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Advances in Solid Dispersion Techniques for Enhancing Drug Solubility, Bioavailability and Controlled Release

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Abstract:- Solid dispersion (SD) refers to the dispersion of active ingredients, whether one or more, within inert carriers in a solid state. This is achieved through methods like fusion, solvent, or solvent fusion. The solid dispersion technique is particularly valuable for enhancing the solubility of inadequately soluble drugs, particularly those falling under BCS Class II. This technique involves the utilization of carriers such as polyethylene glycol 4000, urea, and polyvinylpyrrolidone K 30 to improve the drug's solubility and dissolution properties. The method of solid dispersion has been utilized to improve the solubility, dissolution, and bioavailability of various natural drug components. Furthermore, solid dispersion has been investigated as a strategy for developing natural drug products with controlled or sustained release characteristics. The mechanism of action of this delivery system relies on the specific type of solid dispersion, as well as the interactions among the drugs, carriers, and other components incorporated into the formulation. Currently, there are various methods accessible for characterizing SDs, including X-ray diffraction, differential scanning calorimetry, FTIR spectroscopy, and dissolution testing, among others.

The pharmaceutical uses of the Solid Dispersion technique encompass: augmenting drug absorption, achieving a uniform distribution of a small drug quantity in a solid state, and safeguarding unstable drugs by mitigating processes like hydrolysis, oxidation, and photooxidation.

Keywords:- *Solid dispersion, PEG4000, Urea, Solvent method, Dissolution Studies, Differential scanning calorimeter.*

I. INTRODUCTION

A set of solid products known as a "Solid Dispersion" are those that have at minimum two separate components, often a Hydrophobic Drug and a Hydrophilic Carrier. The substance could be amorphous or crystalline. (Kumar B, 2017; Akiladevi, D *et.al.,* 2011) Solid dispersion has been defined by Chiou as "the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by solvent evaporation, melting (fusion) or melting-solvent method". Solid dispersions can also be named Solid-state dispersion. (Chiou, W. L., and Riegelman, S., 1971). Poorly water-soluble medications become more soluble and dissolve faster the carrier disintegrates and the medication is released in small colloidal particles when the solid dispersion is exposed to wet circumstances. (Sareen, S. *et. al.,* 2012) Though there are several routes of drug administration, Oral medication administration is the most recommended due to the convenience of formulation flexibility, and administration. However, the oral route has several bottlenecks, including lower gastrointestinal absorption of weakly water-soluble medications, which leads to low bioavailability and inferior pharmacological response. (Singh, S. and Singh Baghel, R., 2011).

Most novel chemical compounds being developed today are meant to be used as solid dosage forms that produce an efficient because of the various benefits of this path, such as higher stability, smaller bulk, precise dosage, and simple manufacture, there is repeatable *in-vivo* plasma concentration following oral administration. (Jung, J. Y. *et.al.,* 1999) Due to high lipophilic nature a significant part of drug remains poorly absorbed after administration of the drug by oral route. This causes various issues like low bioavailability of active constituents and absorption of insufficient dosage. (Lewis, D. *et.al.,* 2009) Numerous strategies are used to enhance solubility to remedy the lack of lower solubility associated with such treatments, including pro-drug creation, Cyclodextrin complexation, surfactant use, micronization, salt formation, and so forth. Solid dispersion (SD) technology is one such formulation strategy that has considerably improved such medications' solubility/dissolution. (Kaushik, R. *et.al.,* 2020).

The Biopharmaceutical classification system (BCS) of classification classifies flavonoids and phenols into the Class II category due to their lower solubility and higher permeability. Therefore, everything that can improve in vivo dissolution will likewise improve product absorption. High-fat foods, which increase biliary solubilization and gastrointestinal secretions and are less soluble than Class II medicines, frequently aid in drug absorption. This is especially true for bases and acids with low pKa values that are weak. However, when meals cause the pH of the GI contents to rise, the small intestine and the stomach may tend to precipitate weak bases with low pKa values. (Martinez, M. N. and Amidon, G. L., 2002).

