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SOLID DISPERSION: A NOVEL APPROACH FOR SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

To improve dissolution of poorly water-soluble drugs and hence improving their bioavailability, solid state carrier is used for the dispersion of one or more active pharmaceutical ingredient. This procedure is known as solid dispersion. It has hold remarkable interest as an efficient means of enhancing the dissolution rate. It occurs because of dispersion of inadequately water-soluble drugs with water-dissolvable bearers. Solubility behaviour of drug is one of the challenging aspects in the formulation development. The poorly water soluble compounds number has increased. Comparing with formulations like tablets or capsules which are conventional, solid dispersions formulated by various methods can be used, as they have many benefits over the above conventional dosage form. For the preparation of solid dispersion, there are certain aspects that are to be considered such as; selection of carrier, selection of solvent and methods of physicochemical characterization. In this review, an accentuation is put on solubility, different kind of solid dispersion techniques, mechanism to improve dissolution in solid dispersion, characterization, advantages, disadvantages and the applications of the solid dispersion.

KEYWORDS

Solubility, Solid dispersion, Carrier, Bioavailability and Dissolution.

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INTRODUCTION

Oral route of drug delivery is the most well known, least complex and simplest method of administrating drugs. Solid dosage forms have many advantages compared to other type of oral dosage forms because of the smaller bulk, accurate dosage, greater stability and easy production[1]. The drugs with poor water solubility often show poor oral bioavailabity because of their low levels of absorption. The dissolution rate of drugs under going dissolution rate limited absorption can be

increased by size reduction or micronisation but it leads to poor wettability due to aggregation of particles[2]. The term solid dispersion refers to a bunch of solid products comprising of a minimum of 2 totally different elements, usually hydrophobic drug and hydrophilic matrix. The matrix is either crystalline or amorphous. The drug is distributed molecularly, in amorphous particles (clusters) or in crystalline particles[3-6]. There are variety of formulation strategies reported which may be approached to boost the bioavailability of BCS category II medicine either by increasing the dissolution rate or by maintaining the drug in solution state in the GI tract[7]. The active of drug must dissolve and be absorb within the body to reach adequate concentration within the receptor[8]. When a drug has aqueous solubility less than 100µg/ml, Poor dissolution: Intrinsic dissolution rate <0.1mg/cm2/min, High molecular weight: (>500), Self association and aggregation and high crystal energy (melting point >200°C) is said to be poorly soluble[9].

The term solid dispersion has been used to explain a family of dose forms whereby the drug is distributed in a biologically inert matrix, typically with a view to enhancing oral bioavailability. More specifically, Chiou and Riegelman outlined these systems as, the dispersion of 1 or additional active ingredients in an inert carrier matrix at solid-state prepared by the solvent or melting-solvent method, melting (fusion)[3] method, whereas the definition of a product formed by converting a fluid drug-carrier combination to the solid state is suggested by Corrigan[10]. For improving the oral bioavailability of active agents, two areas of pharmaceutical analysis that targets, include enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs[11]. The incorporation of drug in solid dispersion results in change of crystalline form of drug to amorphous form. The amorphous state is reported to have more solubility as compared to crystalline state and this can be explained by the fact that in the amorphous state no energy is required to break the crystal lattice found in crystalline phase. In the crystalline state, molecules occupy definite positions within the crystal lattice and this well-defined arrangement is repeated several times in all three dimensions of the crystal giving rise to long-range order of crystalline solids. This ordered arrangement requires more energy to break as compared to amorphous state where molecules are arranged randomly. Since 1960 the formulation of drugs having low aqueous solubility using solid dispersion method has been an active area of research[12].

Noyes-Whitney Equation

The rate of dissolution can be expressed by using Noyes Whitney equation. It provides various parameters which can help to improve the bioavailability of a poorly soluble drug.

Dc/dt = AD (Cs-C)/ h

Dc/dt- the rate of dissolution

A- Surface area available for dissolution

D- Diffusion coefficient of the compound

Cs- The compounds solubility in the dissolution medium

C- Concentration of drug in the medium at time t

H- Thickness of diffusion boundary layer adjacent to the surface of dissolving compound[2].

According to Noyes-Whitney equation, the dissolution rate of a drug in a given medium depends on the concentration difference between the dissolving interface and also the bulk solution[13]. The dissolution rate of poorly soluble compounds might be improved to diminish the limitations to oral availability by using modified Noyes- Whitney equation[14]. According to this analysis, chances of increase in dissolution rate are, decreasing the size of the particle present in the solid compound by using wetting phenomenon of the compound surface and enhancing the surface area available for the dissolution. This ensures sink conditions for dissolution, decrease the boundary layer thickness, and under physiologically relevant conditions, the apparent solubility of the drug molecule can be enhanced[15].

