ISSN 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICALSCIENCES

Available online at: http://www.iajps.com *Review Article*

SOLID DISPERSION:APPROACH FOR SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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Abstract:

Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and bioavailability of a range of poorly water-soluble drugs. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The focus of this review articleon advantages, disadvantagesand the method of preparation of the solid dispersion

The review covers concise preface of solid dispersion highlighting various approaches for their preparation, technology involved, selection of carriers.

***Keywords**:*

Solid dispersion; Dissolution; Eutectic mixture; Poorly water soluble drugs

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INTRODUCTION

The oral route is most common preferable route for drug delivery system; it is convenient and easy ingestion. Moreover patient compliance and drug treatment is more effective with oral administration than other routes of administration. Oral drug absorption from solid dosage forms depends on the release of the drug substance from the delivery system, mainly dissolution rate of the drug under the physiological conditions and permeability of the drug across the gastrointestinal tract [1]. Poorly water-soluble drugs are expected to have dissolution-limited absorption. Increasing the drug solubility may substantially improved drug absorption, and consequently drug bioavailability.

About 40% of new chemical molecules are poorly water soluble [2]. Most of the potential drugs are abandoned in initial stages of development due to solubility to overcome this problem by using the various techniques and methods to enhance the solubility and dissolution of poorly water soluble drugs. A poorly soluble drug represents a problem for their bioavailability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract (GIT).Solubility behaviour of a drug is one of the key factor of its oral bioavailability.

Solubility and bioavailability enhancement techniques:

There are various techniques are available to enhance the solubility of poorly soluble drugs. Some of the approaches to improve their solubility are [3].

1) Physical modifications

Particle size reduction

- Micronization
- Nanosuspensions
- Sonocrystalisation

Modification of the crystal habit

- Polymorphs
- Pseudo polymorphs

Complexation

- Use of complexing agents

Solubilization by surfactants:

- Micro emulsions
- Self emulsifying drug delivery systems

Drug dispersion in carriers

- Eutectic mixtures
- Solid dispersions
- Solid solutions

2) Chemical Modifications

3) Other Methods

- Co crystallization
- Co solvency Hydrotropy
- Solvent deposition
- Suitable adsorption on insoluble carrier
- Functional polymer technology
- Nanotechnology approaches

Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability[4].

$$dC / dt = (AD[Cs - C])/h$$

Where,

dC / dt is dissolution rate,

A - Surface area available for dissolution,

D - Diffusion coefficient of the compound,

Cs - Solubility of the compound in the medium,

C - Concentration of drug in the medium at time t and

h - Thickness of the diffusion boundary layer.

These are the techniques to enhance the dissolution and oral bioavailability of many poorly soluble drugs [5]. Hence the researchers focused on two areas:

i) To enhance solubility and dissolution

ii) To increase the permeability of poorly water soluble drugs.

The main use of solid dispersion technique and self-emulsifying drug delivery systems are to improve the dissolution rate and bioavailability of poorly water soluble drugs. Many researches denoted that drugs are poor water solubility and high permeability for solid dispersion systems (BCS classification), this type of drugs shown dissolution rate is limited, and categorized class-II drugs [6]. Therefore by using solid dispersion system and self-nano emulsifying system for class-II drugs the dissolution rate and bioavailability can be increased through oral route of administration.

Solid dispersion contains at least two different components one is hydrophilic matrix and another is hydrophobic drug, the matrix may be either amorphous or crystalline, the drug can be dispersed either as amorphous or crystalline particles [7].

Solid dispersion systems illustrated in literature to enhance the dissolution properties of poorly water soluble drugs. Such as solubilization of drugs in solvents, salt formation, complex forms with cyclodextrins and sometimes particle size reduction also utilized to improve the dissolution of poorly water soluble drugs.

When the solid dispersion exposed to aqueous media, the carrier will dissolves and the drug releases as fine colloidal particles in the media. The resulting enhanced surface area shows higher dissolution rate and bioavailability of poorly water soluble drugs. In solid dispersion drug dissolves immediately to saturate the gastro intestinal tract (GIT) fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron to nano size. Solid dispersion technique was demonstrated by Sekiguchi and Obi. They investigated the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carriers like urea.

A solid dispersion technique who has reported improved results with different poorly water soluble drugs. The first drug whose rate and extent of absorption was significantly increased by using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi[8].

Technique for the preparation of solid dispersions, Lyophilisation technique also been thought for solid dispersion technique .where the drug and carriers were dissolved in cyclohexanol, frozen and sublimed under vacuum to obtain a lyophilized molecular dispersion.

