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SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS: A REVIEW

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ABSTRACT

Among all newly discovered chemical entities about 40% drugs are lipophillic and fail to reach market due to their poor water solubility. Drug with poor water solubility cause slow dissolution rates, generally show erratic and incomplete absorption leading to low bioavailability when administered orally. Aqueous solubility of any therapeutically active substance is a key property, as it governs dissolution, absorption and thus the *in vivo* efficacy. The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. The present review deals in detail about the different techniques used for the improvement of the solubility and dissolution rate of poorly water soluble drugs.

Keywords: Bioavailability, Dissolution rate, poorly soluble drugs, Solubility enhancement.

INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Oral drug delivery is the simplest and easiest way of administering drugs due to its convenience, good patient compliance, greater stability, accurate dosage and easy production.

Drug solubility is the maximum concentration of the drug dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution in a static property

where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate.

It is important to improve the solubility and/or dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability.[3] As solubility is an important determinant in drug liberation hence it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.[1,2]

About 40% of all new chemical entities have poor bioavailability. Increasing the bioavailability of poorly soluble drugs will be one of the biggest challenges for formulation scientists in the future. The bioavailability can be increased by changes in disintegration and dissolution. Aqueous solubility lesser than 1 μg/ml will definitely create a bioavailability problem and thereby affects the efficacy of the drug. There are number of methods through which aqueous solubility of the drug can be increased.

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.

BCS classification: (Amidon *et al.*,1995)[13]

Class I: High permeability and solubility.

Formulation independent:- The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine.

Examples: Benzapril, Loxoprofen, Sumatriptan etc.

Class II: high permeability but low solubility

Formulation dependent:- The bioavailability of class II compounds is limited by drug solubility/dissolution.

Examples: Valsartan, Nimesulide, Loratadine, Aceclofenac etc.

Class III: low permeability but high solubility

Dependent on barrier properties:- The bioavailability of class III compounds is limited by intestinal permeability.

Examples: Gabapentine, Topiramate, Atropine etc.

Class IV: low permeability and low solubility

Formulation and barrier properties dependent:- The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability.

Examples: Hydrochlorthiazide, Furosemide, Meloxicam etc.

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are

1. Micronization: Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug.

Micronization and nanonization techniques are used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability.

Particle size reduction methods include recrystallization of the solute particles from solutions using liquid antisolvents, along with labor intensive techniques like crushing, milling, grinding, freeze drying and spray-drying.

The rapid expansion of supercritical solutions (RESS) is an alternative technique for the micronization of particles using supercritical carbon dioxide to quickly and naturally reduce the particle sizes of various drugs.

Examples of Pharmaceutical compounds using RESS/CO2

Compound	Particle Size (microns)
Aspirin	2 – 5
Caffeine	3 – 5
Cholesterol	2.3
B-Estradiol	<1

Ibuprofen <2

Micronization has some limitations; micronization of sparingly or poorly soluble drugs is by no means a guarantee of better dissolution and absorption. A hydrophobic powder with small particle size leads to aggregation, making it difficult to disperse. The particles float on the dissolution medium because of entrapped air. It is difficult to remove or wet these particles. All these effects, in fact, reduce the rate of dissolution.

2. Nanonization: Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects.[20]

For many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution, the next step is nanonization. There are different techniques used for nanonization of drug including Wet milling, Homogenization, Emulsification-solvent evaporation technique, Pear milling, Spray drying etc. There are many examples of nanonization of drugs.

2.1 Nanocrystals: The term drug nanocrystals imply a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. Drug nanocrystals can be produced by bottom up technologies (precipitation methods) or alternatively by top down technologies (size reduction methods). The at present most industrially feasible methods are the top down technologies, all products on the market are made by size reduction.

2.2 Nanosuspension: Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. Nanosuspension technology solved the problem of drugs which are poorly aqueous soluble and less bioavailability. Stability and bioavailability of the drugs can be improved by the Nanosuspension technology. Nanosuspensions are prepared by using wet mill, high

pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and super critical fluid techniques. Nanosuspensions can be delivered by oral, parenteral, pulmonary and ocular routes.

