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Impacting the Glass-Forming Ability and Long-Term Stability of Spray-Dried Medicines Maintained in Dry and Humid Settings

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Abstract:

Our objectives were to examine (i) how different preparation methods affect the evaluation of GFA and GS in compounds, specifically comparing the GFA class of compounds made by spray-drying vs melt-quenching in the DSC, (ii) how amorphous compounds made by spray-drying fare when stored at <5% RH (dry) and 75% RH (humid) for 168 days, and (iii) whether there is a possible correlation between the long-term physical stability and glass forming ability (GFA) and/or physicochemical characteristics. Twenty-six glass-forming compounds (II and III) with a wide range of physicochemical characteristics were chosen based on their prior reporting.

Keywords: physicochemical, prior, stability, forming reporting.

INTRODUCTION

The primary goal of spray drying medications that are not very water-soluble is to produce amorphous materials. More and more, spray drying is being used as a drying process for nanosuspensions to create nanoparticles or nanocrystalline dispersions of pharmaceuticals that aren't very soluble, and it's also becoming the method of choice for particle engineering, which involves reducing size and increasing surface area. Despite the fact that amorphous forms are typically created as solid dispersions with polymeric carriers, pure drug substances can also be created in spray dried amorphous forms to study their processability in feasibility studies and to compare with other methods of generating an amorphous state. When medications are soluble in volatile organic solvents or combinations of solvents, spray drying becomes an option for those that are not water-soluble. The final product's solid form, however, is entirely dependent on the chemical properties of the medicinal ingredient. It might produce metastable crystals, partly crystalline mixtures, amorphous forms, or crystals with induced imperfections. Domicilethacin and itraconazole are active pharmaceutical ingredients (APIs) that, when spray dried, produce fully vitrified forms with high stability, while naproxen and other medicinal compounds exhibit practically little amorphization.

Coamorphous systems, created by co-spray drying APIs with different glass-forming abilities, have recently attracted the attention of researchers looking for ways to improve the dissolution rates of both components and stabilize them. One example is naproxen, which is poorly water-soluble and has poor glass-forming ability. Another is indomethacin, which has good glass-forming ability. Compared to the crystalline forms produced by precipitation and colloid formation, the solubility of spray dried paclitaxel is significantly enhanced because of the creation of the amorphous form. Amorphous atorvastatin salts that were spray dried recently have their physicochemical characteristics and stability tested for the impact of counter ions. Because the amorphous form was generated and the particle size was reduced, the bioavailability of spray dried atorvastatin calcium was significantly enhanced. Amorphous celecoxib, which is produced via spray drying, has far better surface energy, polar surface distribution, and wettability than its pure crystalline analogue. The authors postulate that the two Tgs seen in the thermal analysis of pure salbutamol sulfate in its entirely amorphous form, produced by spray drying, are caused by the increased plasticization of the bulk fraction relative to the surface of the amorphous state caused by the presence of moisture. Recent research has shown that spray drying may be useful for co-crystal production of carbamazepine with glutaric acid, in addition to generating the drug's amorphous form. Spray drying produced the pure co-crystal, which the authors suggest may be mediated via a glassy state or regulated kinetically, in contrast to the traditional solvent evaporation approach, which produced a mixture of phases.

Literature and review

Shinde, Sunita & Manisha, V. & Shete, S. & Disouza, John & Pranit, A. (2013) One of the main goals of this work was to use the spray drying process to create solid dispersions of the medication fluconazole, which is not very water-soluble. The other goal was to characterize these dispersions. Hydrophilic carriers, such as PVP K30 and the porous carrier Aerosil 200, were prepared into solid dispersions in this investigation by means of a spray drying process. Using scanning electron microscopy (SEM), infrared spectroscopy (IR), dynamic scanning calorimetry (DSC), and XRPD, researchers compared solid dispersions in spray dried powder with pure medication and related physical mixes in the same ratios. Solid dispersion XRPD profiles devoid of fluconazole peaks indicate that crystalline fluconazole has amorphized. the solid dispersions' DSC curves do not show a fluconazole peak. It was shown in the DRIFTS spectra that solid dispersions include hydrogen bonding. A higher rate of dissolution was seen in the solid dispersions compared to pure fluconazole, spray-dried fluconazole, and physical mixes of drug with hydrophilic carriers in the in vitro dissolution test. We may infer that spray drying with hydrophilic carriers effectively produced solid dispersions of the water-soluble medicine fluconazole.

