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A REVIEW ON SOLID DISPERSION: A DISSOLUTION ENHANCEMENT TECHNIQUE

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ABSTRACT
The enhancement of the oral bioavailability is currently one of the greatest challenges in the development of poorly water soluble drugs. To increase the dissolution and hence the bioavaibility it is important to increase the solubility of the poorly water soluble drugs. One of the possible ways to overcome this limitation is the use of solid dispersion technology. This article contains the different methods and mechanism used in the solid dispersion technology also overlooks the various carriers used in the solid dispersion.
KEY WORDS: Solid dispersion, Poorly water soluble drug, Melt agglomeration, Fusion, Solvent evaporation, Spray-drying.

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INTRODUCTION

Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. There have been always certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the Pharmaceutical industry.[1] Oral bioavailability of drugs is affected by a variety of factors which influence their absorption from the gastrointestinal tract. One determinant factor for absorption is drug dissolution which is influenced by the solubility of the drug in the gastrointestinal fluids.[2]

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. When combined with the *In-vitro* dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability and dissolution rate, all of which govern the rate and extent of oral drug absorption from solid oral-dosage forms. It classifies drugs into four classes as shown in **Table 1.**

Poorly water-soluble drug candidates often emerge from contemporary drug discovery programs and present formulators with considerable technical challenges. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids.[3]

Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy.[4]

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. More specifically, Chiou and Riegelman (1971), in their classic review, defined these systems as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-

solvent method', while Corrigan (1985) suggested the definition as being a 'product formed by converting a fluid drug-carrier combination to the solid state'.[5]

Definition of solid dispersion

Chiou and Riegelman, 1971 defined the term solid dispersion as "A dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method"[6]. Dispersions obtained through the fusion process are often called melts and those obtained by the solvent method are frequently referred to as co-precipitates or co-evaporates, for example, Sulfathiazole-Povidone (PVP) and Reserpine-Povidone[7]**.** There are some drugs whose solubility is enhanced by using solid dispersion like Mifepristone[8], Dyhdroartemisinin[9], Furosemide[10], Piroxicam[11] and others.

Advantages of solid dispersions over other strategies

Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a prodrug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others. Solid dispersions are more acceptable to patients than Solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually. Milling or micronization for particle size reduction are commonly performed as approaches to improve solubility, on the basis of the increase in surface area.[12]

The higher dissolution rates of solid dispersions can be ascribed to a number of factors which includes:

1. The formation of higher energy metastable states of the components as a function of the carrier system being used and the proportion of carriers present.
2. The reduction of particle size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption.
3. Formation of amorphous forms of drug and carriers.
4. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug, hence higher dissolution rates. The presence of carrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution.
5. Co solvent effect on the drug by the water soluble carriers.
6. Intermolecular hydrogen bonds between drug and carrier
7. Local solubilization effect of carrier at the diffusion layer.[13]

The different ways of increasing the absorption or bioavaibility are,

1. Micronization
2. Use of soluble salt
3. Use of minuscular form of drug adsorb on the insoluble adsorbants
4. Use of surfactants
5. Use of polymorphs
6. Use of hydrates or solvates and
7. Molecular complexation

Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. In addition micronization is a high-energy process, which causes disruptions in the drugs crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different form that of parent compound.[14] The fusion method can only be applied when drug and matrix are compatible when they mix well at heating temperature.

METHODS OF PREPARATION

The two basic procedures used to prepare solid dispersions are the fusion and co-solvent techniques. Modifications of these methods and combinations of them have also been used.

1. Melting or fusion method

In the melting process, the molecular mobility of carrier is high enough to change the drug's incorporation. A common adaptation to the melting phase consists of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state therefore reducing the process temperature. To cool and solidify the melted mixture, several processes such as ice bath agitation, stainless steel thin layer spreading followed by a cold draught, solidification on petri dishes at room temperature inside a dessicator, spreading on

plates placed over dry ice, immersion in liquid nitrogen or stored in a dessicator were used. After cooling, the mixture must be pulverized regarding its handling[14]. Its simplicity and economy as no solvents are involved. This method may include the tacky and intractable nature of the resulting solidified melt and irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug-carrier system[16].

