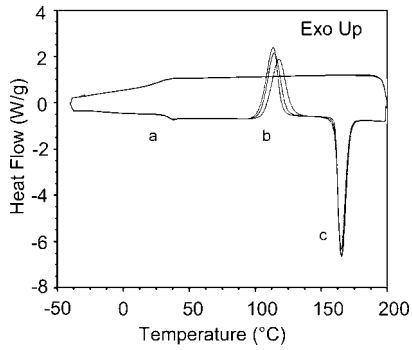

Figure 1. DSC trace of propranolol hydrochloride. Highlighted are (a) a T_g, (b) a recrystallization exotherm and (c) a melting endotherm.

Polarized light and hot stage microscopy was carried out using a Linkam TMS 94 module on a Nikon eclipse E600POL microscope.

Differential scanning calorimetry (DSC) measurements were taken using a TA Instruments Q10 DSC. Approximately 8 mg of sample was placed in a sealed DSC pan with a pinhole in the lid. An indication of the T_g value was obtained by running the following scan: a cool to −40 °C at 30°/min then heating to 20°/min to 250 °C. Traces were then inspected for T_g, recrystallization and melting events. A DSC trace illustrating these events is shown in Figure 1. Once a T_g had been identified further scans were run; in each case the sample was cooled to −40 °C and heated at 20°/min to around 20° above the T_g and cooled back to −40 °C. The cycle was then repeated several times, to erase thermal history and ensure a dry sample, and the T_g was taken from the final heating segment.

Moisture sorption measurements were recorded in a VTI SGA 100 symmetric vapor sorption analyzer. Runs were carried out with a 180 min drying step and subsequent 10% RH increases from 5% to 95% RH. 90 min, or a 0.0001% change in weight, were taken at each RH to allow the sample to equilibrate.

Electronic properties of single molecules of the model drugs and acids were calculated by quantum mechanical methods. Each molecule was fully optimized prior to the single-energy calculation. The methods and basis sets were B3LYP/6-311++g(2d,p)//B3LYP/6-311 g(d,p).[29,30] The program Gaussian 03 was utilized.[31]

PLS models were determined using SIMCA-P+ 11.5 (Umetrics AB, Umeå, Sweden) using the PLS2 NIPALS algorithm.[32]

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Results

After freeze-drying, approximately half of the samples were amorphous, as determined from DSC measurements. Hydrochloride, phosphate and tartrate salts of both compounds were amorphous, but benzoate and acetate salts were never amorphous after freeze-drying. In all, 11 of the 20 salts prepared were amorphous after freeze-drying. Others could be rendered amorphous by heating through the melt and quench cooling. For propranolol besylate, no T_g could be recorded due to its tendency to be crystalline after lyophilization and to recrystallize during cooling from the melt.

Using the DSC method described above, T_gs were measured for amorphous propranolol and nicardipine salts along with the amorphous free bases. Results are shown in Tables 2 and 3. Plots of T_g against pK_a of the counterion for both propranolol and nicardipine salts are shown in Figures 2 and 3. From these figures, two things are apparent. First it can be seen that the T_g of all the salts is raised relative to that of the free base. Second, for the majority of amorphous salts, the T_g scales with pK_a of the counterion: salts containing counterions with a low pK_a have the highest T_gs, and those containing counterions with a high pK_a have the lowest T_g. Hence, the hydrochloride salt has the highest T_g and the acetate salt the lowest for both propranolol and nicardipine. However, as is apparent from Figures 2 and 3, this relationship is not a linear one, especially for those salts made with counterions having a high pK_a, and it is likely that other factors may have an effect including the shape and size of counterion.

The crystallization tendency of the amorphous salts on heating could also be assessed from the DSC data. Only a small number of propranolol salts (hydrochloride, beyslate, tartrate and acetate) and no nicardipine salts were observed to recrystallize on heating (Tables 2 and 3). The recrystallization temperatures (T_c) of the propranolol salts are all elevated compared to that of the un-ionized compound (31 °C) and scale with pK_a of the counterion. Hence the amorphous hydrochloride salt has the highest T_c at 105 °C and the acetate the lowest T_c at 78 °C.

