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REVIEW ON SPRAY DRIED SOLID DISPERSION

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Abstract:

The drug solubility is the most challenging aspect for the formulation development. The poorly soluble drug has poor dissolution and absorption of drug. The low aqueous solubility of drug is required to formulate the drug into more soluble and hence bioavailable drug product. The different technique is being used to enhance the solubility of poorly water soluble drugs. Spray dried solid dispersion of drug is one of the most widely used technology to enhance the solubility of the poorly water soluble drug. For the manufacturing of solid dispersion Spray drying is efficient technology. It converts the liquid drug solution to solid powder form by rapid evaporation of solvent. This method has a contribution to form amorphous solid dispersion.

The formulation parameters such as feed concentration and solvent type and process parameters such as drying gas flow rate or solution spray rate that influence the final physical structure of the solid dispersion particles.

Key words: *Solid dispersion, carriers, spray drying, solubility.*

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INTRODUCTION:

Many recently developed pharmaceutical drug has a low aqueous solubility due to low solubility drug has poor bioavailability and therapeutic effect. This situation provides the opportunities to pharmaceutical scientist pharmaceutical companies to advance multiple methods to solubilize the molecules. [1] Most important parameter is solubility to get a desired concentration of drug in systemic circulation for therapeutic response. The solubility is defined as the maximum quantity of solute that can dissolve in a specific quantity of solvent at specified temperature. It is also define as the ability of one solid substance to form a solution with another liquid substance. The solid substance to be dissolved is called as solute and the other dissolving liquid fluid in which the solute dissolve is called as solvent, which together form a solution. [2] Oral route is most common route for drug delivery. Absorption of drug from the gastrointestinal tract is limited by different factors. Major factor is poor aqueous solubility and low permeability of the drug. Drug is administered by oral route first it dissolve in gastric or intestinal fluids and permeable through the GIT membranes before to reach systemic circulation. Hence, two areas are available to pharmaceutical research that improving the oral bioavailability of active agents including enhancing of solubility and dissolution rate of poorly aqueous soluble drugs. The BCS is a scientific system for classifying a drug substance based on its aqueous solubility and permeability of drug.[3] Many methods are available for the enhancement of solubility. Spray Dried solid dispersion is the one of most convenient technique for the enhancement of the drug solubility. Spray dried solid dispersions (SDs) widely studied recently as an option to improve dissolution rate and in turn bioavailability of poorly water-soluble drugs particularly BCS class II dugs.[4] Spray drying is a unit process have a ability to transforming solutions or suspensions into a solid product.[5] Many poorly water soluble drug solubility is improved spray dried solid dispersion technology. Bhaskar Chauhan et al. (2005) was studied solid dispersions of poorly water-soluble drug etoricoxib using lipid carriers such as Gelucire 50/13 and Compritol 888 ATO by spray drying for the improve the dissolution rate.[6] E. M. Holman et.al(1984) was spray-dried Hydroflumethiazide with polyvinylpyrrolidone to increase the solubility.[7] Makoto Otsuka et.al.(1993) was prepaired Spray-dried solid dispersions of furosemide-Eudragit RS100 and RL100 were studied to determine their stability and dissolution characteristics. Solid dispersions of curcumin in different ratios with PVP were prepared by spray drying. [8] Anshuman A.et.al. (2004) was studied spray dried solid dispersion of curcumin with different ratios of PVP were prepared to increase the solubility and bioavailability. [9] Ke Wu et. al.(2008) studied and prepared spray dried solid dispersion the low aqueous soluble piroxicam with polyvinylpyrrolidone (PVP) were prepared by precipitation with compressed antisolvent (PCA) and spray drying techniques for enhance the solubility and bioavilability.[10] Ilse Weuts et.al.(2005) was prepared Solid dispersions of loperamide a poorly water-soluble agent with polyethyleneglycol 600 were prepared by spray drying to increase the solubility and dissolution.[11] Hirofumi Takeuchi et.al.(2004) Solid dispersion particles of tolbutamide spray dried with nonporous (Aerosil 200 (hydrophilic), Aerosil R972 (hydrophobic)) or porous (Sylysia 350 (hydrophilic), Sylophobic 200 (hydrophobic)) silica as a carrier and applying the spray-drying method.[12] Eun-Sol Ha (1014) was studied to investigate the effect of Soluplus® on the solubility of atorvastatin calcium and develop a solid dispersionby spray drying to improve the oral bioavailability of atorvastatin calcium.[13]Nirmal Marasinia et.al (2013) telmisartan was spray dried with dpolyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC) and sodium carboxymethyl cellulose (Na CMC).[14] Sahilhusen I Jethara et al studied the spray dried solid dispersion improvement in aqueous solubility of aceclofenac with different ratios using HPMC K-15M, PVP-K30 and Eudragit RS-100 at optimized condition. [15] S.Rajarajan et al.(2009) was spray dried itraconazole with Hydroxypropyl Methylcellulose, Polyethyleneglycol 6000 for incrsease the solubility.[16]