Solid dispersion definition

A dispersion mixture of one or more active ingredients in an inert carrier at the solid state

prepared by melting, solvent, solvent-melting or other methods is referred as solid dispersion. The approaches used for preparing Solid Dispersions are referred as solid dispersion techniques[13]. The drug is distributed molecularly, in amorphous particles (clusters) or in crystalline particles[11].

Selection of Carrier[2,9]

A carrier should have the following characteristics to be suitable for increasing the rate of dissolution of a drug

- The carrier should be freely soluble in water with a high rate of dissolution.
- It should be non toxic.
- It should be pharmacologically inert.
- It should have heat stability with a low melting point.
- It should be able to enhance aqueous solubility of the drug.
- It should have chemical compatibility with the drug, and should not form strongly bonded complexes with the drug.
- It should be economical.
- It should be soluble in a variety of solvents.

Generations of Carriers[9]

First generation carriers

Example: Crystalline carriers are Urea, Sugars, Organic acids.

Second generation carriers

Example: PVP, PEG and polymethacrylates like polymers which are fully synthesized. Natural product based polymers, such as (HPMC) hydroxypropyl methylcellulose, ethyl cellulose or hydroxypropyl cellulose which cellulose derivative primarily composes or starch derivates, like cyclodextrins.

Third generation carriers

Example: Surface active self emulsifying carriers such as, Poloxamer 408, Tween 80, and Gelucire 44/14

SOLVENTS USED IN SOLID DISPERSION[16]

Solvent to be used for the formulation of solid dispersion should have the following criteria:

1. The drug and carrier both must be dissolved.
2. Toxic solvents should be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
3. Ethanol can be used as alternative as it is less toxic.
4. Water based systems are preferred.
5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration.

Class I Solvents (Solvents to be avoided)

Solvents included in this class are not to be taken in to use because of their deleterious environmental effects.

Some of the examples are given in Table No.2.

Class II Solvents (Solvents to be limited)

Theses solvent should be limited used in pharmaceutical products because of their inherent toxicity (Table No.3).

Class III Solvents (Solvents with low toxic potential)

Solvents included in this class may be regarded as less toxic and have the low risk to human health and as some are given in Table No.4.

Class IV Solvents (Solvents for which no adequate toxicological information was found)

Some solvents may also be of interest to manufacturers of excipients, drug substances, or drug product for example petroleum ether, isopropyl ether. However, no adequate toxicological information on which to base a PDE was found.

CLASSIFICATION OF SOLID DISPERSION

Depending on the molecular arrangement, solid dispersions may be of the following types

Eutectic mixtures

Solid eutectic mixtures are generally formulated by rapidly cooling the co-melt of the 2 components so as to obtain a physical mixture of very fine crystals of the 2 components[2].

Solid solutions

The two types of solid solutions depending on the miscibility are,

Continuous solid solutions

The components are miscible in all proportions in continuous solid solutions. i.e, bonding strength between the components is stronger than individual component bonding.

Discontinuous solid solutions

The solubility of each of the component in the other component is limited in nature in the discontinuous solid solutions.

The two types of solid solutions depending on the distribution of the solvates in the solvedum are,

Substitutional crystalline solution

These are the type of solid solutions which have a crystalline structure, the solute molecules substitute for the solvent molecules in the crystal lattice.

Interstitial crystalline solid

These type of solid solutions are those in which the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice[2].

Amorphous solid solutions

In amorphous solid solutions, the solute molecules are dispersed molecularly however on an irregular basis within the amorphous solvent[2].

Glass solutions and glass suspension

A glass solution is mainly a homogenous system in which dissolution of the solute in the glassy solvent occurs. The glassy state is characterised by transparency and brittleness below the glass transition temperature. The term glass refers to a pure chemical or a combination of pure chemicals in the glassy state[2].

Carrier-Based Class of Solid Dispersion

First generation solid dispersion

These solid dispersions are prepared by using crystalline carriers. Urea and sugars were the primary crystalline carriers that were utilized in the preparation of solid dispersions. These have a drawback of being thermodynamically unstable and they don't release drug at a faster rate[2]. These solid dispersions produced faster release and better bioavailability than typical formulations of similar drugs. The small particle size and the higher wettability of the drug were the main reasons for the observed improvements in bioavailability[17]. These solid dispersion form crystalline solid dispersions and did not release the drug as quickly as amorphous does and this is the disadvantage of this class[9].