Henriques, Joao & Moreira, Jorge & Doktorovova, Slavomira. (2020) Here we show how to create downstream processes for spray-dried amorphous solid dispersions using a structured approach. Due to the usually poor flow of spray dried powders in tablets, direct compression is usually not the best method to use. As a result, the preferred technique for enabling spray dried dispersion downstream processing is roller compaction (RC). This study used a controlled experimental approach to examine the characteristics of the roller compaction process. We set out to find the optimal processing parameters that would increase powder flow without weakening the tablet's durability. Using varying process settings, ten mixtures were crushed into tablets. We looked at how different process factors affected the characteristics of the granules and tablets. We show that several parameters such as compaction force, mesh aperture, and gap significantly affect the results of RC. The ideal blend compressibility-preserving RC process parameters were determined to be a big gap with little force, which improved the powder flow and ensured little tablet weight change.

Pandi, Palpandi & Bulusu, Raviteja & Kommineni, Nagavendra & Khan, Wahid & Singh, Mandip. (2020) In the development of new therapeutic products, amorphous solid dispersions (ASDs) are often used to increase the bioavailability of molecules that are not very soluble. This is achieved by increasing the pace and extent of dissolution. These systems are made up of a polymer matrix that helps to stabilize an amorphous active medicinal component, making it more stable. With a focus on comprehending and forecasting stability, this study included the approaches of ASD preparation and characterisation. The benefits and drawbacks of various preparation methods, rationale for selecting polymers, and characterisation of polymeric amorphous solid dispersions have all been covered. The ICH recommendations outline the stability elements, which are said to be dependent on the polymer selection and ASD production techniques. Additionally, the process that improves bioavailability was taken into account. The evaluation focused on the regulatory significance of ASD and the intricacies of the present emerging QBD methodology. At the moment, the pharmaceutical industry's most promising frontier is amorphous goods, and ASDs in particular. In terms of improving medicinal product performance in clinical settings and getting them approved by top regulatory authorities to enter the market, this strategic strategy offers significant effect and beneficial qualities.

Ghule, Prashant & Gilhotra, R. & Aukunuru, Jithan & Bairagi, Shripad & Aher, Abhijeet. (2018) Creating amorphous solid dispersions is one of the potential ways to increase the oral bioavailability of medications that are not very water-soluble. The wettability and oral bioavailability of drugs are greatly enhanced when their particle sizes are reduced. To improve the bioavailability and solubility of poorly soluble medicines, new formulation procedures are being developed. Amorphous molecules are much more soluble than their more stable crystalline counterparts due to the increased Gibbs free energy. Also, materials without the periodicity of crystals yet mechanically behaving like solids are known as amorphous forms; they are high energy disordered materials that are kinetically trapped. Slow dissolving rates are associated with partial drug release from dosage forms, low oral bioavailability, an increase in food effect, and substantial inter-patient variability for lipophilic medicines, particularly those in biopharmaceutics classification system (BCS) classes II and IV. Active pharmaceutical ingredient (API) formulation in an amorphous state has so lately become more prominent as one of various formulation options to enhance the solubility and dissolution of medications that are poorly water-soluble. These issues have become less common and the rate of solubility has been improved by formulating amorphous solid dispersions of pharmaceuticals that are not very water-soluble with carriers that are water-soluble. Topics covered in this overview include benefits, solid dispersion categorization, preparation techniques, and amorphous solid dispersion characterization.

Sotthivirat, S & McKelvey, C & Moser, Justin & Rege, B & Xu, W & Zhang, D. (2013) The purpose of this research was to show that solid dispersions of the weakly water-soluble medication MK-0364 may be created to improve the drug's solubility and bioavailability. An oral solid dosage form of MK-0364, either as a monotherapy or combo medication, would be made possible by the potential solid dispersions. Physical characterisation, in vitro dissolution tests, and solvent casting sample preparation were all part of the preliminary screening process. Then, spray-drying (SD) and hot melt extrusion (HME) were used to make lead formulations. Amorphous halo in X-ray powder diffraction (XRPD) analysis, single glass transition temperature (Tg) in differential scanning calorimetry (DSC) measurements, and supersaturation in dissolution media are all features of a single-phase glass that all HME (non-PVP) and SD formulations display. As compared to a liquid-filled capsule reference, monkeys' oral absorption of MK-0364 from certain HME and SD formulations produces somewhat higher exposure with a consistently longer Tmax. Processability, physical characterisation, in vitro dissolution, and animal pharmacokinetic studies support the viability of solid dispersion formulations based on copovidone and hydroxypropyl methylcellulose acetate succinate (HPMCAS). Additionally, under various circumstances, the physical stability of the two solid dispersion formulations was assessed for a duration of 54 weeks. Preserving the solid dispersion based on copovidone from moisture is essential.