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II. ADVANTAGES OF SOLID DISPERSION

The solid dispersion method has the following benefits for pharmaceutical advantages.

- This technology can improve the solubility and bioavailability of medications that aren't very water-soluble.
- It causes a drug's extent and rate of absorption to rise, which causes a quick rate of breakdown.
- It is more applicable and simpler to make.
- The conversion of a drug's liquid form into its solid form.
- Rapidly disintegrating oral pills can more easily be made using solid dispersion.
- Molecular weight, composition, particle porosity, and wettability can all be controlled to increase the bioavailability of medications that aren't very water-soluble.
- It has the purpose to increase the drug's porosity.
- It is used to cover up the drug's unpleasant taste.
- A desirable increase in the bioavailability of the active ingredient.
- Prevent polymorphism alterations and the ensuing bioavailability issues.
- It is possible to achieve homogeneous dispersion of a little amount of medicine in the solid state.(Argade, P. S. *et.al.*, 2013 & Huang, S. *et.al.*, 2016).

III. DISADVANTAGES OF SOLID DISPERSION

The following are some drawbacks of solid dispersion:

- By absorbing moisture, the polymorphs used in a solid dispersion can undergo phase separation and crystallization, and change from an amorphous to a crystalline state.
- Solubility and dissolution rates are consequently decreased.
- It results in an inadequate scale-up for manufacturing.
- It causes reproducibility of physicochemical characteristics.
- The stability of the medicine and vehicle.
- The time-consuming and expensive nature of the preparation process.(Vasconcelos, T. *et.al.*, 2016 & Ma, X. *et.al.*, 2019)

IV. SELECTION OF A CARRIER

The drugs are dissolved in melted carriers while the carriers are heated to a high temperature. Surface active agents are substances that, when present in small amounts, bind to surfaces or interfaces of a system and decrease their free surface or interfacial energy. For a carrier to be effective in accelerating medication dissolution, it must meet the following requirements. Polyethylene glycol 2000, Polyethylene glycol (PEG) 4000 and 6000, Urea, Polyvinyl pyrrolidone, Citric acid, Sugar, etc. are some of the carriers which have been generally used (**Table 1**). They should generally have the following characteristics:

- Freely water-soluble with built-in quick dissolving capabilities.
- Low melting point and heat stability for the melting process.
- Non-toxic and pharmacologically inert.
- Capable of improving the drug's solubility in water.
- Solubility in different solvents.
- Be chemically appropriate with the medicine and fail to bind to it tightly to form a complex.(Van Duong, T. *et.al.*, 2016)

Table 1: Materials Used as Solid Dispersion's Carriers

Materials	**Examples**
Acids	Succinic acid, Citric acid
Sugars	Sucrose, Sorbitol, Galactose, Dextrose, Maltose, Xylitol
Insoluble or enteric polymers	Eudragitl.100, Hydroxypropyl-methyl cellulose
Polymeric materials	Polyethylene glycol(PEG), Povidone (PVP)
Surfactants	Renex, Polyoxyethylene stearate, Spans
Miscellaneous	Urea, Pentaerythritol, Pentaerythrityl tetra acetate

V. SOLID-STATE DISPERSION CATEGORIZATION

As per the recent advancements and molecular arrangements the solid-state dispersions can be classified as follows:

A. Solid dispersion classification According to recent developments, the following SD categories are:

➢ *1st Generation SDs*

These are made using crystallized polymers. First-generation solid dispersions, the first carriers used in solid dispersions, were created. The first crystalline carriers to be employed in the creation of solid dispersions were urea and sugars. Their drawbacks include the tendency to form crystalline solid dispersions and slower drug release than amorphous ones.

