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RECENT SCENARIO OF GELUCIRES IN SOLID DISPERSION TECHNIQUES

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ABSTRACT

Poor water solubility is the major drawback for the various types of drugs and many approaches have been introduced for the solubility enhancement of such drugs. Solid dispersion is one of the techniques adopted for the formulation of such drugs. In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing) products. Presence of the drug in microcrystalline state, improved wettability and formation of high free energy amorphous forms of the drug during solid dispersion formation contribute towards enhancement of drug solubilisation. Despite the promising aspects of dissolution enhancement and simplicity of concept, the solid dispersion has decreased popularity due to manufacturing, stability and scale-up issues. Solid dispersions of poorly water-soluble drugs with water-soluble carriers has been reduced the incidence of these problems and enhanced dissolution. The focus of this review article on advantages, disadvantages of solid dispersions, method of their preparations and current use of gelucires in solid dispersion formulations. This article will also address the physical characterization of a Gelucire based solid dispersion formulation and illustrate some of its potential drawbacks in terms of physical stability.

KEYWORDS: Gelucires, Solubility, Dissolution, Solid dispersion.

INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro- intestinal fluids often cause insufficient bioavailability rather than the limited permeation through the epithelial and the formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industries. A review of new monograph (1992- 1995) in European pharmacopoeia shows that 40% of drug substances have aqueous solubility below 1mg/ml and the 32% have an aqueous solubility below 0.1 mg/ ml. The oral route of drug administration is the most common and preferred method of delivery. Drug absorption from the GIT can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and or poor membrane permeability of drug molecule. While delivering active agent orally it must first dissolve in the gastric and or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: Enhancing solubility and dissolution rate of poorly water soluble drugs and Enhancing permeability of poorly permeable drugs. The use of solid dispersion technique is used to improve the dissolution characteristics of poorly water soluble drugs and in turn their oral bioavailability.[1]

Gelucires are a group of inert semisolid waxy amphiphilic excipients, which are surface active in nature and disperse or solubilise in aqueous media forming micelles, microscopic globules or vesicles. They have been studied as controlled release matrices as well as for improvement of physicochemical properties of drugs. They are identified with respect to their melting point and HLB value. The wide varieties of gelucires are characterized by a wide range of melting points from about 33°C to about 64°C and most commonly from about 35°C to about 55°C, and by a variety of HLB values from about 1 to about 14, most commonly from about 7 to about 14. In the designation of gelucire names, for example, Gelucire 54/02, 54 indicates melting point and 02 indicates its HLB value. Low HLB gelucire can be used to reduce the dissolution rate of drugs. High HLB gelucire can be used for faster release of drugs. Gelucires are vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparation

of sustained release formulations. It has been reported sustained release single unit matrices using Gelucire 43/01, where only 1.7% theophylline was released over a period of 20 hours. Gelucire 43/01 has been also used for the design of multi-unit floating systems of a highly water-soluble drug, diltiazem HCl. The granules were retained in stomach at least for 6 hours. Approximately 65% to 80% drug was released over 6 hours with initial fast release from the surface . The hydrophobic Gelucire 43/01 (GEL) has been used as a coat to extend the release of Felodipine. Caprol PGE-860 was added to this coat as a release enhancer. Caprol PGE-860, by virtue of channel formation in Gelucire coat favoured the Felodipine release. The Felodipine preparation encased within the Gelucire coat was considered to be useful as an extended release composition for lipophilic drugs. The drug release was primarily controlled by diffusion in case of hydrophobic variants of Gelucire (Gelucire 43/01 and 54/02).[2]

There are many techniques which enhances solubility of poorly soluble drugs which include microencapsulation, self emulsifying drug delivery system (SMEDDS), pH adjustment,etc. But every technique has some or the other disadvantage which can be overcome by solid dispersion.

