



A REVIEW ON AMORPHOUS SOLID DISPERSIONS AND RECENT ADVANCES

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ABSTRACT

Amorphous solid dispersion (ASD's) is most widely used and sought after technique by pharmaceutical industries as there is lot of flexibility in choosing the process, polymers to be used and reproducibility. Currently in this article we discussed about the methods used in formulation of ASDs in this hot melt extrusion and lyophilization are the techniques mostly preferred in the industrial processes because of their technical advancement and success ratio is more. Drugs which are having solubility issues can be easily formulated in to ASD's using a suitable solvent system, which is an advantage for many BCS Class II, IV drugs where solubility is main factor which effects bio-availability of drugs. Many marketed products are available in the market formulated using ASD's. Evaluation of ASD's is done by FT-IR, DSC, XRD and SEM. In this article we emphasized about the polymers used in different techniques of the marketed products which will give a strong proof on reliability of the ASDs as the successfully applied technique in industries.

Key words:

Amorphous solid dispersions, BCS classification, solubility, techniques employed.

INTRODUCTION

By using the amorphous solid dispersion (ASD's) technique there is much possibility to increase the solubility and dissolution rate of water insoluble drugs [1]. To increase the stability and to increase drug release various polymers or surfactants are used in amorphous solid dispersion technique [2]. But the disadvantage is that the amorphous materials can easily and rapidly convert to the crystalline form at temporary temperatures, to overcome this stabilizer and plasticizers are used [3]. The BCS classification II will show the low solubility for drugs so that decreases in particle size and nano-particles are used to further increase the solubility of drugs [4]. The ASD's can easily solubilize the drugs which are having solubility issue where solubility is the rate limiting step for better absorption of the drug [5]. The conversion of crystalline form of a drug to amorphous stage is very crucial for any drug, for effective solubility, and this will show its impact on the bioavailability and to maintain the desired therapeutic levels in the body [6,7,8,9,10]. ASD's have lot of advantages and this can be achieved by using various polymers and their combinations. In amorphous solid dispersions the polymers are used to prevent the crystallinity by enhancing amorphous state by physical

stabilities [11, 12, 13, 14]. Especially in case of anticancer drugs the oral route is mostly used [15]. The oral administration offers various factors like frequent administration of drug and also most preferable in administration. In amorphous solid dispersion the amorphous form will accurately enhances their solubility and bio-availability [15, 16, 17]. Therefore, ASDs are most widely used in anti-cancer drugs for effective treatment and to achieve desirable bio-availability as there major drawback like solubility and crystalline issues in most of the anti-cancer drugs, with this technology stability as per ICH guidelines can be maintained [16-17]. Various formulations like tablets and capsules can be formulated using the dry form of amorphous solid dispersed drug. Combination of polymers and matrix type polymers can be employed in the formulation of tablets and capsules to achieve desired drug release patterns and bioavailability.

Methods of preparation of amorphous solid dispersion [Table 1]

1. Fusion method
2. Ball milling
3. Lyophilization technique
4. Hot melt extrusion

5. Supercritical fluid methods

6. Solvent evaporation method

Table 1: Techniques employed in formulation of marketed ASD's

COMPOUND NAME	POLYMERS	METHOD OF PREPARATION	AIM OF THE STUDY
vemurafenib	HPMCP HP-55, Eudragit L-100-55, HPMCAS-L	Micro- precipitated bulk powder technology	Improvement of physical stability, dissolution and human pharmacokinetic profiles.
Itraconazole	Polyvinyl pyrrolidone vinyl acetate co-polymer88 and Hydroxy propyl methyl cellulose acetate succinate	Solvent Evaporation	Evaluation of storage stability.
Atorvastatin	Pluronic F127 and Pluronic F68	Fusion method	Optimization of bioavailability with reduced dose and improvement of solubility. [27]
AZD0837	Polyethylene oxide	Hot melt extrusion	Investigation of controlled release performance of caplet shaped injection molded ASD.
Curcumin	Hydroxy propyl methyl cellulose	Solvent evaporation	Elucidation of impact of HPMC E5 on crystallization and improvement of permeability.
Efavirenz	Soluplus	Spray drying	Improvement of aqueous solubility and bioavailability.
Darunavir	Hydroxy propyl methyl cellulose	Coaxial electro spraying	Introduction of coaxial electro spraying technique and evaluation of encapsulation efficiency.
Phenacetin	Polyvinyl pyrrolidone	Solvent evaporation	Estimation of kinetic solubility of ASD prone to crystallization.
Etoposide	Vitamin E TPGS with Co- povidone: Eudragit L-100 (60:20)	Solvent evaporation	Investigation of solubility and permeability interplay when using TPGS and amorphous solid dispersion
Nifedipine	Polyvinylpyrrolidone Vinyl acetate (PVP/VA 64)	Hot melt extrusion	Investigation of different types of energy input affect the stability and preparation of ASD's. [28]

