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Review Article

REVIEW ARTICLE: SOLUBILITY ENHANCEMENT BY SOLID DISPERSION

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ABSTRACT

The solubility behavior of drug remains one of the most challenging aspects in formulation development. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. Solid dispersion of poorly-water soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. Solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS class II drugs. The focus of this review article on the method of preparation, carrier and solvent use, characterization, advantages, disadvantages, limitations and the application of the solid dispersion.

KEY WORDS: Solid dispersion, Solubility, Carrier, Particle size reduction, Dissolution enhancement, Bioavailability.

INTRODUCTION

Oral drug delivery is by far the most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation, etc. However, in case of the oral route there are several challenges such as limited drug absorption resulting in poor bioavailability and poor pharmacological response resulting into inadequate and erratic oral absorption. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation.[1] Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Therefore, pharmaceutical researchers, focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs.[2] Most of the new chemical entities (NCE's) which are developed or in developing stage fails the phase studies due to their limited solubility and permeation in the biological matrix. These limitations can be overcome by employing the techniques to improve the solubility and permeability which helps in reduction of toxic or adverse effects when they are administered in high doses to produce the pharmacological action and also improves the safety and efficacy of drugs. The solubility of the drug molecules can be enhanced by employing the techniques which mainly act by imparting or inducing the modifications in their physicochemical properties of the drug substance. Various methods which includes reduction in particle size (micronization, nanonization), complexation (inclusion complexes by using cyclodextrins), solid state modification (polymorphs, pseudo polymorphs), salt formation, prodrugs and by alteration of pH in the drug microenvironment.[3]

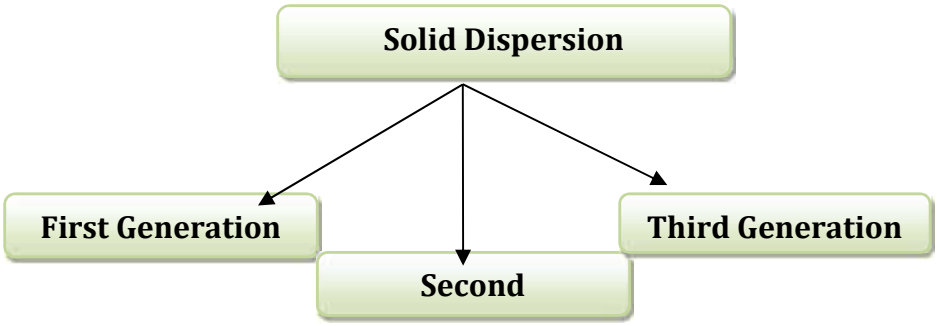
Solubility criteria as per USP and BP

Term	Part of solvent required for one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble or insoluble	>10,000

SOLID DISPERSION

There are various techniques for solubility enhancement. Solid dispersion is one of the best approaches for solubility enhancement. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous; basically amorphous is having good solubility than crystalline substance because no energy is required to break up the crystal lattice of a drug during dissolution process. Drug solubility and wettability may be increased by surrounding hydrophilic carriers. [4]

CLASSIFICATION OF SOLID DISPERSIONS



According to polymers which are used in the dispersion they are as follows-

First generation solid dispersion - These solid dispersions are prepared by using crystalline carriers. Urea and sugars were the first crystalline carriers that were used in the preparation of solid dispersions. These have a disadvantage of being thermodynamically unstable and they do not release drug at a faster rate.

Second generation solid dispersion – These solid dispersions are prepared using amorphous carriers instead of crystalline carriers. The drug is molecularly dispersed in the polymeric carrier. The polymeric carriers are divided into two groups:

- Synthetic polymer – Povidone, polyethylene glycols and polymethacrylates.
- Natural polymers – Hydroxy propyl methyl cellulose, ethyl cellulose, starch derivatives like cyclodextrin.

Third generation solid dispersion – These solid dispersions contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These achieve the highest degree of bioavailability for the drugs that are having poor solubility. The surfactants being used in the third-generation solid dispersion are such as insulin, poloxamer 407 etc. [5]

