REVIEW ARTICLE

Glass transition temperature: Basics and application in pharmaceutical sector

Namdeo R Jadhav, Vinod L Gaikwad, Karthik J Nair, Hanmantrao M Kadam

Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Near Chitranagari, Morewadi, Kolhapur - 416 013, Maharashtra State, India

Glass transition temperature (Tg) is an important tool used to modify physical properties of drug and polymer molecules. Tg 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 Tg. The molecules/atoms in glassy state are subject to only vibration and not translational and rotational motion. Mainly, at Tg, 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 Tg. Techniques like differential scanning calorimetry, elastic modulus, broad-line NMR are used to measure the Tg of substances. The change in Tg 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 (Tg) is used as a tool to modify their physical properties. By knowing the Tg 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 Tg.[2,3] Transition of crystalline solids to amorphous form is carried out mainly to increase the solubility of drug molecules.[4]

Address for correspondence:
Dr. Namdeo R. Jadhav, Bharati Vidyapeeth College of Pharmacy, Near Chitranagari, Morewadi, Kolhapur - 416 013, Maharashtra, India. E-mail: nrjadhav18@rediffmail.com

DOI: 10.4103/0973-8398.55043

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 Tg.[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 (Tm) takes place at a temperature above Tg.[6] Figure 1a and b show the amount of heat added to the solid on the y-axis and temperature

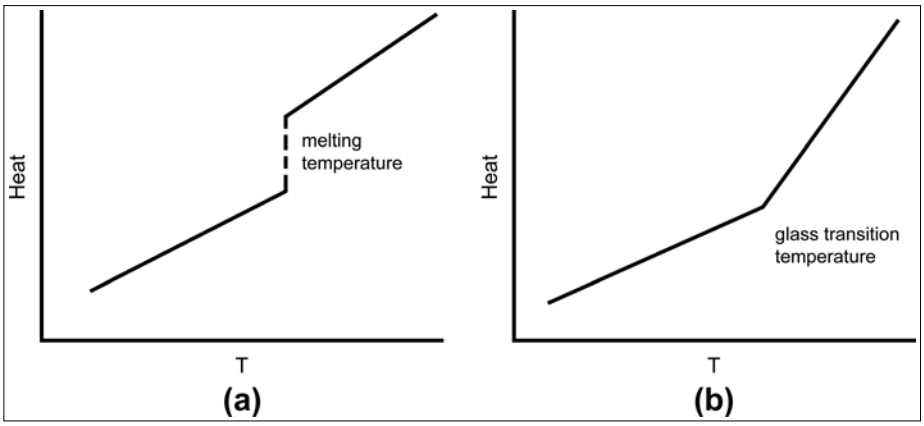

Figure 1: Plot of temperature (T) and heat relationship; (a) melting point and (b) glass transition temperature

obtained by the given amount of heat on the x-axis at Tg and Tm.[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.

Incase 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 Tg is seen no break and latent heat is involved.

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

Specific volume (Vsp) of solid is another factor that changes with the change in temperature as depicted in Figure 2. In this figure, from Tm 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 Tgs are obtained. Rapid cooling gives high Tg (Tg1) while slow cooling rate gives lower Tg (Tg2).[6,8]

Specific heat (Cp) 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 Tg. The temperature

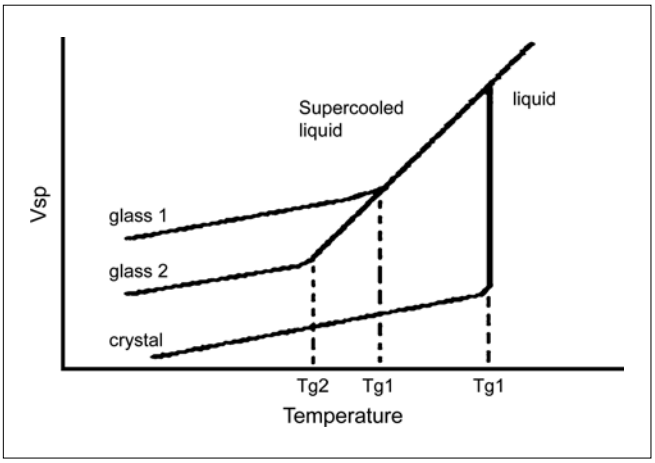

Figure 2: Graph of specific volume against temperature for solids forming glass where, Vsp is specific volume, Tm is melting temperature, Tg1 and Tg2 are glass transition temperatures

