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A Compressive Review on Solubility Enhancement Techniques

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Abstract

Solubility enhancement techniques aim to improve the dissolution and bioavailability of poorly water-soluble compounds. These methods encompass various approaches, including physical and chemical modifications, such as particle size reduction, amorphous solid dispersion, complexation, co-solvency, and lipid-based formulations. These techniques facilitate increased drug solubility and subsequent absorption, ultimately enhancing the therapeutic efficacy of pharmaceutical formulations. This review paper concludes various methods of solubility enhancement techniques used in pharmaceutical industries.

Keywords- Drug, Solubility, Size reduction.

Introduction [3, 10,15]

Solubility is the ability of one substance to dissolve in another substance under specified condition. The solubility is depending on the solvent used as well as temperature and pressure. Solubility equilibrium is important in pharmaceuticals. The word ′soluble ′comes from Latin word solvere meaning to dissolved. The substance which dissolves in liquid is called solute and the liquid in which it dissolves is solvent. The solvent used is generally liquid. Extensive use of solubility term in pharmaceutics leads to express it in various manner, when quantitative data is available. It is commonly expressed as concentration (g of solute per kg of solvent, g per dL (100ml) of solvent), molality, mole fraction or other similar terms of concentration.

Table No.1: Solubility Chart

Terms	Parts of solvent required per part of solute
Very soluble	Less than 1 part
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Insoluble	More than 10,000

Solubilization process

Step 1-The breaking of interionic or intermolecular bonds in solute.

Step 2- Creating a vacant place in solvent molecule for solute molecule.

Step 3-Entrapment of solute molecule in solvent.

Energetic of Solubility

The actual solubility of a substance shows various factors involved in transfer of solute from solid to solution phase. The force involved is interaction between solvent molecule and solute molecule or ions.

Work= W+ W-W

Where,

W- Work to separate solvent molecule.

W- Work to liberate solute particle.

W- Interaction between solute and solvent.

Solubility is property of solid, liquid or chemical substance. Solubility is measured after solute interest has sufficient contact time with the solvent. There are 2 types of solubility

1) Intrinsic solubility

2) Apparent solubility

Intrinsic solubility is defined as maximum concentration to which a solution can be prepared with specific solute and solvent. It is often derived from calculation and it is single numeric number- (0.5 micro gm/mL) and it is independent of environmental factors.

Apparent solubility is dependent on environmental factors such as pH and ionic strength which is obtained from experimental measurement.

Biopharmaceutics Classification System-

It was introduced by US Food and Drug Administration and it classify drug in 4 classes according to permeability and solubility.

Table No 2- Biological Classification of Drug

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

API′s that fall under a BCS Class II designation- They have low solubility and exhibit high tissue permeability means these drugs are ideal candidates for solubility enhancement.

BCS Class II- These have low solubility and low permeability and they require combination of solubility enhancement and permeation enhancement to achieve therapeutic effect.

Importance of solubility[11, 15, 8]

Solubility is the most important thing used in pharmaceutical industry. Oral route is the most common route which is used for administration of drug. This is due to less sterility restriction, cost effective and flexibility in design of dosage form. The major challenge in designing of oral dosage form is poor bioavailability. Bioavailability is the ability of drug or other substance to be absorbed by body. To avoid this condition many generic companies tend to produce bioequivalent oral drug product. If two product containing same active ingredient then it is considered as bioequivalent.

Solubility is also considered while preparing other dosage form like Parentral preparation. Solubility is important term to achieve desired concentration of drug in systemic circulation. Poor water soluble drug require high dose in order to reach therapeutic plasma concentration after oral drug administration. In development of new chemical entity low aqueous solubility is the most common problem associating it.

The improvement of drug solubility and their bioavailability remains one of the most challenging problem in pharmaceutical industry.

Factors affecting solubility [20, 22, 21, 7]

There are various factors which affects rate of solubility.