In solid dispersions, molecular dispersions represents on particle size reduction, after carrier dissolution the drug is molecularly dispersed in dissolution medium. Solid dispersions apply this principle for solid dispersions to drug release by creating a mixture of poorly water soluble drug and highly soluble carriers, if higher surface area is formed, resulting enhanced dissolution rate and bioavailability [9,10]. In solid dispersions drug solubility is related to its wettability to enhance the dissolution rate of drug [11], moreover without surface activity also observed such as urea anyhow carriers will influence the dissolution rate by co-solvents effect and direct dissolution particles shown in solid dispersion particles [12] shown a high degree of porosity, increase the porosity also depends on carrier properties, more porous particles result higher dissolution rate [13].

Poorly water soluble crystalline drugs, at amorphous state drugs were shows higher solubility [14]. Enhancement of drug release can be increased by using the drug in its amorphous state; no energy is required in the dissolution process to break up the crystal lattice [15]. In solid dispersions(SD's)drugs are presented as supersaturated solutions after system dissolution; if drugs are precipitate, it is as a meta-stable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is dictated by the difference in melting temperature between the drug and the carrier, for drugs with high crystal energy shows a higher amorphous compositions can be obtained by choosing of carriers, which show specific interactions with them [16].

First Generation Solid Dispersions:

Sekiguchi and Obi shown in 1961 eutectic mixtures formulations improved the rate of drug release which in turn in enhances the bioavailability of poorly water soluble drugs. Solid dispersions systems were developed by Lev[17], solid solutions by using molecular dispersions instead of using eutectic mixtures, with mannitol as a carrier. These improvements were due to faster carrier dissolution, releasing particles of drug. Firstly using crystalline carriers were described as first generation of solid dispersions. Urea[18] and sugars [19] were the first crystalline carriers to be used in dispersions. The major drawback of this first generation solid dispersion is they form crystalline solid dispersions, which being thermodynamically more stable did not release the drug compared to as amorphous ones.

Second Generation Solid Dispersions:

It was perceived in the late sixties [20], that crystalline solid dispersions are not as effective as amorphous because they are thermodynamically stable [21, 22]. Therefore, the second generation of solid dispersions was introduced having amorphous carrier's alternative of crystalline. Presently, the drugs were molecularly dispersed in amorphous carriers which are ordinarily polymers in random pattern [23].

Third Generation Solid Dispersions:

The third generation solid dispersions show up as the dissolution profile distinctly increased by using carriers having surface activity and self-emulsifying properties. These contain surfactant carriers or a mixture of amorphous polymers and a surfactant as a carrier. The third generation solid dispersions stabilize the solid dispersions, enhancement of bioavailability and reduce recrystallization of poorly water soluble drugs. The use of surfactants such as poloxamer407 as carriers resulted in high polymorphic purity and improved In-vivo bioavailability [24].

PREPARATION OF SOLID DISPERSIONS:

Hot-Melt Extrusion:

Extrusion is broadly elaborated as a technique to "press out", a process of forming a new material (the extrudate) by forcing it through an orifice or die with the unit operations such as temperature, mixing, feed-rate and pressure [25].

HME technology using conventional processing techniques such as aqueous solvent or organic solvent extrusion and spheronization has been since a long time in the pharmaceutical applications. The major advantage of the Hot-melt extrusion is drying step is not involved while compared to traditional process [26].

The important parameter for this hot melt extrusion (HME) is the process temperature. The optimal process temperature is determined by the (*Tm)* of the drug, the *Tm* of the crystalline carrier, the (*Tg)* of the amorphous carrier and the thermoplastic properties of carrier. Over the extruding process, the drug should be completely mixed with the carrier and should not degrade at the process temperature. Commonly, the process temperature has to be higher than *Tm* or *Tg* of the carrier to soften and decrease the viscosity of the carrier allowing a sufficient flow through the extruder. Therefore, the *T*m or *Tg* of carrier should not be too high to limit the risk of drug degradation or to yield a practically process temperature.

This technology was first utilized in the plastic industry and to lesser extent in the food industry since 1930's. Many advantages of hot melt extrusion over conventional solid dosage form manufacturing picked the interest of pharmaceutical industry and researchers for the useful technology to prepare novel drug delivery system [27]. This technique employs the uses of extruders which consists of conveying system, for transportation and mixing of materials, and die system, which shapes the melt into required shape like pellets, granules, or powder [28]. In this method solvents are not used therefore, it is environmentally friendly, economical and no residual solvent in the final product. Advantage of hot melt extrusion technique over melting method is the use of low temperature and short residence time which prevents the drug-carrier mixture from thermal degradation [29]. This method has several disadvantages these are:

(i) High shear forces may produce high local temperature in the extruder therefore it may create a problem for heat sensitive materials.