GFA And Long-Term Physical Stability

Selection of model compounds

We aimed to investigate (i) the influence of preparation method on the assessment of GFA and GS of compounds by comparing the GFA class of compounds prepared via spray-drying vs melt-quenching in the DSC, (ii) the physical stability of amorphous compounds prepared via spray-drying when stored at <5% RH (dry) and 75% RH (humid) conditions for six months (168 days) and (iii) the potential relationship between the long-term physical stability with glass forming ability (GFA) and/or physicochemical properties. Twenty-six previously reported glass-forming compounds (Class II and III) with diverse physicochemical properties were selected [86,87,101,102,105]. Priority was mainly given to poorly water-soluble glass-forming compounds, but com- pounds with satisfactory solubility from an administered dose perspective were also included.

Glass former vs. non-glass former

In the context of this study, a spray-dried compound was considered a glass former (GF) if the amorphous content of the sample was detectable with any or all of the solid-state analyses. This includes both completely amorphous and a mixture of the amorphous and crystalline. If the compound was spray- dried as a fully crystalline solid, it was classified as a non-glass former (nGF). Only 50% (n=13) of the compounds were GFs while the remaining 50% (n=13) were nGFs under the studied spray-drying condition. Of the 13 GFs, seven spray-dried as fully amorphous whereas six were amorphous-crystalline mixtures.

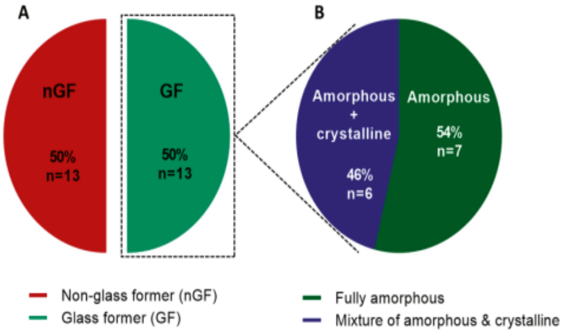

Figure 1 Pie charts showing (A) the glass-forming ability (GFA) of the model compounds produced via spray-drying method, and (B) the solid-state forms of the glass formers (GFs).

The spray-dried compounds were classified as either non-glass formers (nGFs) or GFs. The GFs were further divided into fully amorphous or a mixture of amorphous and crystalline. Glass-forming ability/glass stability classification: melt-quenching vs. spray-drying.

Besides determining whether or not the spray-dried compounds were GFs or nGFs, we were also interested in comparing their GFA/GS classifications against the widely used systems of organic compounds established by Baird et al. via in situ melt-quenching in the DSC [86]. The GFA/GS classes of the compounds obtained via melt-quenching and spray-drying are summarised in Figure 2. In general, the GFA/GS classes varied greatly for the two different preparation methods. Out of the total 26 model compounds, 16 compounds were classified as Class III while 10 compounds were classified as Class II upon melt-quenching.

When spray-drying was used instead, the GFA/GS classification of these compounds was more heterogeneous. Most compounds were down-classified in their GFA/GS classes, and none of the compounds were promoted to a higher GFA/GS class when prepared by spray-drying. Also, a few Class III compounds via melt-quenching showed up as Class I when spray-dried. For the majority of the compounds, the GFA/GS classification is not only influenced by the preparation method used, but also by the specific conditions used for a particular method selected. Our findings are in good agreement with what has been reported by Van Eerdenbrugh et al.

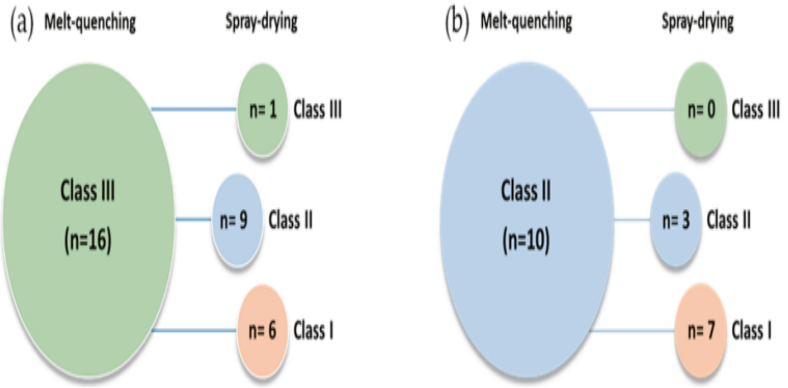

Figure 2 The number of compounds in glass-forming ability/glass stability (a) Class III and (b) Class II according to in situ DSC melt-quenching compared to glass-forming ability/glass stability classes according to spray-drying, respectively. Pink, blue and green represent Classes I, II and III, respectively.