2. Solvent evaporation method

Until the advent of the solvent method, solid solutions were prepared exclusively by the melting method. Tachibani and Nakumara were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vaccum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone (PVP). The evaporation method was then taken up by Mayersohn and Gibaldi. By dissolving both Griseofulvin and polyvinylpyrrolidone (PVP) in chloroform and then evaporating the solvent to achieve a solid dispersion. The release rate of Griseofulvin from the solid dispersion was 5 to 11 times higher than that of micronized drug depending on the drug/carrier ratio. Bates, introduced the term co-precipitates to describe solid dispersions that are manufactured by the solvent evaporation method. Although the term co-precipitate is strictly speaking inaccurate in this case, it is still widely used in this sense today. Simonelli et al. used the term co-precipitate more correctly to describe the solid dispersion of Sulphathiazole and polyvinylpyrrolidone (PVP) that had been precipitated from a solution in sodium chloride by the addition of hydrochloric acid. Solid dispersions and solutions that are manufactured by the solvent evaporation method should really be called co-evaporates and not co-precipitates. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods.

Temperatures used for solvent evaporation usually lie in the range of 23±65^{0}C. The solvent can be removed by freeze-drying or by spray-drying. It must be remembered that when an organic solvent is to be removed small variations in the conditions used can lead to quite large changes in product performance. It form solid dispersions of thermolabile substances. Many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could be now considered as carrier possibilities[17]. The use of large quantities of solvent, difficulty in complete removal of solvent. The possible adverse effect of residual solvent and the selection of common volatile solvent.

3. Hot melt extrusion

Hot melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts or oral dosage forms. Technique offers the possibility of continuous production, which makes it suitable for large-scale production. There may the miscibility problem of drug and matrix. High shear forces resulting in high local temperatures in the extruder which is a problem for heat sensitive material

4. Spray-drying

It is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Van Drooge prepared an alternative solid dispersion by spraying a Povidone and Diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized[19].It is simple and cost effective, as it is 30-50 times less expensive than freeze-drying.

5. Melt agglomeration process

This technique has been used to prepare SD, wherein the binder acts as a carrier. In addition, SD(s) are prepared either by heating binder, drug and excipients to a temperature above the melting point of the binder (melt-in procedure) or by spraying a dispersion of drug in molten binder on the heated excipients (spray-on procedure) by using a high shear mixer[20].

The following five are representative types of solid dispersion.

1. Simple eutectic mixtures

These are prepared by rapid solidification of the fused melt of two components that show complete, liquid miscibility but negligible solid-solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. Thus, the X-ray diffraction pattern of eutectic constitutes which is an additive composite of the two components. A phase diagram of a two-component system is shown in **Figure 1**

2. Solid solution

A solid solution compared to a liquid solution is made up of a solid solute dissolved in a solid solvent. In a solid solution, the two components crystallize together in a homogeneous one-phase system. The particle size of the drug in the solid solution is reduced to its molecular size.

Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture.

Solid solutions can be classified by the two methods.

A) According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous.

(i) Continuous solid solutions

In continuous solid solutions, the two components are miscible in the solid state in all proportions. There are no established solutions of this type, which have shown fast-release dissolution properties, although it is theoretically possible. There would be faster dissolution rate, if the drug is present as a minor component. However, the presence of small amounts of the soluble carrier in the crystalline lattice of the poorly soluble drug also produces a dissolution rate faster than that of the pure compound with similar particle size. This may be due to a small number of the neighbouring drug molecules holding the dissolving drug molecules after the rapid dissolution of the neighbouring water-soluble carrier.

(ii) Discontinuous solid solutions

In this system, there is only a limited solubility of a solute in a solid solvent each component is capable of dissolving the other component to a certain degree above the eutectic temperature.Typical phase diagrams of continuous and discontinuous solid solutions are in shown **Figures 2 and 3** respectively. Discontinuous solid solutions exist at extremes of composition. In general, some solid-state solubility can be expected for all two-component systems.

