MELTING POINT-THERMAL AND KINETIC PARAMETERS (T_{ONSET},T_M AND E_A) FOR DEHYDRATION AS EARLY INDICATORS OF THE STABILITY OF PHARMACEUTICAL HYDRATES AND CLASSIFICATION OF HYDRATES ON THE BASIS OF THESE PARAMETERS.

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ABSTRACT

Assesement of the physical stability of pharmaceutical hydrates is at the forefront of the drug product science and technology research in pharmaceutical industry. We have previously advanced melting point as an early indicator for assessing the physical stability of pharmaceutically relevant hydrates . Now, this new parameter of melting point has been combined with three kinetic parameters –T_{onset},T_m and E_a for dehydration obtained by DSC for predicting the physical stability of the pharmaceutically relevant hydrates. On the basis of the data of these four parameters of a large number of hydrates, the pharmaceutical hydrates have been classified into two types - hydrates with high stability having high MP, high T_{onset}, high T_m and high E_a, and hydrates with medium stability having medium m.p., medium T_{onset}, medium T_m and medium E_a. The generated dataset of a number of pharmaceutically important hydrates with known stability profiles may serve as a reference set for comparison and rank-ordering of the stabilities of novel pharmaceutical hydrates .

INTRODUCTION

During crystallization, solvent may often be incorporated as part of the crystal structure. However, as most of the solvents used are biologically incompatible because of toxicity, such crystals are not acceptable in the development of the solid form of an API. An important exception to that phenomenon are the API hydrates wherein the biologically compatible water forms the part of the crystal structure.1 APIs hydrates are well known in pharmaceutical products. In fact, about one third of the APIs are able to exist as hydrates. One Pharmacopoeia enlists more than 90 hydrates.[2] Hydrates are classified as stoichiometric and non-stoichiometric hydrates. The former type contain a fixed molar amount of water of crystallization in their

crystal lattice. In contrast, the non-stoichiometric hydrates contain varying amount of water which alters reversibly with the partial pressure of the water in the surroundings and hence, *these are not suitable for formulation development*. Although, the anhydrate of an API gets preference over the hydrate form of the API for solid state drug formulation yet, if due to certain reasons like solubility, instability and complicated polymorphism, the anhydride is considered unsuitable, then the hydrate of the API is selected for the said purposes.

The drug products containing the stoichiometric crystalline API hydrates are subject to exposure to a range of temperature and moisture during the manufacturing processes and subsequent storage. 3 As a consequence of these process-induced stresses, the hydrates exhibit the propensity to undergo dehydration that can lead to their completely or partly disordered or chemically decomposed forms.4 Evidently, the dehydration of the API hydrates that can result in significant changes in their physical properties and pharmaceutical behavior such as dosage form appearance and integrity acquires great significance and hence attention . The dehydration of an API hydrate is dictated by the temperature and water vapor pressure of its surroundings.[4] When the API is exposed to higher temperature or to a dry atmosphere having low relative humidity (RH), it can undergo dehydration as the water vapor pressure outside the API is lower than the water vapor pressure inside the API. The resultant dehydrated form has different physiochemical properties such as aqueous solubility, rate of dissolution and bioavailability compared to its hydrate counterpart.4 Thus, if an API is selected for development purposes in a solid dosage form, its physical stability acquires great significance for the reasons of its susceptibility to dehydration and the serious undesirable pharmacotherapeutic consequences. In fact, a change in hydration state is not only of relevance for the API but also for the drug product. When an API loses water of crystallization, the water released may interact with other components in the drug product and lead to their decomposition. Consequently, great emphasis has to be laid upon by pharmaceutical scientists for evaluating the physical and chemical stability of the various crystalline forms of an API including its hydrate forms such as monohydrate, dihydrate etc before selecting the most suitable form for drug development .