➢ *2nd Generation SDs*

The second-generation solid dispersions employed the use of amorphous polymeric carriers in place of crystalline carriers. In these, the drug remains molecularly dispersed throughout the carrier. The polymeric carriers have been classified into the following categories:

- Synthetic carriers: Povidone, polyethylene glycols, etc.
- Natural carriers: Cyclodextrin, HPMC, ethyl cellulose, etc.

➢ *3rd Generation SDs*

These solid dispersions can be made up of polymers that are amorphous and surfactants alone or in combination. Drugs with weak solubility, achieve the highest level of bioavailability. The solid dispersions use surfactants like inulin, poloxamer 407, and others. (Meng, F. *et.al.*, 2015).

B. Classification of solid dispersions according to their molecular arrangement:

➢ *Eutectic mixtures*

To create solid eutectic mixes, the co-melt of the two components is often rapidly cooled. As a result, the two components physically combine to form incredibly thin crystals.

➢ *Solid solutions:*

These are categorized in two categories depending on their miscibility:

- Amorphous solid solutions
- Continuous solid solution

➢ *Glass solutions and glass suspensions*

The substance being dissolved dissolves in the glassy solvent in a homogenous system known as a glass solution. The "glassy" state, which exists below the glass transition temperature, exhibits transparency and brittleness. The term "glass" refers to pure compounds when they are in their glassy state. (Baghel, S. *et.al.*, 2016)

VI. METHODS FOR PREPARATION OF SOLID DISPERSION

Following are the methods for preparation of solid dispersions:

- **Kneading Technique:** The carrier, glass mortar, and solvent are combined in this procedure to create a homogeneous paste. After adding the drug gradually, the mixture was triturated for an hour. Water was changed to preserve the paste's consistency throughout the procedure. The kneaded mixture is next vacuum-dried for 24 hours. And a sieve was used to filter the dry powder. (Modi, A. and Tayade, P., 2006)
- **Solvent evaporation method**: In this procedure, a suitable solvent is used to dissolve both the medication and the carrier. After complete dissolution, the solvent is eliminated via reduced pressure evaporation. The solid mass is pulverized and passes through sieve no. 100 and dried the mixture.(Sethia, S. and Squillante, E., 2004)
- **Co-precipitation method:** This procedure involves adding the necessary amount of medication to the carrier solution. The system is shielded from light and kept in magnetic agitation. To prevent losing the structural water from the inclusion complex, the precipitate has been vacuum separation filtering and dried at ambient temperature**.** (Moyano, J. R. *et.al.*, 1997)
- **Melting method**: The Sekiguchi and Obi melting method calls for preparing a physical combination of the medication and carrier that is water soluble using a mortar and pestle. Then directly heating it till it melts. The melted slurry is then vigorously stirred while quickly freezing in an ice bath and cooled to acquire a solid mass. It is crushed, pulverized, and sieved. (Issa, A. A. *et.al.*, 2013 & Nguyen, T. N. G. *et.al.*, 2013).
- **Co-grinding method**: A blender is used to combine the physical mixture of the medicine and the carrier for some time. A vibration ball mill's chamber is then charged with the mixture, and steel balls are added. The powdered mixture is ground into powder. The sample is then taken and stored in a glass vial with a screw top at room temperature until needed.(Prabhu, P. and Patravale, V. 2016).
- **Spray-Drying Method**: A appropriate solvent is used to dissolve the drug, and water is used to dissolve the necessary amount of the carrier. The following step is to combine the solutions using a sonicator or another suitable method to create a solution with no color, which afterward is spray dried with a spray dryer. (Singh, A. and Van den Mooter, G., 2016).
- **Lyophilization Technique:** Heat and mass must be transferred from one place to the product being prepared during the freeze-drying process. As a substitute for solvent evaporation, this technique was put out. To create a lyophilized molecular dispersion, the drug, and carrier are simultaneously dissolved in one solvent, frozen, and then sublimed. This process is known as lyophilization.(Betageri, G. V. and Makarla, K. R., 1995).
- **Melt Extrusion Method:** This method of solid dispersion uses a co-rotating twin-screw extruder to prepare a hot-stage extrusion of the active ingredient and carrier. 40% (w/w) of the medication is always present in the dispersions. The pharmaceutical industry uses the melt extrusion technique to create dosage forms, such as sustained-release tablets.(Hitzer, P. *et.al.*, 2017).