Long-term physical stability

For the long-term stability assessment, only 13 of the compounds that were fully amorphous or formed a mixture of amorphous and crystalline were included. No further analyses were carried out on the remaining 13 compounds that were spray-dried as completely crystalline samples, except for the initial solid-state characterisation of their freshly spray-dried solids. Figure 3 shows the three main stability patterns. The compounds were either: (i) stable under both dry and humid conditions, (ii) stable under dry conditions but unstable under humid conditions, or (iii) unstable under dry and humid conditions.

Among the studied compounds, indapamide and metolazone displayed exceptional stability when stored under both storage conditions. Glibenclamide, hydrocortisone and hydrochlorothiazide, on the other hand, were stable when stored at dry condition but crystallised with different propensities at humid conditions. Affinity for water is predominantly influenced by the octanol-water partition coefficient (logP), which reflects the hydrophilicity and/or lipophilicity of a compound. These three compounds vary in their logP. Hydrochlorothiazide is the most hydrophilic (logP=-0.1) followed by hydrocortisone (logP=1.6) and glibenclamide (logP=4.8). This trend in hydrophilicity and/or lipophilicity agreed with the observed crystallisation tendency: hydrochlorothiazide > hydrocortisone > glibenclamide. The more hydrophilic compound has higher affinity for interaction with water than the lipophilic ones and hence, the amount of water absorbed may facilitate crystallisation.

Another interesting observation was that a rapid nucleation was not necessarily followed by rapid crystal growth, especially under dry storage conditions. This phenomenon was exemplified by sulfathiazole, prednisone, aripiprazole, glipizide and droperidol. These compounds crystallised completely at different time points when exposed to humid condition. However, the time to complete crystallisation, which reflects the crystal growth rate, was greatly supressed under the dry condition, even though a detectable number of crystals was already present in the sample upon spray-drying and/or after one-day storage. This was especially striking for aripiprazole and droperidol for which minimal crystallisation (≤ 15%) was observed throughout the 6-month storage at dry conditions. These findings strengthen the assumption that interaction with water plays a vital role in influencing the physical stability of amorphous solids.

Probucol, which was spray-dried as a mixture of amorphous and crystalline, behaved rather differently from the rest of the compounds. The tendency to crystallise was similar regardless of the storage conditions. Probucol is very lipophilic (calculated logP=11.3) compared to the other compounds discussed above. Therefore, interaction with water is less likely to contribute to its crystallisation propensity. Nevertheless, the fact that it has a T_g (26°C) that is very close to the storage temperature (25°C), might have caused an increased molecular mobility and thereby enhanced the crystallisation tendency.

Influence of physicochemical properties on GFA and long-term physical stability

No strong correlation was shown between GFA and physicochemical properties of compounds. Nevertheless, glass formers tended to have relatively larger molecular weight (MW), a higher number of hydrogen bond acceptor (HBA), a higher polar surface area (PSA) a higher melting temperature (T_m), a higher crystallisation temperature (T_c), a higher glass transition temperature (T_g), and a higher reduced glass transition temperature (T_{rg}) than the non-glass formers. The increase in heat of fusion (ΔH_f) and entropy of fusion (ΔS_f) appeared to have a negative impact on GFA.

