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Effect of a Counterion on the Glass Transition Temperature (T_g') during Lyophilization of Ganciclovir Salt Forms

Lokesh Kumar,[†] Ankit Baheti,[‡] and Arvind K. Bansal*[,†]

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, Mohali, Punjab 160 062, India, and Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, Mohali, Punjab 160 062, India

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Abstract: This manuscript deals with the effect of a counterion on the glass transition temperature for lyophilization of ganciclovir salts. Salt forms of ganciclovir, namely, sodium, potassium, rubidium, and cesium salts, were prepared by an *in situ* technique and analyzed by modulated differential scanning calorimetry (MDSC) for the determination of the critical process parameter for lyophilization. Nonionized ganciclovir and its salt forms showed a glass transition (T_g') in the reversing MDSC signal, confirming their amorphous nature. T_g' of the nonionized ganciclovir and ganciclovir sodium, potassium, rubidium, and cesium salts followed the order: sodium salt (−34.94 °C) > nonionized ganciclovir (−40.15 °C) > potassium salt (−46.23 °C) > rubidium salt (−49.95 °C) > cesium salt (−53.62 °C). The analysis of the freezable water content for ganciclovir and its salts showed the trend: pure water > nonionized ganciclovir > potassium salt ∼ sodium salt > rubidium salt > cesium salt. This showed that a majority of water in the salts is present as an unfrozen fraction, thus leading to a lowering of T_g' because of the plasticizing effect of unfrozen water. Density functional theory (DFT) further suggested a positive contribution of the strength of intra- and intermolecular force of interactions to the T_g' value, with a higher intramolecular and intermolecular force of interaction leading to a higher T_g'.

Keywords: Lyophilization; ganciclovir; salt form; glass transition

Introduction

Salt formation (salification) is a simple acid−base reaction involving either a proton transfer or a neutralization reaction. It is a commonly employed strategy for an ionizable drug candidate and has the potential to affect a range of physicochemical and/or biopharmaceutical properties, in terms of their solubility, hygroscopicity, stability, and/or processability.[1−7] The importance of salt formation in drug development can be appreciated from the fact that more than 50% of the marketed drugs exist as salt forms of the drug candidate.

A number of existing parenteral formulations in the market are also lyophilized as salt forms. Although biopharmaceutical performance remains the primary driving force during salt screening, prudent selection of the salt form for lyophilization could help to optimize product stability and develop an energy-efficient lyophilization cycle. In this context, it could be interesting to study the effect of a counterion on the critical process temperature (CPT) of the drug for lyophilization.

CPT for lyophilization is routinely determined as it helps in designing an optimal lyophilization cycle. The CPT includes the glass transition temperature (T_g') for an amorphous substance or the eutectic temperature (T_{eu}) for a crystalline component. The product temperature during lyophilization is kept below the T_g' or T_{eu} during the primary

* Corresponding author. A.K.B.: National Institute of Pharmaceutical Education and Research (NIPER), Department of Pharmaceutics, SAS Nagar, Mohali, Punjab 160 062, India. Tel.: +91-172-2214682-2126. Fax: +91-172-2214692. E-mail: akbansal@niper.ac.in.

[†] Department of Pharmaceutics, NIPER.

[‡] Department of Pharmaceutical Technology (Formulations), NIPER.

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drying phase to prevent structural collapse of the solute.[8] Moreover, since primary drying is the most energy intensive step, determination of the CPT enables development of an energy-efficient lyophilization cycle.

During lyophilization, crystallization of ice results in concentration of the solute in the remaining liquid aqueous phase. The resulting solution is frequently termed as the maximum freeze concentrate and may lead to crystallization of solute component(s) in case of favorable nucleation. In some cases, however, even if the solute concentration exceeds the equilibrium solubility in the freeze concentrate, crystallization may not occur. This happens when the solutes in the freeze concentrate are trapped in a metastable liquid phase due to the low degree of molecular mobility, insufficient to otherwise lead to nucleation and crystal growth. Such kinetically stable or metastable highly viscous solution behaves like a supercooled liquid and exhibits a unique glass transition temperature, referred to as T_g', above which it behaves like a viscous liquid, and as an elastic solid below the T_g'.[9]

Reported studies in the literature deal with the effect of the addition of electrolytes on T_g' of lyophilized formulation. Her and Nail demonstrated a reduction in T_g' of dextran, poly(vinyl pyrrolidone) (PVP), and lactose, on the addition of electrolytes like sodium chloride and sodium phosphate.[10] Nesarikar and Nassar similarly reported that the addition of electrolytes to maltose, trehalose, sucrose, dextran, and PVP reduced T_g'.[11] Both of the studies correlated the reduction in T_g' to be primarily due to an increase in the unfrozen water fraction in the formulation.[10,11] However, these studies depicted the effect of exogenous addition of the electrolytes to the lyophilized formulation.