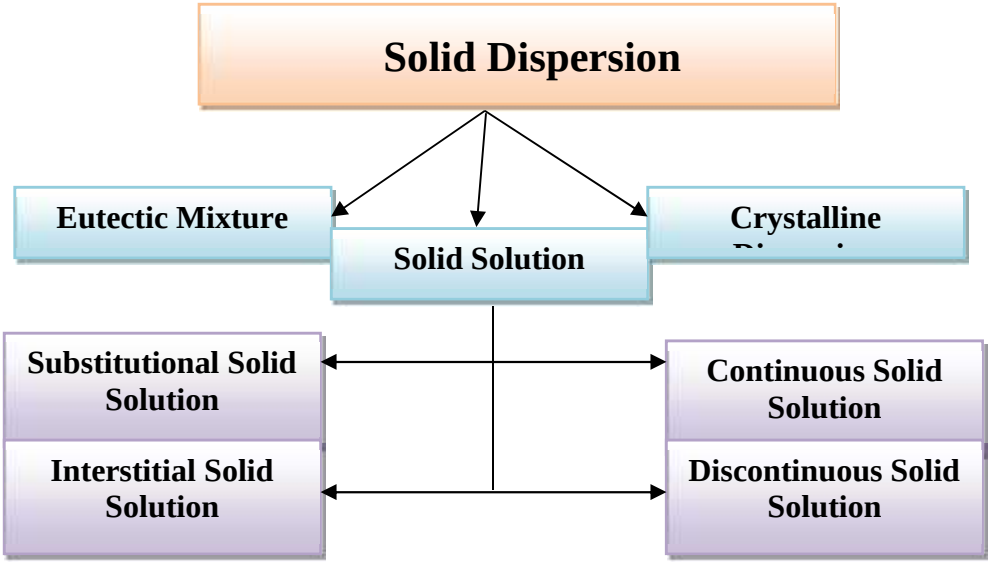
Sr. No.	Solid dispersion type	Matrix *	Drug **	Remarks	No. of phases
I	Eutectics	C	C	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
III	Solid solution Continuous solid solution	C	M	Miscible at all composition, never prepared	1
	Discontinuous solid solution	C	M	Partially miscible	2
	Substitutional solid solution	C	M	Molecular diameter of drug differs less than 15% of matrix diameter	1 or 2
	Interstitial solid solution	C	M	Drug molecular diameter less than 59% of matrix diameter	2
IV	Glass suspension	A	C	Particles size dependent on cooling/evaporation rate	2
V	Glass suspension	A	A	Particles size dependent on cooling/evaporation rate, many solid dispersions are of this type	2
VI	Glass solution	A	M	Requires miscibility or solid solubility	1

Based on their molecular arrangement, six different types of solid dispersions can be distinguished as shown in **TABLE**

*A: matrix in the amorphous state, C: matrix in the crystalline state

: **A: drug dispersed as amorphous clusters in the matrix, **C**: drug dispersed as crystalline particles in the matrix, **M**: drug molecularly dispersed throughout the matrix

TYPES OF SOLID DISPERSIONS



Eutectic Mixture

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. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution. [6]

- **Amorphous precipitation in a crystalline carrier**

Instead of forming a eutectic mixture in which both drug and carrier crystallize simultaneously from a melting or solvent method of preparation, the drug may also precipitates out in an amorphous form in the crystalline carrier. Since the amorphous form is the highest energy form of pure drug, it should under almost all

conditions, produce faster dissolution and absorption rate than the crystalline form. It is postulated that the drug with a high super cooling properties has more tendency to solidify as an amorphous form in the presence of a carrier. [7]

- **Solid solutions**

A solid solution, compared to the liquid solution made up of a solid solute dissolved in a solid solvent. It is often called a mixed crystal because the two components crystallize together in a homogenous one phase system. Solid solution of poorly soluble drug in rapidly soluble carrier achieve a faster dissolution rate than a eutectic mixture because the particle size of drug in solid solution is reduced to a minimum state, in other word dissolution of drug takes place in solid state prior to its exposure to liquid medium. Solid solution generally classified according to the extent of miscibility between the two components or the crystalline nature of solid solution. [8]

Depending on the miscibility, the two types of solid solutions are:

- Continuous solid solutions - In continuous solid solutions, the components are miscible in all proportions i.e. the bonding strength between the components is stronger than the bonding between the individual component.
- Discontinuous solid solutions - In discontinuous solid solutions, the solubility of each of the component in the other component is limited in nature.
- Depending on the distribution of the solvates in the solvendum, solid solutions can be of two types:
- Substitutional crystalline solution- These are those solid solutions which have a crystalline structure, the solute molecules substitute for the solvent molecules in the crystal lattice.
- Interstitial crystalline solid solution – These are those solid solutions in which the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. [9]

Glass solutions and Glass suspension

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature. [10]

SELECTION OF A CARRIER

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

- Freely water-soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.
- Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
- Able to preferably increase the aqueous solubility of the drug.
- Chemically compatible with the drug and not form a strongly bonded complex with the drug. [11]

SELECTION OF SOLVENTS

Solvent to be included for the formulation of solid dispersion should have the following criteria:

- Both drug and carrier must be dissolved.
- Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
- Ethanol can be used as alternative as it is less toxic.
- Water based systems are preferred.
- Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration. [12]

METHODS OF SOLID DISPERSION

1. Melting method
2. Solvent method
3. Melting solvent method (melt evaporation)

4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomeration Process
7. Electrospinning
8. Super Critical Fluid (SCF) technology
9. Inclusion complexes

1. **Melting method:** In melting or fusion method a physical mixture of the drug and a water soluble carrier is prepared, by heating it directly until it melts. The final solid mass that is obtained is crushed, pulverized and sieved. However substances either the drug or the carrier may decompose due to high temperature during the melting process. A method to overcome this problem could be heating the mixture in a sealed container or under vacuum or in the presence of inert gases like nitrogen. The advantage is its simplicity and economical nature.
2. **Solvent method:** this method is also known as solvent evaporation method in which physical mixture of the drug and the carrier is dissolved in common solvent and is evaporated until a clear solvent free film is obtained. The main advantage is that the thermal decomposition of the drug or the carrier can be prevented because the organic solvents require a low temp for evaporation. The disadvantage in this method is difficulty in removing the solvent and higher cost of preparation.
3. **Melting solvent method:** This method involves dissolving the drug in an appropriate liquid solvent and then incorporating the solution formed directly into the melt of polyethylene glycol which is evaporated until a clear solvent free film is obtained. This technique is a combination of fusion and solvent evaporation method.
4. **Melt extrusion method:** using twin screw extruder, the drug/carrier mix is simultaneously melted homogenized and extruded and shaped in different forms such as tablets, granules, pallets, powder etc. The method is applicable for thermo labile drugs as the mixture of the drug and carrier is subjected to elevated temperature for about 1 min.
5. **Lyophilization:** It is a phenomenon of transfer of heat and mass from and to the product. It is an alternative technique to solvent evaporation in which molecular mixture technique is used where the drug and carrier is dissolved in common solvent, frozen and sublimed.
6. **Melt Agglomeration technique:** In this technique binder is use as carrier. There are two method of preparation of solid dispersing, first is by spraying the drug on melted binder plus exipients and other one is melting of binder drug and exipient above the melting temperature of binder used. For using high binder content rotary process might be preferable for controlling temperature. This technique is advantageous in homogenous mixing of drug but larger particle size cause densification and fines cause adhesion of mass.
7. **Electrosipinnig method:** In this technique electric force is used to withdraw a nano size fibre thread from the polymer sol/polymer melt. This a combination of solid dispersion with nanotechnology use in polymer industry. Stream of Polymer solution /melt is subjected to electric force (5 to 30kv) which cause body of the liquid becomes charged, and electrostatic repulsion counteracts the surface tension. This made a strong cohesive force between the particle and droplets of polymer and a stream of fiber is formed. Then thinning and stretching of fiber to nano diameter is done by using whipping process called electrostatic repulsion lead to formation of uniform fiber in nano diameter. This process all depend on rate of feeding surface tension and electric force used.
8. **Supercritical fluid technology:** SCF is a substance above its critical temperature and pressure. Critical point represents the highest temperature and pressure at which the substance exists as vapor and liquid in equilibrium. In this technique SCF is used to form solid dispersion of insoluble material/polymer with drug cause increase in dissolution property. It is superior over conventional technique(spray drying, hot melt etc.), in this technique SCF carbon dioxide is mainly used which cause very rapid precipitation of solid mixture giving no time for separation of drug and polymer in preparation of solid dispersion. It form very stable small particle with higher surface area for good flow and low organic solvent residual. In recent Solid dispersion of carbamazepine with PEG-4000 are made using SCF carbon dioxide in precipitation vessel.

Resulting in formation of carbamazepine with increase rate and extent of dissolution with low solvent residual.

9. Inclusion complexes

1. **Kneading technique-** Mix drug and polymer with the small amount of the solvent i.e. water to form a thick paste by kneading and hence it is dried at 450C in an oven. Pass the mass through the sieve no. 30 and store in the desiccator.
2. **Co-precipitation -** Add required amount of drug to the solution of β- cyclodextrins. Keep the system under magnetic agitation with controlled process parameters and protect from the light. Separate the formed precipitate by vacuum filtration and then dry at room temperature in order to avoid the loss of the structure water from the inclusion complex.
3. **Neutralization-** Add drug in alkaline solution like sodium hydroxide, ammonium hydroxide. Then add a solution of β- Cyclodextrin to dissolve the join drug. The clear solution is obtained after few seconds under agitation. Then neutralize it using HCl solution until the equivalence point is reached. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. Finally filter and dry the precipitate.
4. **Co-grinding-** Weigh the calculated amounts of drug and carriers and mix together with one ml of water. Pass the damp mass obtained, through a 44-mesh sieve; disperse the resultant granules in Petri dishes and dried at 60°C under vacuum, until a constant weight is obtained. Store the granules in desiccators until used for further studies.
5. **Spray-drying method-** Dissolve drug in suitable solvent and the required stoichiometric amount of carrier material like β-Cyclodextrin in water. Mix the solutions by sonication or other suitable method to produce a clear solution. Dry it using spray dryer. [12-17]