2.3 Nanoemulsion: Nanoemulsions are a nonequilibrium, heterogeneous system consisting of two immiscible liquids in which one liquid is dispersed as droplets in another liquid. Emulsions with nanoscopic droplet sizes (typically in the range of 20–200 nm) are often referred to as submicron emulsions. Nanoemulsions are composed of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules. The methods used for the production of nanoemulsions include HPH, microfluidization, ultrasonication and spontaneous emulsification. Commercial products that are nanoemulsions include Estrasorb and Flexogan.

3. Sonocrystallization: Sonocrystallization is a novel particle engineering technique to enhance solubility and dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size by using ultrasound. Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. Most applications use ultrasound in the range 20 kHz-5 MHz.

Melt sonocrystallization (MSC) is promising technique of sonocrystallization to obtain porous, amorphous material with high stability.

4. Supercritical fluid method: A supercritical fluid (SCF) can be defined as a dense noncondensable fluid is a another novel nanosizing and solubilisation technology whose application has increased in recent years. A SCF process allows the micronization of drug particles within sub micron levels. Supercritical fluids are fluids whose temperature and pressure are greater than critical temperature (Tc) and critical pressure (Tp). At near-critical temperature, SCFs are highly compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle size. Carbon dioxide and water are the most commonly used supercritical fluids. The SCF process can create nanoparticulate suspensions of particles 5–2,000 nm in diameter. e.g.

enhancing water solubility of etraconazole with water soluble polymer HPMC by using supercritical fluid processing.[14]

5. Spray freezing into liquid and lyophilization: This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. carbon dioxide, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon or hydrofluroethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders. Use of acetonitrile as the solvent increases drug loading and decreases the drying time for lyophilization. The dissolution rate is enhanced from the SFL powder containing amorphous nanostructured aggregates with surface area and excellent wettability.

6. Evaporative precipitation into aqueous solution: This process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution on the aqueous solution to optimize particle formation and stabilization.

7. Use of surfactant: Surface active agents (surfactants) are substances which at low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface or interfacial tension. Surface active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. Thus, surfactants are said to be amphipathic in nature.

Depending on their charge characteristics the surface-active molecules may be anionic, cationic, zwitterionic (ampholytic) or non-ionic.

Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), Poly (beta-benzyl-Laspartate), b-poly (ethylene oxide) etc used as carrier for solubility and dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to

lowering of surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization of the drugs. To get any substantial solubility enhancement, the surfactant concentration must be at least above the critical micelle concentration (CMC). The CMC will depend upon the surfactant itself and the ionic strength of the media. The amount of surfactant needed depends on the CMC and the degree to which the compound partitions into the surfactant micelles.

8. Use of co-solvent: Cosolvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs.[4,5,6] It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency. Solvent used to increase solubility is known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. The use of mixed solvent system is often necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols, dimethylsulfoxide, ethanol and N, N dimethyl formamide can be used.

9. Hydrotropy method: Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. The term "*Hydrotropy*" has been used to designate the increase in aqueous solubility of various poorly water soluble compounds due to the presence of a large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents and the solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Specific examples include ethanol, aromatic alcohols like resorcinol, urea, sodium ascorbate, pyrogallol, catechol, *a*- and *b*-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene.

Hydrotropy is used for solubility enhancement of different class of drugs such as anti- tumor, anti-viral, anti-inflammatory, antipyretic and analgesic drugs, xanthine derivatives etc.[11,12] Hydrotropy is

successfully applied for solubility enhancement of nimesulide,[8] riboflavin,[7] nifedipine,[9] xanthine derivatives like theophylline and caffeine.[10]

10. Use of salt forms: A major improvement in solubility and dissolution rate can be achieved by forming a salt. Salts of acidic and basic drugs have, in general, higher solubilities than their corresponding acid or base forms. For solid dosage forms, dissolution rates of salt forms of several weakly acidic compounds under gastrointestinal (GI) pH conditions were much higher than those of their respective free acid forms. This may be attributed the higher dissolution rate of a salt to its higher solubility (relative to the free acid form) in the aqueous diffusion layer surrounding the solid. Alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are more water soluble than the parent drug.