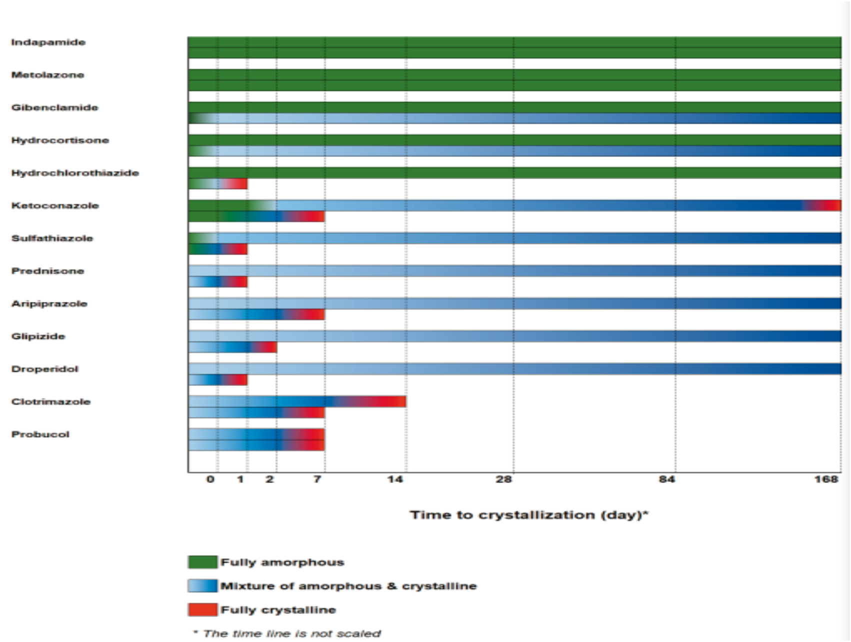

Figure 3 The 6-months (168 days) physical stability of the 13 spray-dried compounds included in the physical stability study.

Gradients of color during the research period indicate the stability of each compound: green for completely amorphous, light to dark blue for varying ratios of amorphous and crystalline, and red for entirely crystal-line. The stability of each component is shown by the top bar under dry circumstances (<5% RH) and the bottom bar in humid conditions (75% RH), therefore.

However, a direct correlation between physicochemical characteristics and physical stability over the long run could not be shown. When humidity is a factor, even a solid GF may not be steady. Furthermore, physical stability could not be predicted by any of the particular physicochemical characteristics.

These results are consistent with earlier research that indicated a relationship between physicochemical characteristics including MW, HBD, Tg, and ΔHf 106 and long-term amorphous stability. While ΔHf was associated with a greater propensity to crystallize and/or physical instability, MW, HBD, and Tg had a beneficial effect on physical stability.

Effect of physical aging and/or crystallisation on supersaturation potential

Seven compounds that were fully transformed to amorphous after spray-drying were studied for their supersaturation potential. The performance of freshly spray-dried amorphous samples was compared with samples that had been stored at 75% RH until they were completely crystallised or for up to six months (168 days), whichever came first. The stability profiles are summarized in Table 1.

Table 1 Physical stability profile of spray-dried amorphous compounds upon storage at 75% RH and 25°C until they were completely crystallised or for up to 6 months (168 days) if no or incomplete crystallisation occurred.

Compound	**Stability after 6-months storage at 75% RH**	**Estimated crystalline content (%)**
Indapamide	Good	0
Metolazone	Good	0

Glibenclamide	Moderate	6
Hydrocortisone	Moderate	11
Ketoconazole	Poor	100
Hydrochlorothiazide	Poor	100
Sulfathiazole	Poor	100

Effect of long-term physical stability on supersaturation potential

The supersaturation profiles of the freshly spray-dried and aged and/or crystallised samples are shown in Figure 4. In general, all of the drugs displayed some degree of supersaturation, but no clear difference in supersaturation pro- files could be observed between the fresh and aged and/or crystallised spray- dried drugs, except for ketoconazole. The completely crystallised spray-dried ketoconazole sample showed a similar dissolution profile as its crystalline form.

Indapamide, metolazone and glibenclamide displayed unstable supersatu- ration. A marked decrease in concentration was apparent after reaching an ap- parent maximum concentration ($C_{max,app}$) above the crystalline solubility. Conversely, the dissolution of hydrocortisone, hydrochlorothiazide, ketoconazole and sulfathiazole generated an apparently stable supersaturation for 60 minutes, at a concentration slightly higher than their crystalline solubility. It is noteworthy that, despite having a comparable estimated crystalline content of 6% and 11%, respectively, glibenclamide and hydrocortisone demonstrated distinct supersaturation behaviours. It is evident, for these two compounds that the presence of small number of crystals did not dramatically influence their supersaturation performance.

