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Recent Breakthroughs in Solid Dispersion: A Review

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Abstract

The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The drugs therapeutic efficacy depends upon the bioavailability and ultimately on the solubility of drugs. Solid dispersion seems to be a viable approach for overcoming this problem. The strategy has proven to improve the bioavailability by dispersing the hydrophobic drug within hydrophilic matrix which resulting increased solubility due to increased surface area available for dissolution. The present article reviews the various preparation techniques of solid dispersion and compiles some of the recent technologies for eg. direct capsule filling method, electrostatic spinning method and dropping method. The different types of solid dispersions based on the molecular arrangement, methods of their characterization and aging of solid dispersion have been highlighted.

Keywords: S*olid dispersions, Recent techniques, Aging effect.*

Introduction

A number of methodologies can be adopted to improve solubility and bioavailability of poorly soluble drug. The techniques generally employed for solubilization of drug includes solid dispersion, micronization, chemical modification, pH adjustment, complexation, co-solvency, micellar solubilisation, hydrotrophy etc. Solubilization of poorly soluble drug is a challenging aspect in screening studies of new chemical entities as well as in formulation design and development 1, 2. Any drug absorbed only when it presents in the form of an aqueous solution at the site of absorption 3, 4, 5. As solubility and permeability are the deciding factor for in vivo absorption of the drug, these can be altered or modified by different solubility enhancement techniques 6.

The term solubility is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution in which the solute in equilibrium with the solvent The solubility of a drug is represented through various concentration expressions such as parts, percentage, molarity, molality, volume fraction and mole fraction 7, 8.

In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bio-availability enhacement of poorly water-soluble drugs can be overcome. This method was later termed solid dispersion, involved the formation of eutectic mixtures of drugs with water soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state 9 Later, Goldberg et al. demonstrated that all the drug in a solid dispersion might not be present in a microcrystalline state; a certain fraction of the drug could be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was

exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water soluble drugs were expected to be high.

Because of such early promises in the bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the area of interest in the pharmaceutical research. Numerous papers on various aspects of solid dispersion were published since 1961; Chiou and Riegelman with Ford reviewed the early research in this area. Despite an active research interest, the commercial application of solid dispersion in dosage form design has been very limited. Only two products, a griseofulvin-in-poly (ethylene glycol) solid dispersion (Gris-PEG, Novartis) and a nabilone—in povidone solid dispersion (Cesamet, Lilly) were marketed during three decades following the initial work of Sekaguchi and Obi. The objectives of the present article are critically review some of the limitations of solid dispersion that prevented its wider commercial application and to discuss how the situation is now changing because of the availability of new types of carriers and the development of new manufacturing technologies.

Various Approaches for Solubility Enhancement

1. Drug dispersion in carriers:
   - Eutectic mixtures
   - Solid solutions
   - Solid dispersions
2. Solubilization with solvent
3. Complexation with polymer
4. Micronization,
5. Nanosuspensions.
6. Modification of the crystal habit
7. Alteration in pH
8. Use of surfactant
9. Use of cyclodextrin
10. Change in physical form
11. Use of prodrug and drug derivatization

Solid Dispersion

Chiou and Riegelman defined solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" 10. The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. 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. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category 22.

Therefore, based on their molecular arrangement, different types of solid dispersions (SDs) can be distinguished and certain combinations can be encountered in the same sample i.e. some molecules are present in clusters while some are molecularly dispersed. In various studies the type of solid dispersions is based on the method of preparation. Since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argue that solid dispersions should preferably designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions and hence it is essential to use terms that indicate the molecular arrangement in the solid dispersion.

Classification of solid dispersion 39, 40

A solid dispersion is a homogeneous mixture of one or more active ingredients in an inert matrix (carrier) in the solid state. Table 1 shows the various classes of solid dispersion that can be produced and the type and number of solid phases present.