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 cp 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 Tg 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 (Tc), melting temperature (Tm) and glass transition temperature (Tg) are seen. Tg and Tc are endothermic and Tm is showed as exothermic.[5] The Tc and Tm are usually showed by crystalline polymers. Complete amorphous polymers show only Tg. Polymers with both amorphous and crystalline region show all the three characteristics.[5]

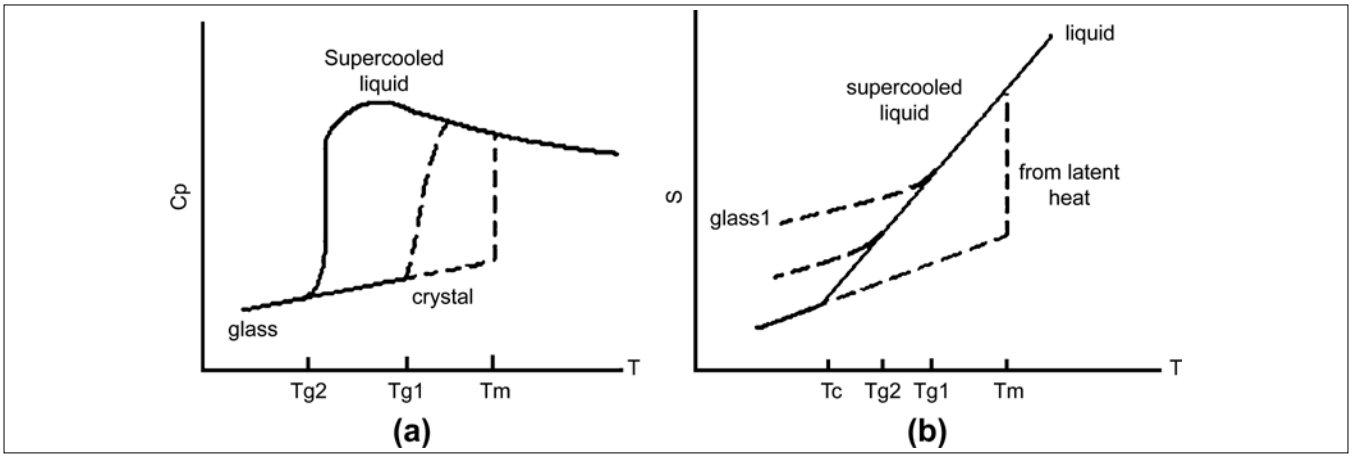

Figure 3: Rate of cooling affecting Tg of solids (a) Glass 1(Tg1) is glass obtained at faster cooling rate; (b) Glass 2(Tg2) obtained at slower cooling rate. (Cp) is specific heat, (S) as specific entropy of crystal, liquid, supercooled liquid and glass 6

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]

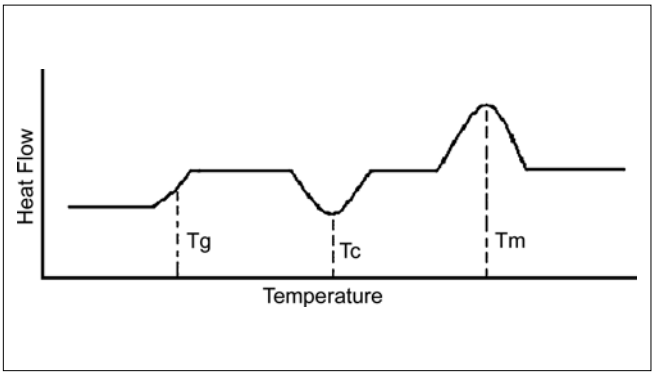

Figure 4: Differential scanning calorimetry plot showing region of crystallization temperature (Tc), melting temperature(Tm) and glass transition temperature (Tg)

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.