1. **Temperature**- The solubility of most solid solute is significantly affected by temperature. Solubility increases with rise in temperature and decrease with fall in the temperature.
2. **Nature of solute and solvent**- Solubility depend on both natures of solute as well as solvent.
3. **Molecular structure**- Each solute has specific molecular structure. Any change in molecular structure can affect rate of solubility.
4. **Complex formation**- The solubility of drug in particular solvent affected by presence of third substance which forms an intermolecular complex.
5. **Solubilizing agent**- Solubilizing agents such as surfactant show property of micelle formation. In aqueous solution the core of these micelle resembles lipophilic phase and organic solute may be taken by these micelles, showing an increase in apparent solubility. This phenomenon is called solubilization.

Solubility determination

The Flory-Huggins solution theory is a theoretical model for determining solubility of polymers. The Hansen solubility parameter and Hildebrand solubility parameter are empirical method to determine solubility of compound.

Solubility can also be determined by using physical constant such as enthalpy of fusion. The partition coefficient (Log P) is measure of differential solubility of compound in hydrophobic solvent (oils & fats) and a hydrophilic solvent (water). The logarithm of these two value can be determined in terms of hydrophilicity or hydrophobicity.

Solubility Enchantement Techniques

While designing a new drug solubility of that drug must be considered. In most of

cases water is used, but some organic component can′t go into aqueous solution. Strong ionized substance are readily free soluble in water. Also some of weakly acidic and weakly basic drugs have sufficient solubility at suitable pH range. Sometimes they are soluble but concentration of solute is very close to limit of solubility and such solute get precipitated on cooling or evaporating solvent.

The aim of enhancement technique is to improve bioavailability by increasing the drug solubility. In study of absorption of drug, solubility and permeability is important factor and these can be modified by enhancement techniques. Solubility enhancement techniques can be classified as Chemical modification & Physical modification of drug substance.

Techniques to overcome poor solubility **10,18,12,3,24,14,11,5,2**

I) Chemical modification

1. Salt formation
2. Co-crystallization
3. Co-solvency
4. Hydrotrophy
5. Use of novel solubilizer

II) Physical modification

1. Particle size reduction-
   a) Conventional method
   b) Micronization
   c) Nanosuspension-
   i) Précipitation technique
   ii) Media milling
   iii) High pressure homogenization
2. Modification of the crystal habit-
   a) Polymorphs
   b) Pseudopolymorphs
3. Complexation-
   a) Physical mixture
   b) Kneading method
   c) Co-precipitation method
4. Inclusion complex formation Based Techniques-
   a) Kneading method
   b) Lyophilization/ Freeze drying technique
   c) Microwave irradiation method
5. Solubilization by surfactant-
   a) Micro emulsion
   b) Self microemulsifyimg drug delivery system
6. Drug dispersion in carriers-
   a) Solid solution
   b) Solid dispersion-
   i) Fusion process
   ii) Solvent method
   iii) Fusion solvent method
   iv) Spray drying
   v) Lyophilization

I) Chemical modification

1) Salt formation-

Salt formation is most common and effective method of increasing solubility and dissolution rate of acidic and basic drugs. Most of times API cannot be formulated in pure form due to various issues of instability. So they are converted to solid forms like salt, co-crystal , solvates, hydrates and polymorphs. Each of those term have different physiochemical property and that will affect on it′s stability, bioavailability, purification and manufacturability of drug. In this technique API is converted to salt by coupling it with a counter ion and crystallization solvent. Salt formation is only possible in ionizable API′s.

Salt formation of poorly soluble drug (weak acid and base) is the property of drug to enhance it′s solubility. When a drug molecule get ionized its salt are formed. In the preparation of Parentral and other liquid formulation it is effective method. In solid dosage form also this method is used.

Examples- Aspirin, Theophylline, Barbiturates, Rosiglitazone maleate.

2) Co-crystallization-

The new approach available for enhancement of solubility is through application of co-crystal. Co-crystallization process alters the molecular arrangement. Co-crystal can be defined as 'Multicomponent crystal that is formed between two compounds that are solid under ambient conditions where at least one component is an acceptable ion or molecule.' Co- crystallization process overcome various problems like physical, chemical or physiological properties of API. An appropriate co-crystal should be selected using analytical technique and rational physiochemical studies that include the solubility and stability study of drug. The difference in solvates and co-crystals is only its physical state. If one of the component is liquid and other is solid then it is termed as solvates and if both components are in solid form then they are called as co-crystals.