Izutsu et al. studied the physical properties of L-arginine and its mixture with acids in frozen aqueous solutions and freeze-dried solids. L-Arginine showed a T_g' of −41.4 °C. Some acids and salts (e.g., H_3PO_4, H_2SO_4, HNO_3, and NaH_2PO_4) raised the T_g', whereas others (HCl, CH_3COOH, HCOOH, Na_2HPO_4, and NaCl) had little effect or lowered the T_g'.[12] Kadoya et al. similarly studied the physical properties of binary frozen aqueous solutions containing various functional groups and deduced the importance of the electrostatic interactions and hydrogen bonding in the relative position of T_g'.[13] However, no investigation of the overall contributors to such behavior was performed in either study.

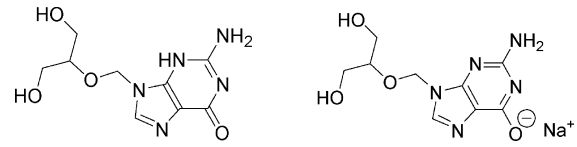

Figure 1. Structure of ganciclovir and ganciclovir sodium.

Drug in a salt form is present as an electrolyte, and the type of counterion may affect the CPT for lyophilization. Moreover, intramolecular interactions between the ionized drug and ionized counterion contribute toward CPT for lyophilization. No study dealing with the effect of counterion on the T_g' for a series of drug salts has been reported in the literature, until date. This manuscript deals with the effect of different alkali metal salts (sodium, potassium, rubidium, and cesium) of a model drug, on the CPT during lyophilization.

Ganciclovir, a model drug for the study, is a synthetic guanine derivative active against cytomegalovirus. It is available as a sterile lyophilized powder in the strength of 500 mg per vial for intravenous administration only (equivalent of 500 mg of ganciclovir as the sodium salt). It exists as a white to off-white crystalline powder with a molecular formula of $C_{19}H_{13}N_5O_4$ and a molecular weight of 255.23. The chemical name for nonionized ganciclovir (hereinafter mentioned as GCV) is 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl] guanine. The pK_a's for ganciclovir are 2.2 (basic) and 9.4 (acidic).[14] The drug is nonionized at a physiological pH but becomes ionized on the addition of a strong base like sodium/potassium hydroxide (Figure 1).

Experimental Section

Materials. GCV was obtained as a gift sample from Strides Arcolab, India, and used as supplied. Sodium hydroxide (Qualigens, India), potassium hydroxide (s.d. fiNE-CHEM, India), rubidium hydroxide (Sigma, USA), and cesium hydroxide (Sigma, USA) were of analytical reagent grade. High-purity freshly glass double-distilled water was used for preparation of solutions.

Methods. Preparation of Salt Forms. Salts of ganciclovir, namely, sodium (GCV-Na), potassium (GCV-K), rubidium (GCV-Rb), and cesium (GCV-Cs), were prepared by *in situ* salt formation. Briefly, 2 M aqueous solution of counterion was prepared and added dropwise to 10 mg of GCV, until complete dissolution (drug:counterion stoichiometry 1:1.5). Preliminary experiments revealed a 1:1.5 (drug:counterion) ratio for complete salt formation. Higher ratios of 1:10 and 1:15 were used to investigate the effect