Second generation solid dispersion

In second generation solid dispersions, the drug is in its supersaturated state due to forced solubilization within the carrier. These systems are mean to reduce the drug particle size to upto a molecular level, for solubilization or co-dissolvation of the drug by the water soluble carrier, so as to supply better wettability and dispersibility of the drug by the carrier material, and to provide amorphous forms of the drug and carriers[17]. These solid dispersions are prepared by using amorphous carriers instead of crystalline carriers. The drug is molecularly dispersed in the polymeric carrier. The polymeric carriers are divided into two groups:

Synthetic polymer

Povidone, polyethylene glycols and polymethacrylates.

Natural polymers

Hydroxypropyl methyl cellulose, ethyl cellulose, starch derivatives like cyclodextrin[2,9].

Third generation solid dispersion

These solid dispersions contain a surface-active agent carrier, or a mixture of amorphous polymers and surfactants as carriers. These achieve the high degree of bioavailability for the drugs that are having poor solubility. The surfactants used in the third generation solid dispersion are like inulin, poloxamer 407 etc[2]. These third generation solid dispersions are meant to stabilize the solid dispersion and to attain the highest degree of bioavailability for poorly soluble drugs and, avoiding drug recrystallization[17].

METHODS OF PREPARATION OF SOLID DISPERSION

1. Melting method
2. Solvent methods
3. Melting solvent method (melt evaporation)
4. Hot melt extrusion method
5. Lyophilization techniques
6. Melt agglomerations Process
7. Co-precipitation method

8. Electrospinning
9. Super Critical Fluid (SCF) technologies
10. Freeze- drying

Melting method

In addition, a super-saturation of a drug or solute in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. When used for simple eutectic mixtures the quenching technique gives a much finer dispersion of crystallites[4]. Sekiguchi *et al* is the first who use a melting method or fusion method consisting of together melting the carrier and drug over the temperature of eutectic point, which is the lowest possible melting point of the mixture[18]. In fusion or melting method a physical mixture of the drug and a water soluble carrier is prepared, by heating it directly until it melts. The final solid mass obtained is crushed, pulverized and sieved. However substances either the carrier or the drug may decompose due to high temperature during the melting process. A method to overcome this problem could be heating the mixture in a sealed container or under vacuum or in the presence of inert gases like nitrogen. The advantage is its simplicity and economical nature[19,20].

Solvent method

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, and then it's evaporated till a clear, solvent free film is obtained. The film is then dried to constant weight[1,21]. The main advantage is that the thermal decomposition of the drug or the carrier can be avoided because the organic solvents need a low temp for evaporation. The disadvantage during this method is higher cost of preparation and problem in removing the solvent[19]. In solid dispersion development, it's essential to eliminate the crystallinity of the drug. This requirement may be achieved by dissolving it in a appropriate solvent. Though a pure amorphous drug can sometimes be obtained, a polymer that stabilizes the amorphous state of the drug through physicochemical and mechanical interactions is usually used during processing. The solvent method consists of a primary stage during which the drug and the carrier are solubilized in a volatile solvent, and in its subsequent evaporation at low temperature, minimizing the risk of thermal decomposition of both the drug and the carrier, to obtain as a result a solid dispersion[22,23]. The first step in the solvent technique is that the preparation of a solution containing each matrix material and drug. The second step involves the removal of solvent(s) leading to formation of a solid dispersion. Mixing at the molecular level is preferred, because this results in best dissolution properties. The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be controlled due to the relatively low temperatures required for the evaporation of organic solvents[24].

Solvent melting method

This method has unique advantages of each the fusion and solvent evaporation methods. By practical viewpoint, its solely limited to drugs with a low therapeutic dose (less than 50mg). In this method, the drug is dissolved in suitable solvent and solution is prepared. Then the solution is directly incorporated into melt of polyethylene glycol, then it is evaporated till solvent free and clear film is left and then further dried to constant weight, the solidified mass is then crushed, pulverized and passed through sieve[4,25]. Spironolactone-polyethylene glycol 6000 and griseofulvin-polyethylene glycol 6000 systems was used for the demonstration of feasibility of this method. However, its application to alternative drugs and carriers, remains to be explored[26]. Liquid compound of 5-10% (w/w) can be incorporated into polyethylene glycol 6000 without loss of its solid property. It is possible that liquid solvent used could have an effect on the polymorphic form of the drug, that precipitates as the solid dispersion as well as the chosen solvent or dissolved drug might not be miscible with the melt of the polyethylene glycol[23].