Results from moisture sorption analysis for amorphous propranolol and nicardipine salts are summarized in Tables 4 and 5. From the data, it can be seen that many of the salts are extremely hygroscopic. It is also apparent that the propensity of an amorphous salt to absorb moisture is altered by changing the counterion. For example, propranolol oxalate did not absorb very much moisture (less than 1% at 75%) while the acetate salt picked up more than 60%. In general, the nicardipine salts appear to pick up less moisture than the propranolol salts. There is no apparent link between the pK_a of the counterion in a salt and the salt's moisture sorption profile although interpretation of the results is complicated by the crystallization of some compounds upon exposure to moisture, as indicated by a decrease in weight after an initial increase. Salts which showed signs of crystallization during the aforementioned measurements were propranolol HCl,

Table 2. Change in T_g against pK_a of Counterion Present for Propranolol and Its Amorphous Salts[a]

salt	pK_a of counterion	T_m, °C	T_c, °C	T_g, °C	ΔC_p, J/g/°C	amorphous after freeze-drying?
hydrochloride	−6	161.6	105.4	35.9 ± 0.6	0.47	y
tosylate	−1.34			16.7	0.59	n
mesylate	−1.2	132.5		29.2 ± 3.7	0.17	y
besylate	0.7	87.1	46.5			n
oxalate	1.271			31.5 ± 2.8	0.23	y
phosphate	1.96	43.9		11.3 ± 0.8	0.28	y
tartrate	3.02	143.1	80.1	23.4 ± 0.9	0.65	y
citrate	3.128	124.7		21.3 ± 1.2	0.61	n
benzoate	4.19	136.5		16.7 ± 0.4	0.08	n
acetate	4.756	119.2	78.4	9.0 ± 5.6	0.32	n
base		85.7	31.2	−9.3 ± 4.0	0.82	

[a] Also listed are melting temperature, T_m, recrystallization temperature, T_c, and change in heat capacity at T_g, ΔC_p.

Table 3. Change in T_g against pK_a of Counterion Present for Nicardipine and Its Amorphous Salts[a]

salt	pK_a of counterion	T_m, °C	T_g, °C	ΔC_p, J/g/°C	amorphous after freeze-drying?
hydrochloride	−6	171.8	81.0 ± 4.2	0.35	y
sulfate	−3		77.2 ± 0.9	0.27	y
besylate	0.7		65.8 ± 0.8	0.32	y
oxalate	1.271	122.5	71.3 ± 2.8	0.22	n
phosphate	1.96		68.1 ± 1.2	0.35	y
tartrate	3.02		58.3 ± 8.7	0.24	y
citrate	3.128		29.3 ± 1.7	0.28	y
benzoate	4.19	99.9	28.5 ± 3.1	1.4	n
base		134.81	3.2 ± 9.6		

[a] Also listed are melting temperature, T_m, and change in heat capacity at T_g, ΔC_p.

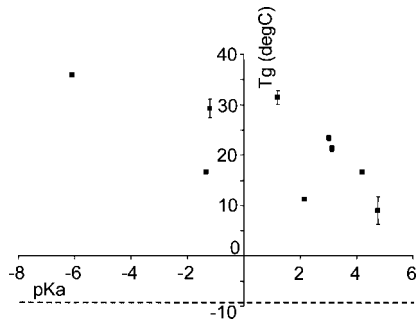

Figure 2. Plot showing change in T_g against pK_a of counterion present for propranolol and its amorphous salts. The dotted line represents the T_g of the free base.

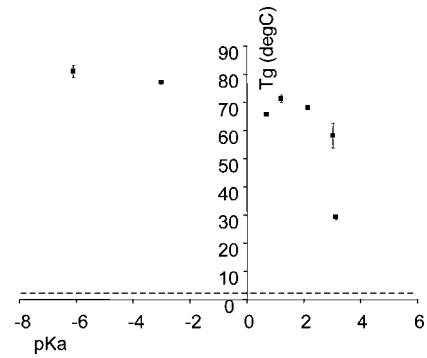

Figure 3. Plot showing change in T_g against pK_a of counterion present for nicardipine and its amorphous salts. The line represents the T_g of the free base.