11. Solvent deposition: In this technique drug is dissolved in a solvent like methylene chloride to produce a clear solution. The carrier is then dispersed in the solution by stirring and the solvent is removed by evaporation under temperature and pressure. The resultant mass is then dried, pulverized, and passed through a sieve. The increase in the dissolution rate is ascribed to the reduced particle size of the drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier. Succesfully solubility of aceclofenac has increase by solvent deposition technique using lactose.

12. Solubilizing agents: Solubilizing materials like superdisintegrants such as crospovidone, crosscarmellose sodium and sodium starch glycolate used as solubilizing agents in many formulation which increase the solubilty and dissolution rate of poorly water soluble drugs. The superdisintegrants acts as hydrophilic carrier for poorly water soluble drug. PEG 400 used to improve the solubility of hydrochlorthiazide. Modified gum karaya (MGK), a developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug nimodipine. The aqueous solubility of the antimalarial agent halofantrine was increased by the addition of caffeine and nicotinamide.

13. Modification of the crystal habit: Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture,

stability etc. Broadly polymorphs can be classified as enantiotrope and monotropes on the basis of thermodynamic properties. In the case of an enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotrope. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area. Generally, the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the organic (nonaqueous) solvates have greater solubility than the nonsolvates. Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is amorphous >metastable polymorph >stable polymorph**.**

Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.

14. Co-crystallisation: The new approach available for the enhancement of drug solubility is through the application of the co-crystals, also referred as molecular complexes. A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces. Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) which includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes

sublimation, growth from the melt, and slurry preparation. The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionisable groups.

15. Complexation: The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methylglucamide. Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring cyclodextrins are α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic, this is due to the arrangement of hydroxyl group within the molecule. Molecules or functional groups of molecules those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. In order to become complex, the "guest molecules" should fit into the cyclodextrin cavity. The cavity sizes as well as possible chemical modifications determine the affinity of cyclodextrins to the various molecules.

16. Drug dispersion in carriers

16.1 Solid solution: A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two compartments crystallize together in a homogeneous one phase system, solid solutions are also called as molecular dispersion or mixed crystals. Because of reduction in particle size to molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersion. They are generally prepared by fusion method whereby physical mixture of solute and solvent are melted together followed by rapid solidification. Such systems, prepared by fusion are called as melts e.g. griseofulvin- succinic acid. The griseofulvin from such solid solution dissolve 6 to 7 times faster than pure griseofulvin.

Mechanism of solid solution for solubility enhancement is when the binary mixture exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles, and when the solid solution, which is said to be in a state of randomly arranged solute and solvent molecules in the crystal lattice, is exposed to the dissolution fluid, the soluble carrier dissolves rapidly leaving the insoluble drug stranded at almost molecular level.

16.2 Eutectic mixtures: When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in microcrystalline state which solubilizes rapidly. Eutectic mixture differs from solid solution in that the fused melt of solute-solvent show complete miscibility but negligible solid-solid solubility i.e. such system are basically intimately blended physical mixture of two crystalline components.

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state (Fig. 1).

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components.

When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

16.3 Solid dispersion: Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs. Solid dispersion is defined as the dispersion of one or more active ingredients in an inert excipient or matrix (carrier), where the active ingredients could exist in finely crystalline, solubilised or amorphous state.

Once the solid dispersion is exposed to aqueous media and the carrier dissolve, the drug is released as very fine to colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs are expected to be high.

The enhanced solubility and dissolution rate of drugs from solid dispersions is based on following mechanisms:

1) Reduction in particle size provides large surface area. 2) Particles with improved wettability and dispersibility of drug. 3) Particles with higher porosity. 4). Drugs in amorphous state. 5) Solubilizing effect on the drug by water soluble carrier. 6) Formation of metastable dispersion.

Various pharmaceutical approaches for the preparation of SDs, include co-precipitation, lyophilization, spray drying, melting solvent method, melt extrusion method, solvent evaporation, fusion and powder mixing methods.