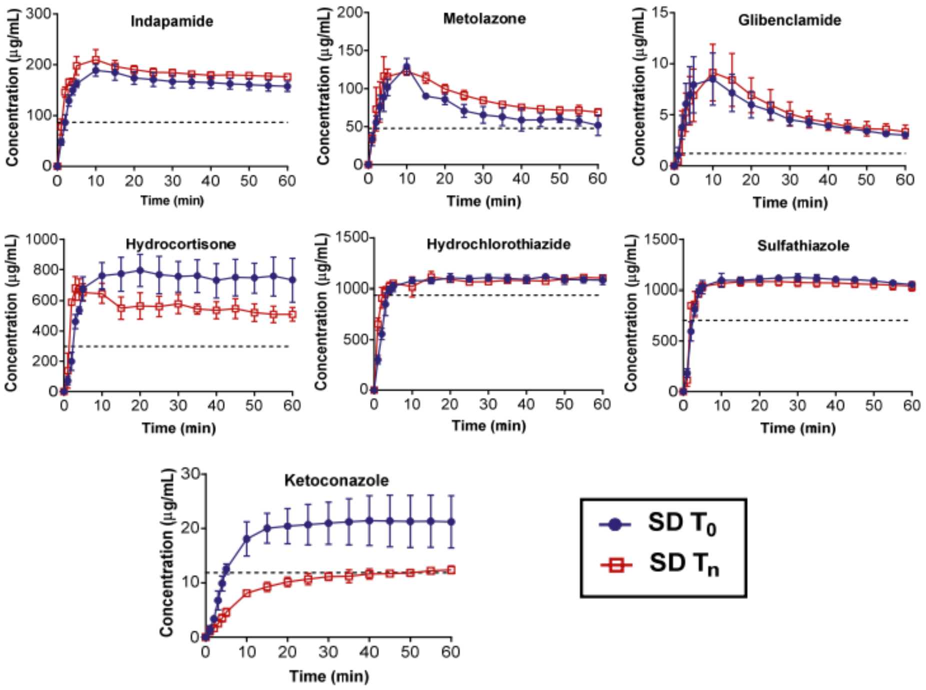

Figure 4. Concentration–time profiles of freshly spray dried (SD T_0) shown in blue circle.

The crystallised and/or aged spray-dried compounds (SD T_n) are shown in red empty squares. The time point, n, depends on: (i) the time point at which the spray-dried samples completely crystallised, or (ii) the last time point of the stability study (i.e., 168 days) if crystallisation was incomplete or did not happen (as indicated in Table 1). The apparent crystalline solubility of each compound is shown as a black dashed line.

$C_{max,app}$ and AUC ratio of fresh, aged and/or crystallised spray-dried solids

To further elucidate the differences in supersaturation profiles of fresh, aged and/or crystallised spray-dried samples, we performed statistical analyses on the $C_{max,app}$ and AUC ratio (indicated as $R_{Cmax,app}$ and R_{AUC}, respectively) of both sample types for each compound (Figures 5). No significant difference in the $R_{Cmax,app}$ of the fresh and the aged and/or crystallised spray-dried drugs was observed, except for ketoconazole (Figure 5a). The completely crystallised spray-dried ketoconazole exhibited a 50% decrease in its $R_{Cmax,app}$. In contrast, no significant impact was detected on the $R_{Cmax,app}$ of glibenclamide and hydrocortisone with estimated crystalline contents of 6% and 11%, respectively. Strikingly, hydrochlorothiazide, hydrocortisone and sulfathiazole, which were fully amorphous freshly upon spray-drying, demonstrated very similar $R_{Cmax,app}$ to the partially or completely crystallised samples after 6 months storage at 75% RH.

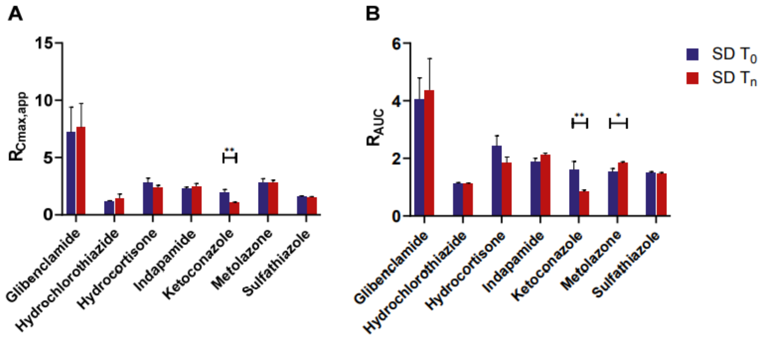

Figure 5 (A) The $C_{max,app}$ ratio ($R_{Cmax,app}$) and (B) the AUC ratio (R_{AUC}) of the fresh and aged and/or crystallised spray-dried APIs at 10-folds supersaturation ratio.

The freshly spray-dried samples are represented as SD T_0 (blue bars), whereas the crystallised and/or aged samples are denoted as SD T_n (red bars) since each of the compounds crystallised at different time points. At 95% confidence interval, a p-value of <0.05 is considered statistically significant.