To understand the mechanism of dehydration of the crystalline hydrates, many researchers have carried out kinetic studies of the dehydration behavior in solid state which, of course, is different to that in the solution form. [5-8] Two approaches , the model-free and model-fitting analyses have been used under the isothermal and nonisothermal conditions for obtaining the energy of activation for dehydration , Ea .[9] The nonisothermal model-free approach called the Kissinger method based on the equation-1 enables us to obtain the energy of activation for dehydration when lnB/Tm is plotted against 1/Tm. [10]. This model-free approach is based on a reaction order model of the form f(x)=(1-a) whence a is the fraction converted.

$$\ln\frac{\beta}{T_m^2} = \ln\left(\frac{AR\left(n(1-\alpha)_m^{n-1}\right.}{E_a}\right) - \frac{E_a}{RT_m}$$

EXPERIMENTAL

MPs of the hydrates were taken from Chemical abstract service (CAS). We also found out the MP of two readily available hydrates-Citric acid monohydrate and lactose monohydrate procured from Fluka. Their melting points were determined by by the readily accessible open capillary method and are uncorrected.

RESULTS AND DISCUSSIONS

On the basis of the melting point of the dehydrated form of the hydrates we have already built a dataset of pharmaceutically relevant hydrates having known stability profiles that can help us predict the stability of the novel hydrates very readily during the form selection phase of the development of the drug hydrate.[11] Recently, the use of a rapid DSC-method for the preliminary assessment of the physical stability of pharmaceutical hydrates was proposed .[12] T_{onset} and T_m and Ea (following the Kissinger equation , Eq 1, for the nonisothermal rate law equation) of dehydration for these hydrate crystal forms were reported, for a number of pharmaceutically relevant and marketed hydrates (collected in Table-1, where a stands for the crystalline form of the hydrate in the commercial products) although, under the unreal conditions

Compound	T_{Onset} (◦C)	T_m (◦C)	E_a (kJ/mol)	M.P (◦C) of compound
Beclomethasone dipropionate monohydrate*a*	31	61	70	< 117
Cefadroxil monohydrate*a*	74	105	63	197[17]
Citric acid monohydrate*a*	47	55	103	100[18]
Indinavir monohydrate	20	57	70	150-153[19]
Lactose monohydrate*a*	138	146	141	214[20]
Neotame monohydrate*a*	31	53	79	83-85[21]
Theophylline monohydrate	60	65	131	270-274[22]
β-Estradiol hemihydrate	72	95	129	178.5[23]
Dicalcium phosphate dihydrate*a*	89	96	138	190[24]
Formoterol hemifumarate dihydrate*a*	82	101	91	138-140[25]
Ampicillin trihydrate*a*	52	75	72	198-200[26]

as determinants or predictors of the physical stability of hydrates although every student of pharmacy knows that the kinetics of dehydration rapidly alter with the experimental conditions, the method adopted and the environment around the sample and that the thermodynamic stability of the pharmaceutically relevant hydrates actually has its origin in the critical water activity across temperatures as is reflected in the RH-temperature(T) phase diagram and not in the kinetics of dehydration; and furthermore, it is the control of RH and temperature (T) that makes sure that the pharmaceutical hydrate under investigation is thermodynamically stable and which is what is done in the pharmaceutical industry in the real practice before a hydrate API comes out in the market as a dosage product for treatment of the disease it stands for. Obviously, the reported work has little meaning or significance in the light of the requirement of the RH-T phase diagram which was not constructed as the RH and T data were not controlled by the authors in that study and in fact, one wonders as to why these parameters of paramount significance in the development of the dosage products containing the hydrate APIs were not taken care of or recorded . The hydrate APIs are different from the APIs which are non-hydrate APIs. That is because the concerns for the stability of non-hydrate APIs differ widely from those required for the stability of hydrate APIs. For API hydrates, the loss of water of hydration or crystallization i.e. dehydration phenomenon assumes great significance while this phenomenon is not a concern for the non-hydrate APIs. There is not much fun or significance in doing analysis for building a dataset of the pharmaceutically relevant and marketed hydrates under conditions which do not fall in line with the real conditions for dehydration of the hydrates -the relative humidity and temperature, they face. Nevertheless , we have attempted to make the determined kinetic data to be of some use to the pharmaceutical industry by associating these with the melting points of the hydrates as discussed below.

