Predicting Onset Temperature Of Crystallization Of Amorphous Drugs On The Basis Of Glass Transition Temperature and Molecular Mass

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Abstract: A strong quantitative relationship has been established among the glass transition temperature Tg, molecular mass MW and crystallisation for predicting the onset temperature of crystallisation, Tcr(onset) of a large number of amorphous drugs.

INTRODUCTION

The modern drug discovery techniques have led to the discovery of many lipophilic drug candidates. Consequently, a majority of new drug candidates within the Biopharmaceutical Classification System (BCS) that belong to class II, III, and IV are characterized by a bioavailability feature that is mainly dependent upon solubility and/or permeability. In the modern pharmaceutical industry, the crystalline active pharmaceutical ingredients in solid oral dosage forms have been commonly employed. However, the crystalline APIs of these classes have poor bioavailabilty and hence are not very effective.

Now a days, there is an increasing inclination towards preferring the amorphous to the crystalline form of an API in oral dosage forms if possible as they have enhanced solubility and bioavailability consequent to increased intestinal absorption compared to that of the crystalline form. The reason for the enhanced solubility of the amorphous forms is the thermodynamic feature of relatively higher Gibbs free energy of these forms. Further, a very significant criterion in assessing whether or not an API is a potentially suitable candidate for an amorphous formulation is determined by its physical stability during the relevant processing as well as subsequent storage conditions. However, as the inherent instability of the amorphous state limits production, handling and use of products based on amorphous compounds, research efforts are aimed at methods that stabilize the amorphous phase. [1-7]

The glassy material preferred to the crystalline form of an API in dosage forms can undergo crystallization during the storage conditions, thereby adversely affecting its desired physical stability. The crystallization from the amorphous solid is highly undesirable because of its adverse effects on the dissolution rate and for these reasons attempts have to be made to prevent these undesirable processes from occurring in the dosage forms. Obviously, even as there is a very much desired advantage in preferring the amorphous state having higher solubility to its crystalline counterpart in cases where low solubility limits its intestinal absorption and also its physical instability stands as an important obstacle preventing its use in solid oral dosage forms. Thus, the inherent instability of the amorphous state of an

API limits production. That also limits the handling as well as use of products based on amorphous compounds. Consequently, one of the important challenges for the pharmaceutical scientists today is to produce amorphous formulations and that too those drugs that are sufficiently stable for practical applications, they stand for.

The production and stabilization of the amorphous phase in dosage forms are of great relevance in pharmaceutical science and industry. Evidently, a thorough and minute comprehension of the parameters that affect and govern crystallization from the amorphous state is of paramount significance in pharmaceutical industry. At the same time, it also becomes very clear that it will be very much advantageous to know and in fact being in a position to predict which crystalline APIs would have a tendency to transform into an amorphous glassy state and that whether or not the resultant glassy state would be stable during the storage conditions i.e. whether or not the glassy state would have a propensity to crystallize during the storage conditions.

RESULTS AND DISCUSSION

Amorphous materials when heated transform into a soft or rubber like state called glass, a phenomenon that is reversible upon cooling and the temperature at which the glass formation or transition occurs is called glass transition temperature,Tg. In the glass state, the molecules are relatively loosely held than in the original unheated form. That is to be anticipated that if the intermolecular forces are weak, the amorphous material will transform into glass readily so that the Tg will be low and in case the intermolecular forces are strong, the Tg will be high. Upon heating the glassy material further above the Tg, the amorphous material may crystallize before it reaches its thermodynamic melting point, Tm. During the transformation into the crystallized form, the molecules undergo change such that the disordered glass now gets converted into the ordered crystalline form. The crystallised state of the drug is represented by the onset temperature of crystallization, Tcr(onset) that is recorded at a well defined heating rate and sample size in the Differential Scanning Calorimetry (DSC) technique.

When the Tg of an amorphous state is low, the drug will have greater propensity for crystallization as it acquires greater kinetic mobility so that the Tcr(onset) of the crystallized state of the drug will be relatively low. In fact, the amorphous state is not stable even far below the Tg temperatures such as (Tg-50) K as there are present primary and secondary mobilities in the amorphous material that can cause crystallization as has recently been revealed by tetrahertz spectroscopy. Evidently, an amorphpus drug stored above Tg will have lower viscosity and consequently greater molecular mobility than at Tg. For these reasons, the amorphous drugs are stored below Tg than at or above Tg. However,the storage of amorphous drugs with low Tg assumes critical significance as it reduces their shelf-life owing to their crystallization propensity. Therefore, special formulation techniques are required for achieving longer shelf-life or greater stability for such amorphous drugs by preventing or suppressing their crystallization propensity.

In fact , the inherent instability disadvantage of the amorphous drugs puts a limit not only on their formation but also on the handling as well as usage of products involving the amorphous drugs. Therefore, this instability is highly undesirable for their usage.