Except for ketoconazole, the extent of supersaturation (R_{AUC}) for the other compounds were not negatively influenced significantly by physical aging and/or crystallisation during storage (Figure 5 b). Ketoconazole showed a 50% decrease in its R_{AUC}, which is in good agreement with the decline in $R_{Cmax,app}$. A significantly positive impact, reflected by an increase in the R_{AUC}, was observed for metolazone. This may be attributed to the removal of electrostatic charges and irregularities via small adsorption of water on the particle's surfaces. This minimizes particle agglomeration, leading to an increase in effective surface area for wetting and dissolution of solid particles. The partial or complete crystallisation of stored hydrochlorothiazide, hydrocortisone, and sulfathiazole did not seem to have a significantly negative impact on their R_{AUC}, compared with their freshly spray-dried fully amorphous counterparts. Of the seven drugs, glibenclamide achieved the highest supersaturation potential from amorphisation, whereas the other compounds demonstrated marginal or no improvement in their supersaturation potential.

4.5.3 Impact of crystallisation pathway on supersaturation potential

As seen in Figure 4, the fully amorphous and partially and/or completely crystallised stored samples of three drugs (hydrocortisone, hydrochlorothiazide and sulfathiazole) exhibited comparable concentration-time profiles. Such concentration-time profiles are usually associated with stable supersaturation, in which there is no 'spring' effect generated by supersaturation. There are two possible explanations for the observed supersaturation profiles of these drugs: (i) the crystallisation of amorphous solid during storage at 75% RH and crystallisation during dissolution followed the same pathway or mechanism, or (ii) the amorphous solid transformed upon dissolution into a meta- stable polymorph with higher solubility than the stable polymorph.

A solvent shift approach was used to probe the factors contributing to the supersaturation profiles observed with these model compounds, especially hydrochlorothiazide, hydrocortisone and sulfathiazole. In the solvent shift, the supersaturation is generated from a concentrated solution of the compound dissolved in dimethyl sulfoxide (DMSO) to evade the dissolution step. On the basis of the supersaturation profiles obtained via this method, one can get in- formation on the predominating crystallisation mechanism or pathway. Our findings were coupled with solid-state analysis to probe any possible poly- morphic changes during the dissolution and crystallisation process. The $R_{Cmax,\ app}$ from the solvent shifts was examined and compared to the spray-dried ones (Figure 6).

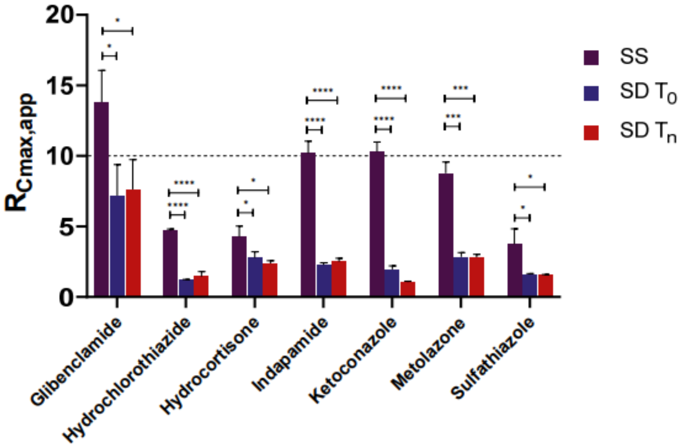

Figure 6 The apparent $C_{max,app}$ ratio ($R_{Cmax,app}$) of the solvent shift for fresh and aged and/or crystalline spray-dried compounds at ten-fold supersaturation ratios.

The sol- vent shift is represented as SS (purple bars), the freshly spray-dried samples as SD T_0 (blue bars), and the crystallised and/or aged samples as SD T_n (red bars), since each of the compounds crystallised at different time points. At a 95% confidence interval, a p-value of <0.05 is considered statistically significant.

In general, the $R_{Cmax,app}$ of all drugs generated from concentrated stock solutions was higher than for those of the spray-dried samples. This indicates the significant role of solids during the dissolution in crippling the ability of the system to reach the highest possible $R_{Cmax,app}$. Two different patterns in $R_{Cmax,app}$ can also be seen in Figure 6. Glibenclamide, indapamide, ketoconazole, and metolazone reached the highest possible $R_{Cmax,app}$ (i.e., 10-folds). However, the $R_{Cmax,app}$ of hydrochlorothiazide, hydrocortisone and sulfathiazole was tremendously lowered (5-folds) compared to their crystalline solubility.

Crystallisation of glibenclamide, indapamide, ketoconazole and metolazone occurred from a relatively high degree of supersaturation. This suggests that they predominantly: (i) nucleated homogeneously from the bulk solution, and (ii) crystallised mainly via a solution-mediated pathway. Glibenclamide, indapamide and metolazone have been previously reported to undergo the same mechanistic pathway of crystallisation.