In fact, the above paper attracted our attention because of our interest in drug stability[13-15]. Although, while MP of a compound is representative of the thermodynamic stability and T_{onset},T_m and E_a represent the kinetic stability, we wanted to give some meaning to the these kinetic parameters by exploring whether the concept of thermodynamic stability as indicated by MP could be combined with the concept of these kinetic and thermal stability parameters for dehydration as determinants or predictors of the physical stability of hydrates . That is to say, we became interested in finding out whether the thermodynamic data, the MPs of the dehydrated solid phase of the hydrate could be compared and related to the kinetic data- the rate of dehydration of the hydrate to the dehydrated solid phase of the hydrate. We chose MP of the dehydrated form of the hydrates, both APIs and excipients as an apt physical parameter of direct relevance to the indication of the stoichiometric hydrate stability as that is readily available in the literature /or is readily determinable, convenient and practical. [15] We envisaged that higher the MP of the dehydrated form of the hydrate, higher its stability; lower the MP of the dehydrated form of the hydrate, lower its stability as MPs are robust indicators of the strength of the intermolecular forces existing between the constituent molecules that bind them together in an orderely crystalline lattice. Of course, it was difficult to envisage a correlation between the dehydration behavior of the pharmaceutical hydrates with the melting points of their completely dehydrated forms even though as already indicated, the MPs are robust

indicators of the strength of the intermolecular forces that exist between the constituent molecules.

Melting point is a fundamental physical property of solid compounds , organic or inorganic, simple or complex, an API or an excipient, salts- organic or inorganic , a free acid or a free base , non-hydrate or a hydrate- semihydrate or monohydrate , dihydrate or trihydrate that is used not only as a marker for chemical identification and as a criterion for judging purity but also for calculating vapor pressure and aqueous solubility. 16 Melting point , a precise end-point , depends upon the molecular arrangement in the crystal lattice and hence is determined by the strength of the crystal lattice. In general, greater the strength of a crystal lattice, higher the melting point, medium the strength of the crystal lattice , medium the melting point, lower the strength of the crystal lattice, lower the melting point. The robustness of a crystal lattice is mainly dependent upon the intermolecular forces , molecular symmetry and conformational degrees of freedom of a molecule. The arrangement of packing of molecules in a molecular crystal is a function of the interplay of the affinity to close packing as well as the strength of the existing intermolecular interactions. 16 Higher melting point for inorganic compounds owe their origin to the presence of the strong electrostatic forces which tightly bind the ions together as reflected by their high lattice energies. Larger the lattice energy , the more stable the solid as more strongly held are the ions , and therefore higher the melting point. Lower the lattice energy, less stable the solid, as the less strongly held are the ions, and hence lower the melting point. Water of crystallization forms an integral part of the structure of the crystals and it may be attached to the anion or to the cation. In dicalcium phosphate dihydrate, water is bound to the calcium ions in the crystal lattice which therefore collapses when water gets eliminated. Four of the water molecules in the copper sulfate pentahydrate that are readily lost upon heating are linked to copper cation but the fifth water molecule is attached more firmly to the sulfate ion, possibly by hydrogen bonding. Ion-coordinated water of crystallization can participate in an ion-water bond that is generally much stronger than any hydrogen bond present in the lattice. In organic compounds, the H-bonding plays a very important role in affecting the structure and consequently the melting point. In effect, the compounds exhibiting intramolecular hydrogen bonding have lower melting point compared to those involving intermolecular H-bonding. [16] In short, melting point of a solid compound is the result of the molecular packing which reflects the molecular shape , size, and symmetry and the H-bonding interactions and forces such as charge transfer and dipole-dipole interactions present in the solid.

Thus, a melting point survey of a number of pharmaceutically relevant hydrates whose three dehydration parameters (T_{onset}, T_m, and E_a) were reported in the above recent study, though under the unreal conditions as mentioned earlier, was carried out very carefully and these have been collected along side their dehydration parameters in Table 1. It should be noted that the desired three dehydration parameters under the investigated conditions of the hydrates other than these ones are not available in the literature and the above paper is the only one that has appeared recently for assessing the dehydration stability of these eleven hydrates via the rapid

DSC-method at a constant rate of heating , needless to say, though, under the unreal conditions which have no connection with the determination or control of the thermodynamic stability that is expected to be tested as well as controlled by the RH and T conditions.