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] triacetine,[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 Tg.[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 Tg has been reported as shown in Table 2.[32]

Cooling rate

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

Example: Study on influence of cooling rate on Tg 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 Tg is also high.[6,9]

Pressure and free volume

Increase in pressure of surrounding leads to decrease in free volume and ultimately high Tg.[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 Tg; increase in film thickness increases compaction and results in an increased Tg. When a polymer is added to substrate, the Tg increases due to decreased mobility. In case of thin free standing films, Tg decreases more due to high mobility than bulk polymer. In case of sandwiched films, compaction leads to increase in Tg.

Example: Polystyrene has shown decrease in Tg 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 Tg and some show low because of the ease with which the polymer chains move. A very low Tg will be shown by the polymer chains which can move around easily, while one that doesn't move will have a high Tg.

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

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

Pregelatinized wheat starch		Native wheat starch	
Moisture (%)	Tg (°C)	Moisture (%)	Tg (°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 Tg. Examples: The major class is of silicones like polydimethylsiloxane. Its backbone is so flexible that it has a Tg-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 Tg. 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 Tg 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 adamantine, gives a high Tg. 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 Tg of 119°C, while adamantine substituted poly (ether ketone) has a Tg of 225°C.

Pendant groups part II[2]

It is observed that the substitution of big bulky pendant groups can also lower Tg 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 Tg, similar to plasticizer. In the series of methacrylate polymers, a decrease in Tg is observed with the substitution of one carbon each time, as seen in poly(methyl methacrylate), Tg 100-120°C; For poly(ethyl methacrylate), Tg: 65°C; poly(propyl methacrylate), Tg: 35°C; poly(butyl methacrylate), Tg: 20°C.

Interfacial energy and thickness[46]

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

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

Branching[3,10,21]

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

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

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.

Functionality[3]

Mono functional aliphatic monomers due to high flexibility exhibit low Tg.

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

Alkyl chain length[5]

Increase in alkyl chain length results in high Tg values.

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

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

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

Importance of glass transition temperature

Improved processing and handling qualities

The materials having low Tg are usually sticky in nature. Hence, if the Tg of material is increased by addition of substance having high Tg 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 Tg material, they are in glassy state at room temperature and show improved dissolution. But in case of low Tg 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 Tg 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 Tg of solids.

ACKNOWLEDGEMENT

The authors are thankful to AICTE, New Delhi, for providing financial assistance in the form of research grant and a JRF.

