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Glass transition temperature: Basics and application in pharmaceutical sector

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Glass transition temperature (T_g) is an important tool used to modify physical properties of drug and polymer molecules. T_g is shown by certain crystalline as well as amorphous solids. During the process of heating, some solid gets melted and if quench cooled, instead of crystallizing, gets converted to amorphous solid form appearing as that of glass. This glass formation is seen because of the dynamic arrest of molecules forming a disordered state at T_g . The molecules/atoms in glassy state are subject to only vibration and not translational and rotational motion. Mainly, at T_g , conversion of glassy (vitrified, amorphous) solid to rubbery (viscous liquid) takes place. Numerous factors like structural change in molecules, cooling rate and incorporation of additives alter the T_g . Techniques like differential scanning calorimetry, elastic modulus, broad-line NMR are used to measure the T_g of substances. The change in T_g has been carried out to improve dissolution and bioavailability, processing and handling qualities of the material.

Key words: Amorphous, crystalline, glass transition temperature

INTRODUCTION

In recent times, the major research focus of pharmaceutical industries has been on manipulation of the existing drug molecules instead of incurring huge costs on search of a new chemical entity (NCE). The maximum biopharmaceutical benefits from existing drug molecules can be reaped by physicochemical modifications in existing drug molecules and modified drug delivery technologies.^[1] In case of certain drug molecules and polymers, glass transition temperature (T_g) is used as a tool to modify their physical properties. By knowing the T_g one can keep material in crystalline or amorphous state, viscous/rubbery/supercooled liquid and less viscous liquid form. When solid is melted, conversion of solid to liquid takes place. And, during the quench cooling of molten solid, melted liquid gets transformed to solid through the intermediate stage called supercooled liquid. With sudden decrease in temperature supercooled liquid gets converted to glassy (amorphous) solid. The temperature below which a solid stays in glassy state and above which goes to viscous liquid form is called T_g .^[2,3] Transition of crystalline solids

to amorphous form is carried out mainly to increase the solubility of drug molecules.^[4]

Phenomenon of glass transition

Glass transition is a phenomenon shown by some crystalline as well as amorphous solids.^[2,5] If such solids are heated, they get melted and if quench cooled, instead of crystallizing get converted to amorphous solid form appearing as that of glass.^[6] When the same molten liquid is cooled at a slow rate, the kinetic energy of molecules does not surpass the binding energy of neighboring molecules and crystal formation begins.^[7] For formation of an ordered crystalline system the time required is more because molecules must move from their current location to an energetically preferred point. As temperature falls molecular motion further slows down and, if cooling rate is fast enough, molecules never reach their energetically preferred point. Ultimately, the substance enters dynamic arrest and forms disordered glass at a certain temperature called T_g .^[7] The molecules/atoms in glassy state are subject to only vibration and not translational and rotational motion.^[2] This process of conversion of crystalline to glassy solid is called vitrification. It has been observed that, cooling rate, cleanliness of liquid, viscosity at melting temperature and similarity of liquid packing during cooling decides the transformation of liquid to glassy or crystalline state. The process of melting of solid (T_m) takes place at a temperature above T_g .^[6] Figure 1a and b show the amount of heat added to the solid on the y-axis and temperature

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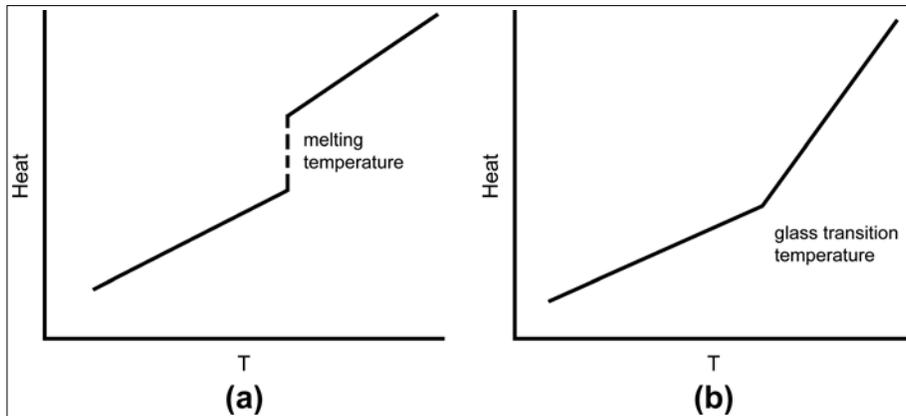


Figure 1: Plot of temperature (T) and heat relationship; (a) melting point and (b) glass transition temperature

obtained by the given amount of heat on the x-axis at T_g and T_m .^[2] A plot of 100% crystalline polymer is discontinuous, in this case, showing break as melting temperature. At that break, lot of heat is taken by the solid without any temperature rise. It is called latent heat of melting. Here, slope is steeper on the high side of the break and the slope of plot is equal to the heat capacity. So this increase in steepness of slope corresponds to increase in heat capacity above the melting point.