tosylate and tartrate. All of these salts showed an initial increase in weight gain, followed by a decrease, which is characteristic of a crystallization event.[33] The moisture sorption profile for propranolol HCl is shown in Figure 4. No nicardipine salts appeared to crystallize during the moisture sorption measurements. To confirm that recrystallization was occurring, the following simple experiment was performed. Samples of the amorphous material were stored at 0% RH and then at 79% RH for 5 days and were examined before and after storage using polarized light microscopy. From these experiments, it was clear that both the propranolol hydrochloride and tosylate recrystallized at the higher relative humidity and data for the tosylate salt is shown in Figure 5. Another compound that apparently recrystallized during the moisture sorption experiments was propranolol tartrate. However, following microscopic examination of samples stored at 0% and 79% RH no crystals were observed (Figure 6). Close inspection of the moisture sorption profile shows that the recrystallization event (at 25% RH) is followed by a large moisture uptake which may indicate that the sample is deliquescing. The microscope image of propranolol tartrate recorded at 79% RH is consistent with that of a sample which has deliquesced (Figure 6).

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Discussion

Both salt formation and rendering the crystalline form amorphous may be used as strategies to enhance dissolution

Table 4. % Weight Change for Amorphous Propranolol Salts and Crystalline Propranolol Free Base at 55% and 75% RH[a]

salt	55% RH	75% RH
hydrochloride	2.20	1.80
tosylate	0.34	0.39
mesylate	4.00	23.50
besylate	0.50	11.10
oxalate	0.30	0.50
phosphate	16.50	21.30
tartrate	1.20	5.34
citrate	8.50	13.10
acetate	28.10	61.90
free base	0.023	2.54

[a] pK_a of counterion is increasing down the series.

Table 5. % Weight Change for Amorphous Nicardipine Salts and Amorphous Free Base at 55% and 75% RH[a]

salt	55% RH	75% RH
hydrochloride	2.9	5.6
besylate	5.2	12.4
oxalate	2.3	4.2
tartrate	3.4	5.2
citrate	5.4	7.8
benzoate	0.8	5.7
acetate	5.2	8.8
free base	0.800	2.890

[a] pK_a of counterion is increasing down the series.

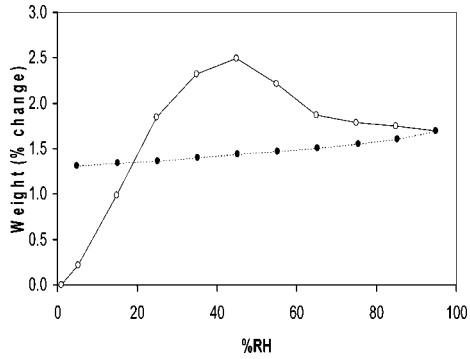

Figure 4. Moisture sorption profile for propranolol hydrochloride. The initial weight gain is followed by a decrease which can be interpreted as recrystallization of the amorphous material. Empty circles show sorption and filled circles desorption.

rates.[34,35] In some circumstances, it may be desirable to combine these two approaches to produce amorphous salts, for example when a lyophilized product is required. In addition, even if a crystalline salt is the goal, small amounts of amorphous material may be present following production, or introduced during processing. The results of this study indicate that the properties of the amorphous salt can be dramatically altered depending on the counterion. For amorphous compounds, the T_g is probably one of the most important properties,[10] and the storage temperature relative to the T_g can influence physical and chemical stability as well as the mechanical properties. It is therefore of interest to examine in more detail which factors influence the T_g of amorphous salts. Eisenberg has described in detail some of the molecular parameters that influence T_g in polymers,[36,37] and some of these would be anticipated to be important for small molecules. They describe the importance of intermolecular interactions, whereby the stronger the intermolecular interactions, the higher the T_g—the greater the intermolecular attraction, the more thermal energy that is required to attain the molecular mobility necessary to undergo the transition. According to the conceptual density functional theory (DFT),[38–40] there are three energy contributions to the intermolecular interaction. The first is the electrostatic contribution, which becomes dominant when the interacting molecules are highly ionic and hard. The concept of hardness refers to the resistance to charge transfer. The second is the covalent contribution, which stems from the flow and sharing of electrons. The third is the polarization contribution, which is of electrostatic nature but is induced by instantaneous fluctuations of electron movement. The last two components are shown to be dominant when interacting molecular systems are soft and their valence electrons have a high tendency to migrate and fluctuate. While interactions such as hydrogen bonding and nonspecific cohesive forces have been found to be important in un-ionized systems,[41] for salts, ionic interactions will be of greater importance in dictating the magnitude of T_g.[20] In addition to intermolecular interactions, structural factors also contribute to T_g through free volume and packing effects.[37] Based on the literature evidence that multiple molecular factors influence T_g, it is of interest to perform multivariate analysis to probe correlations between T_g and a number of molecular descriptors which may reflect the intermolecular interactions formed in the various systems.