REFERENCES

1. Gothoskar AV. Study of softening point of swellable matrices and effect on drug-release pattern. Drug Delivery Technology 2005;5:1-7.
2. The glass transition. Available from: http://www.pslc.ws/mactest/tg.htm. [last accessed on 2007 Feb 4].
3. Glass transition temperatures of sartomer products, Sartomer application bulletin. Available from: http://www.sartomereurope.com. [last accessed on 2007 Feb 4].
4. Forster A, Hempenstall J, Rades T. Investigation of drug/polymer interaction in glass solutions prepared by melt extrusion. The Internet Journal of Vibrational Spectroscopy 2001;5:1-15.
5. Thermal behavior of polymers, Glass transition temperature (Tg). Available from: http: web.missouri.edu/~kattik/katti/Thermal %20 Behavior %20 of %20 Polymers. [last accessed on 2007 Feb 4].
6. Ediger MD, Angell CA, Nagel SR. Supercooled liquids and glasses. Journal of Physical Chemistry 1996;100:13200-12.
7. Glass transition temperature- wikipedia, the free encyclopedia. Available from: http: //www.en.wikipedia.org/wiki/Glass-transition-temperature. [last accessed on 2007 Feb 7].
8. Glass transition. Available from: http://web.umr.edu/~WLF/Bulk/glasstrans.html. [last accessed on 2007 Feb 7].
9. Debenedetti PG, Stillinger FH. Supercooled liquids and the glass transition. Nature 2001;410:259-67.
10. Jenkins M. Polymer science and materials case study, Level 2 (level I), N225, Lecture 3, Factors affecting the glass transition temperature. Available from: http:// www.eng.bham.ac.uk/metallurgy/people/Jenkins-files/L2%20PCS%202006.pdf. [last accessed on 2007 Feb 8].
11. Aloui F, Ahajji A, Irmouli Y, George B, Charrier B, Merlin A. Photostabilisation of the "wood-clearcoatings" systems with UV absorbers: Correlation with their effect on the glass transition temperature. Journal of Physics 2006;40:118-23.
12. Martin A, Swarbrick J, Cammarata A. Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences. 3rd ed. Bombay: Varghese Publishing House; 1991. p. 628-31.
13. Billmeyer FW. Textbook of Polymer Science, 3rd ed. Singapore: A Wiley-interscience Publication; 1994. p. 320-326, 337-340.
14. Sematech provisional test method for evaluating bulk polymer samples of UPW distribution system components (DSC and TGA Methods), Technology transfer # 92010939B-std sematech 1992. Available from: http://www.sematech.org/docubase/document/0939bstd.pdf. [last accessed on 2007 Feb 7].
15. Paradkar AR, Chauhan B, Yamamura S, Pawar AP. Preparation and characterization of glassy celecoxib. Drug Dev Ind Pharm 2003;29:739-44.
16. Phenomenon of the glass transition. Physical properties of polymers, Fall 2004. Available from: http://www.gozips.uakron.edu/~alexei/Lect3-7p2. [last accessed on 2007 Feb 7].
17. Zeng XM, Martin GP, Marriott C. Effects of molecular weight of polyvinylpyrrolidone on the glass transition and crystallization of co-lyophilized sucrose. Int J Pharm 2001;218:63-73.

