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SOLID DISPERSION TECHNOLOGY: RECENT ADVANCEMENTS IN THE DELIVERY OF VARIOUS PHYTOCONSTITUENTS

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ABSTRACT: Nature is an eminent source of potential therapeutic drugs, however; most of the herbal bioactives are left unexploited as precise remedies due to lack of appropriate formulation design and development. Pharmacological interventions of herbal molecules may often be limited due to insufficient solubility, bioavailability as well as instability aspects and it remains one of the most challenging facet for pharmaceutical scientists worldwide. Solid dispersion is one of the well established and convenient techniques for improving the oral absorption of drugs with poor aqueous solubility and dissolution rate. The objective of present study is to enlighten the role of solid dispersion approach for enhancement of solubility and bioavailability profile of various natural moieties. The manuscript also aims to summarize the important features of solid dispersions, carriers utilized, classification, preparation methods and characterization parameters. Numerous and significant research findings in the vistas of phytoconstitutents based solid dispersions are also discussed.

INTRODUCTION: Herb is a plant or part of a plant valued for its medicinal, aromatic or savoury qualities[1]. These botanicals are known to contain one or many chemical constituents that may have significant therapeutic purposes [2]. The belief that natural medicines are much safer than synthetic drugs has gained popularity in recent years and led to tremendous growth of various phytopharmaceutical usage. Herbal medicines are also now in great demand in the developing world for primary healthcare and recent developments in the avenue of herbal drug delivery efficiently manage several human diseases [3].

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These natural drugs are safe, inexpensive, better cultural acceptability, better compatibility, minimal side effects and have fascinated several scientific community worldwide towards herbal drug technological procedures [4, 5]. However, they require significantly more research endeavours for their rational approach and effective utilization in the drug discovery pipeline of natural drugs. Moreover, scientific validation emphasizing on safety and efficacy profile of botanical extracts and compounding is also necessary and can open new doors for herbal drug technology.

The herbal drug technologies have facilitated the drug utilization of phytoconstituents and bioactives in a more precised manner [6]. Interest in natural product research has been rekindled by discoveries of various novel natural molecules. But, therapeutic potential of natural molecules may often be limited by low solubility, bioavailability and instability

associated with herbals. Exploration of solid dispersion technique provides various advantages including enhancement of solubility and bioavailability, protection from toxicity, enhancement of stability, sustained delivery, protection from physical and chemical degradation etc [7].

Hence, there is a great potential for valuable herbal drugs to be formulated into solid dispersions which subsequently facilitates the safe, effective and convenient delivery of natural bioactive constituents in an efficient and controlled manner [8]. The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of administration [9, 10]. Among the various dosage forms available for oral administration, solid dosage forms have many advantages over other types of dosage forms owing to greater stability, diminutive bulk, accurate dosage and easy production.

Therefore, most of the new molecules under development are intended to be utilized as solid that originate an effective *in vivo* plasma concentration after oral administration [11]. But, the major problem associated with most of the drugs is inadequate solubility in biological fluids that ultimately limits their bioavailability and utility after oral administration [12]. The natural products with therapeutic benefits like curcumin[13], dihydroartimisinin [14], biochanin A [15] are poorly water soluble and not well absorbed after oral administration which detract them from inherent efficacy [16]. Moreover, low aqueous solubility and membrane permeability of a drug molecule consequently retard the drug absorption from gastrointestinal tract [11].

The insufficient solubility may be due to high crystallinity/high melting point of pharmacologically active compounds that leads to formation of zwitterion, insoluble salts and H-bonding network. Hydrophobicity/High log P is another reason for inadequate solubility due to lack of ionizable groups and high molecular weight[17, 18]. The drugs can be categorized into four classes according to biopharmaceutical classification system depending on *in vitro* solubility and *in vivo* permeability data as depicted in **Table 1**[19-21].

TABLE 1: BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

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

Among the four classes, class II drugs show poor solubility and high permeability. Therefore, their low ability to dissolve is a limitation to their overall rate and extent of absorption over their ability to permeate through the membrane. Hence, the formulation design for class II compounds should focus on the enhancement of aqueous solubility or dissolution rate [19]. Once these drugs dissolve, they rapidly pass through biological membranes such as the gastrointestinal wall[13, 22].