Melting and solvent evaporation methods are the two major processes of preparing solid dispersions.

a. Melting method: The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melts. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

b. Solvent evaporation method: The solvent evaporation method consists of the dissolving the drug and polymeric carrier in a common solvent, such as ethanol, chloroform, or a mixture of ethanol, dichloromethane, which is evaporated until a clear, solvent free film is left. Normally, the resulting films are pulverized and milled.

In this method, the thermal decomposition of drugs or carrier can be prevented, since organic solvent evaporation occurs at low temperature. The use of organic solvents, the high preparation cost and the difficulties in completely removing the solvent are some of the disadvantages associated with solvent evaporation methods.

Carriers for solubility enhancement: Carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance solubilty and dissolution of drugs.

Various carriers are used for solubilty enhancement listed mentioned in the table 2.

CONCLUSION

The growing percentage of new chemical entities displaying solubility issues demands that technologies for enhancing drug solubility be developed to reduce the percentage of poorly soluble drug candidates eliminated from development as a result.

The delivery of poorly water-soluble drugs has been the subject of much research, as approximately 40% of new chemical entities are hydrophobic in nature and solubility of active pharmaceutical ingredients (API) has always been a concern for formulators.

Because of the solubility problem of many drugs the bioavailability gets affected and hence solubility enhancement becomes necessary. It is now possible to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above. Numerous technological advancements have been introduced for solubility and dissolution enhancement of poorly water soluble drugs.

Table-1: List of carriers used for solubility enhancement.

S.No.	Category	Examples of carrier
1.	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose.
2.	Acids	Citric acid, succinic acid.
3.	Polymeric materials	Povidone (PVP), polyethylene glycol (PEG), Hydroxypropyl methyl cellulose, methyl

		cellulose, hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, galactomannan.
4.	Hydrotrops	Urea, Nicotinamide, Sodium benzoate, Sodium salicylate, Sodium acetate, Sodium-o-hydroxy benzoate.
5.	Surfactants	Polyoxyethylene stearate, renex, poloxamer 188, texafor AIP, deoxycholic acid, tweens, spans.
6.	Insoluble or enteric Polymer	Hydroxy propyl methyl cellulose phthalate, Eudragit L100, Eudragit S100, Eudragit RL, Eudragit RS.
7.	Miscellaneous	Microcrystalline cellulose, Dicalcium phosphate, Silica gel, Sodium chloride, Skimmed milk.

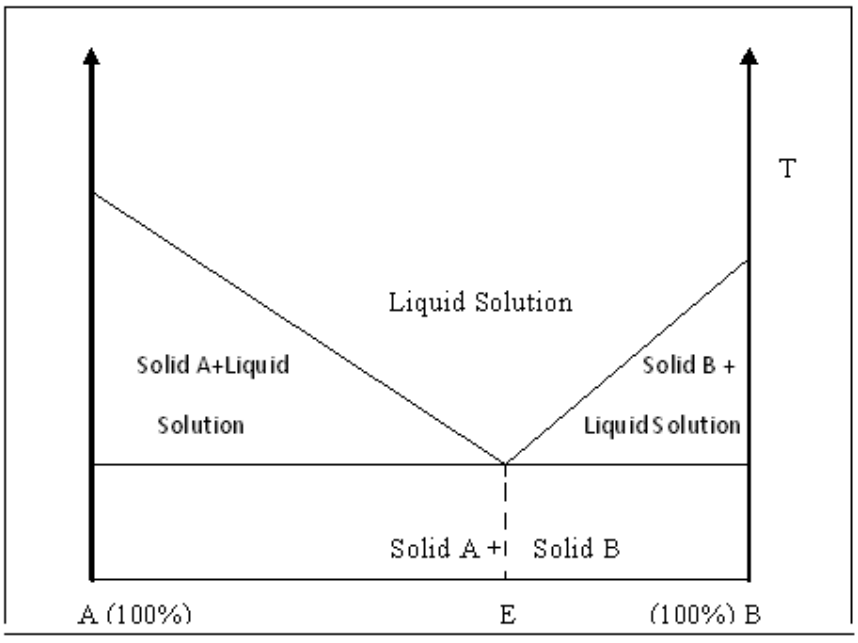

Figure-1: Phase diagram for a eutectic system.

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