B) According to the criteria of molecular size of the two components, the solid solutions are classified as (i) Substitutional and (ii) Interstitial.

i) Substitutional solid solution

In the substitutional type, the solute molecule substitutes for the solvent molecule in the crystal lattice as shown in **Figure 4 (a)**. It can form continuous or discontinuous solid solution. The size and the steric feature of the solid molecule were shown to play a decisive role in the formation of solid solutions. The size of the solute and solvent molecule should be as close as possible. Teresa calculated the degree of molecular isomorphism to express the degree of similarity of the shape of the two components. The dissertation of the crystal lattice of the solvent by the stearic effect or chemical interaction is also important. The solubility of the solute increases until the dissertation of the lattice field of the solvent by the solute molecule can no longer be tolerated.

ii) Interstitial solid solution

An interstitial solid solution is obtained when the solute molecule occupies the interstitial space as shown in **Figure 4 (b)** in the solvent (host) lattice and forms only a discontinuous solid solution. The size of the solute is critical in order to fit into the interstices. Thus, water soluble crystalline polymers of high molecular weight like Polyethylene glycols 4000, 6000 and 20,000 are logical choices for this type of solid solution of insoluble drugs. Low toxicity and lack of absorption from gastrointestinal tract are the advantage of these polymer carriers. In this case, significant amounts of drug can be trapped in the interstitial space when Polyethylene glycol-drug melts are solidified. Griseofulvin, Digitoxin, Methyl testosterone, Pridnisolone acetate and Hydrocortisone acetate dispersed in the matrix of Polyethylene glycol-6000 were shown to produce a faster dissolution rate. The large molecular size of the polymers favors the formation of thermodynamically stable interstitial solid solutions.

3. Glass solutions and suspensions

Chiou and Riegelman, 1971 were the first to introduce the concept of formation of glass solution, a potential modification of dosage forms in increasing drug dissolution and absorption. It is a homogeneous glassy system in which a solute dissolves in a glassy solvent. A glassy state is usually obtained by abrupt quenching of the melt, which usually results in a glassy or vitreous state.

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting points; instead, they soften progressively and continuously on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions. **Figure 5** shows the volume changes associated with glass formation when a melt is cooled down.

Examples of carriers that form glass solutions and suspensions include Citric acid, sugars such as Dextrose, Sucrose and Galactose, Povidone, Urea and Polyethylene glycol.

Glass solution is metastable. It is also amorphous to X-ray diffraction. Glass formation is common in many polyhydroxy molecules, such as sugars, presumably due to their strong hydrogen bonding which may prevent their crystallization. Polymers possessing linear, flexible chains can freeze into glassy state, transparency and brittleness. Glass formation can occur for the pure substance itself or when in the presence of other components. If a water insoluble drug forms a glass

solution with a water-soluble glass-forming carrier, then the *in-situ* dissolved drug is released into the aqueous medium rapidly because the carrier quickly dissolves upon exposure to the aqueous medium. The strength of chemical binding in a glass solution is much less compared to that in a solid solution. Hence, the dissolution rate of drugs in the glass solution is faster than that in solid solution.

4. Amorphous precipitations in a crystalline carrier

The difference between the group of solid dispersions and the simple eutectic mixture is that the drug is precipitated out in an amorphous form in the former as opposed to a crystalline form in the latter. In this method, drug may also precipitate out in an amorphous form in the crystalline carrier from a melting or solvent method of preparation. Amorphous form produces faster dissolution rates then the crystalline form. Amorphous Novobiosin has 10-fold higher solubility than its crystalline form. Amorphous Sulphathiazole dispersed in crystalline urea was believed to be a primary contributing factor in increasing the oral absorption in man. It is postulated that a drug with high super cooling property has more tendency to solidify in an amorphous form in the presence of a carrier. Sulphathiazole was precipitated in the amorphous form in crystalline urea. It is postulated that a drug with a propensity to super cooling has more tendency to solidify as an amorphous form in the presence of a carrier.

5. Compound or complex formation

When the two substances form a molecular compound, it usually gives rise to a maximum in the phase diagram. Dissolution and absorption of a drug can occur from complex or a compound formed between the drug and an inert soluble carrier. An example of this system is the Quinine-Phenobarbital system. It is difficult to generalize, the influence of complex formation on dissolution. A complex between Digoxin and Hydroquinone exhibited a high dissolution rate, whereas the insoluble complex and Polyethylene glycol was shown to reduce both the rates of dissolution and the permeation of Phenobarbital through iverted rat gut. Complexation also implies that dissolution could be retarded, as is observed with Polyvinylpyrrolidone-Hexyl resorcinol and Polyethylene glycol 4000-Phenobarbital. However, the formation of a soluble complex with low association constant results in increased rate of dissolution and absorption. Complex formation between Povidone 25 and Nitrofuranatoin has been established. This dispersion has faster rate of dissolution than the pure drug.[21]

