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Thermal analysis of glassy pharmaceuticals

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Abstract

The glassy state of many solids is achieved when the solids are heated above their melting point (T_m) and rapidly cooled through it. Glassy solids are usually brittle and transparent. The glassy state can be identified through the glass transition temperature (T_g) using differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermomechanical analysis (TMA), dynamic thermomechanical analysis (dTMA), or torsional braid analysis (TBA). Pulsed NMR spectroscopy is also a method used for confirmation of the glassy state.

In this paper most attention is devoted to the low-molecular glassy pharmaceuticals. The influence of cooling rate during glass preparation on T_g, the influence of heating rate on T_g, the influence of heating rate on crystallization, and the influence of annealing on the glassy state are reviewed and discussed with reference to the recently published original research papers. The possibility that glass dispersion systems may be used to improve the stability and useability of glassy pharmaceuticals is also included.

Keywords: Drug; DSC; DTA; dTMA; Glass transition; TMA

1. Introduction

Many solids when heated above their melting point T_m and rapidly cooled through it do not immediately crystallize but form a supercooled liquid. This is usually a brittle and transparent solid commonly called a glass or a glassy solid,

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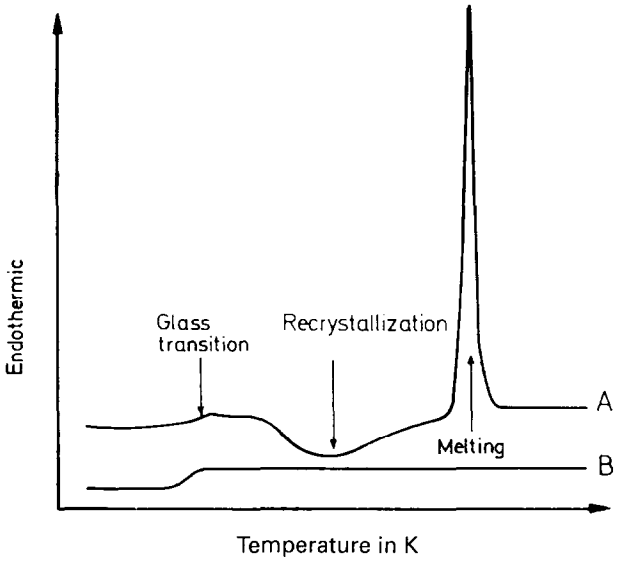

Fig. 1. Typical DSC or DTA scan of a glassy material showing glass transition followed by: curve A, recrystallization and melting transitions; curve B, no recrystallization or melting transitions.

which shows a typical scan (Fig. 1). Depending on the cooling rate, recrystallization may be retarded by only a few degrees but there is a possibility that this supercooled state will itself pass through a heat capacity change, known as glass transition T_g, thereby further inhibiting recrystallization [1]. The glass transition temperature is a kinetic, not a thermodynamic quantity. The translational movements of the molecules freeze below T_g to the glass and diffusion is abandoned. In parallel, the viscosity rises to more than 10^{12} Pa s [2,3]. Crystal seeds can no longer be formed under these conditions. The molecules are randomly distributed in the glass and ordered structures are restricted to next neighbours. Glass is a solid with the structure of a liquid and the energy level of a solution [4]. There has been considerable interest in glasses because their high energy state contributes to fast dissolution rates [5–7].

The properties of glasses are markedly affected by their thermal history and the temperatures involved in their preparation. Factors such as preparation temperature, cooling rates and subsequent annealing conditions contribute to variations in the observed glass transition temperature. Because organic materials tend to soften at the T_g and form a liquid with poor ductile properties either DTA or DSC is used to characterize their T_g.

Polymers often undergo enthalpies of relaxation which display as endothermic peaks. Many drugs, although of low molecular weight, show similar trends. Their glass transitions are apparent either as endothermic drifts in the heating curve or even as small endothermic peaks (anomalous endothermic peaks) (Fig. 1).