Breakthroughs in Solid Dispersion Technology

The recent breakthroughs in the formulation of solid dispersion systems involve (1) Direct capsule filling (2) Electrostatic spinning method (3) Supercritical Fluid technology and (4) dropping method.

Direct Capsule Filling Method:

The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first prepared in 1978 [83]. It was not until much later that the potential application of the technique for solid dispersions is fully realized. Chatam reported the possibility of preparing PEG- based solid dispersions by filling drug- PEG melts in hard gelatin capsules [84]. By using PEG with molecular weights ranging from 1000 to 8000, Serajuddin et al., demonstrated that a PEG itself might not be a suitable carrier for solid dispersion of poorly water soluble drugs intended for direct filling into hard gelatin capsules [17]. Laboratory- scale semiautomatic equipment [85]and large- scale manufacturing equipment for direct capsule filling are commercially available. Direct filling of hard gelatin capsules with the liquid melt of solid dispersion avoids grinding- induced changes in crystallinity of the drug. The filling of hard gelatin capsules has been feasible in molten dispersions of Triamterene-PEG 1500 using a Zanasi LZ 64 capsule- filling machine (Zanasi Co, Bologna, Italy)[86]. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross-contamination and operator exposure in a dust free environment, better fill weight and content uniformity was obtained with the solid plug than the powder fill technique. However, PEG was not a suitable carrier for the direct capsule filling method as the water- soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug [50]. A surfactant must be mixed with the carrier to avoid formation of a drug rich surface layer (eg, polysorbate-80 with PEG, phosphatidylcholine with PEG) [87, 17]. The temperature of the molten solution should not exceed 70ºC because it might compromise the hard gelatin capsule shell.

Elecrtostatic Spinning Method:

The electrostatic spinning technology used in the polymer industry combines solid solution / dispersion technology with nanotechnology [88, 89] this technology is now applied in the pharmaceutical field [90, 91]. Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter scale nozzle [92]. The process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. When the electrostatic field strength up to, but not exceeding, a critical value is increased, the charge species accumulated on the surface of a pendant drop which destabilize the hemispherical shape into a conical shape (commonly known as Taylors cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone due to relieving the charge built up on the surface of the pendant drop. The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the increased viscosity, as the charged jet is dried [95]. Water- soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and non biodegradable) polymers are useful in controlled dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct incorporation into a capsule. Itraconazole/HPMC nanofibers have been developed using this technique. Electro spun samples dissolved completely over time, with the rate of dissolution being dependant on the type of formulation presentation and the drug: polymer ratio. Because the technique has been successfully used in other fields, it has tremendous potential for the preparation of nanofibers and controlling the release of biomedicine, as it is simplest and cheapest [27, 93, 94]. The technique can be extended in the pharmaceutical industry for the preparation of solid dispersions.

Supercritical Fluid Technology:

SCF techniques can be applied to the preparation of solvent free solid dispersion dosage forms. Traditional methods suffer from the use of mechanical forces and excess organic solvents. A solid dispersion of Carbamazepine in polyethylene glycol 4000 (PEG-4000) increased the rate and extent of dissolution of carbamazepine. In this method, a precipitation

vessel was loaded with solution of Carbamazepine and PEG-4000 in acetone, which was expanded with supercritical CO_2 from the bottom of the vessel to obtain solvent- free particles. The physical and thermal properties of SCFs fall between the pure liquid and gas. SCFs offer liquid-like densities, gas-like viscosities and compressibility properties and higher diffusivities than liquids. The properties OF SCFs, such as polarity, viscosity, and diffusivity, can be altered several-fold by varying the operating temperature and/or pressure during the process. This flexibility is enabling the use of SCFs for various applications in the food and pharmaceutical industries. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Out of these, CO_2 is a widely used SCF in the pharmaceutical processing due to its unique properties.