Development of an optimized and more bioavailable formulation of a particular drug is a herculean task [23]. Several methods have been employed to enhance the solubility, dissolution and subsequently bioavailability of drugs with low solubility profile. Some methods comprises of particle size reduction, cyclodextrin complexation, solubilization, co-solvency, solid dispersions, salt formation, polymorphs, solvents or hydrates, pro-drug approach, multiparticulate systems, etc. However each of these methods has some practical limitation [24].

Solid dispersion is one of the most successful and convenient strategic approaches to improve drug release of poorly soluble drugs [11]. This technique molecularly disperses the drug into polymeric carrier, and release rate depends on the nature of carrier [13, 25].

Solid dispersions: Solid dispersions have been traditionally used as an effective method to improve the dissolution property and bioavailability of poorly water soluble drugs [26]. In 1961, Sekiguchi and Obi first proposed the utilization of solid dispersions to increase the dissolution and oral absorption of such drugs[27]. Earlier studies also reveal that solid dispersion systems increased the drug dissolution due to improved solubility, wet ability and dispersability using hydrophilic carriers [26]. The development of solid dispersion as a practically viable method to enhance bioavailability of poorly water soluble

drugs overcame the limitations of several other approaches such as a salt formation, solubilization by co solvents and particle size reduction [28].

The term solid dispersions refer 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. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles based on their molecular arrangement[21]. Chiou and Riegelman defined the term solid dispersions as, 'a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures' [9, 29]. The dissolution of the drug has been enhanced by dispersing a poorly soluble drug in a highly soluble solid hydrophilic matrix[17].

Carriers explored for preparation: The choice of carrier has a tremendous impact on the success rate of the solid dispersion strategies. Following criteria should be considered during selection of carriers:

- High water solubility-improves wettability and enhances dissolution.
- High glass transition point-improve stability.
- Minimal water uptake.
- Soluble in common solvent with drug-solvent evaporation.
- Relatively low melting point-melting process.
- Capable of forming a solid solution with the drug-similar solubility parameter [16].

The excipients employed as carriers in solid dispersions and their nature has been summarized in **Table 2** [30, 31].

TABLE 2: CARRIERS USED IN SOLID DISPERSION

S. No.	Carriers	Nature
1.	Dextrose, Sucrose, Lactose, Sorbitol, Maltose, Mannitol, Galactose	Sugars
2.	Citric acid, Succinic acid, Tartaric acid	Acids
3.	Povidone, Polyethylene glycol, Hydroxyl propyl methyl cellulose, Methyl cellulose, Hydroxy ethyl cellulose, Pectin, Galactomannan	Polymeric material
4.	Polyoxyethylene stearate, Tweens, Spans, Gelucire 44/14, Pluronic F68	Surfactants
5.	Sodium acetate, Sodium-o-hydroxy benzoate, Sodium-p-hydroxybenzoate	Hydrotropes
6.	Urea, Hydroxyalkylxanthines, Silica gel, Sodium chloride, Microcrystalline cellulose	Miscellaneous

Mechanism of dissolution: The enhanced and effective dissolution rate of various drugs from prepared solid dispersions is based on different mechanisms described in the following section. These mechanisms include: (a) wetting of the drug is improved by direct contact of the drug with the hydrophilic polymeric material, (b) the saturated concentration around small particles is higher than around large particles [32], (c) the surface area is increased, and (d) the drug has higher energy in amorphous state than in the crystalline state through which the saturated concentration is increased [33]. Therefore, solid dispersion upgrades the bioavailability of poorly soluble drugs by increasing the drug dissolution rate and their saturated solubility in the gastrointestinal fluids [34].

Advantages: The solid dispersions provide the myriad spectrum of desired characteristics for effective delivery of drugs. Various advantages of solid dispersions are mentioned in the subsequent text: [16, 35-37]

- Improved wettability results in increased solubility.
- Particles having higher porosity. Increase in porosity influence carrier properties and increases the drug release profile.
- Amorphous state of drug leads to enhancement in drug release.
- Pre-systemic metabolism is reduced due to increase in dissolution rate and absorption.
- Liquid form of drug can be transformed into solid form.
- Solid dispersion method is usually preferred over other particle size reducing techniques to enhance the solubility because other size reduction techniques may not cause enough enhancements in drug solubility and improvement in bioavailability.
- Particle size reduction in solid dispersion leads to increased surface area which causes increase in dissolution rate and hence subsequently bioavailability is improved.