Hot Melt Extrusion method

It was observed that solid dispersions of itraconazole/Intec SP1 formulated by hot-stage extrusion presented itraconazole in a fully glassy

state, whereas it was solely partially glassy in solid dispersions formulated by spray drying[27]. In this method extruder is utilized for intense mixing of elements. The elements of the extruder are barrel, hopper, a kneading screw, heating jacket, and a die. Usually physical mixture of each the carrier and drug is introduced into the hopper then passed through screw and eventually it's extruded from the die. The advantage of the strategy is to get varied shapes and styles of the heated drug-matrix mixture into ophthalmic inserts, implants, or oral dosage form[16].

Lyophilization

It is a phenomenon which include transfer of heat from the product and mass to the product. Comparing to solvent evaporation in which molecular mixture technique is used where the drug and carrier is dissolved in common solvent, then it is frozen and sublimed, in order to obtain solid dispersion, lyophilization is an alternative method to it. Sublimed pressure under 8-10mm Hg and condensed onto 75^{o}C[28,19].

Melt Agglomeration technique

In this technique binder is use as carrier. There are 2 methods of preparation of solid dispersing, one is by spraying the drug on melted binder and excipients and other one is melting of binder drug and excipient above the melting temperature of binder used. For using high binder content rotary method may be preferred for controlling temperature. This method is advantageous in homogenous combination of drug however larger particle size cause compaction and fines cause adhesion of mass. It's additionally attainable to formulate stable solid dispersions by melt agglomeration using a rotary processor[27,19].

Co-precipitation method

The drug and polymer of required quantity were mixed and further solvent was added to obtain clear solution. The obtained solution was first dried under vacuum at room temperature and then kept inside the incubator (37^{o}C) for 12 hours and then it was passes through sieves[27]. For increasing dissolution of poorly water soluble drugs, co-precipitation is a recognised technique, so as to consequently improve bioavailability. In this technique non-solvent is added drop wise to the carrier and drug solution, under constant stirring. In this non-solvent addition course, the drug and carrier are co-precipitated for the formation of micro-particles. Finally, the resulted micro particle suspension is filtered and dried[16].

Electrosipinnig method

A polymer solution/melt stream is subjected to the electric force (5 to 30kv) that causes liquid body to become charged, and surface tension is counteracted by electrostatic repulsion. This causes strong cohesive force in between the particles and droplets of the polymer and thus, a stream of fibre is formed. The whipping process called electrostatic repulsion is used for thinning and stretching of fibre to nano diameter which leads to uniform fibre formation in nano diameter. This process depends on feeding surface tension rate and electric force[19]. Electrospinning is methods which involves production of solid fibres from polymeric fluid stream solution or melt which is delivered through a millimeter-scale nozzle[17].

Super Critical Fluid (SCF) Technology

The ability of CO2 to plasticize and swell polymers also can be exploited and therefore the method is dispensed near temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion method by reducing the melting temperature of dispersed active agent. The reason for this depression is that the solubility of the lighter component (dense gas) within the forming phase (heavier component)[17]. The supercritical fluid antisolvent techniques, CO2 is used as an antisolvent for the solute however as a solvent with respect to the organic solvent. Totally different acronyms were used by many authors for denoting micronization method: aerosol solvent extraction system, compressed fluid anti solvent caused precipitation, gas anti-solvent, supercritical fluids caused solution increased dispersion, and supercritical antisolvent. The SAS method involves the spraying of the solution composed of the solute and of the organic solvent into a continual supercritical phase flowing at the same time. Use of

supercritical CO2 is advantageous because it is far easier to remove from the polymeric materials once the method is complete, although a little quantity of CO2 remains strapped within the polymer; it poses no danger to the patient[20,23].

Freeze-drying

This method consists of dissolving the drug and carrier in a common solvent that is immersed in liquid nitrogen until it's absolutely frozen. Then, the frozen solution is then lyophilized. Though it's concluded in literature that this is often a promising and appropriate technique to include drug substances in stabilising matrices, the technique is poorly exploited for the preparation of solid dispersions. A crucial advantage of freeze drying is that the drug is subjected to lowest thermal stress throughout the formation of the solid dispersion. However, the foremost necessary advantage of freeze drying is that the risk of phase separation is decreased as soon as the solution is vitrified[17].