In case of Figure 1b (100% amorphous polymer), heated polymer shows no break.^[2] The only change seen is at the glass transition temperature and an increase in slope shows increase in heat capacity. In amorphous solids though change in heat capacity at the T_g is seen no break and latent heat is involved.

At T_g , changes in hardness, volume, percent elongation-to-break and Young's modulus of solids are mainly seen.^[5] Some polymers are used below their T_g (in glassy state) like polystyrene, poly(methyl methacrylate) etc., which are hard and brittle. Their T_g s are higher than room temperature. Some polymers are used above their T_g (in rubbery state), for example, rubber elastomers like polyisoprene, polyisobutylene. They are soft and flexible in nature; their T_g s are less than room temperature.^[2]

Specific volume (V_{sp}) of solid is another factor that changes with the change in temperature as depicted in Figure 2. In this figure, from T_m onwards, heat supply does not increase the temperature of liquid. Rather, only specific volume gets increased and temperature rise is slowly seen later. If this molten liquid is cooled at different rates then differing T_g s are obtained. Rapid cooling gives high T_g (T_{g1}) while slow cooling rate gives lower T_g (T_{g2}).^[6,8]

Specific heat (C_p) is another parameter associated with solids. It changes with change in temperature. From Figure 3a it is clearly seen that super cooled liquids have largest specific heat and it drops to a lower value near T_g . The temperature

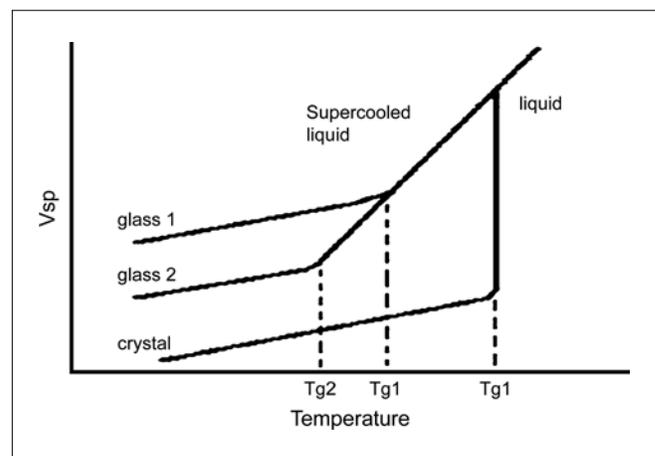


Figure 2: Graph of specific volume against temperature for solids forming glass where, V_{sp} is specific volume, T_m is melting temperature, T_{g1} and T_{g2} are glass transition temperatures

at which specific heat drops rapidly depends on cooling rate of liquid. The two different cooling rates give two different curves. In the plot of specific entropy versus temperature Figure 3b, the slope is largest in liquid and super cooled liquid where c_p is largest. As temperature drops, the entropies of super cooled liquid and crystal quickly approach each other.^[6] At the melting temperature of liquid, its entropy is higher than crystal because liquid has a higher heat capacity than crystal. This entropy difference decreases upon super cooling.^[9] Some reported techniques of T_g measurement are enlisted in Table 1.

The exact picture of glass transition temperature seen in solids can better be visualized in Figure 4 with the help of drawing of DSC plot. In this plot of temperature versus heat flow, region of crystallization temperature (T_c), melting temperature (T_m) and glass transition temperature (T_g) are seen. T_g and T_c are endothermic and T_m is shown as exothermic.^[5] The T_c and T_m are usually showed by crystalline polymers. Complete amorphous polymers show only T_g . Polymers with both amorphous and crystalline region show all the three characteristics.^[5]