- By changing water solubility, drug bioavailability can also be increased.

Limitations: Despite of various merits of solid dispersion techniques, there are some limitations of solid dispersions and these are enumerated in the following section: [16, 36-38]

- Moisture and temperature may affect physical characteristics of solid dispersions.
- Tackiness property of solid dispersions, sometimes makes it difficult to handle.
- Stability problem of vehicle and drug may occur.
- Reproducibility of physicochemical characteristics.
- Large amount of carrier is required to achieve good dissolution.
- During storage of solid dispersion, many problems may be encountered such as phase separation, conversion of amorphous to crystalline form and crystal growth due to which decrease in solubility, dissolution and bioavailability occurs.
- Various synthetic polymers such as polyvinyl pyrrolidone, polyethylene glycol, mannitol are used which are water soluble and has low melting point and are used in large amount but these occasionally show less dissolution enhancement.
- Method of preparation is expensive.

Classification:

Considering mutual spatial arrangement of individual components and their state [39], various types of solid dispersions can be distinguished as presented in **Fig. 1** [36, 40]. The type of solid dispersion and its dissolution behaviour are strongly influenced by physicochemical properties of drug and carrier and the used production process [41].

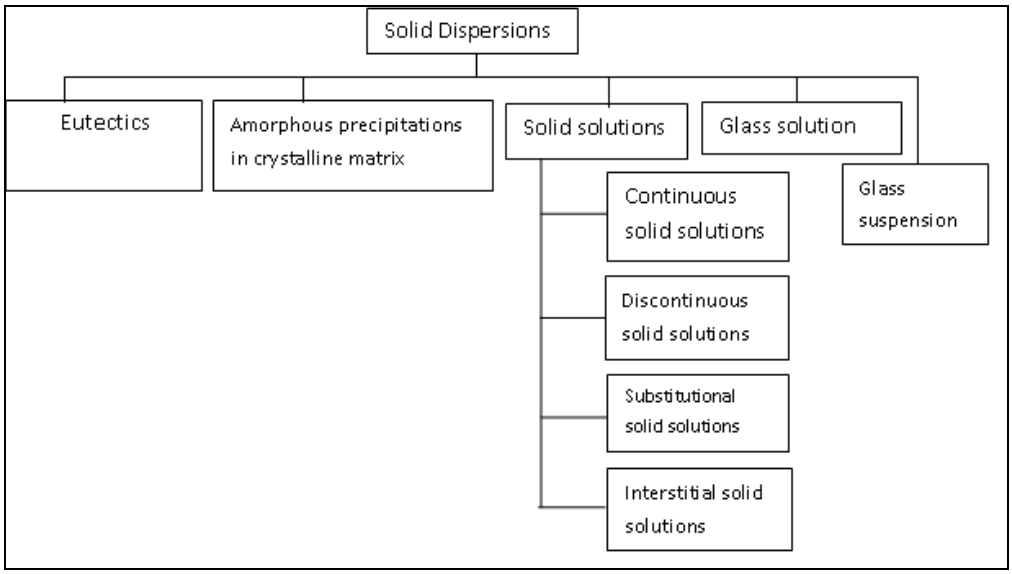

FIG. 1: CLASSIFICATION OF SOLID DISPERSIONS

Manufacturing process: The subsequent section is a brief preface of the various techniques widely accepted for formulation of solid dispersions.

1. Melting (Fusion method): Melting method comprises of heating all components above their melting or glass transition temperatures, followed by mixing and cooling [42]. The uniformly mixed melted mass is allowed to cool at room temperature or under cool conditions. The cooling rate may have great impact on the characteristics and stability of solid dispersion [24]. For cooling and solidification, various processes such as ice bath agitation [43, 44], solidification on petri dishes at room temperature inside a dessicator [45, 46], spreading on plates placed over dry ice [47], immersion in liquid nitrogen [48] or stored in dessicator [49, 50] were used [51]. The most important requirement with this method is that drug and carrier should be stable at the process temperature. Carrier should have a lower melting point (T_m) or high glass transition temperature (T_g) than the drug practically to allow

a more practically processing temperature and decreases the potential of drug degradation [41].