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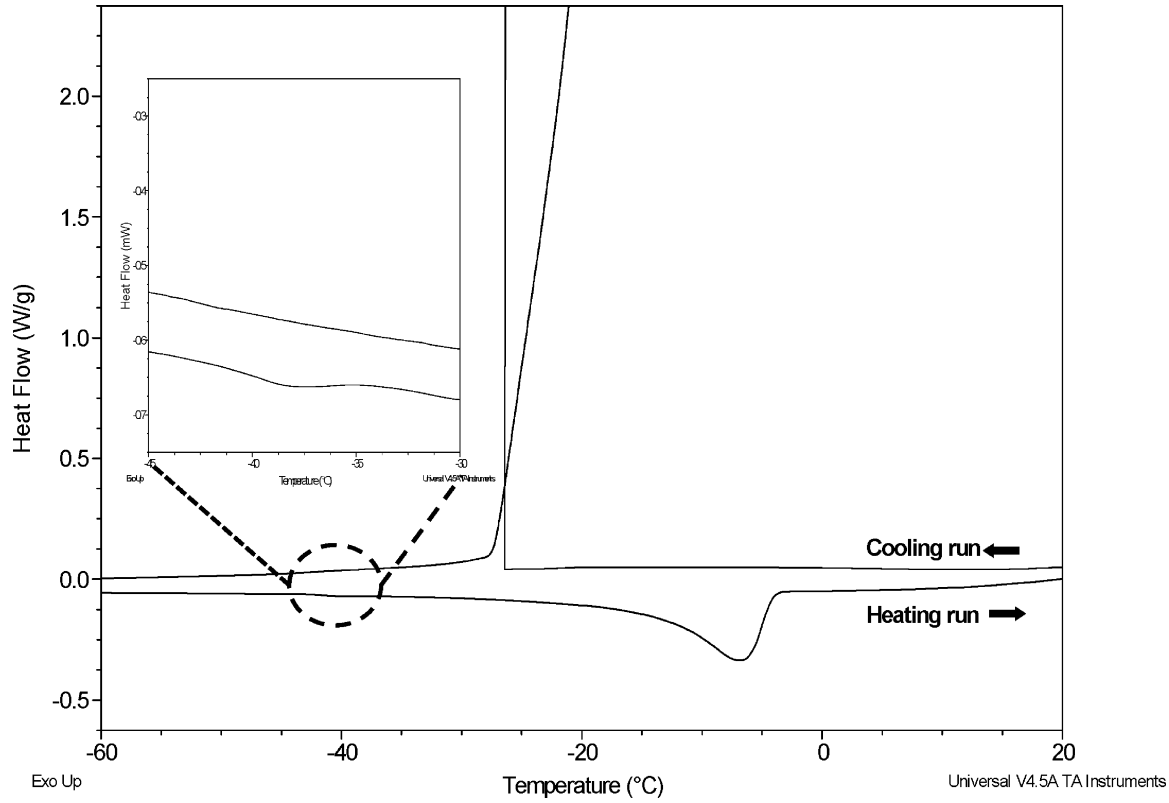

Figure 2. A representative MDSC run for GCV. The upper line denotes the cooling run, and the lower line is the heating run (during which modulation was applied).

of excess counterion on the unfrozen water content. All of the solutions showed a pH greater than 11.5, indicative of complete salt formation. The prepared solutions were immediately analyzed by modulated differential scanning calorimetry (MDSC), for the determination of T_g' or T_{eu}.

Determination of T_g' or T_{eu} by MDSC. The calorimetric response of the sample was measured using MDSC (DSC Q2000, TA Instruments, USA), equipped with RCS90 cooling accessory. Prior to analysis, the instrument was calibrated for temperature and heat flow using the high-purity standard of indium (In). The sample was analyzed in a hermetically sealed aluminum pan, with a blank hermetically sealed aluminum pan as the reference. The following was the MDSC program used for analysis: (a) cooling run (equilibrate at 20 °C; cooling ramp @ 1 °C/min until −80 °C; isothermal hold at −80 °C, for 5 min); (b) heating run (modulation of ±0.2 °C, every 60 s; heating ramp @ 1 °C/min until 20 °C). A baseline shift in the reversing DSC signal, concomitant with a rise in the reversing heat capacity curve, was assigned to be the T_g' of the maximally freeze-concentrated phase of the frozen solution.

GCV (10 mg) was dissolved in water and heated to 50 °C to obtain a supersaturated aqueous solution of GCV, for the determination of the critical temperature of GCV. The solution was then immediately analyzed by MDSC, using a protocol similar to that as described above, except the fact that the equilibration was performed at 50 °C. No degradation of GCV was, however, observed during heating (data not shown). Interpretation of the data was performed with Universal Analysis software (Version 4.5A).

The determination of the freezable water content was performed using the enthalpy of crystallization (ΔH) of ice during the cooling run, by integrating the area under the crystallization exotherm. Prior to determination, DSC was calibrated with indium and double-distilled water.

Results

GCV and its salts showed a T_g' in the reversing heat flow signal, indicating their amorphous nature. Figure 2 shows a representative MDSC heating curve for GCV. The upper line in the curve denotes the cooling run, from equilibration temperature (50 °C) to −80 °C. An exothermic crystallization peak, contributed by the ice formation, was seen at a temperature of around −30 °C. No other peak was observed in the cooling run. The lower line in the curves denotes the modulated heating run from −80 to 20 °C. T_g' event attributed to GCV was obtained at a temperature of −40.15 °C (mid point T_g'; Figure 2).