SCF technology provides a novel alternative method of generating small particles with higher surface area that are free flowing and very low residual organic solvent. The formation of small particles is highly dependent on the materials in research problem and requires optimization of process conditions. These aspects of the technology can be applied to formulate coprecipitates of drug in water-soluble carrier and thus overcome many aforementioned problems of conventional methods. The solid dispersion prepared from this method has been found to increase the dissolution considerably. The technique also used to precipitate homogeneous antracene-phenanthrene crystals of solid solution. The applicability of RESS (Rapid Expansion of Supercritical Solution) for preparation of solid dispersions is limited due to the very low or negligible solubility of most drugs and polymers in the commonly used supercritical CO_2. Another advantage of the method is that the amount of the impregnated drug can be controlled and the process can be immediately stopped by depressurizing the high-pressure cells once the desired level of impregnation is achieved. In addition, the process of impregnation that depends on the drug diffusion rate can be easily tuned by the pressure of the SCF solution, which influences the sorption and polymer swelling. Particle formation in a light-free, oxygen free, and possibly moisture-free atmosphere minimizes their confounding effect during scale-up. Advances in understanding the mechanism of supercritical particle/co precipitate formation and SCF mass transfer form the basis for efficient scale-up. Industrial units, such as Bradford Particle Design have resources for the annual production of 1 ton of cGMP material. The cost of manufacturing in pilot scale with SCF technology is comparable with (or may be better than) conventional techniques such as single-stage spray drying, micronization, crystallition, and milling batch operations.

Dropping Method:

The dropping method is a new procedure for producing round particles from melted solid dispersions was developed by Ulrich et al. to facilitate the crystallization of different chemicals. This technique may overcome some of the difficulties inherent in the other methods. A solid dispersion of a melted drug- carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and size of the pipette, because viscosity is highly temperature dependant, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape. Produced solid dispersions by dropping method at an industrial level developed by Rotoform; Sandvik Process System Co, Sandvik, Sweden. The important advantage of the dropping method does not use organic solvents and therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. A disadvantage of the dropping method is only the thermostable drugs can be used and the physical stability of solid dispersions is a further challenge. Although there is still much work to do in this field (better size distribution, uniformity and stability), the dropping method is a promising approach in the formulation of solid dispersions. Simplifying the formulation process for the dropping may overcome manufacturing difficulties.

The Advantageous Properties of Solid Dispersions

Particle Size

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.

Wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement was seen in solid dispersions [41]**.** It was observed that even carriers without any surface activity, such as urea improved drug wettability[42]. Carriers with surface activity such as cholic acid and bile salts when used can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects [9].

Table: 1 Types of solid dispersion

Sr.	Solid dispersion type	Matrix *	Drug **	Remarks	No. Phases
I	Eutectics	C	A	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	C	C	Rarely encountered	2
III	Solid solutions				
	Continuous solid solutions	C	M	Miscible at all composition, never Prepared	1
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed.	2
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (Solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	1or2
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
VI	Glass solution	A	M	Requires miscibility **or** solid solubility, complex formation or upon fast cooling **or** evaporation during preparation, many (recent) examples especially with PVP	1

*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.

Porosity

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 [40]. The increased porosity of solid dispersion particles also hastens the drug release profile.

Amorphous state

Poorly water soluble crystalline drugs, when converted into 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 [45]. 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 [41]. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them [46]. Formulations for enhancing dissolution rate and consequent bioavailability of poorly water-soluble drugs [27]

Disadvantages

The limitations of this technology have been a drawback for the commercialization of solid dispersions, the limitations include

1. Reproducibility of physicochemical characteristics,
2. Difficulty in incorporating into formulation of dosage forms,
3. Scale-up of manufacturing process and
4. Stability of the drug and vehicle.