As can be seen from the table, of the eleven investigated hydrates, five hydrates have m.p. in the higher range of (178-214^{0}C) and out of these five hydrates four which implies 80% of the five hydrates which exhibited higher melting points in that range, four (beta-estradiol hemihydrate, dicalcium phosphate dihydrate, cefadroxil monohydrate, and lactose monohydrate) which exhibited higher melting points in that range , have high T_{onset} (72-138^{0}C)(see Fig 1), high T_m (95-146^{0}C)(see Fig. 2) and their E_a for the dehydration was also high, in the range 129-141kJ/mol(see Fig 3), as anticipated. We would classify these hydrates as *highly stable hydrates*.

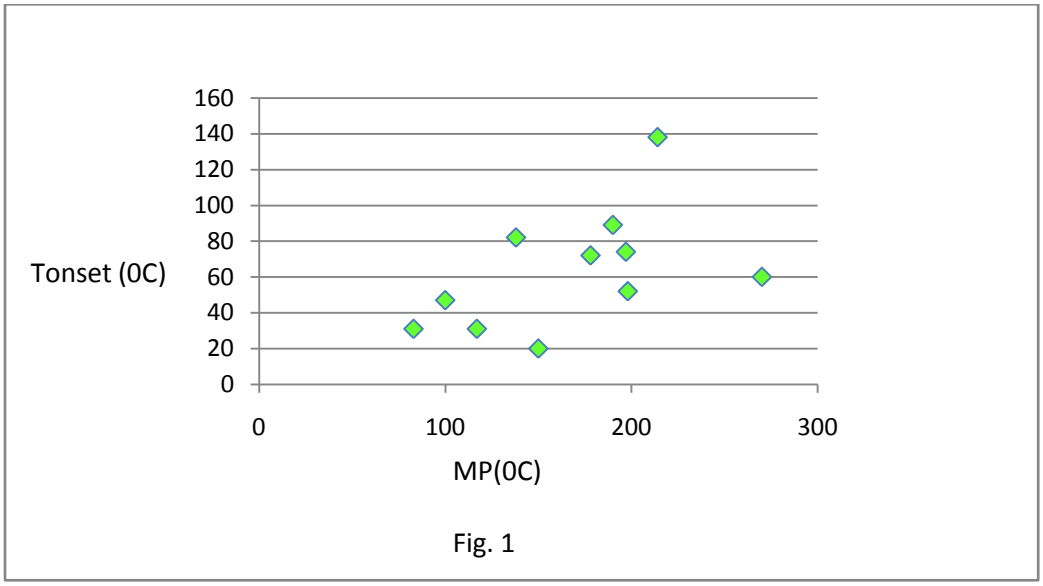

Fig. 1

Of the remaining six hydrates, m. p. of one hydrate, beclomethasone dipropionate monohydrate is unreported hitherto. Out of the remaining five hydrates having m.p. in the medium range (81-151^{0}C), Three (neotame monohydrate, citric acid monohydrate and indinavir monohydrate) of these remaining four hydrates have m.p. in the medium range of 81-150^{0}C with a medium Tonset (20-47^{0}C) and a medium Tm, 55-61^{0}C and their Ea is medium, 70-103kJ/mol , as expected. We would classify these hydrates as hydrates with *medium stability hydrates*. Beclomethasone dipropionate monohydrate whose m.p. is not known in the literature as already stated can be placed in this second category on the basis of its predicted m.p. We predict its m.p. to be below 117-120^{0}C, which is the m.p. of anhydrous beclomethasone dipropionate . That prediction is based on the fact that a hydrated form of a substance always has a lower m.p. point

than the anhydrous form of the substance itself. The values for its T_{onset} (31^0C) ,T_m (61^0C) and E_a (70 kJ/mol) also place it in this category. While theophylline monohydrate is an exception in the first category of highly stable hydrates, formoterol hemifumarate dihydrate is an odd man out in the second category of the hydrate. That is in keeping with the fact that every rule as a rule has got exceptions.