The DSC and DTA methods of the American Standards Institution are among those most used to determine the T_g, the temperatures of fusion and recrystalliza-

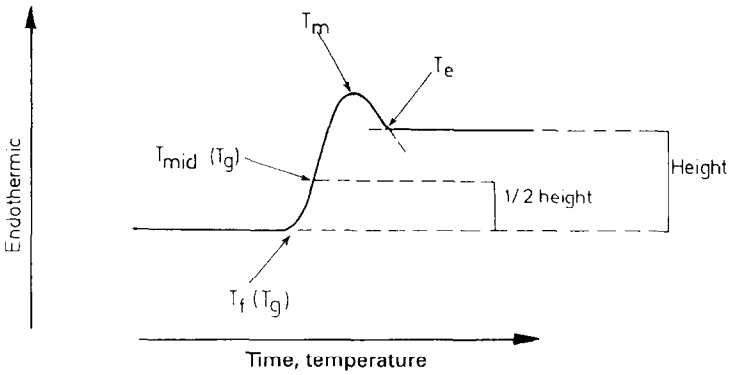

Fig. 2. Transitions of glass-forming material showing onset temperature (T_f), midpoint temperature (T_{mid}), glass transition temperature (T_g), maximum anomalous endothermic peak temperature (T_m), and extrapolated end temperature (T_e).

tion and their related enthalpies for investigated pharmaceuticals. Only DSC and quantitative DTA provide the enthalpies; ASTM D3417-83 [8] recommends power compensation or heat flux DSC be used to determine transition temperatures and enthalpies.

Four characteristic temperatures may be used to define glass transitions of pharmaceuticals (Fig. 2). T_f is the extrapolated onset temperature, T_{mid} is the midpoint temperature, T_m is the maximum temperature of the anomalous endothermic peak, T_e is the extrapolated end temperature. For most applications T_f as well as T_{mid} may be designated as the T_g.

The technique recommended for the determination of T_g suggests recording a preliminary cycle at 20°C min^{-1} to a temperature high enough to erase the previous thermal history, quench-cooling to 50°C below the T_g and holding the sample for 10 min prior to reheating. Care should be taken to ensure that such prior heat treatment does not wipe out the transitions of interest. In such cases the preliminary cycle should be omitted. Repeated runs on the sample are made to ensure that thermal history does not alter the transition temperatures [1].

However, mechanically based methods provide further information on transitions which are not readily detectable by other methods. These methods are thermomechanical analysis (TMA), dynamic thermomechanical analysis (dTMA) and its complementary method, torsional braid analysis (TBA).

TBA has been used in the studies of glassy solids for determination of the glass transition temperature, softening temperature and melting temperature. In this analysis, a constant non-oscillatory load is used and the resultant deformation of the sample is examined. The method evaluates changes such as expansion and contraction. The applied stress produces changes in shape or size as a result of either energy dissipation caused by a relative movement of molecules (viscous response) or energy storage which is released on the removal of the stress (elastic response). The total TMA response is a combination of the expansion behaviour and the viscoelastic effect [9].

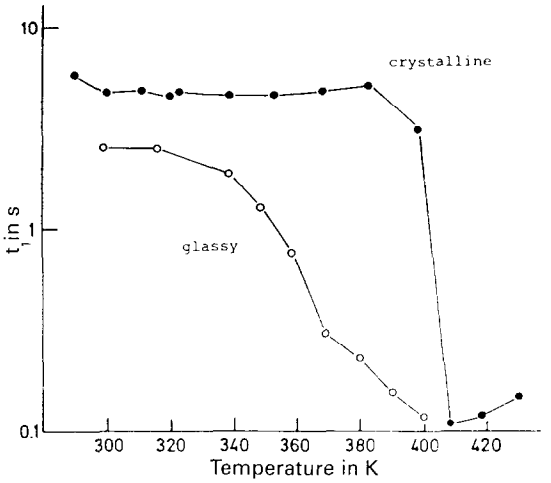

Fig. 3. Spin–lattice relaxation time t_1 determined during heating of crystalline felodipine (●) and its glassy state (○) (reproduced with permission from Ref. [10]).

A rather infrequently used method for confirmation of the material glassy state is pulse NMR spectroscopy. By observing the spin–lattice relaxation time (t_1) and spin–spin relaxation time (t_2), the glassy state can be indisputably confirmed [10]. When heating the crystalline materials, the observed times t_1 and t_2 change owing to a jump in the melting temperature. In contrast, in the case of the glass, the relaxation times t_1 and t_2 undergo gradual alteration. Figs. 3 and 4 demonstrate such behaviour of felodipine and thus provide further confirmation of the drug glassy state [10].