Pharmaceutical Applications of Solid Dispersion

The pharmaceutical applications of solid dispersions technique are numerous. They may be employed

1. To enhance the absorption of drugs.
2. To obtain a homogeneous distribution of a small amount of drug in solid state.
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photooxidation etc.
4. To dispense liquid or gaseous compounds.
5. To formulate fast release priming dose in a sustained release dosage form.
6. To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.
7. 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.
8. To mask unpleasant taste and smell. The very unpleasant taste of anti-depressant famoxetine hindered the development of liquid oral formulations. The bitter taste was greatly suppressed when the solid complex of famoxetine was formulated as aqueous suspension.
9. 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.

Preparation of Solid Dispersions

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete) and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling procedure. Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining the driving force low for example, by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

Fusion method:

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath, immediately after fusion, the sample are poured onto a metallic plate which is kept at ice bath. A modification of the process involves spray congealing from a modified spray drier onto cold metal surface. Decomposition should be avoided and is affected by fusion time and rate of cooling. Another modification of the above method, wherein solid dispersions of Troglitazone-polyvinyl pyrrolidone (PVP) K-30 have been prepared by closed melting point method. This method involves controlled mixing of water content to physical mixtures of troglitazone PVP K -30 by storing at various equilibrium relative humidity levels (adsorption method) or by adding water directly (charging method) and then mixer is heated. This method is reported to produce solid dispersions with 0% apparent crystallinity. On the other hand, the fusion process does not require an organic solvent but since the melting of sparingly water-soluble drug and water- soluble polymer entails a cooling step and solid pulverizing step, a time consuming multiple stage operation is required. To overcome this problem have described a method conceptualizing the formation of a solid dispersions as the solid-to-solid interaction between a sparingly water soluble drug, nilvadipine and water soluble polymer which, unlike conventional production method, comprises mixing a sparingly water soluble drug and water soluble polymer together under no more than the usual agitation force with heating within the temperature region not melting them, instead of heating the system to the extent that the two materials are melted, the sparingly water soluble drug can be made amorphous to have never been achieved by any process heretofore known.

Solvent evaporation method:

The solvent- based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. Identification of a common solvent for both drug and carrier can be problematic, and complete solvent removal from the product can be a lengthy process. Moreover suitable alterations in the concentrations used for solvent evaporation may lead to large changes in the product performance. In addition large volumes of solvents are generally required which can give rise to toxicological problems. Many investigators studied solid dispersions of Meloxicam, Naproxen, Rofecoxib, Felodipine, Atenolol, and Nimesulide using solvent evaporation techniques. These findings suggest that the above- mentioned technique can be employed successfullyfor improvement and stability of solid dispersions of poor water soluble drugs. Bhanbhun M Suhagic suggested a method for preparation of solid dispersions of etorocoxib employing solvent evaporation process wherin carrier is poly ethyl glycol (PEG) and PVP along with drug were dissolved in 2-propanol to get a clear solution and solvent was evaporated. The prepared solid dispersions exhibited improved dissolution attributed to decreased crystallinity, improved wetting and improved bioavailability.

Melt agglomeration on process:

This technique has been used to prepare solid dispersions wherein the binder acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipients to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipients (spray- on procedure) by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersions by melt agglomeration.since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray- on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogeneous distribution of drug

in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

Surface- active carriers:
The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigatiors for preparation of solid dispersions. Recently a new class of surfactants, gelucires has been proposed with different melting points and HLB (hydrophilic and lipophilic balance) values. Gelucire excipients have been used in the formulation of semi solid dispersions. Gelucires are the saturated polyglycolized glycerides consisting of mono-, di-, and tri-glycerides and of mono- and di-fatty acid esters of polyethylene glycol. The nature and proportion of each component are specific to a given grade of gelucire. Gelucires with low HLB can be employed to decrease the dissolution rate of drugs and higher HLB ones for fast release. Gelucire 44/14 and gelucire 50/13 are two examples of this synthetic group where 44 and 50 represent melting point, while 14 and 13 represent HLB values of gelucire respectively. Solid dispersions of antiviral agent uc- 781 – polyethylene glycol 6000- gelucire 44/14 and UC-781-PEG 6000-gelucire 44/14-PVP K-30 were studied and improvement in solubility, dissolution and stability was observed.
Examples of surface active carriers used for dissolution enhancement.