Methods for solubility enhancement: [17]

Physical Modifications

a) Particle size reduction
- ✓ Micronization
- ✓ Nanosuspension,

b) Modification of the crystal habit
- ✓ Polymorphs,
- ✓ Amorphous form
- ✓ Cocrystallization,

c)Drug dispersion in
- ✓ Eutectic mixtures,
- ✓ Solid dispersions,
- ✓ Solid solutions

d)Cryogenic techniques.

Chemical Modifications.
- a) Change of pH,
- b) Use of buffer,
- c) Derivatization,
- d) Complexation,
- e) Salt formation.

Miscellaneous Methods.

a) Supercritical fluid process,

b) Use ofadjuvant like surfactant, solubilizers, cosolvency, hydrotrophy,
and novel excipients.

Solid dispersion:

The concept of solid dispersions was originally proposed by Sekiguchi and Obi.[17] Solid dispersion is a term defined as the dispersion of one or more active ingredients in an inert polymer or polymer matrix or in a carrier, where the active ingredients exist in finely crystalline, solubilised or amorphous form. [18] The solid dispersion consists containing at least two different components, such as a water soluble polymer matrix and a water insoluble drug. The matrix may be either crystalline or amorphous form. The drug can be dispersed in amorphous particles or in crystalline particles molecularly. [19] Molecularly dispersing a poorly water-soluble drug in a hydrophilic carrier leads to increased dissolution and supersaturation of the drug when this system is contact with the water. This is improves a number of factors such as increased wettability of the drug by the polymer, reduces particle size of the drug, separation of individual drug particles by polymer particles, and prevent the drug precipitation in contact with aqueous media.[20]

First generation solid dispersion:

The first generation solid dispersions prepare using crystalline carriers like urea,
mannitol. Eutectic mixtures are binary systems containing poorly water soluble drug and high water soluble carrier and at eutectic point. Only in the specific composition drug crystallizing out simultaneously. When in aqueous medium eutectic mixture is dissolved, the carrier part will dissolve quickly and in the form of fine crystals drug will be released. [21]

Second generation solid dispersion:

Second generation solid dispersions containing amorphous carriers instead of crystalline. The most common solid dispersions use amorphous carriers. The drugs are molecularly dispersed in amorphous carrier they are usually called polymers. polymers like fully synthetic polymers such as povidone (PVP) polyethyleneglycols (PEG) and polymethacrylates and Natural polymers are cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), ethylcellulose hydroxypropylcellulose and starch derivates, like cyclodextrins.[22]

Third generation solid dispersion:

In third generation solid dispersion the surface active self emulsifying carriers are use.the carriers are Poloxamer 407, tween 80, gelucire 44/14, compritol 888 ATO +/- polymer. [23]

Methods of preparation of solid dispersion:

1) Melting method

In this method melting of a physical mixture of carrier and drug convert into the liquid state cool until solidification. Disadvantage of this method is not useful for thermolabile drugs and thus incomplete miscibility is observed between the molten carrier and solid drug.[24]

2) Solvent method:

In this method, the polymer and drug mixture dissolved in a common solvent, which is until a clear, solvent free film is left evaporated. The film is further dried. The main
benefits of this method is thermal decomposition of API or polymers can be prevented because of organic solvent required relatively low temperature.[25]

3) Hot-Melt Extrusion:

Hot melt exstrusion is defined as the process of formation a new material under controlled condition such as temperature, mixing, feed-rate and pressure by forcing it through an orifice or die. It is different from simple extrusion; in this process polymer, drug and excipients blends are mixed in the molten state, solvents not for granulation. The molten polymer use as the thermal binder. [26]

4) Spray drying:

In this type of preparation, the carrier and the drug are suspend or dissolved in a common solvent. In this technique by applying hot air solvent is evaporated. It is fast and quick method because of due to the large surface area of the droplets, the solvent fast evaporates and solid dispersion is formed fast. [27] Spray drying technique is a particle processing technology that liquid feed convert into a powder by spraying the feed to form a droplets, and then evaporating the liquid feed by using a heated drying medium commonly air. The liquid feed may be in the form of a solution, suspension, or emulsion; it should be easily pumpable and capable to droplet formation. [28] The spray drying process works on principle the removal of solvent by heat, the continuous spraying of drug and carrier matrix mixture into the hot drying chamber gives the dried particles. [29]Spray drying is a faster, time- saving technique for obtaining even the smallest quantities of sample in powder form. For particle formation and drying Spray drying is the most widely used industrial process. Spray drying is suitable method to continuous production of dry
solids in powder, granulate or agglomerate particle form of liquid feed stock. This technique the ideal end product properties complies with quality standards that are particle size distribution, residual moisture content, bulk density and particle morphology must comply with precise quality standards.[30]

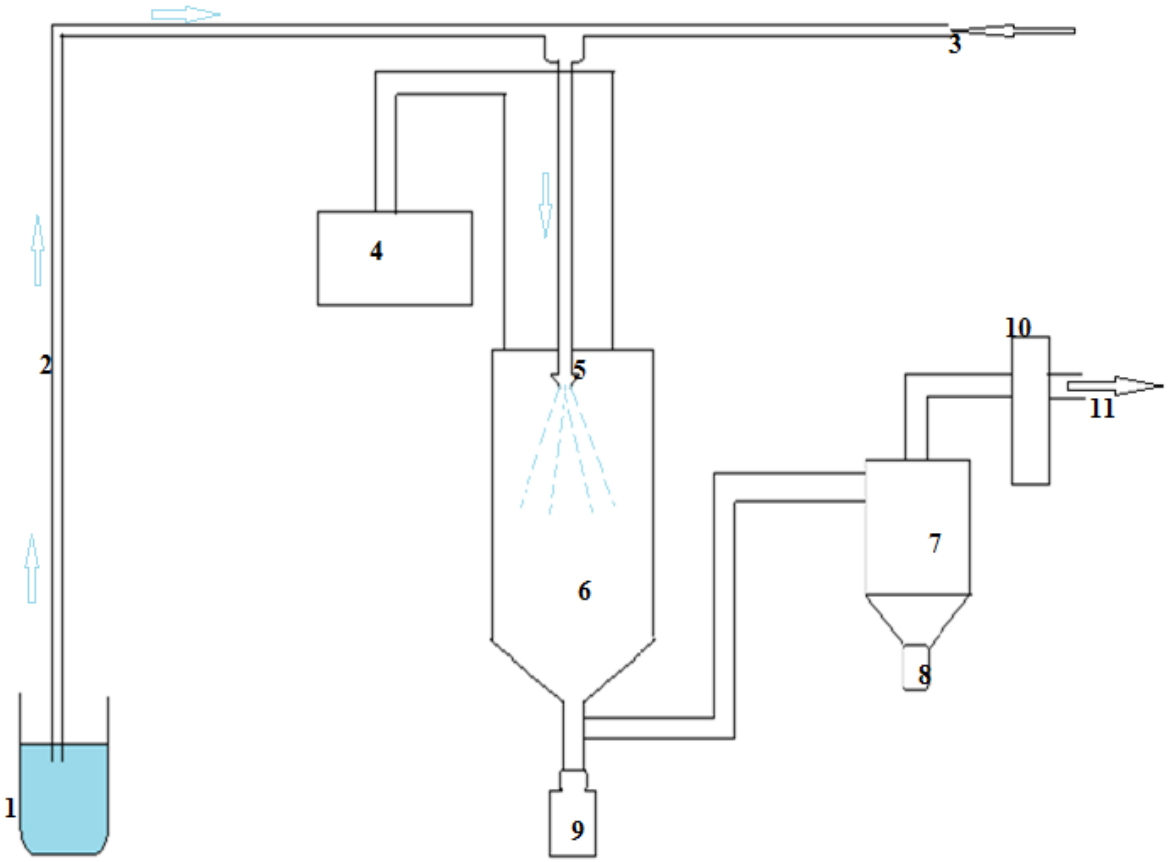

Fig.No.1:Schematic diagram of Spray Dryer.