2. Glassy polymers

Polymers have been investigated from the view of glassy state formation for a number of decades. A T_g is found in all amorphous polymers and in amorphous regions of partially crystalline polymers. The T_g of the latter is independent of the degree of crystallization but the magnitude of the transition decreases with an increase in crystallinity entailing difficult detection of the transition in highly crystalline polymers. The T_g is controlled by three molecular factors [11]. Polymers with a stiff backbone and rigidly held bulky side-groups, which generally restrict polymer movement, possess a high T_g. Thus polyethylene with no bulky side-groups has a low T_g whereas polystyrene with large bulky side-groups has a high T_g. The T_gs of homologous polymers of different molecular weights increase with increasing molecular weight. Some substances, for example, plasticizers, lower the T_g and reduce brittleness of polymers. If the plasticizer reduces the T_g from a temperature above ambient to one below, the material will change from a brittle glass to a soft pliable material.

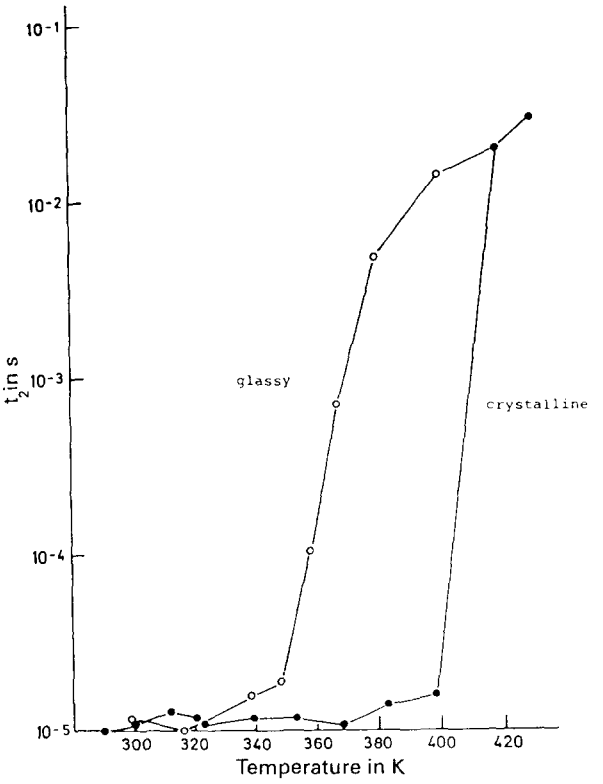

Fig. 4. Spin–spin relaxation time (t_2) evaluated during heating of crystalline felodipine (●) and its glassy state (○) (reproduced with permission from Ref. [10]).

3. Low molecular weight glassy pharmaceuticals

Numerous reports on the glassy state of high molecular weight compounds have been published, whereas the nature of the glassy state of compounds of low molecular weight has been less well investigated.

Glassy pharmaceuticals are usually prepared by cooling the melt and the glassy state is confirmed by detection of a jump of heat capacity and an anomalous endothermic peak in the DSC scan. The values of T_g, T_m and T_g/T_m for some investigated pharmaceuticals are summarized in Tables 1 and 2. It is known that T_g/T_m is, as a rough rule, about 0.5 for many symmetrical polymers such as polyethylene and about 0.7 for many asymmetrical polymers such as polyisoprene [12,13]. As seen from Tables 1 and 2, the T_g/T_m values for low molecular weight pharmaceuticals range between 0.59 and 0.86 and are slightly higher than those of polymers.