Sr.No.	Carrier	Drug	Scientist
1	PEG, Myrj 2, Eudragit E 100	Indomethacin	Hadi et al
2	Gelucire44/14 and PEG 6000	Glibenclamide	Tashtoush
3	Gelucire44/14, Vitamin E TPGS	Carbamazepine	Seong-Wan CHO et al
4	Poloxamer 188	Ibuprofen	Passerini
5	Poloxamer 407	Nifedipine	Chutinawarapan et al

Characterization of Solid Dispersion

Many methods are available that can contribute information regarding the physical nature of a solid dispersion system. In many instances, a combination of two or more methods is required to study its complete picture. The advantages and disadvantages of each method are briefly expounded here.

Thermal Analysis:
This is the most common approach used to study the physicochemical interactions of two or more component systems. Several modified techniques utilizing the principle of change of thermal energy as a function of temperature are discussed separately.

Cooling curve method:
In this method, the physical mixtures of various compositions are heated until a homogeneous melt is obtained. The temperature of the mixture is then recorded as a function of time. From a series of temperature- time curves, the phase diagram can be established [47]. The method suffers from many inherent disadvantages. It is time consuming, it requires a relatively large amount of sample and changes in slopes can be missed, especially if cooling takes place rapidly. In addition, the method cannot be applied to samples that decompose after melting. It is also difficult to detect samples with small solid solid solubility. This method was recently used to determine phase diagrams of deoxycholic acid menadione and caffeine- Phenobarbital [48].

Thaw-Melt Method:
In this method, a sample of a solidified mixture in a capillary melting-point tube is heated gradually. The thaw point is referred to a temperature on crossing a solidus line [47]. This

simple method was used extensively by Rheinboldt, Rheinboldt and Kircheisen, and Guillory et.al. A stirring device in a capillary tube was employed for more accurate results by Sekiguchi et.al [49]. The stirring facilitates the attainment of a homogeneous system; however, such stirring only affects the melting point and not the thaw point. In differentiating between a simple eutectic system and a limited solid solution, the diagnostic point lies at the thaw point. Therefore, the usage of this more complicated device is not necessary for such a purpose. The principal drawback of this thaw-melt method is that it depends on a subjective observation and thereby is not highly reproducible. A range of six degrees of variation was reported in the study of thaw points of a chloramphenicol-urea system [50]. Furthermore, a suitable, upper range of melting points is only limited to about 300 ºC due to the problem associated with capability of visualization. The sample used for study may also be prepared from merely the physical mixture or the evaporated mixture obtained after removing the liquid solvent from the solution [49]. Thaw points are often found at lower temperatures from the samples of physical mixtures, while the melting points are not affected [49]. A special quenching method is proposed for samples exhibiting supercooling properties. A mixture that has not completely solidified results in lower thaw and melting points upon reheating. This was observed in the eutectic composition of a sulfathiazole-urea system [51].

Thermomicroscopic Method:

Goldberg et.al.used polarized microscopy with a hot stage to study phase diagrams of binary systems. The physical mixture is placed on a slide covered with a cover slip and sealed with silicone grease to prevent sublimation. The mixture is heated until it completely liquifies. After cooling, the mixture is heated at the rate of 4º/ min. The thaw and melting points are then determined by visual observation. The advantages of this method are that it is simple and it requires only a small amount of sample. However, it suffers some disadvantages by often being subjective, limited to thermally stable compounds, and potentially inhomogeneous in distribution after resolidification. Furthermore, the melting of isotropic crystals often cannot be detected accurately under a polarizing microscope [52]. The existence of a limited solid solution of griseofulvin in succinic acid determined by this method appears to have been disproved by the DTA and X-ray diffraction method**.** The Kofler contact method, also utilizing polarizing microscopes, was proposed to establish various forms of phase diagrams [52]**.** However, the usage of such a technique seems to require a good knowledge of crystallography.