Evidently,the glass transition temperature,Tg is used as a reference temperature to determine glass formation temperatures as well as temperatures for the storage of amorphous drugs. Nevertheless, it is not possible to use Tg as a predictive tool for determination of physical stability of amorphous drugs with wide differences in their physical stability despite similar Tgs as becomes evident from the following data. Thus, while felodipine with a Tg of 42 has a Tcr(onset) of 51, testosterone with a Tg of 45 has a Tcr(onset) of 51. Nifedipine with a Tg of 42 has a Tcr(onset) of 73 while indometacin with a Tg of 44 has a Tcr(onset) equal to 104. Similarly, albendazole has a Tcr(onset) of 56, and a Tg of 60, while carbamazepine has a Tcr(onset) of 77 despite its relatively high Tg of 61. On the other hand, there are some examples of amorphous drugs that exhibit similar physical stability and similar Tgs. For instance, hydroflumethazide with a Tg of 100 has a Tcr(onset) of 142 while linaprazam with an identical Tg has a Tcr(onset) of 147; D-lactose with a Tg of 105 has a Tcr(onset) of 140 while hydrochlorothiazide with a Tg of 110, has Tcr(onset) of 139.

However, from the preceeding discussion regarding the similarities and dissimilarities of physical stability of amorphous drugs with respect to Tg, it can be concluded that Tg certainly displays a relation with physical stability of the amorphous drugs although when it comes to comparing he physical stability of various amorphous drugs, Tg does not act as the only determinant of the physical stability of the amorphous drugs. Evidently, other factor(s) must be involved and invoked to explain away the differences observed in the physical stability of amorphous drugs as reflected by their Tcr(onset). We suggest molecular weight, MW to be the other prominent parameter that could have impressive effect on the physical stability as does Tg. That suggestion is based on the the universal empirical observation that heavier compounds with higher MW are difficult to crystallize from solution while drugs with relatively lower MW are readily crystallized from solution, in general. That is to be anticipated as molecules with higher MW have complicated structures and would therefore have a lower propensity to get arranged into ordered crystalline form. Furthermore, generally speaking, Tcr(onset) is found to rise with a rise in MW of the drugs. In this work, lighter molecules with lower MW 236-288 exhibit a Tcr(onset) in the range 51-77. Relatively heavier drug molecules with MW more han 300 have, in general, higher Tcr(onset) in the range 90-150. Thus, albendazole with MW 265.3 has a Tcr(onset) of 56, carbamazepine with MW 236.3 has a Tcr(onset) of 77 and testosterone with MW 288.4 has a Tcr(onset) equal to 51. Among relatively heavier molecules, omeprazole with MW 345.4 has a Tcr(onset) of 90, famotidine with Mw 337.4 has a Tcr(onset) of 104, D-lactose having MW 342.3 shows a Tcr(onset) of 140, hydroflumethazide with MW 331.3 records a Tcr(onset) of 142, indometacin with MW 357.8 records a Tcr(onset) of 104, hydrocortisone with MW 366.5 has a Tcr(onset) of 123, linaprazan with Mw 366.5 shows a Tcr (onset) of 147, spironolactone with MW 416.6 shows a Tcr(onset) of 127 and pimozide having Mw 461.5 exhibits a Tcr(onset) of 106.

Of course, there are exceptions to the above generalization. Thus, acemetacin with MW 415.8 has a relatively low Tcr(onset) of 79, acetohexamide with MW 324.4 has a Tcr(onset) of 65, bezafibrate having MW 361.8 records a Tcr(onset) of 61, nifedipine with MW 346.3 crstallizes at a Tcr(onset) of 73. From the preceding discussion, it can be concluded that MW does exert its impact on the Tcr(onset) of the drug although the relation between MW and Tcr(onset) is not linear as was the relation between MW and Tg. Therefore, we decided to develop a tool based on the Tg and MW of these compounds so that the predicted TCr_{onset} values could be compared with the observed values. Having established the existence of two strong parameters, Tg and MW as being closely related to physical stability of amorphous drugs represented by Tcr(onset), we report herein for the first time

that relationship on the quantitative scale by eq 1 for a large number of amorphous drugs which undergo crystallization upon storing below Tg.