Table 1
Pharmaceuticals forming glasses above room temperature (abstracted from Refs. [14–19,27,28])

Pharmaceutical	T_g/K	T_m/K	T_g/T_m
Proxyphylline	295	403	0.73
Acetaminophen	295	447	0.66
Cholocalciferol	296	352	0.84
Paracetamol	297	347	0.86
Eserine	297	378	0.79
Nialamide	297	427	0.70
Chlorotrianisene	298	393	0.76
Chloroamphenicol I	301	349	0.86
Acetaminophen	302	441	0.69
Glucose	303	419	0.72
Nitrendipine	303	429	0.71
Sulphisoxazole	306	460	0.67
Chloramphenicol II	306	414	0.74
Stilbestrol	308	439	0.70
Estradiol-17β-cypionate	309	425	0.73
Dextrose	310	432	0.72
Diphylline	315	438	0.72
Phenobarbital	315	452	0.70
Maltose	316	375	0.84
Felodipine	316	407	0.76
Phenobarbital	321	443	0.72
Norethynodrel	324	453	0.72
Quinidine	326	445	0.73
Sucrose	329	453	0.73
Spironolactone	331	478	0.69
Salicin	333	466	0.71
Sulphathiazole	334	471	0.71
Chlormadinone acetate	334	483	0.69
β-Estradiol-3-benzoate	336	472	0.71
Amlodipine besylate	337	467	0.72
Sulphadimethoxine	339	465	0.73
Glibenclamide	344	447	0.77
Dehydrocholic acid	348	502	0.69
Cellobiose	350	498	0.70
Trehalose	350	476	0.74
17β-Estradiol	354	445	0.80
Nicardipin hydrochloride	358	440	0.81
Griseofulvin I	362	422	0.86
Brucine	365	451	0.81
Griseofulvin II	370	497	0.74
Chenodeoxycholic acid	371	436	0.85
Deoxycholic acid	377	447	0.84
Ursodeoxycholic acid	378	477	0.79
Cholic acid	393	473	0.83

Table 2
Pharmaceuticals forming glasses below room temperature (abstracted from Refs. [14–19,27,28])

Pharmaceutical	T_g/K	T_m/K	T_g/T_m
Glycerol	180	291	0.62
Aspirin	243	408	0.59
Dibucaine	246	336	0.73
Mephenesin	247	340	0.73
Antipyrine	256	380	0.67
Ribose	263	360	0.73
Sorbitol I	270	384	0.70
Methyltestosterone	270	421	0.64
Sorbitol II	271	367	0.74
Phenylbutazone	277	377	0.73
Quinine ethylcarbonate	278	362	0.77
Progesterone	279	399	0.70
Pentobarbital	279	408	0.69
Atropine	281	379	0.74
Ethacrynic acid	282	398	0.71
Citric acid	283	432	0.72
Xylose	283	426	0.66
Tolbutamide	284	403	0.70
Hexobarbital	286	423	0.68
Amobarbital	286	432	0.66
Fructose	286	373	0.77
Tolnaphtate	287	384	0.75
Nimodipine	288	389	0.74
Tartaric acid	289	430	0.67
Flufenamic acid	290	406	0.71
Santonin	290	434	0.67
Ergocalciferol	290	376	0.77

3.1. *Influence of cooling rate during glass preparation on* T_g

It is generally accepted that glass formation depends on the cooling rate of the melt. To examine the effect of the cooling rate on glass formation, glassy felodipine [5], glassy indomethacin [6], glassy spironolactone and glassy griseofulvin [15] were prepared at various cooling rates and the glasses thus obtained were reheated at a constant heating rate. In DSC scans, the endothermic heat capacity change and anomalous endothermic peak (heat capacity maximum) were observed under all cooling conditions employed; this suggested that a glass was formed irrespective of the cooling rate. The magnitude of the heat capacity change was almost the same in all cases (Table 3). The T_g of glassy felodipine varied at various cooling rates only from 317.5 to 318.5 K. However, the area under the anomalous endothermic peak varied from 0.43 cal g^{-1} at the cooling rate of -1 K min^{-1} to 0.11 cal g^{-1} at the cooling rate of 320 K min^{-1} (Table 3). Thus, the area of the anomalous peak increased with decreasing cooling rate of the melt and reflected the dynamics of freezing of molecular movement and quantity of glass relaxation.