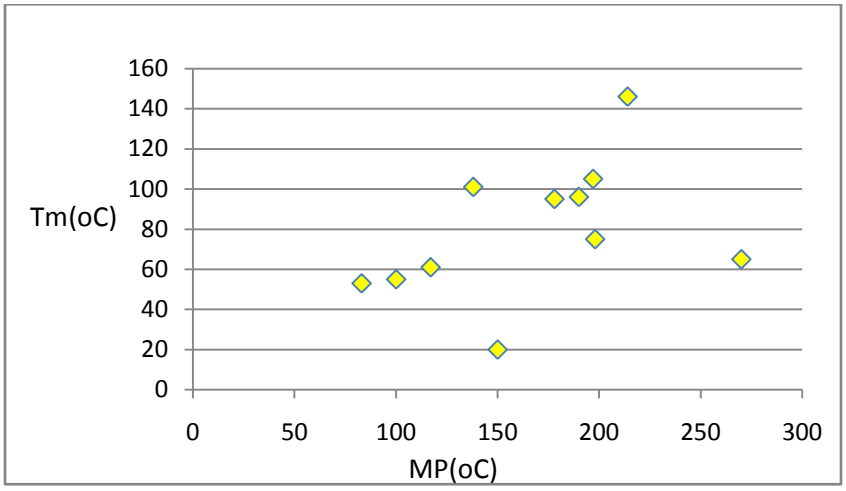

Fig 2

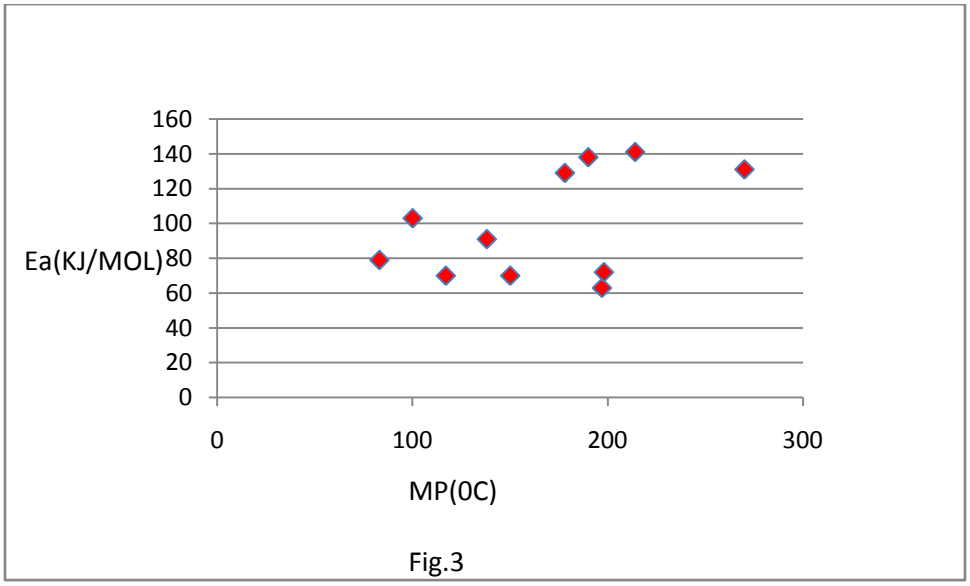

Fig.3

Therefore, it is clear from the preceeding discussion that , in general, there exists an approximate relationship between m.p. and the three dehydration parameters, T_{onset},T_m and E_a recorded under the reported unreal experimental conditions as reported in the reference cited. It needs to be noted tha the rules we have advanced herein for the classification of the pharmaceutically significant hydrates may have exceptions as it is rightly observed that every rule, as a rule, has got exceptions.

Classification of Hydrates on the basis of MP and T_{onset}, T_m and E_a Data

Hydrate Type	***MP and T_{onset}, T_m and E_a***
Higher Stability	Higher MP(178-214^{0}C) and Higher T_{onset} (72-138^{0}C), Higher T_m(95-146^{0}C) and Higher E_a (129-141kJ/mol)
Medium Stability	Medium MP(81-150^{0}C) and Medium T_{onset}(20-47^{0}C),T_m(55-61^{0}C) and E_a 70-103kJ/mol
Lower Stability	Lower MP (less than 81-150^{0}C) and Lower T_{onset} (less than 20-47^{0}C),Tm(less than 55-61^{0}C) and E_a (less than 70-103kJ/mol)