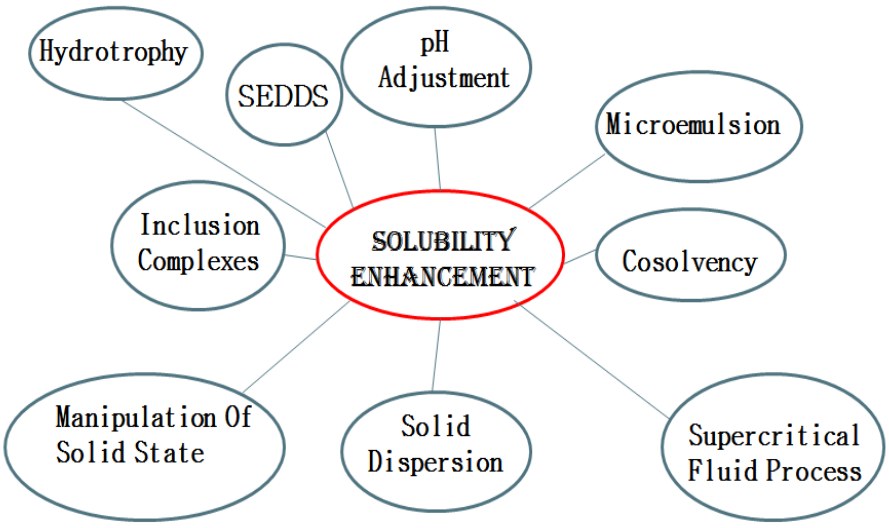

Figure 1: Summarizes various approaches to enhance solubility of poorly solubility of drugs

SOLID DISPERSIONS

Definition of solid dispersions

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. Chiou and Riegelman defined the term solid dispersion as "*a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures"*.

The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Table 1. Moreover, certain combinations can be encountered, i.e. in the same sample; some molecules are present in clusters while some are molecularly dispersed. Confusingly, in various studies the designation of solid dispersions is based on the method of preparation. However, since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argued that solid dispersions should preferably be designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions. Therefore, it is essential to use terms that indicate the molecular arrangement in the solid dispersion. Knowledge about the molecular arrangement will enlarge comprehension of the properties and behaviour of solid dispersions. Furthermore, it will facilitate optimization of their properties required for a specific application. For example, the mechanism underpinning the dissolution of solid dispersions is poorly understood. Many case studies showed accelerated dissolution of hydrophobic compounds using solid dispersions but mechanisms are rarely discussed. The most important reason for that is the lacking knowledge about the mode of incorporation of the hydrophobic drug in the matrix, despite numerous efforts to clarify this. A question like, "is the drug present as a crystalline phase or as amorphous nano-particles or molecularly dispersed throughout the matrix" is rarely discussed. All three situations result in different drug concentrations at the dissolving interface. Still it has not been fully elucidated how this affects dissolution behaviour of solid dispersions. Secondly, the physical and chemical stability of the matrix or the incorporated drug depends on the mode of incorporation. If drug molecules, for example, are present in amorphous nano-particles, crystallization requires only rotational rearrangement. On the other hand, for a molecularly dispersed drug, translational diffusion is necessary before crystallization can occur by rotational rearrangements. The physical state of the matrix is also important for the chemical

stability of the drug: the crystallinity of the matrix influences the translational and rotational rearrangements of the drug necessary for degradation reactions. Finally, the influence of drug load and method of preparation on dissolution behaviour and stability of solid dispersions can only be understood and predicted when the relation between these characteristics and the mode of incorporation is known.[3]

Table 1: Classification of solid dispersions in six subtype

Solid dispersion type		Matrix#	Drug##	Remarks	No. of Phases
I	eutectics	C	C	the first type of solid dispersions prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	rarely encountered	2
III	solid solutions	C			
	Continuous solid solutions	C	M	miscible at all compositions, 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 matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinous: 2 phases even though drug is molecularly dispersed	1 or 2
	Interstitial solid solutions	C	M	drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinous. 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/solid solubility, complex formation or upon fast cooling/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

Advantages of solid dispersions over other strategies[4]

Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a prodrug. Solid dispersion appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Formulation approaches include solubilization and particle size reduction, and solid dispersions. Among others, Solid dispersions are more acceptable to patients than solubilization products since they give rise to solid oral dosage forms instead of liquid as solubilization products usually. Milling or micronization for particle size reduction are commonly performed as approaches to improve solubility, on the basis of increase in surface area.

The higher dissolution rates of solid dispersion can be ascribed to a number of factors which includes:

1. The formation of higher energy metastable states of components as a function of the carrier system being used and the proportion of carriers present.
2. The reduction of particle size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption.
3. Formation of amorphous forms of drug and carriers.
4. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug., hence the higher dissolution rates. The presence of carrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution.
5. Co solvent effect on the the drug by the water soluble carriers.
6. Intermolecular hydrogen bonds between drug and carrier.