DTA:

DTA is an effective thermal method for studying phase equilibria of either a pure compound or a mixture. Differential effects, associated with physical or chemical changes, are automatically recorded as a function of temperature or time as the substance is heated at a uniform rate [53]**.** In addition to thawing and melting, polymorphic transitions, evaporation, sublimation, desolvation, and other types of decomposition can be detected. Apparatus permitting direct observation of samples during heating were used to facilitate the observation of any physical-chemical changes. The greatest advantage of using this technique is in constructing phase diagrams of high reproducibility; a higher temperature range is permitted and greater resolution results [54]**.** A sample size of less than 1 mg can be used for measurement with some commercial instruments. Although the sensitivity and accuracy of the DTA thermograms can be influenced by many factors such as sample size, heating rate, sample geometry, thermal conductivity of the sample container, and method of measurement of the sample temperature, these variables can be adjusted to optimize the desired characteristics of the DTA apparatus. The DTA method was used extensively to construct phase diagrams of a number of binary systems. This technique is especially valuable in detecting the presence of a small amount of eutectic in the mixture, because its melting at the eutectic temperature can be sensitively detected [55]. The observation of such small fractions of melting at eutectic temperature can often be missed when employing thaw-melt or thermomicroscopic methods.

Zone Melting Method:

This technique was first introduced in 1952[56]. It has been primarily used for ultrapurification of metals and inorganic and organic compounds. The phase diagram can be constructed for metals and inorganic and organic compounds. A molten zone affected by a heater traverses a cylindrical ingot or solidified melt at a rate of about 0.5-0.001 cm/ hr. A mechanical stirring device is also required for the mixing of the liquid in the molten zone. After zone melting is finished, the

bar is sectioned and analyzed for its chemical composition. From their chemical compositions and freezing temperatures of the corresponding sections, a phase diagram of a binary or multicomponent system can be constructed. This method is limited to compounds with high thermal stability and low volatility [56, 57]. It is especially valuable in determining the exact chemical composition of a eutectic and the minute solid-solid solubility at the eutectic temperature by merely a single pass. The solubility of InSe in InSb was found to be less than 1%; that of InSb in InSe was also found to be less than 1 by this method [58]. Many phase diagrams of metal systems have been determined by this method [59-61].

X-Ray Diffraction Method:

In this method, the intensity of the X- ray diffraction (or reflection) from a sample is measured as a function of different angles. Counter and film methods detect the diffraction intensity. The advantages and disadvantages of these two methods were well discussed [62, 63]. In the former method, a better resolution of diffraction peaks can be obtained, and it is also easier to compare their relative diffraction intensity. However, it requires more samples and has less reliability and more sensitivity to sample preparation and position. The latter method is more sensitive for the detection of weak lines. The diffraction method is a very important and efficient tool in studying the physical nature of solid dispersions. Recently, it was used to study binary eutectic systems of chloramphenicol-urea and griseofulvin-succinic acid. Many phase diagrams of inorganic and metal compounds were also determined by this method [64, 67]. In simple eutectic systems, diffraction peaks of each crystalline component can be found in the diffraction spectra, in a substitutional solid solution, the lattice parameter of the solvent crystal is either increased unchanged, or decreased, depending on the relative size of the solute atom or molecule. However, a gradual shift in the positions of the diffraction lines with changes in composition, which reflects the resulting change in the lattice parameter, is accepted generally as sufficient evidence for the existence of solid solutions. In a system of a continuous solid solution, there will be a shift from the position in one pure component to those in the other [67]. The interruption of this smooth change is indicative of immiscibility in the system. In an interstitial solid solution, the diffraction spectra of the solvent component may or may not be changed, while those of the solute component disappear. The diffraction method is also particularly valuable in detecting compound or complex formation since its spectra or lattice parameters are markedly different from those of pure components. It has been used to disprove the existence of a patented salt formation between penicillin V and tetracycline [68]. The biggest drawback of using the diffraction method to study dispersion systems is its frequent inability to differentiate amorphous precipitation from molecular dispersion if the lattice parameter of the solvent component is not changed. This is because of the disappearance of the diffraction peaks or lines of the crystalline solute compound in both systems. This problem is encountered in the lower concentrations of drugs dispersed in polyethylene glycol [41] or polyvinylpyrrolidone polymers. The solidified eutectic of sulfathiazole-urea has a broad (instead of sharp melting point as found for its physical mixture) and lower melting range. This is attributed to the presence of amorphous sulfathiazole. The amorphous form is transformed into a crystalline form after annealing at high temperature, as shown by the appearance of its sharp diffraction peaks. The diffraction method has been used to study quantitatively the concentration of a crystalline component in the mixture [68, 69]. The ability of this method to quantitate the crystalline component in solid dispersion systems may be limited by its low concentration or weak intrinsic intensity of diffraction. The height of diffraction peaks may be attenuated by a reduction of crystallite size, usually below 0.2 µ. This is also accompanied by a broadening of the peaks [68]. An extremely fine crystalline dispersion of Sulfathiazole in polyvinylpyrrolidone has also been considered one reason leading to the disappearance of sulfathiazole diffraction peaks. Integrated diffraction peak areas were used to study particle-size distribution between 0.002 and 0.2 µ [12].

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 polyvinylpyrrolidone 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 iopanoic acid in polyvinylpyrrolidone. The application of the electron microscope technique is, however,

usually limited to chemicals with high atomic numbers [76].

Spectroscopic Method:

Visible absorption spectroscopy was used to study the low concentration dispersion of β-carotene in polyvinylpyrrolidone [78]. The spectrum of the dispersed β- carotene resembles that of β- carotene dissolved in organic solvents but not that of β-carotene particles. These results indicated that β- carotene is dispersed molecularly in the polymer. The undetected shift of IR bands of the dispersed β-carotene was thought to indicate the absence of the marked interaction between β-carotene and polyvinylpyrrolidone. IR spectroscopy was also used to studythe solid solutions of nitrite ion in many inorganic halides such as KBr, NaCl, and KI [79, 80].

Dissolution- Rate Method:

The dissolution- rate method was recently proposed by Allen and Kwan [80] to study the degree of crystallinity in solid-solid equilibria, especially in temperature regions below solid-liquid equilibria. The method involves comparing the in vitro dissolution rates of the solute component from a constant- surface tablet made from molecular dispersion (i.e., solid or glass solution) with a physical mixture of the same chemical composition. The technique is simple to perform, except that in some binary systems the tablet surface may not remain constant due to the leaching of particles into the dissolution medium. Such difficulty was encountered in the mechanical mixture of the high sulfathiazole to polyvinylpyrrolidone ratio tablets [68], solid dispersion of barbital-polyethylene glycol 6000 system [41], and physical mixture of 10 % griseofulvin-90 % polyethylene glycol 6000 [41]. Tablets made up of 10% sulfathiazole- 90 % urea physical mixture under various pressures were also found to disintegrate almost immediately in the aqueous medium [56]. This was primarily due to the almost instantaneous dissolution of urea into water because the solubility of this small molecule compound in water is very high, approximately 1 g. in 1 ml. The dissolution of 10 % sulfathiazole-90 % urea solid solution from 10-20-mesh granules was also found to be complete almost immediately upon their exposure to water [56]. The almost instantaneous dissolution from such dispersion systems will make them difficult to compare quantitatively with the dissolution from physical mixtures.