(ii) Just like traditional fusion method, miscibility of drug and carrier matrix can be a

problem[30]. 17β-Estradiol hemihydrates (17β-E2) is a poorly water soluble drug therefore, Hülsmann, 2000, prepared solid dispersion by melt extrusion technique with an objective to overcome many of conventional methods.

Different compositions of excipients such as PEG 6000, PVP (Kollidon® 30) or a vinylpyrrolidone-vinylacetateco-polymer(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% 17β-E2, 50% PVP and 40% Gelucire® 44/14. The SDs was then processed into tablets and the improvement in the dissolution behaviour 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[31].Some examples of pharmaceutically approved polymeric materials which are used in hot-melt extrusion include vinyl polymers (polyvinylpyrrolidone(PVP), PVP-vinyl acetate (PVP-VA), polyethylene oxide (PEO), Eudragit® (acrylates), Polyethylene glycol (PEG) and cellulose derivatives.

The Hot-Melt Extrusion Process:

The different zones of the barrel are pre-set to specific temperatures before the extrusion process. The feed stock is placed in the hopper and transferred into the heated barrel by the rotating screw. The feed stock must have good flow properties. This requirement is usually met by insuring that the angle of the feed hopper exceeds the angle of repose of the feed materials. When this prerequisite is not met, the feed stock tends to form a solid bridge at the throat of the hopper resulting in erratic flow in these situations; a force feeding device can be used. As the feed stock is moved along the length of the barrel, heat is generated by shearing imposed by the rotating screw in addition to conduction from the electrical heating bands. The efficiency of the feeding section is dependent upon the friction coefficient between the feed materials and the surface of the barrel and screw. High friction along the barrel and low friction at the screw interface contribute to efficient mass flow in the feed section. Obviously, the bulk density, particle shape, and compression properties of the raw materials impact the feeding efficiency. The transfer of the material should be efficient in order to maintain an increase in pressure in the compression zone and the metering zone. The pressure rise in these zones insures efficient output of the extrudate. It is possible to fine-tune the barrel temperature at the feeding section in order to optimize the friction at the surface of the barrel. Incompatible material feed may result in a "surge" phenomenon that will cause cyclical variations in the output rate, head pressure and quality. The normal temperature of the melting zone is 15-60ºC above the melting point of semi-crystalline polymers or the glass transition temperature of amorphous polymers [32,33].

Solvent Evaporation Method:

In this method both the drug and carrier are dissolved in a organic solvent. After an entire dissolution the solvent is evaporated. The solid mass is sieved and dried. Example Solid dispersion of furosemide with eudragits was prepared by solvent evaporation method [34].

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. However, several drugs can be degraded by the use of high temperatures can be a limitation of this method. The incomplete miscibility of drug and carrier that may occur because of the high viscosity of a polymeric carrier in the molten state is another limitation of this process.

Direct Capsule Filling:

In 1978, Francois and Jones [35], further developed the solid dispersion method by directly filling hard gelatine capsules with semisolids materials as a melt, which solidified at room temperature. Chatman [36] reported the possibility of preparing PEG-based solid dispersions by filling drug-PEG melts into hard gelatine capsules [37].

Kneading Technique:

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The final mixture is then dried and passed through sieve if necessary.

Co-Precipitation Method:

Required amount of drug is added to a carrier solution. The system is kept under magnetic agitation and protected from the light. The precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex [38].

Melting Method:

Drug and carrier are mixed using mortar and pestle. To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components. It is then cooled to acquire a congealed mass. It is crushed and sieved. Ex. albendazole and urea solid dispersion was prepared by this method [39].

Co-Grinding Method:

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized then the sample is collected and kept at room temperature in a screw capped glass vial it's until use. Ex. chlordiazepoxide and mannitol solid dispersion was prepared by this method [40].

Gel Entrapment Technique:

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in particle size by mortar and sieved [41].

Spray-Drying Method:

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer [42].

Lyophilisation Technique:

Freeze-drying involves transfer of heat and mass to from the product under preparation. This technique was alternative method to solvent evaporation. It is a molecular mixing technique where the drug and carrier are co dissolved in a solvent, frozen and sublimed to obtain a lyophilized molecular dispersion [43].