18. Montserrat S, Colomer P. The effect of the molecular weight on the glass transition temperature in amorphous poly (ethylene terephthalate). Polymer Bulletin 1984;12:173-80.
19. Roth CB, Pound A, Kamp SW, Murray CA, Dutcher JR. Molecular-weight dependence of the glass transition temperature of freely-standing poly(methyl methacrylate) films. Eur Phys J E Soft Matter 2006;20:441-8.
20. Champion D, Meste M, Simatos D, Roudaut G, Contreras-Lopez E. Molecular mobility around the glass transition temperature: Amini review. Innovative Food Science and Emerging Technologies 2004;5:127-34.
21. The Glass transition in polymers, Doitpoms teaching and learning packages, University of Cambridge. Available from: http://www.doitpoms.ac.uk/tlplib/glass-transition/theory1.php. [last accessed on 2007 Feb 7].
22. Sauvant V, Duval S, Method of evaluating the glass-transition temperature of a polymer part during use. US Patent 6543931; 2003.
23. Wu C, McGinity JW. Influence of ibuprofen as a solid-state plasticizer in eudragit RS 30D on the physicochemical properties of coated beads. AAPS PharmSciTech 2001;2:1-9.
24. Nakagami, Hiroaki, Kojimam, Masazumi, Sagasaki and Shinji, Sustained-release granular preparations and production process thereof, US Patent 6030644; 1998.
25. Sobral PJ, Monterrey QE, Habitante AM. Glass transition study of nile tilapia myofibrillar protein films plasticized by glycerin and water. Journal of Thermal Analysis and Calorimetry 2002;67:499-504.
26. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publishing House; 1987. p. 368-9.
27. Vesey CF, Farrell T, Rajabi-Siahboomi AR. Evaluation of alternative plasticizers for surelease, an aqueous ethylcellulose dispersion for modified release film-coating, Modified release, Controlled Release Society, Annual meeting, Poster reprint, 2005,1-4.
28. Okarter TU, Singla K. The effects of plasticizers on the release of metoprolol tartrate from granules coated with a polymethacrylate film. Drug Dev Ind Pharm 2000;26:323-9.
29. Scapin SM, Silva DR, Joazeiro PP, Alberto-Rincon MC, Luciano RM, Duek EA. Use of triethylcitrate plasticizer in the production of poly-L-lactic acid implants with different degradation times. J Mater Sci Mater Med 2003;14:635-40.
30. Ljungberg N, Andersson T, Wesslen B. Film extrusion and film weldability of poly (lactic acid) plasticized with triacetine and tributyl citrate. Journal of Applied Polymer Science 2003;88:3239-47.
31. Honary S, Orafai H. The effect of different plasticizer molecular weights and concentrations on mechanical and thermomechanical properties of free films. Drug Dev Ind Pharm 2002;28:711-15.
32. Zeleznak KJ, Hoseney RC. Glass transition in starch. Cereal Chemistry 1987;64:121-4.
33. Yang B, Huang W M, Li C, Chor JH. Effects of moisture on the glass transition temperature of polyurethane shape memory polymer filled with nano-carbon powder. European Polymer Journal 2005;41:1123-8.
34. Ohkuma C, Kawai K, Viriyarattanasak C, Mahawanich T, Tantratian S, Takai R, *et al*. Glass transition properties of frozen and freeze-dried surimi products: Effects of sugar and moisture on the glass transition temperature. Food Hydrocolloids 2008;22:255-62.
35. Goula AM, Karapantsios TD, Achilias DS, Adamopoulos KG. Water sorption isotherms and glass transition temperature of spray dried tomato pulp. Journal of Food Engineering 2008;85:73-83.
36. Surana R, Randall L, Pyne A, Vemuri NM, Suryanarayanan R. Determination of glass transition temperature and in situ study of the plasticizing effect of water by inverse gas chromatography. Pharm Res 2003;20:1647-54.
37. Millington S, Shaw SJ. Adhesives for elevated-temperature applications, Materials research society, MRS BULLETIN 2003, 428-433. Available from: www.mrs.org/publications/bulletin. [last accessed on 2007 Apr 25].
38. Royall PG, Craig DQ, Doherty C. Characterisation of moisture uptake effects on the glass transitional behavior of an amorphous drug using modulated temperature DSC. Int J Pharm 1999;192:39-46.
39. Moynihan CT. The glass transition and the nature of the glassy state. Annals of the New York Academy of Sciences 1976;279:15-36.