There are some marketed products which are prepared by using solid dispersion technology such as

1) Griseofulvin in PEG (Gris-PEG)- Novartis
2) Nabilone in PVP (Cesamet)- Lily

The various carriers can be used for the solubility enhancement are shown in **Table 2**

CONCLUSION

The solid dispersion technology is very useful tool to enhance the dissolution of the poorly water soluble drug. Though, it very popular and widely used in research but its commercial application is limited. The most frequent concerns with solid dispersions have been the ability to scale-up the manufacturing method, the physical stability of the dispersion and the amount of carrier needed to facilitate the required increase in the release rate. Various factors affecting dissolution of drug from solid dispersion includes the method of preparation of the solid dispersion, amount and properties of the polymer carriers, drug polymer contact and drug-polymer interactions.

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Table1: Biopharmaceutical classification system

Permeability	Solubility: Low	Solubility: High
High	III	I, II, IV
Low	III, IV	I, II

Table 2: Materials used as Carriers for Solid Dispersions [22]

Materials	Examples
Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol, Mannitol, Lactose.
Acids	Citric acid, Succinic acid.
Polymeric materials	Povidone (PVP), Poly- ethylene glycols (PEG), Hydroxypropyl-methyl- cellulose, Methyl cellulose, Hydroxyethylcellulose, Cyclodextrins, Hydroxypropylcellulose, Pectin, Gal.
Insoluble or enteric polymers	Hydroxypropyl-methylcellulose phthalate, Eudragit L-l00, Eudragit S- l00, Eudragit RL, Eudragit RS.
Surfactants	Polyoxyethylene stearate, Renex, Poloxamer 188, Texafor AIP, Deoxycholic acid, Tweens, Spans.
Miscellaneous	Pentaerythritol, Pentaerythrityl tetracetate, Urea, Urethane, Hydroxyalkylxanthins.

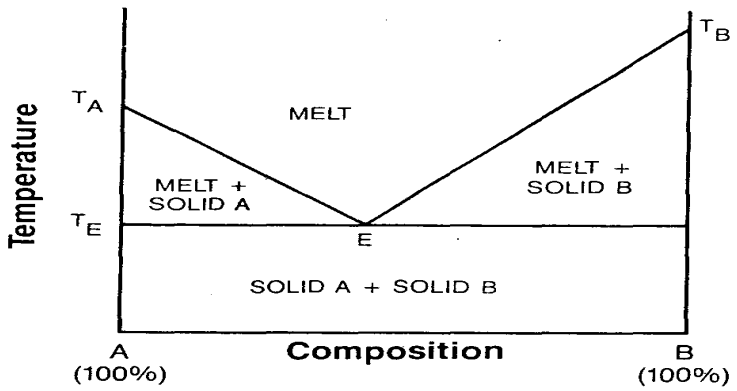

Figure 1: Simple Binary-Phase Diagram with Eutectic Formation. T_A is Melting Point, Pure A: T_B is Melting Point of Pure B: and E is Eutectic Point

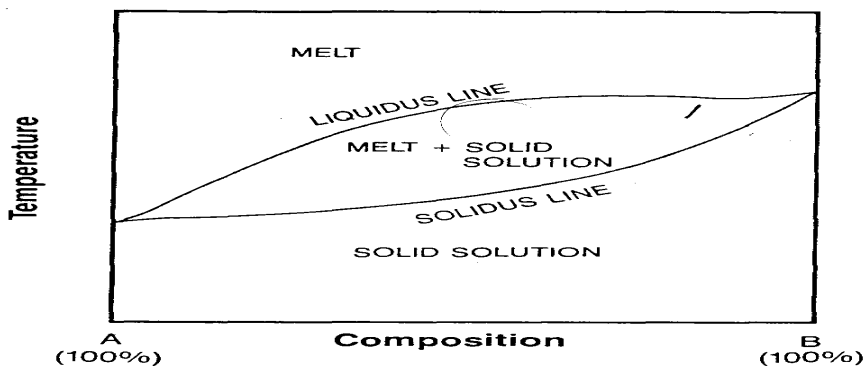

Figure 2: Phase Diagram of Continuous Solid Solution for a Binary System A and B.