Table 3
Influence of cooling rate of the melt on felodipine glass transition (abstracted from Ref. [5])

Cooling rate/ (K min^{-1})	T_{mid} (T_g)/ °C	ΔC_p/ (cal g^{-1} K^{-1})	Anomalous peak/ (cal g^{-1})
−1.0	45.37	0.1006	0.43
−2.5	45.02	0.0829	0.32
−5.0	44.31	0.1061	0.26
−20.0	44.79	0.0966	0.18
−50.0	44.92	0.1102	0.12
−150.0	45.22	0.0840	0.11
−320.0	45.16	0.0983	0.11

3.2. *Influence of heating rate on* T_g

The choice of the proper heating rate is of vital importance in ascribing the correct temperature and enthalpy value to a transition. Rapid heating rates give large peaks but small details may be lost, whereas at slower rates the temperature difference between the sample and the reference becomes too small and some transitions may not occur on the scan [1].

In the studies of the influence of heating rate on glass transition [5,6,15], the melts were cooled below T_g and reheated at various heating rates. In the DSC scans of glassy felodipine (Fig. 5) the endothermic heat capacity change and the anomalous endothermic peak can be observed at all heating rates employed. The glass showed different DSC scans due to the structural relaxation process during heating at different heating rates. Thus, a fast heating rate was desirable in order to prevent the glass from recovering enthalpy or relaxation during heating. Studies of the effect

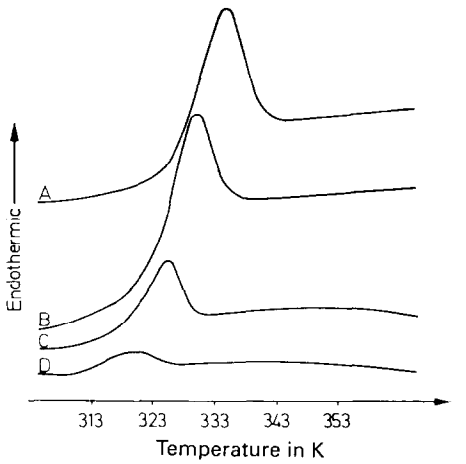

Fig. 5. Variation of T_g with heating rate of glassy felodipine. Heating rate: curve A, 80 K min^{-1}; curve B, 40 K min^{-1}, curve C, 20 K min^{-1}; curve D, 10 K min^{-1} (reproduced with premission from Ref. [5]).

of the heating rate on T_g revealed that the latter increased with increasing heating rate. A linear relationship was observed when the logarithm of the heating rate was plotted versus $1/T_g$. The apparent activation energies of the glass transition for felodipine, indomethacin, chenodcoxycholic acid, griscofulvin, and tolnaphtate were 132.2, 212.5, 273.6, 270.3, and 127.6 kJ mol^{-1}, respectively [5,6,15].

3.3. *Influence of heating rate on recrystallization*

When a glassy substance shows a recrystallization exotherm in the DSC scan, the influence of heating rate on the glass recrystallization can be studied through DSC analyses. Two methods, a "heat evolution method" [20,21] and a "variable heating rate method" [22], can be employed for evaluation of the kinetic parameters of glass recrystallization.

In the heat evolution method, the heat flow signal is, to a good approximation, directly proportional to the instantaneously evolved heat on condition that the samples are not too large (below 20 mg). Accordingly, the instantaneous reaction rate can be derived from the measured heat flow and the reaction rate constant k at any temperature T_i may be calculated under these conditions [20,21]. After the order of crystallization has been assessed (most crystallizations follow a first order mechanism), the kinetic crystallization parameters, i.e. the pre-exponential factor A and activation energy E_a, which are related to the rate constant k are derived by the Arrhenius equation. The kinetic parameters obtained with this heat evolution method are dependent on the heating rate used in the DSC (Table 4).

The variable heating rate method is a DSC method based on the work of Ozawa [22] and measures the variation in the maximum temperature of the exothermic peak which depends on changes in the linear programmed DSC heating rates. Table 5 presents the peak temperatures obtained at various heating rates for glassy felodipine, solidified at room conditions and thereafter pulverized in a mortar. The plot of natural logarithm of the heating rate as a function of the reciprocal peak maximum temperature was linear in the range from 10 to 80 K min^{-1}. An activation energy of crystallization of 21.7 kcal mol^{-1} was obtained from an Arrhenius plot.