One more approach can be used as well to indicate the stability of the hydrates on the basis of their m.p. and T_{onset} parameters alone . It needs to be noted that between T_{onset} and T_m parameters, the former is a better indicator for assessing the stablility of a hydrate than the latter. That is because while the T_{onset} represents the temperature at which the process of dehydration actually begins, the T_m is the temperature at which dehydration process gets completed. Moreover , while T_{onset} remains constant , T_m shifts with the change in the rate of heating in the DSC- method. The energy of activation for dehydration as determined by the Kissinger method indicates the activation energy for the completion (maximum conversion at T_m) of the process of dehydration rather than for the dehydration process when it just begins at T_{onset}. The beginning of the process of dehydration is of great concern as is the completion of the process of dehydration to a pharmaceutical scientist as that poses challenges to the development of the hydrates .

When we consider the hydrates having m.p. above 138^{0}C (i.e. in the range 138-270^{0}C), then seven out of a total of eight such hydrates which means a significant figure of 87.5%, have T_{onset} in the range 60-138^{0}C . As the accelerated stability tests often involve studies at temperatures of 50^{0}C, 60^{0}C(or higher), evidently , this puts them in the category of the hydrates having high desirable stability. The remaining three hydrates having m.p. below 138^{0}C, and T_{onset} in the range 31-47^{0}C fall in the second category of the relatively less stable ones. As ampicillin trihydrate has a high m.p. (198-200^{0}C) hence, as anticipated, its T_{onset} is not too low to disallow its subsequent development.

Classification of Hydrates on the basis of MP and T_{onset} alone

Hydrate Type	**MP and T_{onset}**
Higher Stability	Higher MP(138-270^{0}C) and Higher T_{onset} (72-138^{0}C)
Medium Stability	Medium MP(81-138^{0}C) and Medium T_{onset} (20-47^{0}C)

Thus, a general relationship between the melting point (MP) and the T_{onset} alone is clearly indicated under the investigated unreal experimental conditions in the DSC experiments even though, neither were the RH and T data controlled or reported by the authors of that study and in fact, one wonders as to why these parameters of paramount significance in the development of the dosage products containing the hydrate APIs were not carried out and recorded and why for the lack of such parameters was the paper published in the journal, particularly, in view of the fact that the thermodynamic stability of the pharmaceutical hydrates has its origin in the critical water activity that is a function of RH across temperatures (T) and not kinetic parameters of dehydration. Nevertheless , we have attempted to make the kinetic data determined to be of some use to the pharmaceutical industry by associating these with the melting points of the hydrates.

From the preceeding discussion, it is clear that a simple look at the melting point of the hydrate can enable us to predict the stability of a hydrate without having to take recourse to the expensive DSC method as previously reported by us recently. 15 A higher melting point of the hydrate can act as an early indicator to predict its higher physical stability which can then be confirmed by doing the DSC experiments for determining the T_{onset} of its dehydration. Further , we have observed a general empirical relation between the MP and the kinetic and thermal parameters, T_{onset},T_m and E_a for predicting the stability of the hydrates. The observed empirical correlation between the melting points and the three kinetic and thermal hydration parameters for determining physical stability of solid stoichiometric crystalline hydrates is interesting and therefore, requires some discussion.

First of all, we need to know as to what does the MP of a hydrate exactly imply. The MP of the hydrate should, in theory, represent the MP of the presumably completely anhydrous solid form (anhydrate) of the hydrate after it has lost all its water of crystallization. In fact, the anhydrate may be just one or several polymorphs of the anhydrate. However, despite all these concerns, there does seem to exist as we have shown a general empirical relation between the MP of the hydrates and the kinetic and the thermal parameters investigated by DSC, of course, *under the unreal experimental conditions as already discussed.* As the hydrate gets dehydrated to the anhydrate form, evidently, it becomes difficult to envisage a correlation between the dehydration behavior of a pharmaceutical hydrate with the melting point of its completely dehydrated form even though as already indicated, the MPs are robust indicators of the strength of the intermolecular forces that exist between the constituent molecules. However, we believe that the anhydrates with higher MP have higher stability and those with lower MP have relatively lower stability in keeping with the generally accepted viewpoint. As the hydrates with higher values of the kinetic parameters discussed above have higher MPs(as per our interpretation), which actually represent the MPs of their dehydrated anhydrate forms, therefore, we are led to the conclusion that in general, unless proven otherwise very solidly, the hydrates which have higher MPs of their anhydrate forms have higher stability compared to the hydrates whose anhydrates have lower MPs and lower values of the kinetic parameters . Of course, if that