The application of this method also requires: ***(a)*** the observed dissolution rate to be proportional to the surface area, ***(b)*** a reasonably large difference between the dissolution rate of the physical mixture and the corresponding solid solution, and **(c)** the use of the same polymorphic form of a drug in the tablet of the physical mixture as that precipitated out from the solid dispersion [68]. Most commercially available sulfathiazole, which was often used to prepare solid dispersions, is polymorphic Form I, while the precipitated sulfathiazole in the sulfathiazole-urea system is polymorphic Form II [56]. The dissolution rate of Form I was found to be 1.6 times higher than that of Form I [56]. Furthermore, one must assume in this dissolution method that the distribution of particle size (maybe as small as in the subcolloidal range) precipitated from the solid solution or glass solution does not affect the dissolution rate. Such assumption needs to be proved experimentally. The dissolution-rate method has been shown to be applicable to simulated systems of indomethacin-polyethylene glycol 6000 and sulfathiazole-urea. The validity of this principle, however, needs further confirmation by other methods.

Thermodynamic Method:

The phase diagrams of eutectic and solid solution systems can be constructed on the basis of some thermodynamic parameters [71, 73]. Knowledge of heats of fusion, entropies, and partial pressures at various compositions enables one to determine the solubility gap below the solid- liquid equilibrium temperature. A solubility gap in the continuous solid solution of the AgBr-NaBr system was also found from thermodynamic data obtained from an electromotive force study by galvanic cell [81, 82]. The detailed mathematical discussion of such an approach is beyond the scope of this article.

Aging of Solid Dispersions

The solid dispersion appears to be a potential dosage form modification for increasing dissolution and absorption rates of poorly soluble drugs. However, the results of aging or storage under various conditions and the effects on the fast-release characteristics and chemical stabilities have not been reported extensively. Hence, this will be an interesting and important research subject for pharmaceutical scientists before the wide and long-range practical applications of this unique approach are feasible. The effects of aging in many nonpharmaceutical

systems such as alloys and inorganic compounds have been well studied [10]. The purpose of this section is to review these studies with a hope that similar principles and methodologies can be utilized to apply to our systems. Ageing of the solid dispersions has deleterious effects on the dissolution of bropirimine whereas such ageing has no effects on the dissolution of the drug from the prepared inclusion complex [30].

Aging Effects of Eutectic Mixture:
It is well known that the dispersed-phase particles tend to coarsen on aging because the interfacial energy of the system is reduced by the concomitant reduction in interface area [31].This phenomenon occurs in eutectic systems with or without solid solution formation. The extent of coarsening increases with time and aging temperature. The morphology and transparency of a freshly prepared eutectic mixture of naphthalene phenanthrene were found to change after standing primarily due to recrystallization of fine grains [32].

Aging Effects of Glass Solution:
Since a glass solution is a metastable form, it may be subjected to aging transformation, yielding a more stable form. This may take place rapidly or extremely slowly, as in the case of untreated ordinary window glass kept at room temperature. Small-angle X-ray scattering and electron microscope methods were used to study the kinetics of a metastable amorphous phase separation from CaOMgO- SiO2 glass at 825' [33].

Aging Effects of Solid Solution:
The most important aging effect from solid solutions is the precipitation from supersaturated solid solutions along with the subsequent changes of physical-chemical properties [34]. The effect of precipitation from supersaturated solid solutions on the age-hardening of alloys is well known [34, 35]. Therefore, the hardening effect is also a function of composition, aging temperature, and time. Holding or aging the preparations for too long a period at a given temperature may also cause them to lose their hardness. This effect is known as overaging [35].

Conclusion

Most of the promising NCEs are poorly water soluble drugs, which may present a lack of therapeutic effect, because of their low bioavailability. Solid dispersions are one of the most attractive processes to improve drug's poor water solubility. Solid dispersions can improve their stability and performance by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity. Moreover, new optimized manufacturing techniques that are easily scalable are also coming out of academic and industrial research.

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