1. Feed
2. Feed flow
3. Nozzle gas flow
4. Heater
5. Fluid nozzle
6. Drying chamber
7. Cyclone
8. Waste material
9. Collecting vessel
10. Exhaust air
11. Filter bag

Solvent system:

Different solvents, separately or in combination, has been used to prepare feed stock solutions for spray drying. These solvents are aqueous, alcohols such as methanol, ethanol or isopropanol and some organic solvents such as dichloromethane (DCM), acetone, methyl ethyl ketone, dioxane, tetrahydrofuran (THF), chloroform, ethyl acetate, and acetonitrile. Out of these, the most commonly used solvent system is DCM.DCM has low boiling point (39.8 °C), excellent solubilizing power and high volatility for various drug and polymers. The critical parameter is a common solubility of feed components in a solvent to obtain molecularly dispersed solid dispersions. [31]

Carriers:

Carriers used for solid dispersion:

The carriers should be melted elevated temperatures and in melted carriers drug should be dissolved in carriers. Surface-active agents are adsorb on the surface and alter the surface energy and surface tension at low concentration. They have polar and non-polar region in same molecule. They should have soluble in water and gastrointestinal fluid ,thermally stable ,low vapour pressure and carrier not have

melting point much higher than the drug, should be nontoxic in nature.[32]

Ideal properties of carriers:

It should have improves wettability and enhances dissolution.
It should be improving stability.
It should have Minimum uptake water.
It should be Soluble in common solvent with drug.
It should have relatively low melting point. [33]

Examples of carriers: [31]

***Polymers*:** Hydroxypropyl-methyl cellulosephthalate, EudragitL100

Polymeric materials: Povidone (PVP), Poly-ethyleneglycols (PEG)

Insoluble or enteric Surfactants: Polyoxyethylene stearate, Renex, Poloxamer 188, Spans

Sugars: Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol

Acids: Citric acid, Succinic acid

Miscellaneous: Pentaerythritol, Pentaerythrityl

Process variables of spray drying:

The operation of the process of spray drying considered as one of the most complicated
types of drying. The operator of a spray dryer has direct influence on:
Inlet temperature of the drying air;
Flow rate
The supply rate of the liquid stream
Atomizing air pressure
(For the pneumatic nozzle, for other atomizing devices—other appropriate parameters related
to atomization)
Other process parameters, such as:
Outlet temperature of the drying air
The droplet size;
The drying efficiency
The physical properties of the dried product (e.g., the particle size, moisture content, and hygroscopicity); are depends on the parameters adjusted by the operator, on drying air humidity, and on the feed properties. [34]

Inlet temperature and outlet temperature:

Inlet air temperature and aspirator capacity both increased and that increases the outlet air temperature due to the increased supply of heat energy. Due to Increasing feed flow rate it lowers the outlet air temperature hence the volume of evaporation of liquid is increase. [35]

Due to increasing heater outlet or air inlet temperature causes increasing outlet temperature. [36]

Flow rate:

The effect of flow rate on process of spray drying due to increasing feed flow rate decreasing total solid product because of increase in water introduction in drying chamber under constant drying conditions. Increasing feed flow rate causes increasing particle size and increasing bulk
density this is resulting higher water content in the particles and increase density as compare to dry solids and this causes the decreasing solubility. [37]

Atomizing Air Pressure:

Atomization refers a formation of droplets or mist by transfer of bulk liquid solution through a nozzle.[38]If the atomization air pressure is increase then the mist size will be decreases, then the
Possibility of agglomeration will also decrease. However, if the Atomization air pressure set high in lab model, then the pilot scale process also required too high atomization pressure. The atomization air must be maintained to avoid agglomeration. Droplets are very small to achieve fastest possible process during the optimization of spray rate. Droplet will be small in case of pressure is high. It is also necessary to understand that beyond a certain pressure the particle size reduction will be negligible. [39]