(a) Techniques employed in formulation of marketed ASD's**Fusion method:**

The fusion method is a kind of melting method, is a technique for creating amorphous solid dispersions, in this method drug and the polymer mixture are melted until they melt and form a homogenous mixture forming a homogenous molten mixture that is then rapidly cooled to solidify, resulting in a molecularly dispersed amorphous form of the drug encapsulated in the polymer matrix, where solubility and dissolution rate can be improved. [18]

Ball milling:

Ball milling is a simple method used to achieve amorphous solid dispersions, in this technique amorphous forms are achieved during milling process because of particle size reduction, in these solvents are not used. The carrier is mixed with the drug while milling. Mixing miller is used

to mill the drugs. Using a 50ml chamber for 240 min at 4% w/v with 4-24 mm diameter and 6-7 mm diameter stainless steel ball bearing. [19]

Lyophilization technique:

Lyophilization, also known as freeze-drying, is a technique used to create amorphous solid dispersions (ASDs) by dissolving a drug and carrier in a solvent and then the mixture is allowed to freeze, then the solvent is removed from the frozen product by sublimation process under vacuum, leaving behind a uniformly mixed, amorphous solid dispersion with improved drug solubility due to its high surface area and molecular dispersion and is often preferred for its ability to avoid harsh organic solvents and produce fine, stable amorphous particles. [20]

Hot melt extrusion:

Hot melt extrusion (HME) is a technique used to create amorphous solid dispersions (ASDs), in this combination of poorly soluble drug and matrix forming polymers are taken and are mixed in a molten state under heat and mechanical shear within a screw extruder, resulting in a homogenous mixture that is then extruded and cooled to form a solid dispersion with enhanced drug dissolution properties; this process is solvent free and relies on the combined forces of heat and mechanical stress to achieve molecular level dispersion of the drug and the polymer matrix, offering advantages like high production efficiency and flexibility in formulation design.[20]

Super critical fluid methods:

In these technique organic solvents like carbon-dioxide is used as anti-solvents for the solute in supercritical fluid anti-solvent procedures. Different micronization techniques like gas anti-solvent, anti-solvent, and supercritical anti-solvent were used. The SAS procedure entails spraying the solute and organic solvent solution into a continuous supercritical phase that flows simultaneously. [21]

Solvent evaporation method:

In this method, the ASDs are formulated by removing the solvent from the solution containing drug and polymer in a suitable solvent and is the most popular method at industrial level for improving the solubility of poor water soluble drugs. In this method the identification of suitable solvent is a critical step, where it can effectively dissolve both the drug and the polymer without compromising their stability and compatibility it requires proper selection of solvents to ensure that no adverse interactions such as drug degradation, precipitation or phase separation occurs.

In this method using a same solvent for both the drug and polymer can be challenging when there are significant differences in their polarities. Polar and non-polar substances tend to have poor solubility in each other. In poor drug-polymer interactions, the stability, solubility and function of formulation can be affected if there is difference in their polarity. In this method i.e., solvent evaporation method, the used solvent should be free from toxic components and should have proper stability for the drug and carrier. In solvent evaporation method, the ASDs are prepared by dissolving the drug-polymer using a suitable solvent system and their action to evaporation. In amorphous solid dispersions the amorphous form of drug-polymer can be achieved by evaporating the solvent from drug-polymer solution. The solvent evaporation technique is very useful for formulations which are thermolabile. The

various solvents are used in this method such as water, alcohols (i.e., methanol, ethanol or iso propanol).[22]

Bioavailability enhancement through amorphous solid dispersion:

Carrier-controlled, dissolution controlled, dissolution controlled and drug-controlled dissolution are the three main mechanisms involved in enhancing the bioavailability.

Mechanisms of amorphous solid dispersion dissolution:

i. Carrier - controlled dissolution:

Polymer matrix acts as rate controlling barrier for drug release and the mechanisms involved in drug release through polymer-matrix are hydrating, swelling and dissolving.

ii. Dissolution - controlled dissolution:

Dissolution rate is determined by the intrinsic dissolution properties of the drug and polymer.

iii. Drug - controlled dissolution:

The drug is highly soluble or when the polymer dissolves rapidly, leaving the drug to control the release. Amorphous solid dispersion dissolution is indeed influenced by several factors such as amount of drug, uniformity in the amorphous solid dispersion, matrix formation of drug-polymer, and the type of surfactants used. [23]

Increased drug absorption in amorphous solid dispersions is primarily attributed to two key factors:

1. Increased concentrations of molecularly dissolved active pharmaceutical ingredient.
2. Flux through the unstirred water layer. [24]

Surfactants are very important for the dissolution and stability of amorphous solid dispersions (ASDs). Enhancement of dissolution properties, stabilization of supersaturated solutions, potential destabilization, and reduction in dissolved active pharmaceutical ingredient fraction. [25]

BCS Classification:

In the pre-oral drug absorption solubility and permeability plays important role. BCS classification data is crucial for pharmaceutical industries for product development and for FDA approval. The BCS data is very frequently used for in-vitro dissolution in industrial quality control is also frequently used by the ICH. Not only the solubility and the permeability, other factors like absorption, dosage and dissolution have a significant effect. Several BCS system shortcomings were noted and are covered below. Formulation strategies of each BCS class were discussed in the table [3] [Table 2].