40. Bruning R, Samwer K. Glass transition on long time scales. Physical Review B 1992;46:318-22.
41. Hsu CL, Heldman DR, Taylor TA, Kramer HL. Influence of cooling rate on glass transition temperature of sucrose solutions and rice starch gel. Journal of Food Science 2003;68:1970.
42. Simulations of amorphous polyethylene glass transition. Available from: http:// www.wag.caltech.edu/home/gao/thesis/chapter6. [last accessed on 2007 Feb 7].
43. Forrest JA, Dalnoki-Veress K, Stevens JR, Dutcher JR. Effect of free surfaces on the glass transition temperature of thin polymer films. Phys Rev Lett 1996;77:2002-5.
44. He T, Li B, Ren S. Glass transition temperature and chain flexibility of 1,2-polybutadiene. Journal of Applied Polymer Science 2003;31:873-84.
45. Schut J, Bolikal D, Khan IJ, Pesnell A, Rege A, Rojas R, *et al*. Glass transition temperature prediction of polymers through the mass-per-flexible-bond principle. Polymer 2007;48:6115-24.
46. Fryer DS, Peters RD, Kim EJ, Tomaszewski JE, Pablo JJ, Nealey PF. Dependence of the glass transition temperature of polymer films on interfacial energy and thickness. Macromolecules 2001;34:5627-34.
47. Melting and glass transition temperatures for some of the more common polymeric materials, Available from: http://www.tech.plym.ac.uk/sme/Interactive-Resources/ tutorials/ Failure Analysis/ Hail-Damage/Glass-Transition. [last accessed on 2007 Feb 8].
48. Mallapragada SK, Peppas NA, Colombo P. Crystal dissolution-controlled release systems, II, Metronidazole release from semicrystalline poly (vinyl alcohol) systems. Journal of Biomedical Materials Research 1997;36:125-30.
49. The role of plasticizers as functional excipients in pharmaceutical dosage forms prepared by hot-melt extrusion, Pharmaceutical Coatings Bulletin, Available from: http://www.morflex.com/pdf/Bul102.6.pdf. [last accessed on 2007 Feb 8].
50. Colas A, Dow corning, Silicones in pharmaceutical applications, Dow corning healthcare industries, 2001, Dow corning corporation, 2001:1-21, Available from: http://www.dowcorning.com/content/publishedlit/51-993a-01.pdf. [last accessed on 2007 Feb 8].
51. Buenviaje C, Dinelli F, Overney RM. Investigations of heterogeneous ultrathin blends using lateral force microscopy, "Scanning probe microscopy of polymers: The next generation" ACS 2000 fall meeting, Washington, D.C. 2000:1-12. Available from: http://www.depts.washington.edu/nanolab/publications/2000ACSDC.pdf. [last accessed on 2007 Feb 8].
52. Afantitis A, Melagraki G, Makridima K, Alexandridis A, Sarimveis H, Iglessi-Markopoulou O. Prediction of high weight polymers glass transition temperature using RBF neural networks, Journal of Molecular Structure: Theochem 2005;716:193-8.
53. Brechet Y, Cavaille JY, Chabert E, Chazeau L, Dendievel R, Flandin L, Gauthier C. Polymer based nanocomposites: Effect of filler-filler and filler-matrix interactions. Advanced Engineering 2001;3:571-7.
54. Hibbs MR, Holtzclaw J, Collard DM, Liu RY, Hiltner A, Baer E, Schiraldi DA. Poly(ethylene terephthalate) modified with aromatic bisester diamides: Thermal and oxygen barrier properties. Journal of Polymer Science: Part A: Polymer Chemistry 2004;42:1668-81.
55. Max GJ. Intra-pocket drug delivery devices for treatment of periodontal diseases, US Patent 4764377; 1987.
56. Walther LE, Israeloff NE, Russell EV, Gomariz HA. Mesoscopic-scale dielectric relaxation at the glass transition. Rapid Communications Physical Review B 1998;57:15112-5.
57. Herzog B, Gardner D J, Lopez-Anido R, Goodell B. Glass transition temperature based on dynamic mechanical thermal analysis techniques as an indicator of the adhesive performance of vinyl ester resin. Journal of Applied Polymer Science 2005;97:2221-9.
58. Durig T, Salzstein RA, Skinner GW, Harcum WW, Grasso RP, Lau SF. Advanced structure-function properties of ethylcellulose: Implications for tablet compactibility, Hercules, Pharmaceutical Technology Report 2002, PTR-021: 1-9. Available from: http://www.herc.com/aqualon/product-data/ptr/ptr-021.pdf. [last accessed on 2007 Feb 8].
59. Gomez-Carracedo A, Alvarez-Lorenzo C, Gomez-Amoza JL, Concheiro

