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Review Article

A Review on Solid Dispersion and Polymers Used For Solubility Enhancement through Lyophilization Technique

Suryawanshi Abhijeet*, Sawant Ganesh, Dr. Prakash Jadhav, Velhal Atish, Bhongale Ashish, Dr. Vivek kumar Redasani

Department of Pharmaceutics, YSPM's Yashoda Technical Campus, Satara 415011, Maharashtra, India.

A B S T R A C T

There are very few marketed treatments that use solid dispersions, despite their enormous potential to improve medication solubility. Solid dispersion has shown promise among the several techniques available to increase the new drug's solubility. Numerous hydrophilic carriers have been studied to improve the bioavailability and dissolving properties of medications that are not very soluble in water.It has been determined that solid dispersion is a better dose form for medications with low water solubility. Solid dispersions can be made using a variety of techniques, including lyophilization, hot melt extrusion, melt agglomeration, fusion, kneading, melting, solvent evaporation, fusion, spray drying, co-grinding, and supercritical fluid (SCF) technology. Pharmaceutical excipients that are utilized to make solid dispersions come in a wide variety of hydrophilic and hydrophobic carriers. This article provides an overview of the several types of natural, semisynthetic, synthetic, and modified hydrophilic carrier that are utilized to formulate solid dispersions through lyophilization technique.

Keywords: Solid dispersion, hydrophilic carrier, lyophilization, solubility

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*Address for Correspondence:
Suryawanshi Abhijeet, YSPM's Yashoda Technical Campus, Faculty of Pharmacy, Wadhe, Satara 415011, (M.S.) India.

INTRODUCTION

The "Solubility" describes the highest concentration of a material that can dissolve in a specific solvent. It is a fundamental concept in many fields, such as chemistry, physics, pharmaceuticals, and biology. In the pharmaceutical industry, solubility is especially important because it directly affects a drug's bioavailability, which affects how well the body can absorb and use the medication[1]. Three major factors, namely solubility, permeability, and dissolution, affect a drug's bioavailability; a poorly soluble drug causes problems in bioavailability[2]. Pharmaceutical scientists have always faced a difficult problem when formulating poorly water-soluble drugs [3].There are many different methods available and documented in the literature to improve the solubility of poorly water-soluble drugs [4].

1) Physical Modifications-Drug dispersion in carriers such as eutectic mixtures, solid dispersion, solid solutions, and cryogenic procedures; decrease of particle size such as micro-ionization and nanosuspension; and alteration of the crystal habit such as polymorphs, amorphous form, and crystallization.

2) Chemical Modifications-pH change, buffer usage, complexation, derivatization, and salt production.

3) Miscellaneous Methods-Adjuvants such as surfactants, solubilizers,cosolvency, hydro trophies, and new excipients are used in supercritical fluid processes[5].

Solid dispersion is the process of dispersing one or more hydrophobic active ingredients in a hydrophilic inert carrier in a solid state using the melting (fusion) method, solvent, or melting solvent method[6].

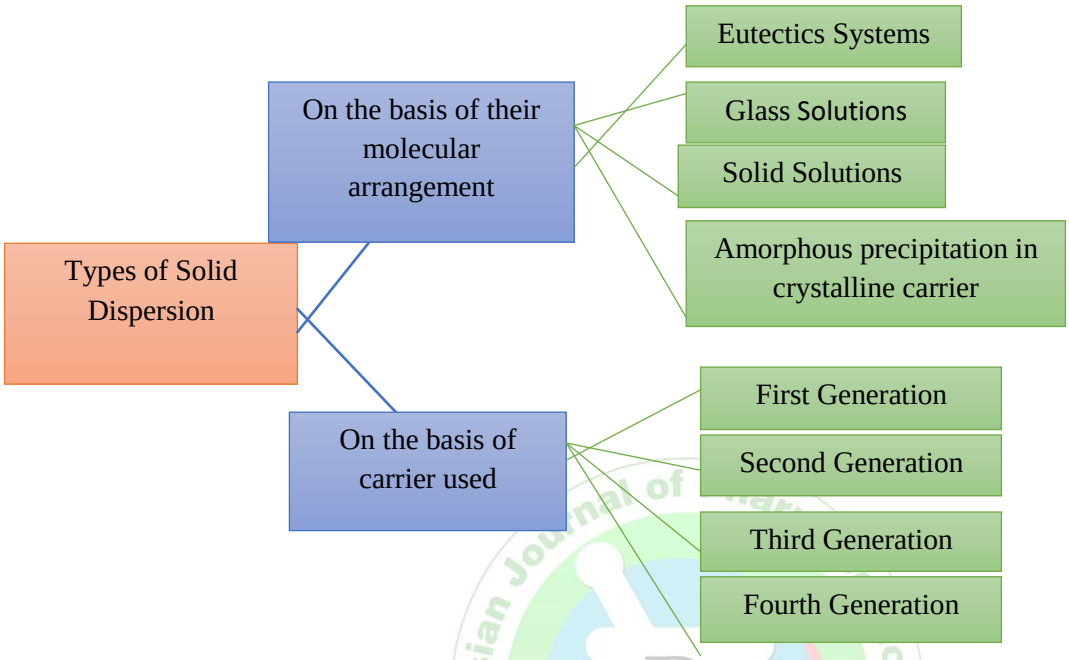
Solid Dispersion:

Sekiguchi and Obi carried out the first investigation into SD in 1961 [7]. Solid dispersions, which are often made via the melting (fusion) process, solvent method, or fusion solvent method, are defined as the dispersion of one or more active substances in an inert carrier in a solid state. The medication may be distributed in crystalline particles, amorphous

particles or molecules [8]. The classification of solid dispersion is as follows: (1)Eutectic systems consist of two compounds mixed in a particular ratio,possessing a single melting point that is lower than the component part's melting temperatures; (2) Microfine crystalline dispersions are crystalline dispersions of drugs in the carrier matrix; (3) solid solutions that are further separated into amorphous solid solutions with solute randomly distributed in an amorphous carrier, substitutional solid solutions (solute molecule replaces a solvent molecule), interstitial solid solutions (solute molecule is present in the interstices) [9].

The following describes the several types of solid dispersion [10]

Types of Solid Dispersion:



Based on their molecular arrangement:

Eutectics System- A mixture of two substances that melt at the same temperature is called a eutectic system. At the eutectic point, where the mixture's melting point was lower than each component's alone, components co-melted. The first eutectic combination of urea and sulfathiazole was made in 1961 by Obi and Sekiguchi [7]. In order to create a physical mixture of extremely thin crystals of separate components, solid eutectic mixes are typically made by quickly cooling the melted components [11]. A fused melt of two components that exhibit total liquid miscibility but little solid-solid solution is quickly solidified to create it [12].

Solid Solutions- Making a solid solution was initially suggested by Chiou and Riegelman as a way to improve a substance's solubility and absorption. In this system, a single homogeneous phase system is formed when the two constituents crystallize together. In the solid solution, the drug particle size is reduced to its molecular size.As a result, the solid solution will dissolve more quickly than the eutectic combination. Depending on the degree of miscibility between the two chemicals or the mode of circulation of the solvate molecules (interstitial or substitutional), the solution can be classified as continuous or discontinuous [10].

Continuous solid solutions-In a steady solid solution, the constituentsare compatible in every ratio. From a theoretical perspective, this implies that the binding between the two components is stronger than the bond between the molecules of each individual component [10].

Discontinuous solid solutions-Each component's solubility in the other component is restricted in discontinuous solid solutions [15]. Goldberg et al. have proposed that the term "solid solution" [13] Due to practical considerations, it should only be utilized when the two components' mutual solubility is larger than 5%. [8].

Substitutional solid solutions- Only when the size difference between the solute and solvent molecules is less than 15% is substitution feasible. The crystalline structure of classical solid solutions allows the solute molecules to either fit into the gaps in the crystal lattice between the solvent molecules or swap out the solvent molecules [8].

Interstitial solid solutions- The dissolved molecules in interstitial solid solutions take up the interstitial gapsbetween the solvent molecules in the crystal lattice. The molecular diameter of the solute molecules in interstitial crystalline solid solutions should not exceed 0.59 times that of the solvent molecules. Additionally, the solute molecules' volume should not exceed 20% of the solvent [14].

Glass Solution: A solute dissolves in a glass carrier to form homogeneous glassy systems known as glass solutions**.** [12] and the concept of making a glassy solid solution was first put up by Chiou and Riegelman as a way to improve a substance's solubility and absorption [10].

Amorphous precipitation in crystalline carrier: Two categories of amorphous precipitations were identified based on molecular structure. In the former, the drug material is distributed throughout the amorphous carrier as amorphous

agglomerates. The latter consists of an amorphous drug material and a crystalline carrier [11].