Conversely, heterogeneous nucleation and solid-to-solid crystallisation seemed to be the predominating nucleation and crystallisation pathways for hydrochlorothiazide, hydrocortisone and sulfathiazole. They appeared to crystallise at a relatively lower supersaturation than the other four compounds. The large number of solid particles provides a large surface area for the solutes to nucleate on. Similarly, there is a greater likelihood for the formation of local supersaturation on the surface of particles as they are present in large numbers. It is a known fact that nucleation proceeds more rapidly for compounds with higher solubility in the media. This may also explain why the crystallisation of hydrochlorothiazide, hydrocortisone and sulfathiazole occurred at lower supersaturation compared with the other compounds. As solubility in- creases, the solute molecules have higher probability to see each other in the solution. It also causes more changes in the composition of the solution, hence, lowering the interfacial energy between the crystal and solution. As a result, the solute has more affinity for the crystal than the solution.

4.5.4 Role of polymorphism on supersaturation potential

Why did the supersaturation profiles of hydrochlorothiazide, hydrocortisone, and sulfathiazole appear like a stable supersaturation, even though they partially or completely crystallised upon storage? To investigate this, we per- formed solid-state analyses (i.e. Raman spectroscopy and DSC) on the solids collected after the dissolution experiments.

For all of the three compounds, the melting temperature and heat of fusion of the crystallised samples – either from storage at 75% RH or upon dissolution – were lower than the original crystal forms. This indicates the formation of metastable crystalline forms which, provides an explanation why the con- centration of the crystallised samples of these compounds was higher than that of the original crystalline. These analyses emphasised the importance of understanding the solid-state changes that may occur during dissolution. A stable supersaturation might not be the result of the amorphous nature of a given compound. Rather, it could be due to the crystallisation to a metastable poly- morph with higher solubility.

4.5.5 Crystallisation rate constant (k) and crystallisation kinetics

The overall supersaturation decreases as nucleation and crystal growth ensue. As the system approaches equilibrium, the kinetics of nucleation and crystal growth decelerate. As a result, the thermodynamic aspects begin to dominate over the kinetic ones. The crystallisation rate constants (k) of hydrochloro- thiazide, hydrocortisone and ketoconazole and sulfathiazole was not possible to calculate. This was due to the fact that their concentration-time profiles did not show the characteristic "spring" pattern associated with a supersaturating system. As such, no decline in concentration was detected after reaching the $C_{max,app}$. The crystallisation rate constant of the three remaining compounds is shown in Figure 7.

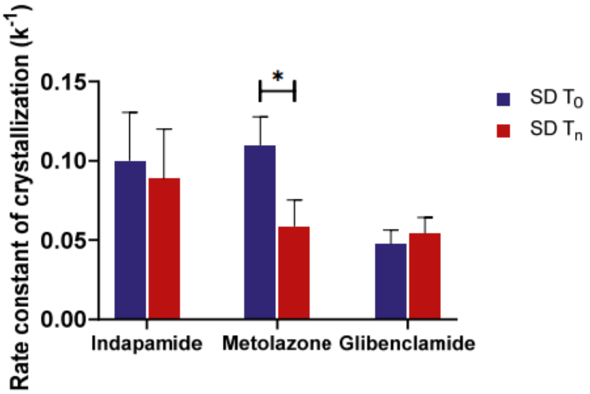

Figure 7 Crystallisation rate constants, k (min^{-1}), of fresh and aged and/or crystallised spray-dried indapamide, metolazone and glibenclamide.

Out of these three compounds, only the crystallisation rate constant of the aged, spray-dried metolazone showed significant decrease compared with its fresh counterpart. No significant differences were measured for indapamide and glibenclamide. The crystallisation rate constant of the partially crystallised glibenclamide was expected to decrease more than the other two compounds since the system is approaching equilibrium as it crystallised. However, the small amount of crystalline material in the stored spray-dried glibenclamide samples did not affect the crystallisation rate. It was also unclear why the crystallisation rate constant of metolazone decreased significantly, despite it being stable upon storage.

Conclusion

The glass forming ability/glass stability (GFA/GS) classification of drug compounds are influenced by preparation methods. Spray-drying produces more heterogeneous distribution across the GFA/GS classes than the in-situ melt-quenching using differential scanning calorimetry (DSC). The efforts to investigate long-term physical stability and the implications of physical aging and the extent of solid crystallisation during storage on the supersaturation performance of amorphous compounds. Very limited number of studies have, till date, investigated both solid crystallisation during storage and supersaturation potential in the same study with more than one model compound.

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