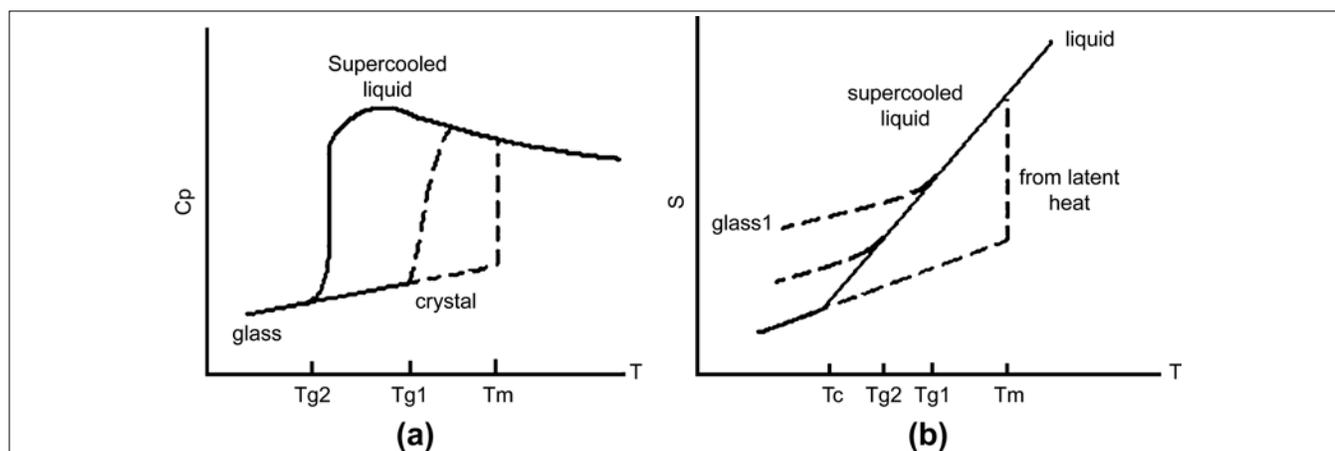


Figure 3: Rate of cooling affecting Tg of solids (a) Glass 1(Tg1) is glass obtained at faster cooling rate; (b) Glass 2(Tg2) obtained at slower cooling rate. (Cp) is specific heat, (S) as specific entropy of crystal, liquid, supercooled liquid and glass 6

Table 1: Techniques of Tg measurement

Techniques

- Differential scanning calorimetry^[2,5,10,11]
- Refractive index^[12,13]
- Dynamic mechanical measurements^[8,11]
- Specific heat measurements^[8]
- Thermo mechanical analysis^[11,14]
- Thermal expansion measurement^[12]
- Micro-heat-transfer measurement^[15]
- Isothermal compressibility^[12]
- Heat capacity^[12]
- Elastic modulus or hardness^[12]
- Broad-line NMR^[12,13]

Factors affecting Tg

Molecular weight^[16-19]

In case of straight chain polymers, increase in molecular weight leads to decrease in chain end concentration. This results in decreased free volume at end group region- and increase in Tg. If end groups of chain are changed molecular weight dependence of Tg can be changed. Decrease in chain end concentration (low molecular weight) and stronger interactions at end groups increase Tg.

Example: Effects of molecular weight of polyvinylpyrrolidone on glass transition temperature and crystallization of sucrose.

Molecular structure

Bulky, inflexible side group^[10,16,20]

Insertion of bulky, inflexible side group increases Tg of material due to decrease in mobility, viz: Poly-N-vinylcarbazole shows increased Tg due to substitution of bulkier group (carbazole).

Length of side group^[10,16]

As length of side group increases the polymer chains move apart from each other and that increases free volume in the molecule resulting in decreased Tg.

Example: Polyvinyl n-butyl ether showed decreased Tg with increase in chain length.

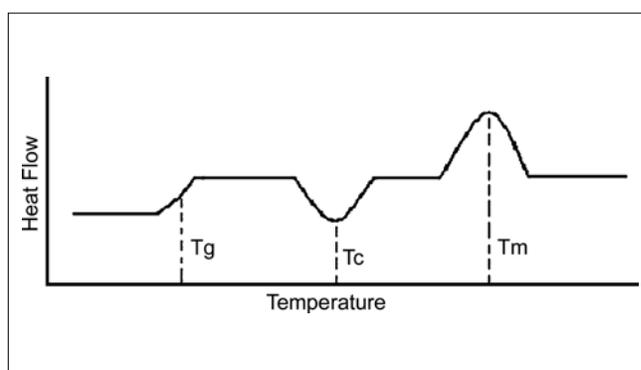


Figure 4: Differential scanning calorimetry plot showing region of crystallization temperature (Tc), melting temperature(Tm) and glass transition temperature (Tg)

Double bond in back bone^[10,16]

Double bonds in backbone of molecule decrease bond rotation leading to increase in free volume and ultimately decrease in Tg.