Evaluation parameters:

Saturation solubility:

The saturation solubility of drug and Sold dispersion is determined in distilled water and phosphate buffer saline (PBS pH 7.4) by adding an excess of drug and SD to sufficient quantity of distilled water or PBS in glass stoppered tubes. The stoppered tubes rotate for24 h in water bath shaker at 37oC. The saturated solutions filtered through a 0.45 µm membrane filter, suitably diluted with water and analyzed by UV-spectrophotometer. [40]

Drug content determination:

The drug content percentage of solid dispersions determine by dissolving the solid dispersions equivalent to10 mg of drug in 100 mL of given solvent. Each of these aliquots ware further diluted with phosphate buffer of suitable pH and absorbance were measure by UV –spectroscopy. [41]

Differential scanning calorimetry (DSC):

Thermal characteristics of the solid dispersions were determined by a differential scanning calorimeter. Samples placed in aluminum pans. [42] Accurately weighed samples placed in aluminum pans heat at constant rate and by purging a nitrogen gas inert atmosphere maintain. [43]

Transform infrared spectroscopy (FT-IR):

the IR spectra of the spray-dried products determined by IR-spectrophotometer. [44'45]

X-Ray Diffraction studies (XRD):

The powder X-ray diffraction patterns were determined for pure drug, and SSDs. X-ray diffractograms were obtained using the X-ray diffractometer. [46]

X-Ray Powder Diffraction (XRPD):

The crystalline state of drug and solid dispersion in the different samples determine by XRPD. A

diffraction pattern is obtained on X-ray Diffractometer. [47]

Dissolution study:

Dissolution study carried in triplicate according to the United States Pharmacopeia Paddle method (Apparatus II). Take a solid dispersion equivalent quantity of drug weigh and placed into
900 ml of pH 1.2 Hcl or pH 6.8 phosphate-buffered saline(PBS) or distilled water as dissolution media.50 rpm paddle revolution speed 37.0+/- 0.5 0C temperature should be set respectively. The samples (2 ml or 5ml) collect at specific time interval replacement by an equal volume of dissolution medium. Drug content determine by UV-spectrophotometer. [47, 48]

Advantages: [49, 50]

1. Spray drying has been used to for sterile pharmaceutical processing to ceramic powder production.
2. It can be designed to virtually any capacity required. (Feed rates range from a few pounds per hour to over 100 tons per hour).
3. The spray drying process is very fast, with the major quantity of evaporation taking place in less than a few seconds.
4. It is fully automated control system that allows continuous monitoring and recording of very large number of process variables simultaneously.
5. Wide ranges of different spray dryer designs are available to get various product specifications.
6. It can be used for both heat-resistant and heat sensitive compounds.
7. Spray-drying method mostly used in the pharmaceutical, chemical, cosmetic and food industries

Disadvantages: [49]

There is a some disadvantages of spray drying;

1. The equipment is very heavy and equipment is expensive.
2. The overall thermal efficiency is low, as the large volumes of heated air pass through the chamber without contacting a particle, thus not contributing directly to the drying.
3. Product yield is very low and high quantity of sample is required.

Applications: [51]

1. To improve the solubility absorption of active pharmaceutical ingredient.
2. In small quantity of drug to get a homogeneous distribution of drug in solid state.
3. Protect drug against decomposition processes like hydrolysis, oxidation racemization, photo oxidation to stabilize unstable drugs.
4. For the formulation of a fast release dose in a sustained release dosage form.
5. The damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound.
6. Unpleasant taste and smell of drug masked by complex with different polymers.
7. Used to convert liquid compounds into solid formulations like powders, capsules or tablets.

CONCLUSION:

Spray drying is an efficient drying technique and particle engineering for the formulation of the pharmaceutical product. By using the spray drying we can formulate the dry amorphous powder of the product we can use this for direct compression or for the encapsulation. Spray drying technique is helpful to enhance the solubility of the poorly water soluble drug. It converts the liquid drug solution dry amorphous form of drug by using hot air and increases the bioavailability and oral absorption of the drug. Spray drying is a unit operation produces a uniform quantity of the product with constant physical properties.

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