Various DFT-based concepts have been developed for characterizing interatomic and intermolecular interactions. Hardness and softness are derived to characterize the polarizability of an electronic structure, and the hardness has been proven to be related to Klopman's frontier molecular

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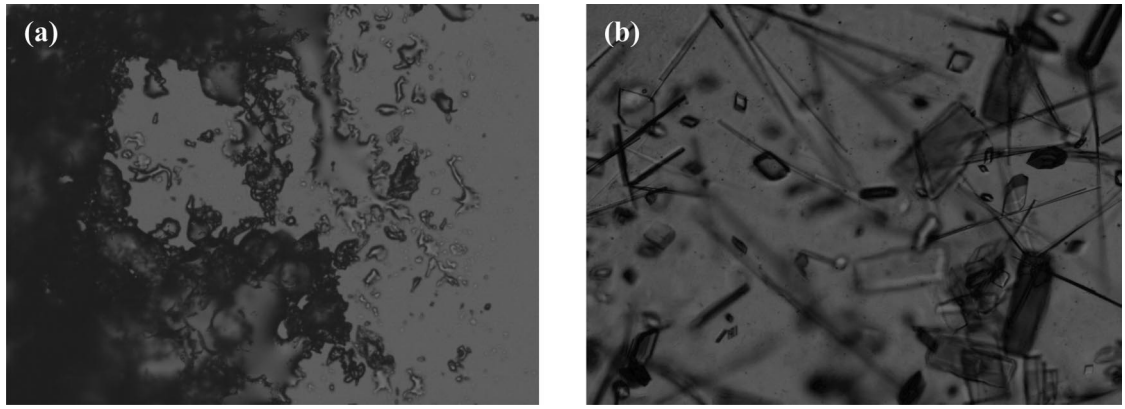

Figure 5. Optical micrographs of propranolol tosylate taken at 10× magnification. Picture (a) shows amorphous material stored at 0% RH. Picture (b) shows the material after being stored at 79% RH for 48 h and having recrystallized.

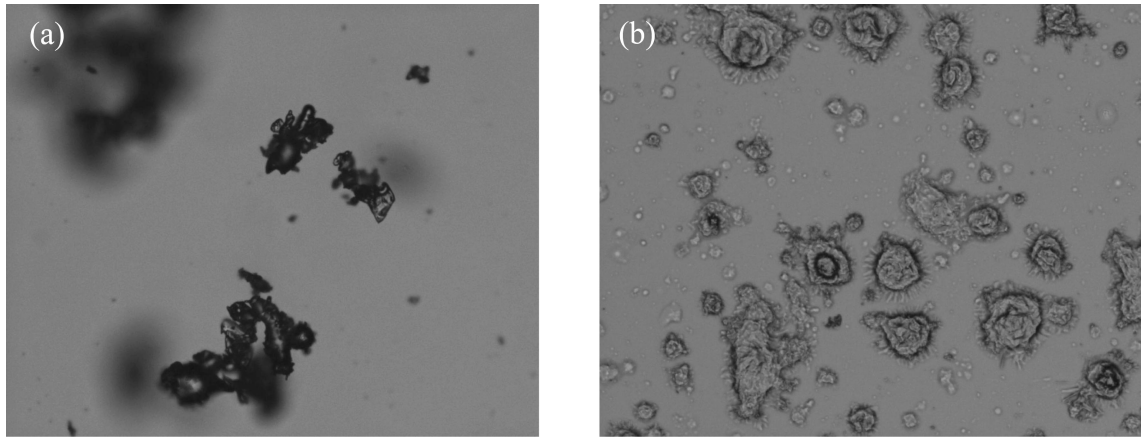

Figure 6. Optical micrographs of propranolol tartrate taken at 10× magnification. Picture (a) shows amorphous material stored at 0% RH. Picture (b) shows the material after being stored at 79% RH for 48 h in which the sample has deliquesced.