Pharmaceutical co-crystals consist of 2 components-

1) API
2) Co-crystal formers

Different techniques for co-crystallization-

1) Solvent evaporation
2) Grinding
3) Slurry co-crystallization
4) Solvent drop grinding (modification of grinding)
5) High throughout co-crystallization
6) Hot melt extrusion
7) Sonocrystallisation method

Co-crystal characterization methods-

1) Solubility
2) Maximum wavelength
3) Stability
4) Bioavailability
5) Intrinsic dissolution
6) Melt (Hot stage microscopy)
7) Melting point
8) Scanning Calorimetry (DSC)
9) XRD
10) Vibrational spectroscopy

Examples- Flurbiprofen, Itraconazole, Carbamazepine.

These co-crystals are formed in research work.

3) Co-solvency

The solubility of poorly water soluble drug can be frequently increased by addition of water miscible solvent in which drug has good solubility known as co solvent. The co solvency term is used to increase the solubility of electrolytes and non-electrolytes in water. This can be achieved by adding a co solvent that is miscible with water and in which the substance is soluble. The co solvent work by modifying affinity of solvent for solute through a decrease in interfacial tension between solute and solvent or by changing dielectric constant. The expected dielectric constant values for solvent and co solvent should be in range of 25-80.

The drugs which are poor soluble they are either lipophilic or highly crystalline that have high solubility in solvent mixture when appropriated to use of co solvent. These cosolvents are mainly used in Parentral preparation due to less toxicity of many co- solvent and relatively greater ability to solubilized non-polar drugs.

Examples- Ethanol (for paracetamol), Isopropyl alcohol (betamethasone valetrate), Glycerine & propylene glycol (for co-trimazole), other examples- glycerin, polyethylene glycol, sorbitol, mannitol, etc.

4) Hydrotropy-

It is solubilization phenomenon where addition of large amount of second solute result in an increase in the aqueous solubility of existing solute. The mechanism involved in this process is like or cations that are themselves very soluble in water result in ′salting in ′of non-electrolytes called as ′**Hydrotropic Salt** ′a phenomenon is known as hydrotropism.

Examples-

1) Aromatic anions- Sodium benzoate, Sodium Salicylate, Sodium benzene sulphonate, Sodium benzene disulphonate.

2) Aromatic cations- Para aminobenzoic acid hydrochloride, Procaine hydrochloride.

3) Aliphatic and linear anionics- Sodium alkanoate

This hydrotropes also influence on surfactant aggregation leading to micelle formation, phase manifestation of Multicomponent system with reference to nanodispersion and conductance percolation clouding of surfactant and polymers.

5) Use of novel Solubilizer-

Using various solubilising materials solubility of poorly soluble drugs can be enhanced.

Examples- conventional solubilizer polysorbates, PEG 400 sepitrap, soluplus povacoat, dendrimers.

- PEG- PEG 400 is colorless and tasteless liquid at room temperature.It is readily soluble in water, ethanol, acetone and insoluble in paraffin and ether.
- Sepitrap- Sepitrap is available to solubilized drug substance because in less than 5 minutes 80% of solubilizer desorbed from it. It′s ratio of sepitrap and drug is 2:1 which is good for enhancing the dissolution rate and also at same time it does not affect tablet characteristics and can be used without any formulation constraint.
- Dendrimers- It acts as host for hydrophilic and hydrophobic drugs and these are known for their three dimensional, monodispersed, highly branched, macromolecular, nano- scopic architecture with number of reactive end group obtained by reiterative sequence of reaction. Dendrimers are static unimolecular micelles and their micellar structure remains stable at high concentration. This micelle like behaviour of dendrimers are useful to solubilise hydrophobic drugs. The solubility of hydrophobes can be enhanced due to hydrophobic interaction, hydrogen bonding between terminal functional group of dendrimers and hydrophobes.

Example- Polyamidoamine (PAMAM) dendrimer, Polypropyleneimine(PPI) dendrimer.