A. Chemical structure and glass transition temperature of non-ionic cellulose ethers. Journal of Thermal Analysis and Calorimetry 2003;73:587-96.
60. Eerikainen H. Preparation of nanoparticles consisting of methacrylic polymers and drugs by an aerosol flow reactor method, Academic Dissertation. Vol. 563. Espoo: Vtt Publications; 2005. p. 1-112.
61. Albano AA, Phuapradit W, Sandhu HK, Shah NH. Stable complexes of poorly soluble compounds in ionic polymers, US Patent 6350786; 2002.
62. Polymer chemistry, The glass transition, Available from: http://www.faculty.uscupstate.edu/llever/Polymer%20Resources/GlassTrans.htm. [last accessed on 2007 Feb 8].
63. Slade L, Levine H. Non-equilibrium behavior of small carbohydrate-water systems. Pure and Applied Chemistry 1988;60:1841-64.
64. Ambike A, Mahadik K, Paradkar A. Spray-dried amorphous solid dispersions of simvastatin, a low Tg drug: *In vitro* and *in vivo* evaluations. Pharm Res 2005;22:990-8.
65. Chang BS, Beauvais RM, Dong A, Carpenter JF. Physical factors affecting the storage stability of freeze-dried interleukin-1 receptor antagonist: Glass transition and protein conformation. Arch Biochem Biophys 1996;331:249-58.
66. Papageorgiou GZ, Bikiaris D, Karavas E, Politis S, Docoslis A, Park Y, *et al*. Effect of physical state and particle size distribution on dissolution enhancement of nimodipine/PEG solid dispersions prepared by melt mixing and solvent evaporation. AAPS PharmSciTech 2006;8:E623-31.
67. Keymolen B, Ford JL, Powell MW, Rajabi-Siahboomi AR. Investigation of the polymorphic transformations from glassy nifedipine. Thermochimica Acta 2003;397:103-17.
68. Correia NT, Moura Ramos JJ, Descamps M, Collins G. Molecular mobility and fragility in indomethacin: A thermally stimulated depolarization current study. Pharm Res 2001;18:1767-74.
69. Javadzadeh Y, Siahi MR, Asnaashari S and Nokhodchi A. Liquisolid technique as a tool for enhancement of poorly water-soluble drugs and evaluation of their physicochemical properties. Acta Pharmacetica 2007;57:99-109.
70. Tong P, Zografi G. Effects of water vapor absorption on the physical and chemical stability of amorphous sodium indomethacin. AAPS PharmSciTech 2004;5:1-8.
71. Gupta P, Bansal AK. Molecular interactions in celecoxib-PVP-meglumine amorphous system. Journal of Pharmacy and Pharmacology 2005;57:303-10.
72. Royall PG, Craig DQ, Doherty C. Characterisation of the glass transition of an amorphous drug using modulated DSC. Pharm Res 1998;7:1117-21.
73. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. AAPS Pharm Sci Tech 2005;6:E405-12.
74. Paradkar A, Maheshwari M, Tyagi AK, Chauhan B, Kadam SS. Preparation and characterization of flurbiprofen beads by melt solidification technique. AAPS PharmSciTech 2003;4:E65.
75. van Drooge DJ, Hinrichs WL, Visser MR, Frijlink HW. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. Int J Pharm 2006;310:220-9.
76. Moroni A. A novel copovidone binder for dry granulation and direct-compression tableting, Pharmaceutical Technology Drug Delivery 2001,8-12.
77. Madeka H, Kokini JL. Effect of glass transition and cross-linking on rheological properties of zein: Development of a preliminary state diagram. Cereal Chemistry 1996;73:433-8.
78. Wang W. Lyophilization and development of solid protein pharmaceuticals. Int J Pharm 2000;203:1-60.
79. Albano AA, Phuapradit W, Sandhu HK, Shah NH. Amorphous form of cell cycle inhibitor having improved solubility and bioavailability, US Patent 6482847; 2002.
80. Gothoskar AV. Study of effect of polymer viscosity and polymer: Exipient ratio on drug release pattern from swellable matrices. Drug Delivery Technology 2005;5:1-7.
81. Fukuoka E, Makita M, Yamamura S. Some physicochemical properties of glassy indomethacin. Chem Pharm Bull (Tokyo) 1986;34:4314-21.
82. Srcic S, Kerc J, Urleb U, Zupancic I, Lahajnar G, Kofler B, *et al*. Investigation of felodipine polymorphism and its glassy state. Int J Pharm 1992;87:1-10.
83. Jans FH, Mielck JB. Stability of drugs in solid dispersions: Effect of glass transition on degradation kinetics under stress in systems of reserpine and PVP. European Journal of Pharmaceutics and Biopharmaceutics 1996;42:303-12.

Source of Support: AICTE, New Delhi, **Conflict of Interest:** None declared.