Electro spinning Method:

The electro spinning technology is used in the polymer industry combines solid solution/dispersion technology with nanotechnology. In this procedure a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces prevail over the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are produced. As the solvent evaporates, the formed fibers can be collected on a screen to give a non woven fabric[44]. This technique has tremendous potential for the preparation of nanofibers and controlling the release of biomedicine as it is simplest and the cheapest this technique can be utilized for the preparation of solid dispersions in future [45].

Dropping Method Solution:

The dropping method was developed by Ulrich, 1997. The crystallization of different drugs, it is a new technique for developing of solid dispersions. This technique may be overcome some of the difficulties inherent in the other methods. For laboratory scale preparation a solid dispersion of a melted drug-carrier mixture is pipette and then dropped into a plate, where it solidifies into round particles. The dropping method not only simplifies the manufacturing process, it gives a higher dissolution rate [46].

Melt Agglomeration Process:

This technique has been used to prepare solid dispersion where the binder acts as a carrier. SD(s) are prepared by heating the carrier, drug and excipients to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer [47]. A rotary processor has been shown to be alternative equipment for melt agglomeration because of easier control of the temperature and because higher binder content can be incorporated in the agglomerates[48]**.**

MATERIALS USED IN HOT-MELT EXTRUSION

For a pharmaceutical material to be processed by hot-melt extrusion, it must be able to deform easily inside the extruder and solidify upon its exit. Materials must meet the same levels of purity and safety as those prepared by traditional techniques. Most of the raw materials used in hot-melt extruded pharmaceuticals have been used in the production of other solid dosage forms such as tablets, pellets, granules and transdermals. Thermal stability of the individual compounds is a prerequisite for the process, although the short processing times encountered in this process may not limit all thermolaible compounds.

Hot-melt extruded dosage forms are complex mixtures of active medicaments and excipients. Excipients may be broadly classified as matrix carrier's release modifying agents, bulking agents, antioxidants, thermal lubricants and miscellaneous additives. The incorporation of plasticizers may lower the processing temperatures necessary for hot-melt extrusion thus reducing drug and carrier degradation. Drug release from these systems can be modulated by the incorporation of various excipients. The dissolution rate of the active compound can be increased or decreased depending on the rate-modifying agent. Oxidative or free radical degradation during the processing or storage the addition of an acid acceptors and light absorbers may be warranted.

Carriers

In hot-melt extruded drug delivery systems the active compound is embedded in a carrier formulation comprised of one or more meltable substances and other excipients. The meltable substances may be polymeric materials [49] or low melting point waxes[50].

The selection of polymer for hot-melt extrusion process mainly depends upon drug-polymer miscibility, polymer stability and final dosage form. A many of carrier systems have been studied or used in hot-melt extrusion dosage forms. Drug release kinetics from hot-melt extruded dosage forms is highly dependent upon the choice of the carrier material. Carriers used in hot-melt extruded dosage forms have included water insoluble polymers and waxes such as ethyl cellulose or carnauba wax in which the rate of drug release are diffusion controlled. Water soluble polymers have included hydroxy propyl cellulose, poly vinyl pyrrolidone, polyethylene oxide in which the drug is released by a diffusion and erosion mechanism [51,52]. Functional excipients have also been used to modify drug release rates in these systems. Depending upon the physical and chemical properties of these additional excipients, various release profiles may be achieved. Functional excipients have been formulated into hot-melt extruded dosage forms to modify the drug release rate by altering the porosity of the dosage form. Viscosity increasing agents have been incorporated into polymeric matrices to limit and reduce the initial burst often observed with these systems.

Hydroxy Propylmethyl Cellulose (HPMC):

HPMCs are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% is derivative with hydroxy propyl groups. For example, Type 2910 has an average methoxy content of 29% and hydroxy propyl content of 10%. The molecular weight of the HPMCs ranges from about 10 000 to 1 500 000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane[53]. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nilvadipine[54] and benidipine.

Hydroxypropylcellulose (HPC):

Hydroxypropylcellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 400C),

ethanol, methanol and chloroform. The average Molecular Weight of the HPCs ranges from 37 000 (Type SSL) to 1 150 000 (Type H)[55]. Yuasa *et al*. carried out extensive studies of the influence of the chain length and proportion of HPC in the solid dispersion on the release behaviour of flurbiprofen.

Carboxy Methyl Ethyl Cellulose (CMEC):

CMEC also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. CMECs readily dissolve in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8.