DISADVANTAGES[5, 6]

The rare occurrence of solid dispersion based pharmaceutical dosage forms in the clinic are due to problems in scale-up of preparation methods, difficulties in dosage form development and poor and irreproducible physical and chemical stability of drug and matrix . Knowledge about the behavior of solid dispersions during preparation, storage and dissolution can help to tackle these problems. A thorough understanding of processes that occur place on the molecular level is a prerequisite for rational and more efficient design of solid dispersions. However, development of solid dispersions has often been a trial-and-error approach. Unfortunately, most reports deal with a case, in which the authors used a specific matrix to accelerate the dissolution of a specific drug in-vitro or to show increased bioavailability.

PREPARATION OF SOLID DISPERSIONS[7,8]

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 SD(s) 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 k30 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 SD with 0% apparent crystallinity.

Supercritical fluid process

This process includes dissolving the drug and carrier in supercritical CO2 under precise conditions of temperature and pressure, followed by rapid depressurization. Supercritical CO2 is nontoxic and it has the potential as an alternative for organic solvents.

Solvent Evaporation Method

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or

carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as

1) The higher cost of preparation.

2) The difficulty in completely removing liquid solvent.

3) The possible adverse effect of traces of the solvent on the chemical stability

4) The selection of a common volatile solvent.

5) The difficulty of reproducing crystal form.

6) In addition, a super saturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties.

Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid-state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding. The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties using the solvent method, the pharmaceutical engineer faces two challenges. The first challenge is to mix both drug and matrix in one solution, fusion method is poly (vinyl pyrollidone) PVP. PVP, supplied in the amorphous state, is heated to above its Tg. The drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V or VI are obtained. The mode of incorporation of the drug depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle. Although frequently applied, the fusion method has serious limitations.

Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture, which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose a temperature of 169°C was required and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. PEG's melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.

Lyophilization

It is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices, the technique is poorly exploited for the preparation of solid dispersions . One of the reasons might be the low freezing temperature of most organic solvents. Obviously, sublimation during freeze drying is only possible when the solvent stays frozen. In addition when the formation of a glass is envisaged, the sample temperature should be kept below the Tg of the maximally freeze concentrated fraction. Therefore, low sample temperatures are required which slows down the process. Betageri and Makarla used a condenser temperature of -75°C, to dry a solution with cyclohexanol as the solvent. In table 2 an overview is presented of several organic solvents. To obtain a lyophiliation process of acceptable duration, the solvent should have a sufficiently high vapour pressure. As can be seen in table 2, dimethylsulphoxide DMSO has a high melting temperature but it has a very low vapour pressure. Therefore, DMSO is not suitable as a solvent for freeze drying. A suitable solvent that meets both requirements is 2-methyl-2-propanol or tertiary butanol (TBA), because it has a high melting temperature as well as a high vapour pressure. The application of TBA in lyophilization is discussed by Teagarden. Also mixtures of solvents can be considered. However, in that case the phase diagram of the mixture should be consulted. For example, while water and DMSO have melting points of 0°C and 19°C, the mixture has eutectic points below -60°C. The sample temperature of such a mixture should be kept below this value, which causes a slow sublimation.

An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified.

An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum. Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary, or nasal administration.

Table 2: Atmospheric Melting And Boiling Temperature And Vapour Pressure Of Organic Solvents

Solvent	Melting Point (°C)	Boiling Point (°C)	Vapour Pressure At 25°C (Kpa)
water	0	100	3.16
methanol	-93.9	65	16.9
ethanol	-117	78.5	5.79
1-propanol	-85.8	97.4	2.27
2-propanol	-127	82.4	5.85
chloroform	-63	62	26.1
Dimethylsulphoxide(DMSO)	19	189	0.08
acetic acid	17	118	1.64
1,4-dioxane	12	102	4.92
2-methyl-2-propanol (TBA)	25	82	5.49

Spray Drying

Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes the drug may be partially crystallized during processing.

Electrostatic Spinning Method

Electrostatic spinning method involves the introduction of a liquid into an electric field whereby the liquid is caused to produce fibres. After being drawn from the liquid the fibres

harden, which may involve mere cooling, chemical hardening or evaporation of solvent, and then hardened fibres may be collected upon a suitably charged surface. Tubular products comprising polyurethane fibres can be prepared by this electrostatic spinning method. One example of this type of tubular product is a vascular prosthesis, particularly a synthetic blood vessel. Other applications of this type of tubular products include the use of different kinds of ducts, e.g. urinary, air or bile as well as conduit through which for example a wire or other device or structure may pass or lie. The electrostatic spinning method has a few applications in pharmaceutical industry. In this method a drug-matrix solution is pumped through an orifice and then subjected to an electrical field to form fibres with a diameter of micro- or nano-scale. This method is limited to a few matrices because only a few high molecular weight materials are fibre forming materials. In this method electrical forces are used to overcome the surface tension of drug-polymer solution at air interface, the fibres of submicron diameters are formed whose diameter depends upon feeding rate, dielectric constant, surface tension, electric field strength.