Table 1 and Figure 3 depicts the order of T_g' for different salts as: GCV-Na (−34.94 °C) > GCV (−40.15 °C) > GCV-K (−46.23 °C) > GCV-Rb (−49.95 °C) > GCV-Cs (−53.62 °C).

The freezable water content of GCV and its salts was quantified in terms of the enthalpy of crystallization, as determined by DSC. The enthalpy of crystallization per unit weight of a sample is directly proportional to the amount of

Table 1. Glass Transition Temperature (T_g') and DFT Parameters for Ganciclovir and Its Salt Forms

sample	T_g' (mid point; reversible; °C)	freezable water content (ΔH; J/g)	unfrozen water content (%)[a]	hardness factor η (KJ/mol)	chemical potential μ (KJ/mol)	electrophilicity index ω ($\times 10^6$) (KJ/mol)
GCV	−40.15 (0.9)[b]	255.15 (1.6)	9.42 (0.4)			
GCV-Na	−34.94 (1.3)	137.35 (0.3)	51.39 (0.1)	442.9	−274.3	16.7
GCV-K	−46.23 (0.9)	146.27 (5.4)	48.24 (1.3)	370.4	−233.6	10.1
GCV-Rb	−49.95 (0.7)	126.95 (0.1)	55.07 (0.0)	356.1	−224.9	9.0
GCV-Cs	−53.62 (0.1)	115.85 (1.2)	59.00 (0.3)	330.2	−210.6	7.3

[a] Calculated based on the enthalpy of crystallization of pure water (282.6 J/g); $n = 3$. [b] Parentheses indicate the standard deviation.

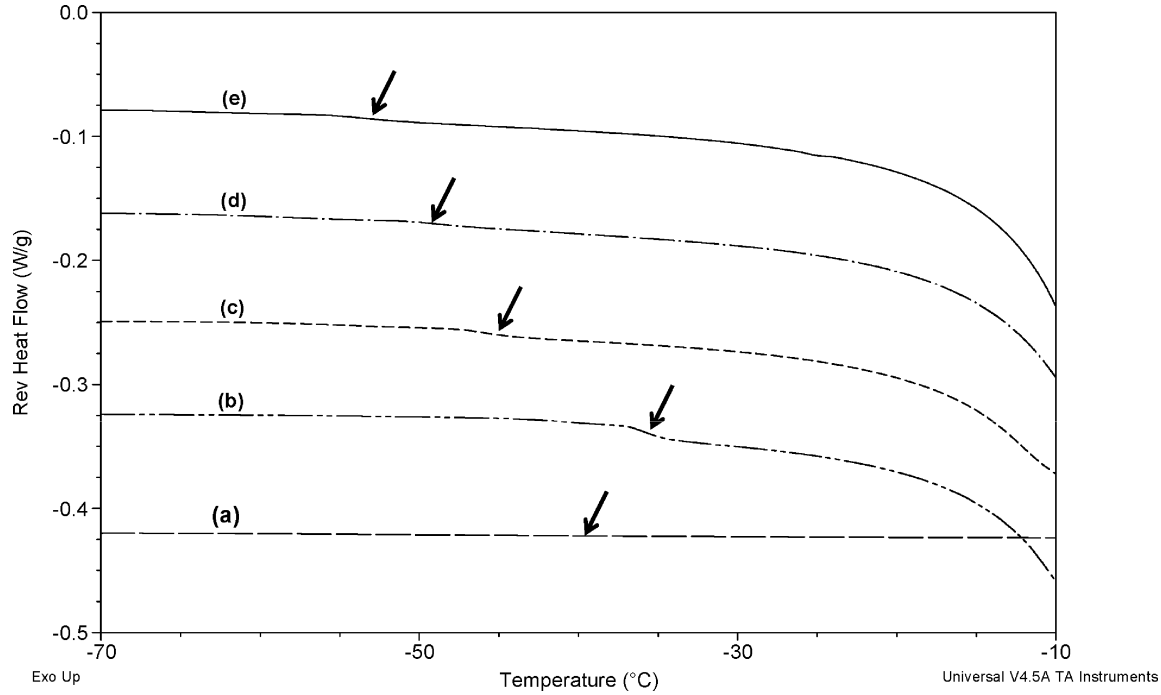

Figure 3. Reversing heat flow signal of (a) GCV, (b) GCV-Na, (c) GCV-K, (d) GCV-Rb, and (e) GCV-Cs, showing a baseline shift in the heat flow. The arrows denote the position of T_g'.