6) Nanotechnology-

In this technique the study and use of materials & structure at nanoscale level of 100 nanometer (nm) or less occurs. Now-a-days there are so many chemical entities are complexation involving weak interaction between hydrotropic agent like sodium benzoate, sodium acetate and poorly soluble drug Several salts with large anions

discovering and till research is continues. But this new chemical entities have low solubility and for that oral bioavailability enhancement by micronization is not sufficient because micronized product has low effective surface area for dissolution and next step taken was nanonisation. The methods of preparation such as milling,

high pressure homogenization, vaccum deposition and high temperature evaporation may be used.

II) Physical Modification-

1) Particle size reduction- Particle size reduction can be achieved by

a) Conventional method

b) Micronization

c) Nanosuspension

Solubility of drug depend on size of particle. If the particle size is small then ratio of surface area & volume increases. Larger the surface area greater will interaction with solvent and which leads to increase in solubility of drug. The bioavailability of poorly soluble drugs is related to particle size of drug. If surface area is increased by reducing particle size then it will improve dissolution properties & allows wider range of formulation approach & delivery techniques.

a) Conventional method-

The mechanism like cutting, compression, impact, attrition are involved in conventional method of particle size reduction. The conventional methods like comminution & spray drying dependent on mechanical stress to disaggregate active compound. This method of enhancing solubility is economic as well as effective. The mechanical forces natural to comminution like milling & grinding produce significant amount of physical stress upon drug leads to degradation. Thermal stress also produced during comminution and spray drying while processing thermo sensitive or unstable active agents. It is not possible to enhance solubility of drug by traditional technique up to desired level.

b) Micronization-

Micronization is also conventional method for particle size reduction. In this method high energy particle size reduction occur so it convert coarse particle into particles of less than 5µ in diameter. This technique help in uniform and narrow particle size distribution which is essential for developing uniform dosage form. When micronization occur surface area increases with decrease in particle size and solubility increases. The properties of drug like particle size, size distribution, shape, agglomeration behaviour are affected by the type of micronization technique used. Mechanical communition, spray drying are the most commonly used technique for production of micronized drug particle. According to Noyes-Whitney postulations the administration of drug in micron size is most convenient method to improve bioavailability of drug.

Techniques for Micronization-

a) Jet milling

b) Rotor stator colloids mills

c) Micro précipitation & Micro crystallization

d) Controlled crystallization

e) Spray freezing into liquid

c) Nanosuspension-

This technology is applicable to drugs that are insoluble in oil & water. A pharmaceutical nanosuspension is biphasic system consist of nanosized drug particle in aqueous vehicle, stabilized by surfactant for oral as well as topical use or Parentral & pulmonary administration. Various method for preparation of nanosuspension are precipitation technique, media milling, high pressure homogenization in water, high pressure homogenization in non-aqueous media.

i) Précipitation technique-

In precipitation technique drug is dissolved in solvent and after then added to Antisolvent to precipitate crystals. This is

simple method and equipments used in this method are of low cost. The challenge in this method is addition of growing drug crystal to avoid formation of micro particles.

Example- Nanosuspension of Danazol and Naproxen have been prepared by precipitation technique to improve dissolution rate and oral bioavailability.

But in this technique the drug needs to be soluble in at least one solvent and this solvent needs to miscible with Antisolvent is the only limitation of this method.

ii) Media milling-

In this technique nanosuspension are prepared by using high shear media mills. The milling chamber is charged with milling media, water, drug & stabilizer is rotated at very high shear rate under controlled temperature for several days(at least 2-7 days). The milling medium is composed of glass, zirconium oxide or highly cross linked polystyrene resin. As impactation of milling media with drug causes breaking of microparticulate drug to nanosized particle high energy shear forces are generated.

iii) High pressure homogenization-

To prepare nanosuspension of many poorly water soluble drugs this technique is used. In this technique the suspension of drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle is based on cavitation in the aqueous phase. To convert the drug microparticles into nanoparticles cavitation forces within particles are sufficient. We can increase dissolution rate, bioavailability of poorly soluble drugs by this technique.

Example- Spironolactone, budesonide.

2) Modification of crystal habit-

a) Polymorphs-

Polymorphism is ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drug are chemically identical but they exhibit different physiochemical properties including solubility, melting point, density. An amorphous form of drug is always more suited than crystalline form due to higher energy associated & increase in surface area. Order of dissolution is Amorphous > metastable polymorphs > stable polymorphs.