Verreck et al., in 2003, used electrostatic spinning method for the preparation of drug-laden nonbiodegradable nanofibre for potential use in topical drug administration and wound healing. Itraconazoleand ketanserin were selected as model compounds while segmented polyurethane (PU) was selected as the nonbiodegradable polymer. For both Itraconazole and ketanserin, an amorphous nanodispersion with PU was obtained when the drug/polymer solutions were electrospun from dimethylformide (DMF) and dimethylacetamide (DMAc), respectively.

Current Trends In Solid Dispersions Techniques,[7]

It is intended to discuss the recent advances related on the area of solid dispersions. The classification of solid dispersions according to implementation and recent advancement.

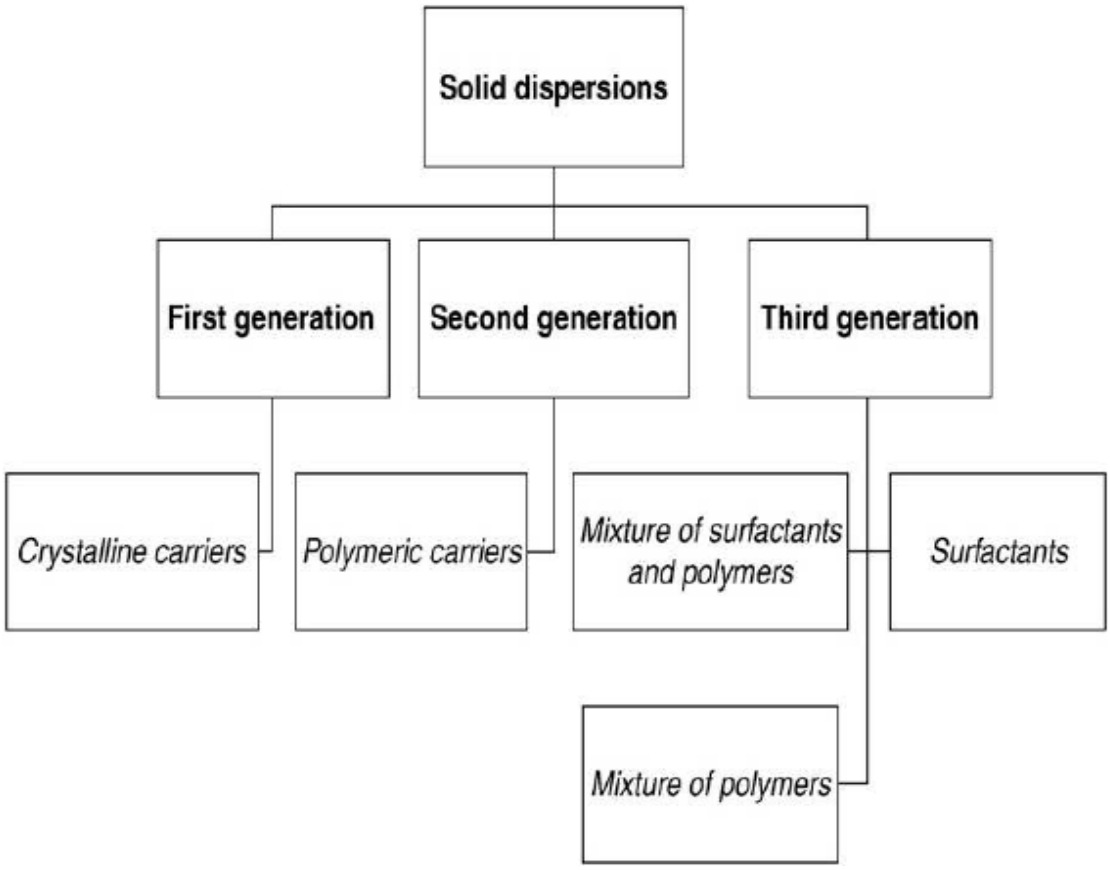

Figure 2: New trend classification of solid dispersion

First Generation Solid Dispersions

The first description of solid dispersions was from Sekiguchi and Obi in 1961. They noted that the formulation of eutectic mixtures improves the rate of drug release and consequently, the bioavailability of poorly water soluble drugs. In the same decade, several solid dispersions were described using poorly water soluble drugs, such as sulfathiazole and chloramphenicol using urea as high water soluble carrier. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs.