Example: Polybutadienes show low Tg (175°K), which is less than corresponding polybutane containing side chain double bond.

Chemical cross-linking^[13,16,21]

Increase in cross-linking decreases mobility leads to decrease in free volume and increase in Tg.

Plasticizer

On addition of plasticizer to polymer, plasticizer gets in between the polymer chains and spaces them apart from each other increasing the free volume.^[2] This results in polymer chains sliding past each other more easily. As a result, the polymer chains can move around at lower temperatures resulting in decrease in Tg of a polymer^[2,13,21-23]

Example of plasticizer includes, nitrobenzene, β-naphthyl salicylate, carbon disulphide;^[2] glycerine,^[24-27] propylene glycol,^[24,26-28] triethyl citrate,^[24,27-29] triacetin,^[24,27,30] polyethylene glycol,^[31] etc.

Water or moisture content

Increase in moisture content leads to increase in free volume due to formation of hydrogen bonds with polymeric chains increasing the distance between polymeric chains. The increased free volume between polymeric chains result in decreased T_g.^[32-38] Simultaneously, low hydrogen bonding between drug and polymer provides more hydrogen bonding sites for water molecules resulting in decreased physical stability.^[4,35,38]

In case of wheat starch, available in pregelatinized and native form, with increase in moisture content decreased T_g has been reported as shown in Table 2.^[32]

Cooling rate

If rate of cooling of molten solid is higher, T_g is higher^[39,40] and if rate of cooling is slower, then T_g obtained is low as seen in Figure 3.^[6,8,41]

Example: Study on influence of cooling rate on T_g in sucrose solutions and rice starch gels.^[41]

Effect of entropy and enthalpy

The value of entropy for amorphous material is higher and low for crystalline material. If value of entropy is high, then value of T_g is also high.^[6,9]

Pressure and free volume

Increase in pressure of surrounding leads to decrease in free volume and ultimately high T_g.^[16] Free volume is the unoccupied space arising from inefficient packing of disordered chains and is the space available for polymer to undergo rotation.^[42]

Polymer film thickness^[16,19,43]

Mobility of molecules increase when polymer film thickness decreases, resulting in decrease in T_g; increase in film thickness increases compaction and results in an increased T_g. When a polymer is added to substrate, the T_g increases due to decreased mobility. In case of thin free standing films, T_g decreases more due to high mobility than bulk polymer. In case of sandwiched films, compaction leads to increase in T_g.

Example: Polystyrene has shown decrease in T_g with decrease in its film thickness.^[16,43] Similar effect has been observed in poly (methyl methacrylate) films on Au.^[19,43]

Flexibility of polymer chain^[2,10,44,45]

Some polymers show high T_g and some show low because of the ease with which the polymer chains move. A very low T_g will be shown by the polymer chains which can move around easily, while one that doesn't move will have a high T_g.

Factors affecting mobility of polymer chains responsible for easy movement of one polymer chain than the other are:

Table 2: Decrease in T_g with increase in moisture content of wheat starch^[32]

Pregelatinized wheat starch		Native wheat starch	
Moisture (%)	T _g (°C)	Moisture (%)	T _g (°C)
0.0776	127	0.151	90
0.0811	120	0.149	85
0.105	108	0.159	81
0.110	105	0.171	77
0.122	92	0.164	67

Backbone flexibility^[2,21]

More flexible backbone chain results in better movement of the polymer chain and lowers its T_g. Examples: The major class is of silicones like polydimethylsiloxane. Its backbone is so flexible that it has a T_g-127°C and is in liquid state at room temperature. In case of poly (phenylene sulfone) backbone is so stiff and rigid that it doesn't have a T_g. It will stay in the glassy state up to the higher temperature. It will decompose before it undergoes a glass transition. By substituting flexible group like ether in the backbone chain, the polymer's T_g can be decreased.