frozen water (the water capable of forming the ice phase surrounding the unfrozen solution) present per unit weight of the sample. A higher enthalpy of crystallization, therefore, suggests a higher proportion of the freezable water. GCV salt solution exhibited a decrease in the enthalpy of crystallization as compared to pure water alone, confirming higher water content in unfrozen state. This leads to a reduction in T_g', as unfrozen water acts as a strong plasticizer (T_g' of water $= -131$ °C).[10,11]

Discussion

The difference between the T_g' of GCV-Na and GCV-Cs is of the order of about 19 °C, which is very significant in terms of the energetics of a lyophilization cycle. It has been reported that for every 1 degree rise in drying temperature, the sublimation rate during lyophilization increases by about 13%. Therefore, primary drying is preferably carried out at the highest possible temperature below the CPT (T_g' or T_{eu}), to maintain product stability.[15] GCV-Na would be the preferred salt for lyophilization of ganciclovir, because of its highest T_g', compared to other GCV salts, thus providing an energy efficient lyophilization cycle.

Analysis of the freezable water content (ΔH; J/g) for GCV and its salts showed the following trend: GCV (255.15) > GCV-K (146.27) ≥ GCV-Na (137.35) > GCV-Rb (126.95) > GCV-Cs (115.85).

The influence of the counterion on freezable water content and T_g' was investigated further, by using different stoichiometry of drug:counterion in GCV-K. An increase in the drug:counterion stoichiometry led to a further reduction in the T_g' for all of the salts. It should be noted that the excess of counterion is present as free ions in the solution. T_g' of GCV-K shifted from −46.23 °C (1:1.5 drug to counterion stoichiometry; enthalpy of crystallization $\Delta H = 146.2$ J/g) to −50.87 °C (1:2.5 drug to counterion stoichiometry; enthalpy of crystallization $\Delta H = 129.1$ J/g) and further to −62.75 °C (1:10 drug to counterion stoichiometry; enthalpy of crystallization $\Delta H = 104.1$ J/g). This observation established that the increase in drug:counterion stoichiometry increased the unfrozen water content (decrease in enthalpy of crystallization) in the glass matrix. A similar trend was observed for other salt forms.

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The glass transition is known to be influenced by the intermolecular as well as the intramolecular force of interactions.[16−18] It has been reported that an increase in the intramolecular force of interaction between the ionized drug and the counterion leads to an increase in the glass transition temperature. Networking of intense electrostatic interactions and hydrogen-bonding between the multiple functional groups has been reported to raise the T_g' value.[12,13] Further investigations were therefore carried out to understand the effect of the counterion on the intramolecular and intermolecular force of interaction between the ionized fragments of the drug and the counterion.

Density functional theory (DFT) has been applied to explain the trend in glass transition of different salts in the solid state.[18,19] According to the theory, there are three energy contributions to the glass transition. The first is the electrostatic contribution, which dominates when the interacting molecules are highly ionic and hard. The second is the covalent contribution, which arises 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. Interactions such as hydrogen bonding and nonspecific cohesive forces have been found to be important in nonionized systems,[20] whereas ionic interactions are of greater importance for salt forms.[18,19]

The concept of hardness has been used in DFT to characterize covalent and polarization interactions induced by charge transfer and sharing. Hardness is also useful to understand the electrostatic interactions, typically dominant among hard species. Hardness (η) is calculated as the energy gap between the ionization potential and the electron affinity and is given by eq 1:

$$\eta = I - A \tag{1}$$

Also, parameters like chemical potential and electrophilicity index indicate a contribution of the covalent and polarization interactions.[19,21,22] The chemical potential μ is given by eq 2:

$$\mu = -\frac{I + A}{2} \tag{2}$$

The electrophilicity index ω denotes the molecular interactions for an intermolecular process involving charge transfer. It is given by eq 3:

$$\omega = \frac{\mu^2}{2\eta} \tag{3}$$

A high electrophilicity index shows a tendency to form strong covalent and polarization interactions with other similar molecules.