VII. CHARACTERIZATION OF SOLID DISPERSION

A. Drug-carrier Miscibility

- **Differential Scanning Calorimetry:** The concentration of crystalline material can be determined by using DSC. This method involves heating samples at a consistent rate while measuring the energy required for doing it. The temperatures at which thermal events take place can be found using DSC. The amount of crystalline substance can be determined using the melting energy.
- **Powder X-ray Diffraction:** Long-range order in a material can be qualitatively detected using PXRD. The more crystalline material is indicated by sharper diffraction peaks.

B. Interaction between drug-carrier

- **Fourier Transformed Infrared Spectroscopy (FTIR):** This method is employed to find variations in the energy distribution of medication and carrier interactions. Crystallinity is indicated by sharp vibrational bands 37.
- **Raman Spectroscopy (Confocal):** Confocal Raman to assess the solid mixture's homogeneity, spectroscopy is used. It is stated that homogenous distribution was indicated by a standard deviation in drug content of less than 10%. Uncertainty surrounds the existence of nano-sized amorphous drug particles due to the 2 μm, pixel size.(Karolewicz, B. *et.al.*, 2014).

C. Dissolution Enhancement

- ***In-vitro* Dissolution Studies:** Dissolution behavior is discovered by in-vitro dissolution research. The *in-vitro* dissolution research can be utilized to show the level of bioavailability or bioequivalence of the therapeutic product.

- **Dissolution Calorimetry:** Dissolution calorimetry, which depends on the sample's crystallinity, estimates the energy of dissolution. Typically, crystalline material dissolves endothermically while amorphous material dissolves exothermically. (Jafari, E., 2013 & Paradkar, A. *et.al.*, 2004).

D. Various Applications of Solid Dispersion

Pharmaceutical applications for solid dispersion include:

- Increasing the rate of solubility and dissolution of medicines that are weakly water soluble will increase their bioavailability.
- The damage caused to the mucosa of the stomach by several non-steroidal anti-inflammatory medicines can be lessened by delivery as an inclusion substance.
- To provide homogeneous drug distribution in the solid state for modest doses.
- Drugs, for instance, are less able to bind to the erythrocyte membrane when their inclusion is made complicated.
- To create formulations from liquid components. Essential oils with unsaturated fats, nitro-glycerine, prostaglandin, clofibrate, and other liquid medications can be produced as powders, capsules, or tablets which are solid pharmaceutical formulations.
- To cover up bad flavors and odors and prevent undesired incompatibilities.
- To lessen the pre-systemic inactivation of medications like progesterone and morphine.(Ozeki, T. *et.al.*, 1997 & Tambosi, G. *et.al.*, 2018)

VIII. CONCLUSION

Based on this review, it's evident that solid dispersion technology represents an advanced approach for overcoming the solubility challenges faced by poorly water-soluble drugs. Therefore, prior to creating a new solid dispersion system for a specific drug, it becomes imperative to examine the physical and chemical properties of both the drug and the carrier in order to identify the most suitable match between them. Furthermore, the preparation methodology and the ratio of carrier to drug are also significant factors influencing the enhancement of the drug's solubility and dissolution rate. This article systematically presents our efforts to address all these aspects and outlines how they can be orchestrated to achieve this objective. Consequently, in the realm of innovative drug delivery applications, the evolution of solid dispersion technology is set to continue in the future, effectively resolving challenges associated with delivering poorly soluble drugs.

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