TABLE:2 Amorphous Solid Dispersion of marketed Drugs with BCS classification [32]

Product name	Drug	BCS class	Carrier polymers	Preparation method	Therapeutic category	Dosage form	FDA approval year
Cesamet (US) Canemes	Nabilone	II	PVP	Solvent evaporation	Cancer	Capsule	1985
Onmel	Itraconazole	IV	HPMC	HME	Onychomycosis	Tablet	2010
Advagraf /Astagraf XL	Tracrolims	II	HPMC	Wet granulation	Organ transplantation	Capsule	2013
Gris-Peg	Griseofulvin	IV	PEG600	Melt extraction	Fungal infection	Tablet	1975
Kletra	Lopinavir/ ritonavir	II	PVP	PME	AIDS	Tablet	2005
Eucreas/ Galvusmet	Vildagliptin Metformin HCL	III	HPC	Melt extraction	Diabetes	Tablet	2007
Intelence	Etravirine	IV	HPMC	HME	AIDS	Tablet	2008
Prograf	Tacrolimus	II	HPMC	Kneading, drying	Organ transplantation	Tablet	1994
Samsca	Tolvaptan	IV	N/A	Granulation	Hyponatremia	Tablet	2009
Lozanoc	Itraconazole	IV	HPMCP	Spray drying	Fungal infection	Capsule	2012
Kalydeco	Ivacaftor	II/V	HPMCS	Spray drying	Cystic fibrosis	Tablet	2012
Sporanox	Itraconazole	IV	HPMC	Spray drying	Fungal infection	Tablet	1992

b) Amorphous Solid Dispersion of marketed Drugs with BCS classification

Marketed drugs on ASD's data were also provided where it shows the applicability of the technique and its reproducibility. [Table 3]

TABLE: 3 Marketed drugs and polymers used

TRADE NAME	CHEMICAL NAME	POLYMERS USED
Mavyret	Glecaprevir	Hypromellose, Co-povidone
Lynparza	Olaparib	Co-povidone
Erleada	Apalutamide	Hypromellose acetate succinate
Trikafta	Elexacaftor	Hypromellose, Hypromellose acetate succinate
Alvaiz	Eltrombopag olamine	Polyvinyl Phosphonic Acid
Jaypirca	pirtobrutinib	Hydroxypropyl methyl cellulose Acetate Succinate
Paxlovid	nirmatrelvir	Polyvinyl Phosphonic acid
Phyrago	Dasatinib	Methacrylic acid-ethyl acrylate copolymer
Sotyktu	Deucravacitinib	Hydroxypropyl methylcellulose acetate succinate
Sunlenca	Lenacapavir	Poly (vinylpyrrolidone-co-vinyl acetate)
Xtandi	Enzalutamide	Hydroxypropyl methylcellulose acetate succinate
Welireg	Belzutifan	Hydroxypropyl methylcellulose acetate succinate
Tukysa	Tucatinib	Polyvinylpyrrolidone-co-vinyl acetate
Ubrelvy	Ubrogepant	Polyvinylpyrrolidone-co-vinyl acetate

c) Marketed drugs and polymers used

CHARACTERIZATION:

1. Differential scanning calorimetry
2. Powder X-ray diffraction
3. Fourier transform infra-red spectroscopy
4. Scanning electron microscopy

Differential scanning calorimetry:

Differential scanning calorimetry, is a standard method and is used to determine the amount of crystalline material (DSC), In this formulation in powder form is heated at a steady rate, and the melting temperature and enthalpy are measured. The DSC curve will show the peaks where melting of the formulation started. Thermal events include melting, recrystallization, and the shift from glass to rubber. The amount of crystalline material can be determined using the melting energy. [26-28]

Powder X-ray diffraction:

Materials with long-range order can be qualitatively detected using powder X-ray diffraction. More crystalline material is indicated by sharper diffraction peaks. Diffraction techniques are arguably the most reliable way to identify and quantify molecular order in any system. When temperature and ambient conditions are controlled, conventional PXRD, can be used to track the kinetics of phase transformation and quantify non-crystalline material down to 5%. [29]

Fourier transform infra-red spectroscopy:

Using an FT-IR spectrophotometer with the traditional KBr pellet approach, FT-IR spectroscopy can be used to identify potential interactions between the medication and the carrier in the solid state.[30]

Scanning electron microscopy:

SEM can be used to determine a solid particle's size and shape, and occasionally to identify medication polymorphism. One can see how the drug particles are finely dispersed throughout the carrier matrix [31].

SEM provides information on:

Particle shape, size and distribution- surface topography and roughness presence of defects, cracks, or agglomerates- Sample morphology and texture. [32]

Conflicts of interest:

The authors declare no conflicts of interest.

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