The method is advantageous due to its simplicity and economy [29]. In addition, a super saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature [52]. The major disadvantage of this method is that the texture of solid dispersion after cooling is quite hard. Therefore, size reduction of the solid dispersion may be difficult [41].

2. Solvent method: Solvent method aims to dissolve both the drug and carrier in organic solvent, followed by evaporating the solvent. Solvent is allowed to evaporate by various processes including vacuum drying [53, 54], heating on a hot plate [55], using rotary evaporator [56], a stream of nitrogen [57], spray drying [58], freeze drying [59] and using supercritical fluids [60, 61].

The advantage of this method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents [29]. The major challenge in the preparation of solid dispersion by solvent method is to mix both the drug and the matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution [40, 62].

3. Melting solvent method: The method is a combination of melting method and solvent evaporation method [63]. It is performed by dissolving the drug in a suitable solvent and mixing of this solution with the molten carrier followed by cooling, resulting in solidification [64, 65]. Such a unique method possesses the advantages of both the melting and solvent methods. Unfortunately, from a practical standpoint, it is only limited to drugs with low therapeutic dose, e.g. below 50 mg [29].

4. Hot melt extrusion: Hot melt extrusion is a combination of melting and a mechanical process in which the drug, polymer and optionally plasticizer are mixed and melted under controlled conditions of temperature and shear forces. The mass of co-melts is mixed with the help of transport screws and extruded through a die plate, yielding solid dispersions [41]. This method offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms [40, 66]. Metrex® process is a technology based on hot melt extrusions and applied for the development of a ritonavir-lopinavir combination tablet with improved dissolution characteristics [41]. Another technology based on molten substances is Meltdose® for improving the dissolution of fenofibrate [41].

5. Spray drying method: In this method, where a solution of drug and carrier is evaporated by spraying the solution as fine droplets into a chamber under controlled conditions of heat, humidity and air flow [63]. It is cheap, fast and a one-step process and is widely used for processing solutions, emulsions, suspensions into powders, efficiently controlling size, density and morphology of the particles [67]. However, the formation of a sticky product at the outlet of spray drier may occur [41].

6. Freeze drying method: Freeze drying consists of three successive steps: freezing, primary drying and secondary drying. A sample to be freeze dried consists of a drug, excipients and one or more solvents [41]. High freezing rates can be achieved by using cryogenic liquids such as liquid nitrogen. Either vials containing the solution can be immersed in the cryogenic liquid or the solution is sprayed directly into the cryogenic liquid [41]. It is preferred for the preparation of solid dispersion of thermolabile materials but also has a disadvantage of being time consuming and expensive process[24].

7. Supercritical fluid technology: Supercritical fluids can dissolve nonvolatile solvents, with the critical point of carbon dioxide; the most widely used supercritical fluid. This technique offers tremendous potential as it is safe, environmentally friendly and economical [68]. Supercritical micronization processes such as rapid expansion of a supercritical solution [69], gas anti solvent process [70, 71], particles from gas saturated solutions and precipitation with compressed fluid antisolvent [72]

have gained increasing attention and may be considered as interesting alternatives and most effective processes for microionization of solid dispersions [73].

8. Kneading method: The physical mixture of drug and carrier is triturated to thick paste utilizing small volume of solvent. The solvent used can be organic (alcohol, dichloromethane, acetone) or aqueous or mixture thereof. The kneaded paste is dried in an oven and the dried mass is pulverized and subsequently stored in dessicator. This process is economical but residual solvent may be an issue [24].

Characterization aspects: Characterization of solid dispersion is intended for identification of physical state (amorphous or crystalline), various properties (such as particle size, degree of crystallinity, shape, morphology etc.), drug-carrier interactions, drug-carrier miscibility, dissolution testing and stability parameters.

Various techniques employed in the characterization of solid dispersions includes microscopic techniques (polarized light optical microscopy, scanning electron microscopy, atomic force microscopy and hot stage microscopy); spectroscopic techniques (fourier transform infrared spectroscopy, H^1 nuclear magnetic resonance, Raman spectroscopy); thermal analysis technique (conventional differential scanning calorimetry, temperature modulated differential scanning calorimetry, isothermal microcalorimetry) and various other miscellaneous techniques such as powder X-ray diffraction, water vapour sorption etc [29, 40, 74-85].