CHARACTERISATION OF SOLID DISPERSIONS

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion

Thermal Analysis Techniques: Thermal analysis comprises a group of techniques in which a physical property of a substance is measured as a function of temperature, while the substance is subjected to a controlled temperature programme. In deferential thermal analysis, the temperature difference that develops between a sample and an inert reference material is measured, when both are subjected to identical heat. [18]

Powder X-Ray Diffraction

Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi-quantitative. [19]

Infrared Spectroscopy (IR)

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material. [20]

Microscopic Method:

Microscopy has been used quite often to study the polymorphism 70 and morphology of solid dispersions 50, 71-75.The fine particles of crystallization in the glassy polyvinyl pyrrolidone matrix can be readily detected by the polarizing microscope. The high resolution of an electron microscope was used to study the dispersed particle size of ionic acid in polyvinyl pyrrolidone. The application of the electron microscope technique is, however, usually limited to chemicals with high atomic numbers. [21]

Scanning Electron Microscopy: The morphology of the spray-dried ternary solid dispersions can be characterized with a Philips XL30 ESEM FEG environmental scanning electron microscope carbon tape that was mounted on conventional SEM stubs. [18]

Differential Scanning Calorimetriy (DSC)

Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetriy (DSC). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is

detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material. [20]

In Vitro Dissolution Studies

In vitro dissolution studies are done for the find out dissolution behavior. The in-vitro dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through in vitro –In vivo correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed in-vivo dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. [22]

ADVANTAGES OF SOLID DISPERSION

Solid dispersions are promising drug delivery forms which offer the possibility to disperse a hydrophobic drug in a hydrophilic matrix and thereby improve the dissolution behavior and the bioavailability of the drug. Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.

Particles with reduced particle size

Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium. Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area isformed, resulting in an increased dissolution rate and consequently, improved bioavailability.

Particles with improved wettability

The solubility enhancement of the drug is related to the drug wettability improvement verified in solid dispersion. A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as bile salts, when used, can significantly increase the wettability properties of drugs. Recently, the inclusion of surfactants in the third generation solid dispersions reinforced the importance of this property.

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process.

- To enhance the absorption of drug.

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.
- To dispense liquid or gaseous compounds.
- To formulate a fast release priming dose in a sustained release dosage form.
- To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.
- To reduce side effects (a) the binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex, (b) the damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound.
- To mask unpleasant taste and smell. The very unpleasant taste of antidepressant famoxetine hindered the development of oral liquid formulations. The bitter taste was greatly suppressed when the solid complex of famoxetine was formulated as aqueous suspension. [23]

DISADVANTAGES OF SOLID DISPERSIONS

- Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a Meta stable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate.
- Drawback of solid dispersions is their poor scale-up for the purposes of manufacturing. [24]

LIMITATIONS OF SOLID DISPERSIONS

Although a great research interest in solid dispersion in the past four decades, the commercial utilization is very limited.

Problems of solid dispersion involve

- The physical and chemical stability of drugs and vehicles
- Method of preparation
- Reproducibility of its physicochemical properties
- Formulation of solid dispersion into dosage forms
- Scale-up of manufacturing processes. [25]

PHARMACEUTICAL APPLICATIONS OF SOLID DISPERSION

The pharmaceutical applications of solid dispersion techniques include:

- To increase the solubility of poorly soluble drugs thereby enhance the dissolution rate, absorption and bioavailability.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.
- To dispense liquid or gaseous compounds
- To formulate a fast release priming dose in a sustained release dosage form;
- To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier;
- To reduce side effects-(a) the binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex, (b) the damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound;
- To mask unpleasant taste and smell and avoid undesirable incompatibilities.
- To convert liquid compounds into formulations. Liquid drugs can be manufactured as solid drug formulations such as powders, capsules or tablets e.g., unsaturated fatty acids, essential oils, nitroglycerin, benzaldehyde, prostaglandin, clofibrate etc. [1]

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