Table 4
Influence of heating rate on crystallization kinetic parameters for glassy felodipine, using heat evolution method (abstracted from Ref. [5])

Heating rate/ (K min^{-1})	Activation energy E_a/(kcal mol^{-1})	Pre-exponential factor $\ln(A/min^{-1})$
10.0	35.22	48.81
20.0	26.64	36.39
40.0	20.42	27.35
80.0	21.00	28.41

Table 5
Influence of heating rate on glassy felodipine crystallization, using variable heating rate method (abstracted from Ref. [5])

Heating rate/ (K min^{-1})	Onset T/ °C	T_m/ °C
10.0	67.71	80.17
20.0	71.70	87.10
40.0	77.18	97.96
80.0	83.72	104.60

3.4. *Influence of annealing of the glassy state*

The properties of glasses are markedly affected by their thermal history and the temperatures involved in their preparation. Several authors [6,15,23] have published comprehensive data on the influence of isothermal ageing process below T_g on the glassy state.

Serajuddin et al. [23] characterized the glassy state of indapamide. DSC of the melt that had been quench-cooled through its T_g showed only an endothermic heat capacity change at 98°C equivalent to the T_g. An endotherm of its T_g developed with decreasing cooling, i.e. its area increased as the cooling rate was decreased from 10 to 1 K min^{-1}. The influences of annealing were examined in quench-cooled samples following storage at 85°C (Fig. 6). The area of the endotherm that developed increased with the annealing time to reach a maximum in 168 h. The

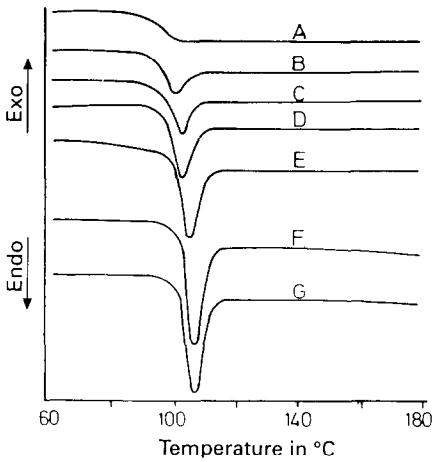

Fig. 6. DSC scans of indapamide glass showing the effect of duration of annealing at 85°C on the size of endotherm at the glass transition temperature. Annealing time: curve A, 0 h; curve B, 2 h; curve C, 4 h; curve D, 21 h; curve E, 45 h; curve F, 168 h; and curve G, 336 h (reproduced with permission from Ref. [23]).

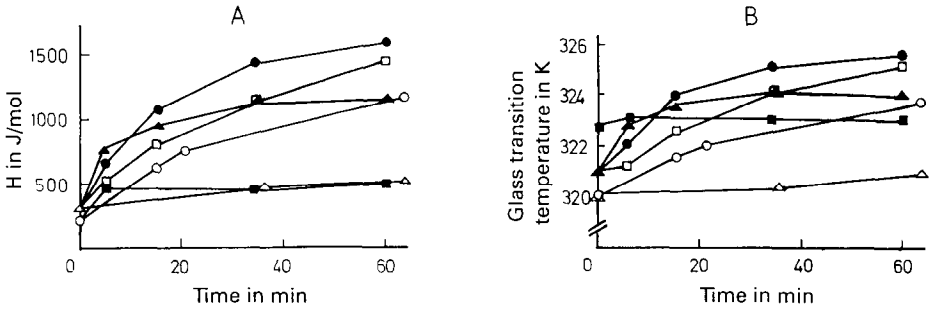

Fig. 7. Influence of temperature on the rate of enthalpy relaxation during isothermal ageing of indomethacin below T_g: (A) the area under the anomalous endothermic peak of the DSC curve; (B) T_g. Temperature for isothermal ageing: △, 283 K; ○, 293 K; □, 298 K; ●, 303 K; ▲, 308 K; ■, 313 K (reproduced with permission from Ref. [6]).

explanation was that large-scale molecular motion is frozen without a change in structure when a liquid is quench-cooled to become a glassy solid. A glassy solid formed by quenching or under atmospheric cooling condtions therefore has an excess of enthalpy relative to the corresponding equilibrium glassy state. It reaches equilibrium during annealing by enthalpy relaxation, i.e. by releasing the strain produced by cooling.