orbital theory,[42] calculated (eq 1) by the energy gap between ionization potential, I, and electron affinity, A,[43]

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_v = \left(\frac{\partial \mu}{\partial N}\right)_v \cong I - A \qquad (1)$$

where E is the system energy, N is the number of electrons, μ is the electronic chemical potential, opposite of the electronegativity,[44] and $v(\mathbf{r})$ is the external potential defined by nuclear charges and positions in the system. The inverse of hardness is softness, S.[45] Accordingly, the chemical potential (eq 2) is the first-order derivative of the system energy:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_v = -\frac{I + A}{2} \qquad (2)$$

For an intermolecular process in which charge transfer is invoked, the molecular interaction may be characterized by a so-called electrophilicity index (eq 3), ω:[46]

$$\omega = \mu^2/2\eta \qquad (3)$$

Thus, if a molecular system has a large value of electronegativity and is soft (i.e., small hardness value), its electrophilicity index is expected to be significant. Intuitively, the molecule may form strong covalent and polarization interactions with other similar types of molecules.

Because it is difficult to explicitly model interacting molecules and calculate the intermolecular interactions, particularly when the molecules are in the solution or

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Table 6. Table of General Molecular Descriptors for Counterions Used in This Study[a]

acid	ClogP	MW	CMR	PSA	vol	p*K*a1	H bond donors	H bond acceptors	rotatable bonds	ClogD	flex index
hydrochloric acid	−1.316	36.46	0.669	0	29.05	−6	0	0	0		0.00
sulfuric acid	−2.174	98.08	1.356	74.6	61.68	−3	2	4	0	−10.2	0.00
methanesulfonic acid	−2.424	96.11	1.667	54.37	72	−1.2	1	3	0	−6.4	0.00
toluenesulfonic acid	−0.146	172.2	4.178	54.37	147.19	−1.34	1	3	1	−4.1	5.81
benzenesulfonic acid	−0.645	158.18	3.714	54.37	128.12	0.7	1	3	1	−4.6	6.32
oxalic acid	−1.745	90.04	1.483	74.6	68.68	1.271	2	4	1	−8.811.	11
maleic acid	−0.166	116.07	2.357	74.6	95.54	1.92	2	4	2	−5.9	17.23
phosphoric acid	−2.174	98	1.427	77.76	69.36	1.96	3	4	0	−6.3	0.00
malonic acid	−0.712	104.06	1.946	74.6	85.04	2.826	24	2	−6.5	19.22	
tartaric acid	−3.22	150.09	2.716	115.06	124.03	3.02	46	3	−10	19.99	
citric acid	−1.998	192.13	3.68	132.13	160.94	3.128	4	7	5	−10	26.02
benzoic acid	1.885	122.12	3.341	37.3	114.16	4.19	1	2	1	−1.4	8.19
acetic acid	−0.194	60.05	1.294	37.3	57.12	4.756	1	2	0	−3	0.00

[a] ClogP: calculated log *P*. MW: molecular weight. CMR: molar refractivity. PSA: polar surface area. Vol: molecular volume; Flex index: flexibility index.

amorphous state, the DFT-based concepts have been explored for studying various molecular behaviors including chemical reaction and physical attraction.[47–50] Being intrinsic electronic properties that can be calculated directly from individual systems, the concepts are believed to be capable of characterizing the inherent tendency of how a molecule interacts with other systems. The hardness and softness may be used for characterizing covalent and polarization interactions induced by charge transfer and sharing. The concepts date back to Pearson's HSAB (hard and soft acids and bases) principle,[43,51–54] and have been used for evaluating intermolecular interactions between Lewis acids and bases.[55,56] The hardness is also useful for understanding the electrostatic interaction, which is typically dominant among hard species. Similarly, the electronic chemical potential and electrophilicity index have been used for providing insights about intermolecular interactions. Based on the results of this study, we believe that the glass transition temperature of the amorphous salts is strongly affected by the interaction between the acidic and basic components. As such, we have utilized molecular descriptors, including the discussed DFT-based concepts, to seek for correlations that support our hypothesis.