$$Tcr(onset) = Tg + 0.101MW \quad \text{.....Eq 1}$$

From eq 1, it becomes evident that Tcr(onset) quantitatively depends upon the twin parameters of Tg and MW. Further, greater the Tg, greater will be the effect of Tg on Tcr(onset) i.e.the Tcr(onset) will rise as the MW term is a fixed quantity for that drug molecule. Lower the Tg, lower will the contribution of Tg towards the Tcr(onset) so that lower will be the Tcr(onset) for that drug. Similarly, it also becomes evident from the eq 1 greater the MW, greater will be the Tcr (onset), lower the MW, lower will be the the contribution of MW to Tcr(onset). As only about 10% (0.101MW) of the actual MW of the drug is required in eq 1, so we can say higher the magnitude of the 0.101 MW of the amorphous drug, higher will be the the Tcr(onset) of the drug. Lower the magnitude of the 0.101MW of the amorphous drug, lower will be the Tcr(onset) of the drug. Furthermore, it is evident from eq 1 that if Tg> 0.101 MW for any drug compound, then Tg plays the role as a major parameter in deciding the Tcr(onset) of that particular compound. On the other hand, if Tg< 0.101 MW for a compound, then obviously 0.101 MW parameter assumes dominant role in governing Tcr(onset) of that particular drug compound. For instance, in case of acemetacin, it is evident that it is the 0.101 MW (equal to41.58) that plays the dominant role over Tg which is equal to 37. In D-lactose, it is the Tg (equal to 105) that plays the dominant role over 0.101 MW (equal to 34.23). Similar is the relation in the case of acetohexaide whose Tg (26) is lower than its 0.101 MW that is equl to 32.44. That is worth noting that only in a couple of cases in this study, Tg < 0.101 MW (in acemetacin and acetohexamide), while in all other cases, it is the other way around i.e. the Tg part of eq 1 that is dominant over the 0.101 MW part in contributing towards the Tcr(onset). Therefore, in conclusion, in majority of the cases, it is the Tg parameter that overweighs the 0.101 MW part in governing or predicting the Tcr(onset).

That needs to be noted that all the compounds whose Tcr(onset) have been reported are the ones that were amorphized by the duel techniques of spray drying and melt-cooling. These TCr_{onset} could be considered highly accurate as these were recorded at a well defined heating rate of $20^{o}C$ per minute by DSC, a rate that allowed complete separation of crystallisation and melting peaks and also at a well defined sample size.

We were able to predict the TCr_{onset} values employing eq 1 for a large number of compounds mentioned earlier as illustrated below.

1 Acemetacin

Tg of acemetacin is 37 and its MW is 415.8. Fitting these values in eq 1 we get a TCr_{onset} equal to 78.99, which is in excellent agreement with the observed value of 79.

2 D-Lactose

Mw of D-Lactose is 342.3 and its Tg is 105. Using the eq 1 we get the predicted TCr_{onset} of 139.5 which is very close to the observed TCr_{onset} of 140.

3 Hydrochlorothiazide

Application of eq 1 to this compound having Tg equal to 100 and MW 297.7 predicts a TCr_{onset} of 140, a value that agrees well with the observed TCr_{onset} of 139.

4 Hydrocortisone

Hydrocortisone has a Tg of 86 and MW 362.4 and the predicted value of TCr_{onset} comes to 122.6 that is very close to the observed TCr_{onset} of 123.

5 Pimozide

Tg of pimozide is 57 and its MW is 461.5. Applying eq 1 we predict TCr_{onset} as 103.6 that is also close to the observed TCr_{onset} of 106 (97.1% accuracy).

6 Omeprazole

Mw of omeprazole is 51 and its MW is 345.4. Application of eq 1 predicts its TCr_{onset} of 86 which is close to the observed TCr_{onset} of 90, accuracy being 96%.

7 Bicalutamide

Bicautamide has Tg equal to 50 and its MW is 430.4. Its predicted TCr_{onset} as per eq 1 comes to be 93 which is close to the observed TCr_{onset} of 97 with an accuracy of 96%.

8 Spironolactone

Spironolactone has a Tg of 91 and MW as 416.6. As per eq1, its TCr_{onset} is predicted to be 132.6 while its observed TCr_{onset} is 127 which is only 4% higher.

9 Hydroflumethazide

This drug shows a Tg of 100 and its MW is 331.3. The eq 1 predicts its TCr_{onset} to be 133 which is close to its real TCr_{onset} is 142 being 94% of this value.

10 Linaprazan

Linaprazan has a Tg of 100 and a MW of 366.5 so that as per eq 1 its predicted TCr_{onset} equals 136.5 that is 93 % 0f the observed value of 147.

11 Felodipine

Felodipine has a Tg equal to 41 and aMW of 384.3 so that as per the eq the predicted TCr_{onset} comes to be 79 that is close to the real value of 86 being 91% of it.

12 Nifedipine

Nifedipine which has a Tg of 45 amd a MW of 346.3 exhibits a predicted TCr_{onset} of 79 that is just 8% more than the real observed value of 86.

13 Acetohexamide

This drug with a Tg of 26 and a MW of 324.4 shows a predicted value of TCr_{onset} as per eq 1 of 58.5 that is 89% of the observed value of 65.

14 Carbamazepine

Carbamazepine having a Tg of 61 and a MW of 236.3 shows a predicted value of TCr_{onset} of 85 using eq 1 which is only 11% higher than the recorded value of 77.

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