Fukuoka et al. [6] also examined the influence of the temperature and time on the rate of enthalpy relaxation during isothermal ageing of indomethacin below the T_g. Fig. 7(A) shows the increase in the area of the endotherm of the glass during standing at various temperatures. The rate of relaxation increased as the temperature increased up to 303 K and decreased at higher temperatures. In the same manner, T_g reached a maximum at 303 K as shown in Fig. 7(B)

The area under the anomalous endothermic peak of the DSC scan increases with ageing time, showing that the enthalpy relaxation proceeded gradually during standing at room temperature (Fig. 8(A)). The variation of mechanical properties of glassy pharmaceuticals by enthalpy relaxation can be studied by TMA where the effect of relaxation is shown by change of shape of the TMA curves [24].

The TMA curves (Fig. 8(B)) for glassy indomethacin immediately after preparation showed gradual expansion at around room temperature and the expansion reached a peak at about 315 K followed by a smooth curve toward shrinkage. A shoulder was seen at 318 K. The expansion curve became sharper with a more distinct shoulder portion with ageing, but after 15 days the shoulder disappeared and shrinkage occurred rapidly. Below T_g the expansion curve became sharper with increasing ageing time.

4. Glass dispersion systems

When at least one of the components in the binary system is capable of glass formation there are various possibilities for the structure of the appropriate

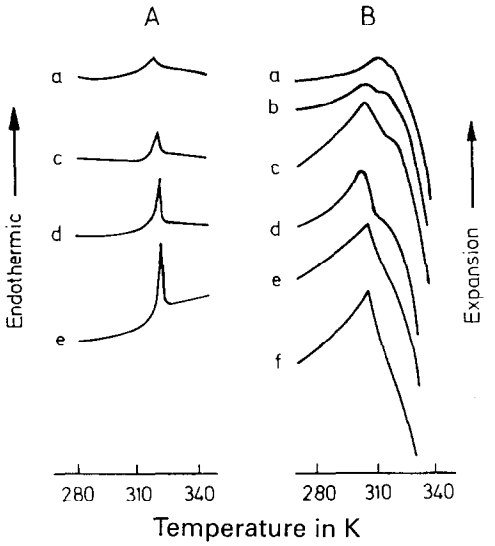

Fig. 8. Effect of relaxation at room temperature on DSC and TMA scan of glassy indomethacin: (A) DSC scans; heating rate 5 K min^{-1}. (B) TMA scans; heating rate 5 K min^{-1}; load 4 g; range 50 μm. Curve a, immediately after preparation; curve b, 1 day; curve c, 2 days; curve d, 5 days; curve e, 15 days; curve f, 22 days (reproduced with permission from Ref. [24]).

dispersion. Thus, both materials may form glasses or either or neither material may form a glass. Additionally, total miscibility, total immiscibility or partial miscibility may be found. The relationship between T_g and the composition can be either linear (phenobarbital–salicin [14], hexobarbital–dextrose [18]), or nonlinear (antipyrine–indomethacin [14], acetaminophen–citric acid, sulfonamide–citric acid, sulphathiazole–citric acid [18]). The data for the glassy phenobarbital–salicin system showed linear relationships between the weight ratio of salicin and T_g (Fig. 9(A)) and when plotted according to the Gordon–Taylor equation (Fig. 9(B)). The system thus obeys the ideal situation described by the Gordon–Taylor equation [25]. These results indicate that salicin and phenobarbital were mixed randomly in the binary glass system without any interaction.

Glassy systems which show fluctuations in T_g either less than or greater than the T_g of its glassy components, as seen with the sulphonamide–citric acid system (Fig. 10), suggest a reaction and/or incompatibility between the components [18].

In a study of drug–PEG 6000 systems [16], it was predicted that systems which displayed PEG melting endotherms at drug contents of 0 to more than 70% drug and drug melting endotherms at contents in excess of 50% drug, would make unsuitable solid dispersions because increases in dissolution rate occurred over a limited range of low drug content. Graphs of reciprocal T_g and dispersion drug content indicated a T_g for PEG 6000 at -71°C. Using this value and the observed T_g values of the drugs, estimates of T_g values were compared with observed values throughout the drug–PEG 6000 phase diagrams. Systems where the observed T_g