The small particle size and the better wettability of the drug were the main reasons for the observed improvements in bioavailability. Later, Levy and Kaning developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. The observed improvements were attributed to a faster carrier dissolution, releasing microcrystals or particles of drug .These solid dispersions, which could be designed as first generation solid dispersions, were prepared using crystalline carriers. Crystalline carriers include urea and sugars, which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming

crystalline solid dispersions which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

Second Generation Solid Dispersions

In the late sixties it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable. Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline carriers but amorphous. In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier . These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material, and to produce amorphous forms of the drug and carriers. In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile.

Third Generation Solid Dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The use of surfactants such as inulin , inutec SP1 , compritol 888 ATO, gelucire 44/14 and poloxamer-407as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability. The association of amorphous polymers and surfactants has also been reported. For instance, the dissolution rate and bioavailability of LAB68, a poor water soluble drug, were improved after being dispersed in a mixture of PEG and polysorbate 80. The bioavailability of this solid dispersion was 10-fold higher compared to the dry blend of micronized drug. In addition, the solid dispersion system was physically and chemically stable for at least 16 months. HPMC was also associated with poloxamer and polyoxyethylene hydrogenated castor oil to prepare an amorphous felodipine solid dispersion. The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles.

Characterization Of Solid Dispersion[8]

Currently, the following techniques are available to detect (the degree of) crystallinity:

Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi-quantitative.

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99% in pure material. However in solid dispersions only qualitative detection was possible.

Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

Isothermal microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg). This technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

Dissolution calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

Macroscopic techniques that measure mechanical properties that are different amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity for and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solids.

Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which

thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

Confocal Raman Spectroscopy is used to measure the homogeneity of the solid mixture. It is described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2 μm^3, uncertainty remains about the presence of nano-sized amorphous drug particles.

Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC Therefore this technique can be used to assess the amount of molecularly dispersed drug and from that the fraction of drug that is dispersed as separate molecules is calculated.

In vitro dissolution studies are done for the find out dissolution behavior. The in-vitro dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through in vitro – in vivo correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed in-vivo dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. There are some apparatus used in United States pharmacopoeia for dissolution testing these are following.

GELUCIRES[9]

Also known as lauroyl polyoxylglycerides. [British Pharmacopoeia (BP, 2005)].A non ionic water dispersible surfactant composed of well characterized PEG esters, a small glyceride fraction and frees PEG. It is a bioavailability enhancer could be assocaiated with inhibition of enterocytic efflux transporter. Gelucires are a family of lipid-based excipients comprising glycerides and esters of polyethylene glycol (PEG), these two components conferring

hydrophobic and hydrophilic properties to the vehicle. Each Gelucire is characterized by two numbers, the first referring to the nominal melting point of the base and the second to the HLB value. Gelucires come in a variety of grades with different melting points (from 33 ºC to 65 ºC) and HLB values (from 1 to 14). (Gelucire 54/02, 50/13, 43/01) are used in preparation of sustained release formulations. It has been reported sustained release single unit matrices using Gelucire 43/01, where only 1.7% theophylline was released over a period of 20 hours. Gelucire 43/01 has been also used for the design of multi-unit floating systems of a highly water-soluble drug, diltiazem HCl. The granules were retained in stomach at least for 6 hours. Approximately 65% to 80% drug was released over 6 hours with initial fast release from the surface.

Pharmaceutical Applications of Gelucires

The wide range of materials within the Gelucires group results in a wide range of properties, particularly in terms of melting/crystallization behavior and hydrophobicity. Consequently, it is possible to choose the Gelucire according to the particular formulation requirement, either in terms of manufacturing metho or the rate of drug release (Craig, 1995). Different rates of drug release can be obtained by mixing the same active substance with Gelucires of different melting points and HLB values (Howard & Gould, 1987). Table 3 shows different applications of different Gelucires.

Table 3: Pharmaceutical Uses Of Some Gelucires

Types of gelucires	Uses
Gelucire 33/01, Gelucire 39/01, Gelucire 43/01	Vehicle, oily phase for ointment.
Gelucire 44/14	Emulsifier for solid and semi solid self-microremulsifying drug delivery systems, bioavailability enhancer.
Gelucire 50/02, Gelucire 50/13, Gelucire 54/02, Gelucire 70/02	Coating and matrix agents for sustained release formulations.
Gelucire 50/13, Gelucire 53/10	Hydrophilic glyceride for semi-solid formulations.