On the basis of carrier used:

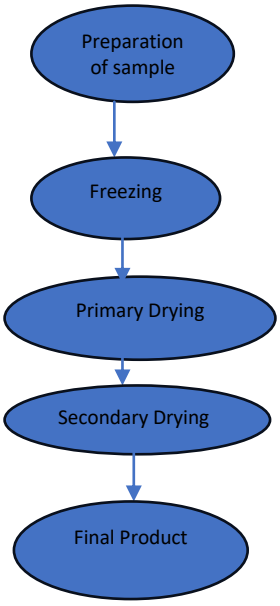
First generation -The creation of eutectic mixes or molecular dispersions enhanced the rate of drug release in the first-generation solid dispersion, which in turn raised the bioavailability of medications that were not very water soluble. Urea, sugars, and organic acids are examples of ex-crystalline carriers [15]. Because the drug and the carrier will crystallize concurrently after cooling, a eutectic combination is always preferred. This will lead to a well-dispersed drug in the carrier and a notable increase in the drug's dissolution rate compared to the actual API's dissolution rate [16].

Second generation - The amorphous carriers found in second-generation solid dispersions are primarily polymers. Depending on the drug's physical condition, these solid dispersions, also called as amorphous solid dispersions, can be categorized as glass solid solutions, glass suspensions, or a combination of the two [17]. Polyvinylpyrrolidone (PVP), crospovidone, PVPVA, polymethacrylates, cellulose derivatives (such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), ethyl cellulose (EC), starch, and cyclodextrins are a few examples of polymers utilized in second generation solid dispersions. [18].

Third generation - We use carriers with surface activity and self-emulsifying properties in the third generation. The surfactants increase the drug's solubility by reducing its recrystallization. For instance, Gelucire 44/14, Tween 80, and Poloxamer 408 are surface active self-emulsifying carriers [19].

Fourth generation- The goal of adding SD in the fourth generation is to improve solubility and provide regulated extended release in controlled manner [20]. Ethyl cellulose, hydroxypropyl cellulose, carboxyvinyl polymer, Eudragit RS, RL, and poly (ethylene oxide) are among the polymers that are utilized [21].

Lyophilization cycle[52]:



Different methods of solid dispersion [22]**:**

1. Lyophilization technique
2. Solvent evaporation method
3. Co-precipitation method
4. So-grinding method
5. Gel trapping method
6. Spray-drying method
7. Melt aggregationmethod
8. Electrospinning method
9. Melting extrusion method
10. Kneading technique

Lyophilization method:

Heat and mass are transferred to product being prepared during lyophilization. This method was put out as a substitute for solvent evaporation. The drug and carrier in a lyophilized molecular dispersion are co-dissolved in a shared solvent, frozen, then sublimed. This process is known as lyophilization. A lyophilization, also called freeze drying, allows ice to proceed directly from solid to vapor without passing through a liquid phase by extracting water from a product after it has been frozen and placed under vacuum. [24]. Three steps make up a standard lyophilization process: freezing, primary drying, and secondary drying [23].

Freezing: It is the lyophilization process's initial step. In this process, water is transformed into ice crystals at a low temperature, and the solute stays in the space between the ice crystals [25].

Primary Drying: This process, also known as sublimation, occurs when a product is frozen and then placed under vacuum, allowing the frozen solvent to evaporate without going via the liquid phase [26].

Secondary Drying: The step where the temperature of product increases above the primary drying stage is known as the secondary drying stage. Reducing the ultimate residual water content to a manageable level is the aim of secondary drying [27].

Table: 1 Polymers/Carriers used to prepare solid dispersion through lyophilization technique:

Carrier	Drug	Conclusion	Reference
Arginine	Simvastatin	Simvastatin-arginine (SMV-ARG) complex exhibited solubility enhancement by 12 000-fold in both acidic and alkaline dissolution media	[28]
Skimmed milk	Simvastatin	In-vitro drug release studies exhibited a cumulative release of 86.69% as compared to 25.19% for the pure drug	[29]
Gelatin 50PS	12 Active pharmaceutical ingredients	The viability of using gelatin 50PS as a carrier in the lyophilization process to create solid dispersions was evaluated.	[30]
Aegle marmelos Gum	Atorvastatin calcium	The SD's prepared using the lyophilization method displays faster dissolution rates compared with those prepared using other method	[31]
EudragitE, Plasdone S and Soluplus	Theobromine	Improved dissolution profile	[39]
Sodium acetate	Docetaxel	Enhanced dissolution rate resulting in enhanced bioavailability	[32]
PEG 4000, PEG 6000	Glyburide	In conclusion, physical mixtures, solid dispersions and lyophilized solid dispersions increase dissolution of glyburide	[33]
HPMC K15	Lovastatin	prepared Lovastatin solid dispersion to increase solubility and dissolution rate	[34]
Eudragit E PO,Gelucire 44/14	Resveratrol	Gelucire 44/14 as a surfactant and Eudragit E PO as the hydrophilic carrier will optimize RES's solubility and dissolution, hence increasing its oral bioavailability.	[35]
Soluplus	Carvedilol	Using a solid dispersion approach, Soluplus®, a novel polymeric carrier, was studied for improving the solubility of a medication called CAR that is poorly soluble in water.	[36]
PVP K30	Telmisartan	Using PVP K30 as a polymeric carrier and Na2CO3 as an alkalizer, a solid dispersion formulation of telmisartan was created by the lyophilization process.	[37]
PEG 6000, Poloxamer 407	Fenofibrate	In conclusion, fenofibrate dissolves more readily in physical mixtures, solid dispersions, and lyophilized solid dispersions.	[38]
PVP K30, PEG 6000, pluronic F127	Flutamide	lyophilized solid dispersions of FLT are obtained in which FLT transformed from crystalline to partially amorphous form	[40]
Sodium dodecyl sulfate	Mebendazole	SD is a good candidate for improving the bioavailability and anticancer effects of MBZ	[41]
Skimmed milk	Atorvastatin	The formulation was successful in significantly enhancing the solubility and dissolution rate of atorvastatin.	[42]
Poloxamer	Gliclazide	Solubilityand oralbioavailability are increased by using lyophilization technique.	[43]
Poloxamer	Glibenclamide	Solubility is enhanced by using lyophilization method	[44]
Eudragit	Promethazine HCl	The solubility of PHC was markedly decreased after formation of polymeric dispersions	[45]
Natural gum, maltodextrin biopolymers	Artemisinin	Solubility and dissolution rateis enhanced by using lyophilization technique	[46]
PVP K-30	Meloxicam	Polyvinylpyrrolidone K-30 (PVP) has an improving effect on the properties of MX as the solubility, dissolution rate, and permeation through cellophane membrane or hairless mouse skin	[47]

Eudragit L100-55	Ibuprofen	Ibuprofen loaded Eudragit L100- 55 nanoparticles prepared with different drug loadings (9, 16, 20 and 23 w/w % of solid in organic phase) were prepared.	[48]
Poloxamer 188	Sildenafil citrate	This comparative study reveals that both direct compression of SD and freeze-dryingwere successful techniques is prepared	[49]
PVP-K30	Valsartan	It was determined that the new PVP-based SDs were effectively made using a freeze-drying technique, which significantly improved VAL's dissolution.	[50]
PEG 6000	Artemether	Poly ethylene glycol-6000 with artemether can be the most appropriate carrier to enhance drug-polymer interaction in solid dispersion system	[51]

Table 2: Processing Parameters of lyophilization:

Steps	**Parameters**
Freezing	Freezing rate, Freezing temperature
Primary Drying	Shelf temperature, Chamber pressure, Primary drying time
Secondary Drying	Secondary drying temperature, Secondary drying pressure, Secondary drying time

Advantages of lyophilization:

1. Easy removal of water without using the heat [53].
2. Vacuum conditions provide good protection for oxidizable materials [54].
3. It can enhance product stability in a dry state [55].
4. Simple reconstitution preserves the quality of food, biochemicals, and chemical reagents while drastically lowering weight and making them easier to carry [55].

Disadvantages of lyophilization:

1. The process is time-consuming and expensive [56].
2. A strong vacuum can be used to eliminate volatile substances [57].
3. It requires heavy cost which intern increases the cost of the product[57].

Conflict of interests

There is no conflict of interest.

CONCLUSION

Various techniques are created to improve the medications' solubility and dissolution. One of the best methods for improving the solubility of medications that are not very soluble in water is solid dispersion. The amount of the carrier and the preparation technique are also important factors in increasing the rate of medication dissolution. An alternate and the best option for increasing the solubility of the weakly water soluble BCS-II medication is a solid dispersion with a synthetic or natural carrier that is less toxic, biocompatible, and more readily available. the use of solid dispersion and careful carrier selection to increase the oral bioavailability and release rate of poorly water-soluble medications.

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