Pendant groups I^[2,10,20]

It has been observed that pendant groups affect chain mobility by acting as a fish hook that will catch on nearby molecules when the polymer chain tries to move. Pendant groups can also catch on each other when chains try to slither past each other. The pendant groups like big bulky adamantyl group derived from adamantane, gives a high T_g. This adamantyl group acts not only like a hook that catches on nearby molecules and avoids the polymer movement, but also its mass is such a load for its polymer chain that, it allows the movement of a polymer chain much more slowly. It has been reported that unsubstituted poly (ether ketone) has a T_g of 119°C, while adamantane substituted poly (ether ketone) has a T_g of 225°C.

Pendant groups part II^[2]

It is observed that the substitution of big bulky pendant groups can also lower T_g because of the limitation of the close packing of the polymer chains together. Thus they are away from each other giving more free volume. This facilitates easy movement, resulting in decrease in the T_g, similar to plasticizer. In the series of methacrylate polymers, a decrease in T_g is observed with the substitution of one carbon each time, as seen in poly(methyl methacrylate), T_g 100-120°C; For poly(ethyl methacrylate), T_g: 65°C; poly(propyl methacrylate), T_g: 35°C; poly(butyl methacrylate), T_g: 20°C.

Interfacial energy and thickness^[46]

The T_g of polymer films was less than their bulk values for low values of the interfacial energy, while on other hand, the T_g of polymer films was greater than their bulk values for high values of the interfacial energy. The deviations of the T_gs of the films from bulk values have shown increase with decrease in film thickness.

Example: Tgs of polystyrene and poly(methyl methacrylate).^[46]

exhibit low Tg.

Branching^[3,10,21]

Increased branching gives rise to decreased mobility of polymer chains and increased chain rigidity results in high Tg.

Example: Isooctyl acrylate, tridecyl acrylate, laurylacrylate. Higher functionality materials have similar molecular weights due to higher cross-link density results in higher Tg.

Example: Tgs of polystyrene and poly (methyl methacrylate).^[3]

Alkyl chain length^[5]

Increase in alkyl chain length results in high Tg values.

Bond interactions^[3]

High secondary forces due to the high polarity or hydrogen bonding lead to strong crystalline forces that require high temperatures for melting. So, these high secondary forces give rise to high Tg due to the decreased mobility of amorphous polymer chains.

Example: Increase in Tg has been observed with addition of number of methylene units in side group chain of phosphazene polymer.^[5]

Functionality^[3]

Mono functional aliphatic monomers due to high flexibility

Polar groups^[12]

Presence of polar groups increases intermolecular forces; inter chain attraction and cohesion leading to decrease in free volume resulting in increase in Tg.

Table 3: Reported Tgs of some polymers and drug molecule

Polymers and drug molecules	Tg (°C)	Polymers and drug molecules	Tg (°C)
Polyethylene (low density) ^[47]	-110	Sucrose ^[32]	56.6
Polyethylene (high density) ^[47]	-90	Lactose ^[32]	101.2
Polypropylene (atactic) ^[47]	-18	Maltose ^[32]	87
Polyvinyl acetate ^[7]	28	Fructose ^[32,63]	100
Polyvinyl alcohol ^[7,48]	85	Maltodextrin DE 20 ^[32]	141
Polyvinyl chloride ^[47]	87	Maltodextrin DE 25 ^[32]	121
Poly ethylene Glycol 400 (PEG 400) ^[49]	41	Maltodextrin DE 36 ^[32]	100
Polydimethylsiloxanes ^[50]	-127	Chewing gum ^[62]	Between 0 to 37
Polybutadiene ^[10]	-85	Galactose ^[32,63]	110
Polystyrene ^[5,7,47,51]	100	Xylose ^[32,63]	9
Poly (oxyethylene) ^[52]	-67	Glycero ^[32,63]	-93
Poly (oxymethylene) ^[52]	-55	Sorbitol ^[32]	-2
Poly (acrylic acid) ^[52]	106	Simvastatin ^[64]	Lower Tg
Poly (methyl acrylate) ^[52]	8	Felodipine ^[65]	42.7
Poly (methyl methacrylate) (atactic) ^[7]	105	Nimodipine ^[66]	20
Poly (butyl methacrylate) ^[2]	20	Nifedipine ^[67]	48
Poly (butyl acrylate) (PBA) ^[53]	-50	Indomethacin ^[68,69]	42
Poly vinyl Pyrrolidone (PVP) ^[4]	168	Amorphous sodium indomethacin ^[70]	121
Poly (ethylene terphthalate) (PET) ^[54]	80	Celecoxib ^[71]	58.1
Ethylene vinyl acetate ^[55]	< 28	Saquinavir ^[72]	107
Poly-vinyl-acetate ^[56]	35	Meglumine ^[71]	18.9
Vinyl ester resin ^[57]	< 60	Etoricoxib ^[73]	40.8
Ethyl cellulose (with high ethoxyl content) ^[58]	Low Tg	Ibuprofen ^[74]	< -30
Methylcellulose (MC) ^[59]	184 to 197	Flurbiprofen ^[74]	-4.65
Sodium carboxy-methyl cellulose ^[32]	-57	Silica ^[7]	1175
Hydroxypropylcellulose (HPC) ^[59]	105	Beclomethasone dipropionate ^[60]	66
Hydroxy propyl methylcellulose (HPMC-powder) ^[1]	180	Ketoprofen ^[60]	-14
Eudragit L 100 ^[60]	67	Naproxen ^[60]	29
Eudragit E 100 ^[60]	45	Diazepam ^[75]	46
Eudragit RS 100 ^[60]	64	Inulin ^[75]	155
Eudragit.RTM. S100 ^[61]	160	Copovidone ^[76]	105 to 108
Eudragit.L100-55 ^[61]	110	Water ^[77]	-135
Eudragit.RTM. L100 ^[61]	150	Triethyl citrate (TEC) ^[27]	74.4
Eudragit.RTM. E ^[61]	50	Triacetin ^[27]	79.6
Maltodextrin DE 5 ^[32]	188	Propylene Glycol ^[27]	91.1
Maltodextrin DE 10 ^[32]	160	Glycerin ^[27]	128.5
Maltodextrin DE 15 ^[32]	99	Glycine ^[78]	-42
Glucose ^[32]	29		