CHARACTERISATION OF SOLID DISPERSIONS

Several different molecular structures of the drug within the matrix are encountered in solid dispersions. Certain techniques are available and used to investigate the molecular arrangement in solid dispersions. However, most effort has been done to differentiate between amorphous and crystalline material. Several techniques used that find the quantity of crystalline material within the dispersion.

Thermal Analysis Techniques

Thermal analysis is techniques in which a physical property of a substance is measured as a function of temperature. In this technique, subjection of the substance to controlled temperature program is done. In differential thermal analysis, the sample and an inert reference material produces temperature difference that is measured, when both of them are subjected to an identical heating condition[15].

Powder X-Ray Diffraction

Power X-ray diffraction technique is used for quantitative detection of material with long range order. Sharper diffraction peaks indicates that the material is more crystalline. Recently developed X-ray equipment is semi- quantitative[19].

Infrared spectroscopy (IR)

Infrared spectroscopy (IR) is used for identification of variation in the energy distribution of interaction in between matrix and drug. Crystallinity is indicated by sharp vibrational bands. For accurate detection of crystallinity ranging from 1 to 99% in the pure material, Fourier Transformed Infrared Spectroscopy was used[17].

Microscopic Method

Microscopy method is use to study the polymorphism 70 and morphology of solid dispersions 50, 71-75. The fine particles of crystallization in the glassy polyvinyl pyrrolidone matrix can be readily detected by the polarizing microscope. To study the dispersed particle size of ionic acid in polyvinyl pyrrolidone the high resolution of an electron microscope was used. The application of this technique is usually limited to chemicals with high atomic numbers[19].

Scanning Electron Microscopy (SEM)

SEM is useful in ascertaining the morphology, particle size of solid particles and sometimes polymorphism of drug. The fine dispersion of drug particles within the carrier matrix could also be visualized. The application of the electron microscope technique, however usually limited to chemicals with high resolution[9].

Differential Scanning Calorimetry (DSC)

Frequently used technique to detect the quantity of crystalline material is Differential Scanning Calorimetry (DSC). In DSC, samples are heated with a constant heating rate and therefore the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur are often detected. Thermal events are often a glass to rubber transition, (re)crystallization, melting or degradation. The melting and (re)crystallization energy can be quantified further. The melting energy may be used to detect the quantity of crystalline material[17].

***In Vitro* Dissolution Studies**

In vitro dissolution studies are performed for the determination of dissolution behavior. The *in-vitro* dissolution studies are often used to demonstrate the bioavailability or bioequivalence of the drug product through *in vitro - in vivo* correlation (IVIVC). On the opposite hand if absorption of the drug is dissolution rate limited meaning the drug within 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 are going to be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately[19].

ADVANTAGES OF SOLID DISPERSION[19]

In solid dispersions as a drug delivery forms that supply the possibility to disperse a hydrophobic drug within a hydrophilic matrix and therefore the reby improve the dissolution behavior and the bioavailability of the drug. Drug release profile management using solid dispersions is done by manipulation of the properties of carrier and solid dispersion particles. Carrier relative molecular mass and composition, particle porosity and drug crystallinity and wettability like parameters, when controlled successfully, they can cause improvements in bioavailability.

Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and the drug is molecularly dispersed in the dissolution medium after carrier dissolution. Solid dispersions apply this principle to drug release by creating a mix of a poorly water soluble drug and highly soluble carriers. A high surface area is created, leading to an increased dissolution rate and consequently, improved bioavailability.

Particles with improved wettability

The solubility enhancement of the drug is concern to the drug wettability improvement verified in solid dispersion. A powerful contribution to the enhancement of drug solubility is said to the drug wettability improvement verified in solid dispersions. It was observed that even carriers with none surface activity, like urea improved drug wettability. Carriers with surface activity, like bile salts, when used, can significantly increase the wettability properties of drugs. Recently, the inclusion of surfactants within the third generation solid dispersions reinforced the importance of this property.

Particles with higher porosity

Particles in solid dispersions are found to possess a better degree of porosity. Increase in porosity is affected by carrier, for example, those solid dispersions which contains linear polymers, they produce larger and more porous particles than the solid dispersions containing reticular polymers, hence they cause better dissolution rate. The improved porosity of solid dispersion particles also hastens the drug release profile.