Tables 6 and 7 list various molecular descriptors that have been calculated/measured for the various counterions used in this study. These molecular descriptors might be expected to influence T_g, as discussed above. Using these values, together with the T_gs measured for the various nicardipine and propranolol salts, PLS modeling was explored. Citrate and phosphate salts were found to be outliers when the models were built with all the data, probably as a result of their trivalent character. By excluding these salts, good correlations could be found between the glass transition temperature and several of the molecular descriptors input into the model. The correlation coefficient (R^2) of the model was 0.909, and the cross-validation coefficient (Q^2) was 0.668, indicating that the predictability of the model is adequate.[32] The resulting observed vs predicted plots are shown in Figures 7 and 8 for propranolol and nicardipine respectively. In those plots the T_g predicted by the PLS model is plotted versus the measured T_g. The RMSEE for the T_g of propranolol and nicardipine was 3.8 and 3.4 °C respectively, i.e., the calibration error was 3−4 °C for the best model that was constructed.

It can be seen from the loading weights plot (Figure 9) that the T_g of nicardipine salts is dependent on μ (−0.30) and I (0.29) primarily, but also to some degree on vol (−0.26), pK_a (the lowest, −0.26) and rotatable bonds (−0.25) and that for propranolol salts the T_g is mainly dependent on ω (0.52), μ (−0.46), and log D (−0.47), but also to some degree on pK_a (the lowest, −0.42) and E (0.39). The numbers in parentheses represent the distance of the loading weights (w^*) in the direction of the regression coefficient (c) from the origin and provide an indication of the relative importance of each factor. A positive number means that an increasing value of that property will increase the T_g, whereas a negative

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Table 7. Selected Molecular Descriptors for the Counterions Utilized in These Studies Calculated Using Density Functional Theory[a]

counterion	E (eV)	I (eV)	η (eV)	S (eV^{-1})	μ (eV)	ω (eV)
hydrochloride	−0.486	12.765	13.251	0.075	−6.139	1.422
sulfuric acid	0.771	11.359	10.587	0.094	−6.065	1.737
methanesulfonic acid	0.321	10.769	10.448	0.096	−5.545	1.471
bezenesulfonic acid	0.353	9.569	9.216	0.109	−4.961	1.335
toluenesulfonic acid	0.305	9.122	8.817	0.113	−4.713	1.26
oxalic acid	0.714	10.407	9.692	0.103	−5.561	1.595
phosphoric acid	0.012	10.498	10.486	0.095	−5.255	1.317
tartaric acid	−0.040	9.522	9.562	0.105	−4.741	1.176
citric acid	0.426	9.507	9.081	0.110	−4.967	1.358
benzoic acid	0.208	9.272	9.064	0.110	−4.740	1.239
acetic acid	−1.004	10.516	11.520	0.087	−4.756	0.982

[a] E: electron affinity. I: ionization potential. η: hardness. S: softness. μ: chemical potential. ω: electrophilicity index.

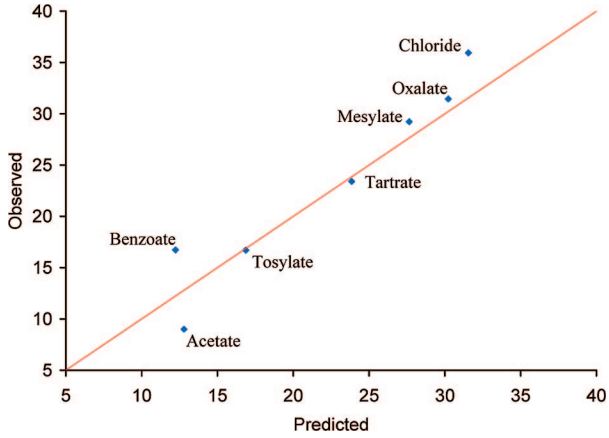

Figure 7. Observed vs predicted plot for modeling the T_g (°C) of propranolol.