Polymer solutions, co-polymers and blends^[16]

It has been shown that T_g strongly depends on solvent used and the composition of polymer solutions. T_g is found to be decreased with addition of solvent to polymer due to plasticization. Hence, T_g becomes inversely proportional to concentration of solvent. Immiscible blends show separate T_g for each of the individual components. So, two T_gs are observed for binary blends. In case of miscible blends, a single T_g appears in between T_gs of mixed components.

Example: Decrease in T_g of polyvinyl chloride due to plasticization by di(ethylhexyl)phthalate;^[16] immiscible blend of polystyrene and styrene-butadiene co-polymer has shown separate T_gs. Table 3 shows a list of reported T_gs of some polymers and drug molecules.

Importance of glass transition temperature*Improved processing and handling qualities*

The materials having low T_g are usually sticky in nature. Hence, if the T_g of material is increased by addition of substance having high T_g values, then product obtained won't be sticky, rather it becomes harder and easy to process. In this glassy state, the substance gets tougher and has good strength.

Improved dissolution and bioavailability

Amorphous materials show better aqueous solubility than crystalline material.^[15,79,80] This is because, in case of amorphous material, minimal is energy required by randomly arranged molecules for dissolution. In case of high T_g material, they are in glassy state at room temperature and show improved dissolution. But in case of low T_g material, they are in rubbery state at room temperature/body temperature. Hence, rubbery nature of drug/polymer leads to erratic dissolution.^[81]

Indomethacin^[82] and nifedipine are poorly water-soluble drugs exhibiting dissolution rate limited oral bioavailability.^[4] So both drugs are prepared as glass solutions by melt extrusion with amorphous (hydrophilic) polymer-poly vinyl Pyrrolidone (PVP).^[4] Glass solutions of both have showed increased drug dissolution rate than crystalline form of drug.^[4,15,82]

Improved physical stability

Glass solution is formed when drug and polymer are entirely miscible in molten state and remain as an amorphous one-phase system when cooled. Extensive hydrogen bonding between drug and polymer leaves fewer sites available for bonding with water/moisture.^[4,83] Hence, addition of polymers like PVP to drug in amorphous state (Nifedipine and Indomethacin) has showed improved physical stability.^[4] Also, any material in glassy state shows improved storage capability and physical stability.^[38,65,70,81]

CONCLUSION

Glass transition temperature can be used to modify physical properties of solids. By altering the T_g of drug or polymer molecules they can be maintained in amorphous solid form at ambient or body temperatures. Improvement in handling characters, solubility and reproducibility in dissolution of solids can be achieved by increasing the T_g of solids.

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