Table 1 shows the DFT calculations for counterions used in this study. The values of ionization energy (KJ/mol) for Na, K, Rb, and Cs are 495.8, 418.8, 403.0, and 375.7, respectively. The corresponding values of electron affinity (KJ/mol) for Na, K, Rb, and Cs are 52.9, 48.4, 46.9, and 45.5, respectively.[23] The hardness factor η decreases progressively from Na to Cs, indicating a decrease in the intramolecular force of interaction between the drug and the counterion. Other DFT parameters, like the electrophilicity index, also showed a similar downward trend from Na to Cs, corresponding to the decreasing ability to form covalent and polarization interactions with other similar molecules.

Therefore, the intramolecular interaction between GCV and Na is greater (higher η value), in comparison to GCV and Cs, contributing to a higher T_g' of GCV-Na. A lower degree of intramolecular force of interaction between the ionized ganciclovir and the potassium ion (GCV-K) as compared to GCV-Na justifies a higher T_g' of GCV-Na, in spite of having a lower enthalpy of crystallization (and hence higher unfrozen water content). The intermolecular force of interactions between GCV and Na is also higher as compared to other salts of GCV (higher μ and ω value), thus possibly contributing to a higher T_g' value.

In contrast, hydrogen bonding is predominant in the nonionized GCV, thus becoming the overriding factor of glass transition.[18,19] The presence of hydrogen bonding in GCV and lesser unfrozen water content, as compared to GCV salts, justifies a relatively higher T_g' of GCV, compared to all GCV salts, except GCV-Na.

A higher T_g' of GCV-Na compared to GCV further suggests that the ionic interaction is the major contributor among the factors affecting T_g'. Therefore, the T_g' value of GCV-Na is higher than GCV, in spite of the higher unfrozen water content of the former.

Apart from the drug−counterion interaction, water also plays a prominent role in dictating the observed T_g'. The nature and strength of interaction with the counterion and the corresponding degree of unfrozen water contribute to the observed T_g'. During solvation of a cation (Na/K/Rb/Cs), water molecules are aligned in a defined manner, surrounding the counterion. Water molecules in a primary hydration shell have strong hydrogen bonding with the cation. A secondary

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hydration shell is further created by the hydrogen bonding interaction of water molecules of primary hydration shell, with additional neighboring water molecules. The water molecules in primary and secondary hydration shells together constitute the total hydration sphere of the cation. Na and K cations have a primary hydration number of four water molecules, whereas Rb and Cs have a primary hydration number of six water molecules. However, Na and K cations, being smaller in size, have a greater polarizing power and a higher total hydration number on account of a larger secondary hydration shell. The total hydration number of Na, K, Rb, and Cs follows the order as: Na (17) > K (11) > Rb (10) ∼ Cs (10).

However, the water present in the secondary hydration shell does not contribute to T_g', as this water is able to diffuse, owing to weaker binding, thus resulting in their crystallization over the course of lyophilization.[24] In contrast, water molecules in the primary hydration shell remain associated with the solute as unfrozen water, thus reducing the observed T_g', by virtue of their plasticizing effect. Since Na and K have a lower primary hydration number, compared to Rb and Cs, an increase in unfrozen water content was observed, as we move down from Na to Cs.

The study highlights the importance of salt screening of drugs meant for the development of lyophilization-based products. Certain classes of drugs, for example, penicillins and cephalosporins, are commonly used as lyophilized formulations, and a careful consideration of the effect of the salt form on the CPT (T_g' or T_{eu}) would help in the development of a lyophilization cycle. The study also suggests that the excess of counterion, if used in the preparation of *in situ* salt forms, could lead to a reduction in the CPT. Therefore, care should be undertaken to prepare the salt form, preferably with an optimal stoichiometry, to develop an energy-efficient lyophilization cycle.

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Conclusion

The present study demonstrates the effect of salt forms on CPT during lyophilization. A higher CPT is desirable to economize on the time and energy requirements of lyophilization cycle. T_g' is affected by the ionic interaction between the drug and the counterion and the hydrogen bonding strength, as well as the freezable water content of the system. The effect of the salt form on the CPT of lyophilization should be an integral part of the preformulation and drug development program of lyophilized formulations.

Abbreviations

CPT, critical process temperature; T_g', glass transition temperature; T_{eu}, eutectic temperature; GCV, nonionized ganciclovir; pK_a, ionization constant; MDSC, modulated differential scanning calorimetry; GCV-Na, ganciclovir sodium salt; GCV-K, ganciclovir potassium salt; GCV-Rb, ganciclovir rubidium salt; GCV-Cs, ganciclovir cesium salt; DFT, density functional theory; Na, sodium; K, potassium; Rb, rubidium; Cs, cesium.

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