3) Complexation- It is association between two or more molecules to form a non-bonded entity with a well defined stoichometry. It is of 3 types-

a) Physical mixture

b) Kneading method

c) Co-precipitate method

a) Physical mixture- Using a mechanism of trituration in mortar a suitable polymer & drug are mixed together & passes through appropriate sieve to get desired particle size in final product. It is simple trituration method.

b) Kneading method- This method is based on soaking a suitable polymer with little amount of water or hydroalcoholic to convert it into paste. After that add the drug in above paste and kneaded for specified time. Then dry this mixture and passed through sieve.

c) Co-precipitate method-This is the simple method of solubility enhancement. In this method required amount of drug is added in solution of suitable polymer. Then kept this complex under agitation. The complex should be protected from light. The formed precipitate is separated by vaccum filtration and dry at room temperature to avoid loss of structure water from inclusion complex. This method is used in industry.

4) Inclusion complex-It is formed by insertion of non-polar molecule or non-polar region of one molecule (guest) into cavity of another molecule or group of molecule (host). The cavity of host must be large enough to accommodate the guest & small enough to eliminate water. Solid inclusion complexes are prepared by various method such as kneading method, co-precipitatoion, neutralization, co-grinding.

Example- Cyclodextrine

b) Lyophilization-

In this method solvent system from solution containing both drug & suitable polymer eliminated through a primary freezing.

Lyophilization process dependent on unique properties of water and it′s role as solvent, gas, diluents. It is an alternative to solvent evaporation. It involves mixing of drug and carrier in common solvent.

c) Microwave irradiation method-

It involves microwave irradiation reaction between drug and Complexing agent using microwave oven. The drug and a suitable polymer in definite molar ratio are dissolved in mixture of water & organic solvent in specified proportion in round bottom flask. The mixture is kept for 1-2 minutes at 600C in microwave oven. After reaction completes add sufficient amount of solvent in mixture to remove residual, uncomplexated drug. The precipitate is separated by Whatman filter paper and dry in vaccum oven at 400C for 48 hours.

5) Solubilization by surfactant-

Surfactants molecule have polar and non-polar region. Most of surfactant have hydrocarbon segment connected to polar region. The polar group is cationic, anionic, zwitterionic or non-ionic. The addition of surfactant decreases the surface tension and increases the solubility of drug by increasing dissolution of lipophilic drug in aqueous medium. To stabilize the drug suspension surfactants are also used.

The formation of micelle occur when concentration of surfactant more than critical micelle concentration (CMC), which is in the range of 0.05-0.10% for most surfactant. This method entrap the drug within the micelle and is known as micellization & this result in elevated solubility of the drug.

It is of 2 types-

a) Microemulsion

b) Self-emulsifying drug delivery system

a) Microemulsion- A microemulsion is optically clear preconcentrate, isotropic, thermo dynamically stable transparent & translucent system which contain mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poorly water soluble drug. When the contact of this microemulsion occur with water the formulation self emulsifies and forms a very clear emulsion of small and uniform oil droplet containing solubilised poorly water soluble drug. This method is widely used for the poorly water soluble drug along with incorporation of proteins for oral and parentral route. Microemulsion can also enhances the oral bioavailability by reducing droplet size (<100nm) and so increases rate of absorption by surfactant induced permeability changes. This method is widely used due to incorporation of wide range of drugs of varying solubility.

b) Self-emulsifying drug delivery system

This method involve the in situ formation of emulsion in GIT (gastrointestinal tract). The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvent and co-solvent forms a transparent isotropic solution that is known as the self emulsifying drug delivery system (SEDDS)

and self micro emulsifying drug delivery system (SMEDDS). This both SEDDS & SMEDDS are isotropic solution of oil & surfactant which forms oil-in-water microemulsion on mild agitating with presence of water. In oral administration these colloidal formulation behave as oil-in-water micro emulsions.

6) Drug dispersion in carriers-

In this technique a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix which increases dissolution of the drug.