CURRENT USE IN SOLID DISPERSION

Spray Drying

Spray drying usually yields drugs in the amorphous state, but sometimes the drug may be partially crystallized during processing. Polyglycolized glycerides (Gelucire) are available with a range of properties depending on their hydrophilic lipophilic balance (HLB) over the range of 1 to 18 and melting point between 33^{o} and 70°C. Preparation of SDs by conventional

spray drying with polyglycolized glycerides has been problematic because a sticky and tacky mass of polyglycolized glycerides is obtained. Therefore, spray drying technique for polyglycolized glycerides has been used with its combination high melting lipids to solve this problem. Chauhan et al. in 2005, prepared solid dispersions of etoricoxib using spray drying technique with lipid carriers, mainly polyglycolized glycerides (Gelucire 50/13) and high melting lipids, namely, Compritol (atomized glyceryl dibehenate) or Sterotex K NF (hydrogenated cottonseed oil). They concluded that SDs of the purely watersoluble drug etoricoxib was successfully prepared by spray drying using lipid carriers. Solid dispersion using polyglycolized glycerides creates some problem as already discussed above and this can be solved by using silicon dioxide as an adsorbent. Due to presence of surface silanol groups, silicon dioxide is able to form hydrogen bond with drug molecule leading to the increase in wettability and consequently enhanced dissolution rate. SD of glibenclamide with Geluride was successfully prepared using silicon dioxide as an adsorbent by spray drying technique with enhanced dissolution rate. Al-Obaidi et al., in 2009, prepared solid dispersions of griseofulvin by using spray drying technology. Spray dried dispersions of griseofulvin (GF), poly [N-(2-hydroxypropyl)methacrylate] (PHPMA) and polyvinylpyrrolidone (PVP) were prepared from acetone and water. The glass transition temperature for the ternary solid dispersion (GF, PHPMA, and PVP) shifted from 83°C (acetone/water) to 103°C for the acetone/methanol system. They found that the SDs that was prepared using lower concentrations of drug and polymers in solutions resulted in the formation of particles that display a lower relaxation rate.

Melting or Fusion Method

In this method, a physical mixture of the drug and the carrier is heated until it is melted. The melt is then cooled, and the resultant solid dispersion is pulverized and sieved. Carbamazepine was first mixed with microcrystalline cellulose or pre-gelatinzed starch and then granulated in the heated mortar with molten Gelucire 44/14. Finally, the granules were passed through a 1.25 mm sieve. To enhance the dissolution rate of the carbamazepine, a series of granules were fabricated with the addition of, excipients that should enhance the distintegration of the granules.

Hot-Melt Extrusion

Estradiol hemihydrate (17_-E2) is a poorly watersoluble drug therefore, Hülsmann et al., in 2000, prepared solid dispersion by melt extrusion technique with an objective to overcome

many of the shortcomings of conventional methods. Different compositions of excipients such as PEG 6000, PVP (Kollidon® 30) or a vinylpyrrolidone-vinylacetatecopolymer (Kollidon® VA64) were used as polymers and Sucroester® WE15 or Gelucire® 44/14 as additives during melt extrusion. A 30-fold increase in dissolution rate was obtained from a formulation containing 10% 17_-E2, 50% PVP and 40% Gelucire® 44/14. The SDs was then processed into tablets and the improvement in the dissolution behavior was also maintained with the tablets. Atorvastatin is a selective competitive inhibitor of HMG CoA reductase and its absolute bioavailability is 14% and therefore to increase its solubility solid dispersion was prepared by using this technique. Solid dispersion preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with mannitol, PEG 4000 and PVP-K30. They found that the solid dispersions obtained by this method were tacky enough.

CONCLUSION

Solid dispersions provide a simple and effective method of increasing solubility and oral bioavailability of poorly water-soluble drugs. More specifically, solid dispersions prepared with self-emulsifying carriers, such as Gelucires, are of a special interest due to their unique properties. Hence, the present study was carried out to investigate the utility of Gelucires for formulating solid dispersions of poorly water soluble drugs with aim of enhancing their oral bioavailability. Previous techniques used to improve the oral bioavailability of poorly water soluble drugs, such as co-micronization and microcoating, are time-consuming and/or costly. Hence in this study it was shown the different advantages of using current techniques in preparing solid dispersions.

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