Drugs in amorphous state

Poorly water soluble crystalline drugs, when within the amorphous state tend to possess higher solubility. The increase in the drug release can usually be achieved using the drug in its amorphous state, because no energy is required to interrupt up the crystal lattice during the dissolution process. In solid dispersions, when system dissolution drugs are introduced as supersaturated solutions and it is speculated that, it is as a metastable polymorphic form with greater solubility than the foremost stable crystal form if drugs precipitates.

LIMITATIONS OF SOLID DISPERSION[28]

- It is not using commercially due to its stability problems.
- During processing and storage due to mechanical stress, temperature & humidity more chances of amorphous state undergo crystallization.
- Phase separation may occur because most polymers used will absorb moisture.
- Chances of conversion of metastable crystalline form to more stable structure.
- Poor scale up for manufacture.

- Too expensive.
- It is not applicable to thermo labile substances.
- Also cooling and soldifying methods are difficult to carry out.
- In case of hydrophobic drugs solvent used will be more and the drug concentration will be less to get desired therapeutic effect.
- Selection of a carrier is important because only a small number of carriers are currently available for oral use.
- Low solubility of drug in available carrier is a major Limitation.

APPLICATIONS OF SOLID DISPERSIONS[23]

1. To increase the solubility of poorly soluble drugs and hence increase the absorption, dissolution rate and bioavailability.
2. Stabilization of unstable drugs against recrimination, oxidation, hydrolysis, isomerization, photo oxidation and several decay procedures.
3. To reduce side effect of some drugs.
4. To mask unpleasant taste and smell of drugs.
5. Enhacement of drug release from ointment creams and gels.
6. To avoid incompatibilities which are undesirable.
7. To acquire a similar distribution of a small amount of drug in solid state.
8. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
9. To formulate a quick release primary dose by using a sustained released dosage form.
10. To formulate sustained release product of soluble drugs by using poorly soluble or insoluble carriers.
11. Reduction in pre systemic in activation of drugs like morphine and progesterone.

Table No.1: Different carriers used in solid dispersion

S.No	Category	Carriers
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
2	Acids	Citric acid, succinic acid
3	Polymeric materials	Polyvinyl pyrrolidine (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxypropyl cellulose, pectin, galactomannan
4	Insoluble or enteric polymer	Hydroxypropyl methyl cellulose phthalate (HPMCP), eudragit L100, eudragit RS, eudragit E100, eudragit RL
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans
6	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urethane, urea, hydroxy alkyl xanthins

Table No.2: List of some class I solvents

S.No	Solvent	Concentration limit (ppm)	Effect
1	Benzene	2	---
2	Carbon tetrachloride	4	Carcinogenic, toxic, environmental hazards
3	1, 2-dichloroethane	5	Toxic
4	1, 1-dichloroethane	8	Toxic
5	1, 1, 1-trichloroethane	1500	Environmental hazards

Table No.3: Class II solvents in pharmaceutical products

S.No	Solvent	PDE (mg/day)	Concentration limit (ppm)
1	Chlorobenzene	3.6	360
2	Chloroform	0.6	60
3	Cyclohexane	38.8	3880
4	1, 2-dichloroethene	18.7	1870
5	Ethylene glycol	6.2	620
6	Methanol	30.0	3000
7	Pyridine	2.0	200
8	Toluene	8.9	890

Table No.4: Class III solvents: these should be limited by gmp or other quality based requirements

S.No	Acetic acid	Ethyl ether
1	1-butanol	Formic acid
2	2-butanol	Heptane
3	Acetone	Isobutyl acetate
4	Butyl acetate	Isopropyl acetate
5	Dimethyl sulfoxide	Methyl acetate
6	Ethanol	3-methyl-1-butanol
7	Ethyl acetate	Pentane
8	1-propanol	1-pentanol
9	2-propanol	Propyl acetate

CONCLUSION

Improving the dissolution and solubility enhancement properties of poorly water-soluble drugs, when the solid dispersion is exposed to aqueous media, the carrier dissolves and therefore the drug releases as fine colloidal particles. The resulting enhanced area produces higher dissolution rate and bioavailability of poorly water soluble drugs. Carriers with or with none any surface activity, when used, can significantly increase the wettability properties of drugs. The carrier properties affects porosity and increases it, as an example, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate and increases the solubility of poorly water soluble drug. Solid dispersion has also been used to produce sustained release microsphere using tedious methods. New optimized techniques are also useful in the industries.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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