It is of two types-

a) Solid solution

b) Solid dispersion

a) Solid solution-

Solid solution is the mixture of two crystalline solid that exists into as new crystalline solid. Due to two components of crystals get crystallizes together in a homogeneous one phase system, a mixed crystal is formed. In solid solution form, the drug could be partially or completely soluble in the dispersing matrix.

b) Solid dispersion-

Solid dispersion technique can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing). Eutetic dispersion are homogeneous dispersions of crystalline or amorphous drugs in crystalline or amorphous carriers. This ′Solid Dispersion ′technique was invented by Sekiguchi and Obi. They proposed that generation and dissolution performance of eutectic melts of sulphonamide drug and a water soluble carrier in early 1960s. It is one of the useful technique in pharmaceutics for increasing dissolution, absorption & therapeutic efficacy of drug in dosage form. Solid dispersion consist of two components which are hydrophilic matrix and a hydrophobic drug. This is useful for the hydrophobic drugs to enhance it′s solubility in water.

Hydrophilic carriers.

Example- 1. Polyvinylpyrrolidone (Povidone, PVP)

2. Polyethylene glycols (PEGs)

3. Tween-80 (surfactant)

4. Sodium lauryl sulphate (surfactant)

The solubility of the drugs like celecoxib, halofantrine can be enhanced by solid dispersion using celecoxib with povidone (PVP) as a suitable hydrophilic carrier.

It is of 5 types-

a) Fusion process

b) Solvent method

c) Fusion-solvent method

d) Spray Drying

e) Lyophilization

f) Hot melt extrusion

g) Dropping method

a) Fusion process-

In this method a carrier is heated to a temperature just above it′s melting point and drug is incorporated into matrix, the melted mixture is then cooled and solidified rapidly in ice bath with rigorous stirring. The final solid mass is then crushed, pulverised & sieved which can be compressed into tablet with help of tableting agents. This method was proposed by Sekiguchi and Obi for preparation of fast release solid dispersion dosage form. This a very useful technique due to it′s simplicity as well as economical.

b) Solvent method

In this method the carrier and active ingredient are dissolved in suitable organic solvent. This solvent is evaporated at an elevated temperature or under vaccum. As solvent is being removed, supersaturation occurs which causes simultaneously precipitation of constituents resulting in

solid residue. The methods like Differential Thermal Analysis (DTA), Differential Scanning Calorimetry (DSC) are highly sensitive techniques used for demonstrate complete removal of solvent.

c) Fusion- Solvent Method

In this technique carriers are melted and drug is incorporated in the form of solution. If the carrier is capable of holding a certain proportion of liquid yet maintain it′s solid properties and if liquid is innocuous the need for removal of solvent is eliminated. This method is used for drugs having high melting point and for thermolabile drug.

d) Spray Drying-

In this method carrier and active ingredient are dissolved, suspended in suitable solvent. This solvent is evaporated by drying it by using steam of heated air to remove the solvent present in solution. Due to availability of large surface area of droplet, the solvent gets readily evaporated and solid dispersion forms quickly.

e) Lyophilization-

It is also called as Spray Freeze Drying. In this method solid dispersions are prepared under ambient temperature and avoiding heating during preparation of thermo sensitive drug. It involves atomization of a feed liquid containing poorly water soluble or insoluble API′s and excipients into cryogenic liquid at ambient temperature to produce micronized powder and that can be subsequently dried.

f) Hot melt extrusion-

This method is generally used in polymer industry. A melt extrusion consist of

1. An opening to feed raw materials
2. A heated barrel that consist of extruder screws to convey and mix the feed
3. Exit portion consist of optional die to shape extruding mass

In this method the active ingredient and carrier are fed into heated barrel of extruder at a constant rate. When mixture of active ingredient and carrier is conveyed through heated screw it is transformed as fluid like state. This state initiates homogeneous mixing by the high shear of extruder screws. After when the mixture is comes to exit portion the shapes is given to melt by optical die in required form like pellets, films or powder. A mixture is subjected to elevated temperature for 1min which enables the drug that are thermo labile to be processed.

g) Dropping method

In this method a solid dispersion of melted drug-carrier mixture is pipette then dropped into plate, where it gets solidified. The size, shape of the particle can be influenced by many factors such as viscosity of melt & size of pipette. It is important to adjust the temperature because viscosity is highly temperature dependent so that when the melt is dropped on plate it solidified to spherical shape.

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