Hydroxy Propylmethylcellulose Phthalate (HPMCP):

HPMCPs are cellulose esters which are often used as eccentric coatings. They dissolve first at pH 5 .They are having a type-dependent solubility in organic solvents. Molecular weights ranges from 20,000 to 20, 00,000. The griseofulvin dissolution rate at pH 6.8 could be greatly enhanced by incorporating it in a co evaporates of HPMCP (Hilton, 1986). Using a spray-drying technique to form a solid dispersion in HP 55, the dissolution rate of the anti-fungal drug MFB-1041 could be increased by a factor of 12.5 as compared to the best possible dissolution achievable by micronizing the drug [56].

Polyacrylates and Polymethacrylates:

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid and derivatives of these polymers such as esters nitriles and amides. Commonly they are referred to by the trade name Eudragit drug. When benidipine was formulated as a co-evaporate with eudragit E, the rate of dissolution was much higher than from the pure drug powder[57]. On the other hand, dissolution of griseofulvin dissolution has been increases by using of Eudragit L and spironolactone at a pH value of 6.8.

Urea:

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000. A two-fold increase in the dissolution rate of phenytoin has also been achieved with urea; however, in this case PEG 6000 was far more efficient.

Sugar, Polyols and their Polymers:

Although sugars and related compounds are highly water soluble. The melting point of most sugars is high, making preparation by the hot melt method problematic and their solubility is poor in organic solvents, making it difficult to prepare co-evaporates. Mannitol, which has a melting point of 165-168^{0}C and decomposes only above 2500C, can be employed in some cases to prepare dispersions by the hot melt method [58].

Emulsifiers:

Emulsifying agents will influence the drug release rate; mainly two possible mechanisms are involved: 1.improvement of wetting properties and solubilization of the drug. 2. Owing to their potential toxicity problems of drugs, such as mucosal surface damage, emulsifying agents are usually in combination with another carrier. For example, the release of naproxen from solid dispersions in PEG 4000, 6000 and 20000 could be further enhanced when either sodium lauryl sulphate (SLS) or Tween® 80 was added to the system [59]. Inclusion of alkali dodecylsulphate surfactants in carrier systems can lead to conversion of a solid dispersion to a solid solution. Melts of griseofulvin and PEG 6000 normally contain crystalline areas; in the presence of SLS a solid solution is formed [60].

Plasticizers:

The main uses of polymeric carrier's are usually low molecular weight compounds capable of softening polymers to make them more flexible. Incorporation of a plasticizer into the formulations in order to improve the process conditions during the manufacturing of the extruded dosage form or to improve the physical and mechanical properties of the final product[61]. Plasticizers are added to HME formulations to facilitate the extrusion of the material and to increase the flexibility of the extrudate. This approach may reduce the degradation problems that are associated with temperature-sensitive drugs or polymers. Mainly plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains [62]. In doing so, the ease of movement of polymer chains with respect to each other is dramatically reduced. Plasticizers were also found to facilitate the fusion process of semi crystalline polymers [63,64]. Less energy is usually required to melt semi-crystalline polymers following the addition of one or more plasticizers. With the addition of a plasticizer, a HME process can be conducted at lower temperatures and with less torque. Generally, both the active ingredient and the polymer will be more stable during the extrusion process due to these improved processing conditions. Materials commonly used as plasticizers that are approved by the Food and Drug Administration (FDA) for use in pharmaceutical dosage forms, according to their chemical structure. Plasticizers used for the preparation of pharmaceutical dosage forms must have good efficiency, stability, polymer-plasticizer compatibility and permanence. In hot-melt extruded system triacetin, citrate esters, and low molecular weight polyethylene glycols have been investigated as plasticizers.

Recently, surfactants have also been shown to be promising plasticizers in producing solid dispersions by HME in addition to acting as Solubulizer [65]. Additionally, several drug substances have been reported to function as plasticizers in hot-melt extruded dosage forms [66].

Limitations of Solid Dispersions:

Despite an active research interest, the commercial application of solid dispersion in dosage form design has been very limited. Only two products, griseofulvin in

polyethylene glycol and nabilone in polyvinylpyrrolidone solid dispersions.

Main problems limiting the commercial application of solid dispersion involve

(a) The physical and chemical stability of drugs and vehicles

(b) Method of preparation

(c) Reproducibility of its physicochemical properties

(d) Its formulation into dosage forms

(e) The scale-up of manufacturing processes.

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