is so, one is likely to infer that any stoichiometric crystalline compound which does not contain water of crystallization but has a higher MP(being stable for the reasons discussed herein) should form a hydrate which should be more stable than the anhydrate itself. We are merely talking about the relative stability of the hydrates based upon the MPs of their corresponding anhydrates.

Further, in general, the water of crystallization forms an integral part of the structure of the crystals whatever the reasons for the incorporation of the water molecules as water of crystallization including the steric factors but because the water of crystallization of the hydrate is not present in the anhydrate formed from the hydrate, so it is not possible to correlate the MP of the anhydrate of the hydrate with the dehydration behavior of the hydrate. As dehydration of a hydrate occurs before melting point of the compound is reached therefore, the escape of water of crystallization should serve as a marker for the strength of the intermolecular forces that exist in the crystal structure(in which the water of crystallization serves as an integral part of the structure due to whatever reasons including the steric factor) and that govern and allow the presence of water of crystallization including the steric reasons. However, as we have interpretted that the stoichiometric hydrates whose anhydrates have very high MPs are more stable compared to the stochiometric hydrates having anhydrates with relatively lower MPs, we can conclude that, the water of crystallization in such stable stoichiometric hydrates is relatively tightly held in their crystal lattice, irrespective of the nature and causes of forces that stand responsible for tightly holding the water of crystallisation. Consequently, these more stable hydrates should require higher E_a for dehydration and that is why they exhibit higher T_m and higher T_{onset} as well as shown in the Table. On the other hand, a medium melting point of a hydrate implies the presence of relatively weaker intermolecular forces in the crystal lattice of the hydrate. Therefore, the water of crystallization in such type of relatively less stable hydrates is not so tightly held compared to their counterparts in the stable hydrates with higher melting points. As a result, these moderately stable hydrates require medium Ea for dehydration to occur. Because of these reasons, their T_{onset} and T_m are medium as observed .

CONCLUSION

A new parameter , melting point which we advanced earlier (ref 15)as an early indicator for assessing the physical stability of pharmaceutically relevant hydrates has been combined with the three kinetic and thermal parameters for predicting the stability of the hydrates. The MPs of the dehydrated form of the hydrates have been shown to have a direct connection with the values of $T_{onse,t,,}$ T_m, and E_a for dehydration. On the basis of these four parameters, two types of hydrates have been identified among a large number of the pharmaceutically significant hydrates for which the kinetic and the thermal parameters were reported recently with some consistency, the more stable ones whose dehydrated forms exhibited higher melting points (178-214^{0}C), had high T_{onset} (72-138^{0}C) , higher T_m (95-146^{0}C) and their E_a for the dehydration was also high (129-141 kJ/mol) as anticipated. The second type of hydrates , the relatively less

stable had melting points of their dehydrated forms in the medium range (81-150^{0}C), had medium T_{onset} (20-47^{0}C), medium T_m(55-61^{0}C) and their E_a was also medium (70-103 kJ/mol) as expected. Clearly, hydrates with values of these four parameters lower than those of the hydrates with medium stability possess would fall in the third category of hydrates with lower undesirable stability in pharmaceutical industry. As all these hydrates discussed above are marketed and have known stability profiles, whether they belong to the first category or the second category of the hydrate types we have proposed on the basis of the four parameters, their dataset can serve as a reference for comparing and rank-ordering pharmaceutically relevant novel hydrates . The results presented here are preliminary and it is hoped that they will inspire further investigations into melting point -thermal and kinetic parameters (MP, T_{onset},T_m,and E_a) as early indicators of the stability of a hydrate.

CONFLICT OF INTERST

We report no conflict of interest.

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