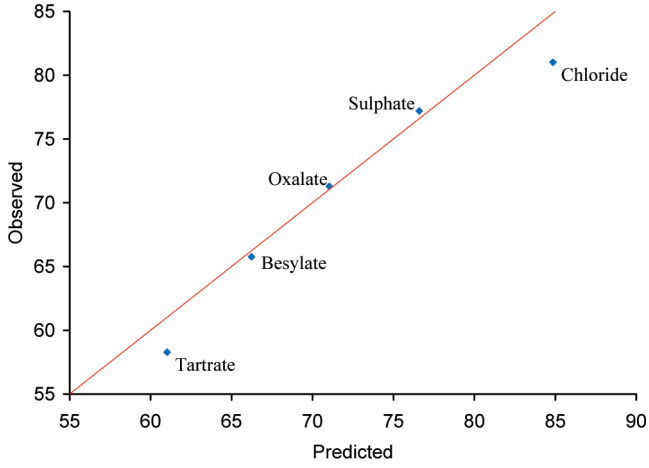

Figure 8. Observed vs predicted plot for modeling the T_g (°C) of nicardipine.

relative importance value will decrease the T_g when the value of such a property increases. For instance, pK_a has a negative relative importance value for both nicardipine and propranolol. This means that as the pK_a of the counterion is raised, the T_g of the corresponding salt should be lowered.

As mentioned previously, literature evidence suggests that multiple molecular factors might influence T_g. Multivariate analysis confirms this, highlighting that many properties of

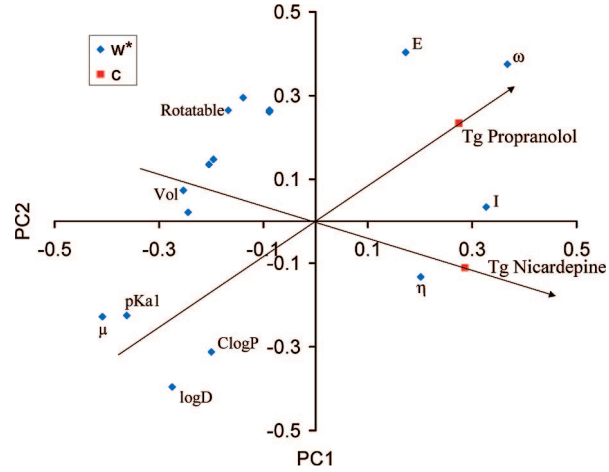

Figure 9. Loading weights plot for the PLS2 model. Loading weights (w^*) regression coefficient (c).

the counterion appear to contribute to the T_g of an amorphous salt. Some of these properties (ω, μ and pK_a) are not unexpected and can be related to the strength of the interaction formed between acid counterion and free base. Others are less intuitive and further investigation is required to understand the underlying reason that these factors influence the T_g of amorphous salts.

Another important property of amorphous salts is their propensity to crystallize. It is clear from the results presented above that different salts of a given compound had varying tendencies to crystallize. Propranolol salts were overall more likely to crystallize than nicardipine salts. However, the susceptibility of the propranolol salts to crystallization depended on the type of stress (freeze-drying, heating in the DSC or exposure to moisture). No one salt crystallized in all three instances, although both the HCl salt and the tartrate salt crystallized in response to elevated temperature and exposure to moisture. Thus although it is apparent that the crystallization tendency of amorphous salts will be affected by the counterion, it is clear that more work needs to be performed in this area to better understand the important factors underlying this process.

Conclusions

A number of amorphous salts of nicardipine and propranolol have been made and characterized by measuring T_g and moisture sorption properties. The properties of each of the amorphous salts have been found to be different. The T_gs of the amorphous salts are raised relative to that of the free base, and the extent of this increase can be related to a number of factors. Broadly speaking, a good approximation is that those salts made with counterions having low pK_a (and high electrophilicity index) have the highest T_g.

The moisture sorption properties of the amorphous salts are also different although currently these differences cannot be linked to any of the properties we are able to calculate for the counterions.

As with crystalline salts, it is apparent that the counterion has an effect on the properties of amorphous materials such that at some point in the future it may be possible to select a counterion to impart required properties and hence to engineer amorphous properties.

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