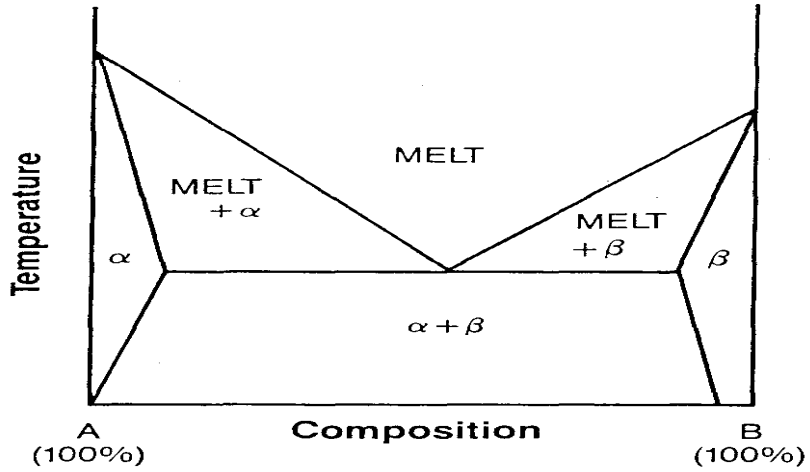

Figure 3: Phase Diagram of a Discontinuous Solid Solution for a Binary System A and B: α and β are Regions of Solid Solution Formation.

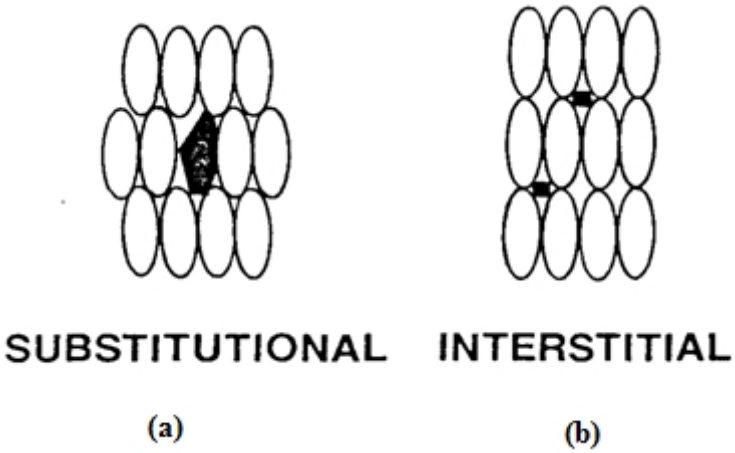

Figure 4: Schematic Representations of Substitutional and Interstitial Solid Solutions (Dark Symbols Represent Solute Atoms or Molecules) (Open symbol Indicate Solvent Atoms or Molecules).

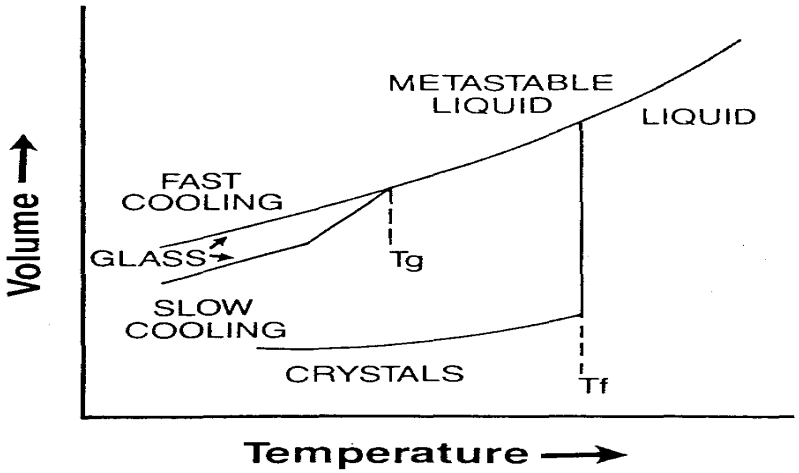

Figure 5: Volume Changes Associated with Cooling of a Melt: T_g is the Glass Transition Temperature and T_f is the Melting Point of the Material.