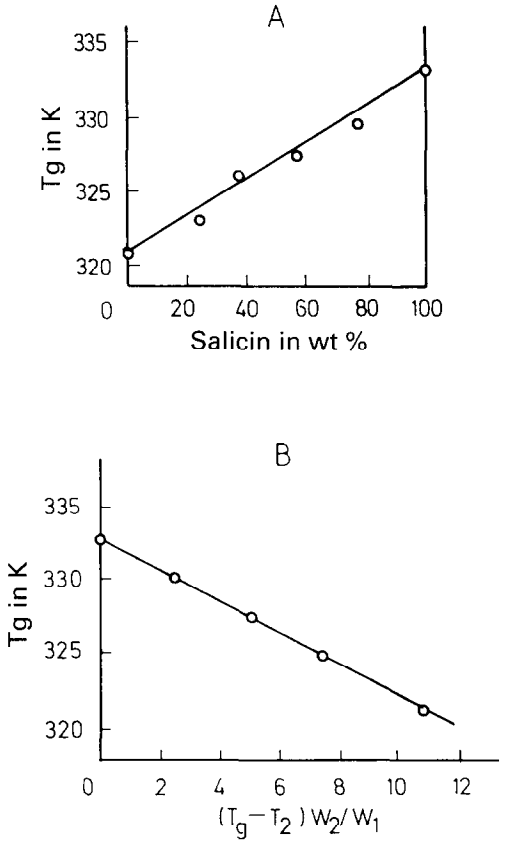

Fig. 9. Phenobarbital–salicin glass system: (A) variation of T_g with salicin weight ratio; (B) analysis in terms of the Gordon–Taylor equation (reproduced with permission from Ref. [14]).

values were higher than calculated T_g values (paracetamol or chloramphenicol) were less prone to age-mediated dissolution changes than those systems where the calculated T_g values exceeded the observed values (glutethimide, griseofulvin or indomethacin).

The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions [26]. Examples of carriers that form glass solutions and suspensions include citric acid, PVP, urea, PEG, and various sugars such as dextrose, sucrose and galactose [26].

Most of the glasses are mechanically and/or thermally unstable. By mixing two compatible miscible glasses in a particular ratio, it is possible to obtain greater physical stability than can be realized from the individual glassy components. The glass dispersion technique is presently in the development stage, and a number of technical problems must be overcome before its full potential can be achieved.

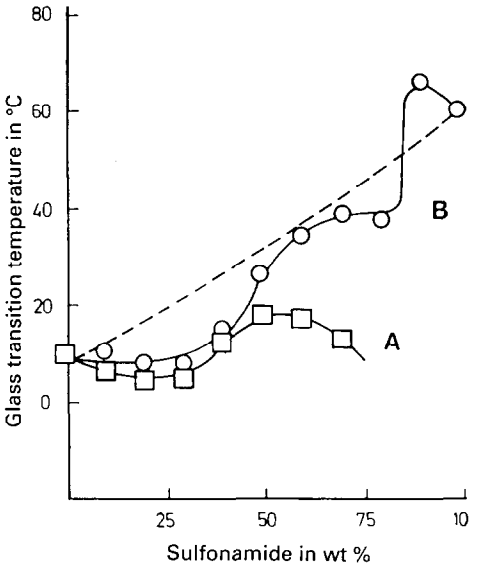

Fig. 10. The T_g for the sulfanilamide–citric acid (curve A) and sulphathiazole–citric acid (curve B) glass system. The dashed line represents the values of T_g for the sulfathiazole–citric acid predicted by the Gordon–Taylor equation (reproduced with permission from Ref. [18]).

5. Conclusions

From the pharmaceutical point of view, glass represents a relatively important state. The glassy state of low molecular weight pharmaceuticals can play an important role, especially in the enhancement of dissolution rate. The glassy states of pure drugs show low stability. Therefore, glassy drug dispersions, solutions or suspensions are favoured.

It is expected that the glassy state could serve as the starting position for controlled crystallization–crystal engineering. The drug diffusion control and the switch on–off principle in polymers as vehicles may be possible by controlling the polymer glassy state.

Very little is understood about the comminution and consolidation of the glassy state, the two processes of paramount importance in tablet production. It seems that the glassy state will be an important aspect in the field of pharmaceutical research.

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