Careful analysis of literature on solid dispersions provides prominence to their success in enhancing solubility, dissolution and subsequently bioavailability of several natural moieties. **Table 3** highlights the favourable outcomes and reported method of preparations of various solid dispersions of natural constituents. Several research endeavour have been carried out by large number of investigators worldwide in order to enhance the dissolution rate and thereby bioavailability of diverse naturally active constituents.

TABLE 3: LIST OF NATURAL DRUGS INCORPORATED INTO SOLID DISPERSIONS

S. No.	Natural drugs	Ingredients utilized	Method of Preparations	Objectives	References
1	Curcumin	Cellulose acetate	Solvent evaporation method	Enhanced bioavailability, solubility and sustained release	13
2	Dihydroartemisinin	PVP K30, PVP K25, PVP K15 and inclusion complexes with HPβCD	Solvent evaporation method	Improved solubility and bioavailability	14
3	Cryptotanshinone, Tanshinone I, Tanshinone IIA	Poloxamer 407, 2-Hydroxypropyl-β-cyclodextrin, PVP K-30, PEG 8000,PEG 3400, Microcrystalline cellulose	Solvent method	Enhanced solubility, dissolution and bioavailability	34
4	Paclitaxel	Poloxamer 188, PEG	Melting method	Improved drug release	86
5	Ginsenosides	Sodium dodecyl sulphate	Hot melt extrusion and cogrinding	Improved dissolution and bioavailability	87
6	Tanshinone II A	Nano silica, Poloxamer 188	Solvent method	Improved dissolution and stability	88
7	Camptothecin	Soluplus, Citric acid	Solvent evaporation	Increased aqueous	89

			method	solubility, stability	
8	Evodiamine	PVP K-30	Solvent method	Increased dissolution rate, improved solubility and oral bioavailability	90
9	Carvedilol	Porous silica (Sylysia)	Solvent evaporation method	Improved wettability and dissolution	91
10	Quercetin	PVP, Pluronic F127	Evaporative precipitation of nano suspension	Enhanced drug dissolution	92
11	Silymarin	HPMC E 15LV	Kneading, spray drying and co-precipitation methods	Improved solubility and dissolution, reduction in crystallinity	93
12	Artemether	PVP K25, PEG 4000	Freeze drying and melting method	Improved rate of dissolution	94
13	Dihydroartemisinin	PVP K30	Solvent evaporation method	Improved water solubility	95
14	Curcumin	Hydroxypropyl cellulose SL, Hydroxypropylmethyl cellulose acetate succinate	Nanomill-01 system, Freeze drying	Improved dissolution, bioavailability and high photochemical stability	96
15	Cinnamon oil	Stearic acid, PEG 6000, Gluceryl monostearate	Melting method	Sustained release	97
16	Pilocarpine hydrochloride	Ethylcellulose, Hydroxypropyl methyl cellulose phthalate	Solvent method	Sustained release	98
17	Etoposide	PEG	Co-precipitation method	Enhanced solubility and dissolution rate	99

Therefore, several scientific advancements have been undertaken in the avenue of phytoconstituents based solid dispersion technology which reflects the successful and effective utilization of various natural drugs.

CONCLUSION: The naturally active constituents have tremendous pharmacological significance, however; their effective utilization has been limited due to various constraints such as poor solubility, bioavailability and instability. Large number of investigators across the globe developed numerous techniques to overcome several problems associated with herbal drugs. Solid dispersion technology has been explored by scientific community as an efficient and successful methodology for improving solubility profile and bioavailability of natural drugs. Moreover, it is a promising and convenient method for achieving sustained release characteristics of natural moieties.

The present manuscript is an attempt to provide an insight view on the design and development of solid dispersion of natural constituents. Furthermore, the wide availability of carriers and various preparation techniques along with characterization aspects of solid dispersions are also discussed. Despite remarkable achievements in solid dispersion technologies, this arena still has promising potential for future innovations and

advancements in the delivery of various botanicals. Investigational research can also be persuaded to improve the feasibility and proper utilization of new herbal drug delivery systems. Furthermore, these exciting opportunities will also quicken the expansion of research and commercialization of this advanced approach in the fascinating arena of phytoconstituents.

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