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The role of surfactants in preserving the stability of amorphous solid dispersions: A review

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Abstract

In recent years among various formulation strategies, amorphous solid dispersions (ASDs) has gained tremendous recognition for improving the solubility of poorly soluble drug substances. Among various manufacturing strategies, hot melt extrusion (HME), spray drying, kinetisol, and electrospinning are the most widely employed for developing ASDs. Despite the improving solubility and bioavailability, the stability of ASDs is the major problem haunting the pharmaceutical industries. Various factors, such as miscibility, the solubility of the drug in polymer, drug-polymer interactions, glass transition temperature, hygroscopicity, and storage conditions, determine the stability of ASDs. The poor stability of amorphous drugs also limits the drug loading capacity, resulting in an increased volume of the dosage form affecting patient compliance. Apart from the physical stability of ASDs, solution-mediated recrystallization of the drug when present in a supersaturated state is another factor affecting the quality and performance of the formulations. In recent years incorporation of surfactants to hinder solution-mediated recrystallization of drugs, thereby improving the stability and performance of ASD formulations, is being most widely investigated. The incorporation of surfactant in the HME process will also act as a plasticizer, thereby allowing the process to be carried at lower temperatures. This review article mainly focuses on the role of surfactants in ASD systems and recent advancements. Still, research is warranted to understand the mechanism of surfactants and to establish screening criteria.

Keywords: Amorphous solid dispersions; Hot melt extrusion; Spray drying; Kinetisol; Surfactant; Poor solubility

1. Introduction

In today's world, the main focus of the pharmaceutical industry lies in improving the solubility and bioavailability of poorly soluble drug substances. Around 60-70% of the new chemical entities (NCEs) within the developmental pipeline are claimed to be poorly soluble, belonging to the biological classification system (BCS) class II and IV [1–6]. The poor solubility of drug substance will affect the bioavailability and therefore require the administration of larger therapeutic doses to achieve the required pharmacological action. Knowledge of solubility will not only help the design of dosage forms but will also provide information for developing liquid formulations required for toxicological and pharmacokinetic studies. In addition, it will also aid the process of analytical method development, which requires the knowledge of drug solubility for developing a robust analytical method [7–12]. Thus, improving solubility is the major prerequisite for the developmental scientist and is one of the major physiochemical properties affecting *in vivo* performance.

Among various dosage forms such as injectables and transdermal medications, oral formulations has huge demand attributing to various advantages in terms of business activity and patient compliance. The oral medications are cost-

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effective and easy to administer when compared with the medications intended for other routes. Among various oral dosage forms such as liquids and solids, the solid dosage forms (capsules and tablets) have huge demand attributed to their longer shelf life and easy transportation [13–20]. Among tablets and capsules, the tablets are mostly preferred attributing to this low manufacturing cost and no possibility of adulteration. In addition, the tablets provide the flexibility of dose division for the pediatric patient population. The division of dose remains impossible for capsule dosage forms and making them prone to adulteration. Thus, owing to the advantages of oral medications, the pharmaceutical industries are left with no choice of improving the solubility of drug substances.

For the last three decades, various formulation approaches such as self-emulsifying drug delivery systems (SEDDS), liposomes, pro-liposomes, complexation, salts, cocrystals, prodrugs, amorphous solid dispersions, solid crystal suspensions, and co-amorphous systems have been investigated for improving the solubility of drug substances. The low oral bioavailability can be due to poor solubility or poor absorption of the drugs. The bioavailability of the drug substances experiencing solubility as a rate-limiting step can be improved by employing suitable solubility enhancement approaches [21–26]. In the case of drug substances experiencing poor absorption or permeability across the biological membrane, the bioavailability can be improved by employing permeation enhancers. Among the various formulation strategies, amorphous solid dispersions (ASDs) have gained tremendous recognition and attention from researchers across the pharmaceutical industries and regulatory bodies. Within ASDs, the drug loses its crystal habitat and exists in a molecularly dispersed high-energy state, resulting in improved wettability and solubility. Various manufacturing techniques such as high shear granulation, fluid bed granulation, hot melt extrusion (HME), spray drying, and Kinetisol have been investigated for developing ASDs. Among various manufacturing strategies, the HME and spray drying process has gained commercial viability for manufacturing ASDs [23, 27–58]. To date, there have been various products launched into the market which are manufactured by these techniques and are listed in Table 1. This review article mainly focuses on the role of surfactants in improving the stability of ASDs, along with a note on the advantages and limitations of ASDs.

Table 1 Various commercial ASD formulations [45]

Trade Name	Drug Substance	Year of Approval
Isoptin® SR	Verapamil	1987
NuvaRing®	Etonogestrel/Ethinyl Estradiol	2001
Kaletra®	Lopinavir/Ritonavir	2007
Norvir®	Ritonavir	2010
Onmel®	Itraconazole	2010
Noxafil®	Posaconazole	2013
Belsomra®	Suvorexant	2014
Viekira® XR	Dasabuvir/Ombitasvir/Paritaprevir/Ritonair	2014
Venclexta®	Venetoclax	2016
Mavyret®	Glecaprevir/Pibrentasvir	2017
Lynparza®	Olaparib	2018
Braftovi®	Encorafenib	2020
Oriahnn®	Elagolix/Estradiol/Norethindrone Acetate	2020

2. Factors affecting the stability of ASDs

The ASDs are identified as a commercially viable approach for improving the solubility of poorly water-soluble drug substances. Within ASDs, the drug substance exists in a molecularly dispersed high-energy state. Over some time, the mobility of the drug molecules will increase and results in the recrystallization of the drug affecting the stability and performance of the formulation. Various factors, such as storage conditions, atmospheric humidity, glass transition temperature, miscibility, and drug-polymer interactions, play an important role in preserving the stability of ASD systems. In order to develop a stable ASD system, the drug and polymer need to be miscible, resulting in the formation

of a single-phase system with one glass transition temperature. If the concentration of the drug is maintained above the miscibility levels, the mobility of the drug upon storage will increase, leading to recrystallization[59–68]. The formation of drug-polymer interaction will hinder the mobility of the drug inside the polymeric carrier, thereby improving the shelf life of the product. The storage temperature needs to be maintained below the glass transition temperature of the ASD system since storage of formulation above the glass transition will trigger mobility and recrystallization. The formulations of ASDs need to be protected from environmental moisture since the moisture acts as a plasticizer and results in reduced glass transition temperature of the system. The utmost care must be taken while milling the ASDs since the generated heat affects the glass transition temperature resulting in mobility and recrystallization of the drug.

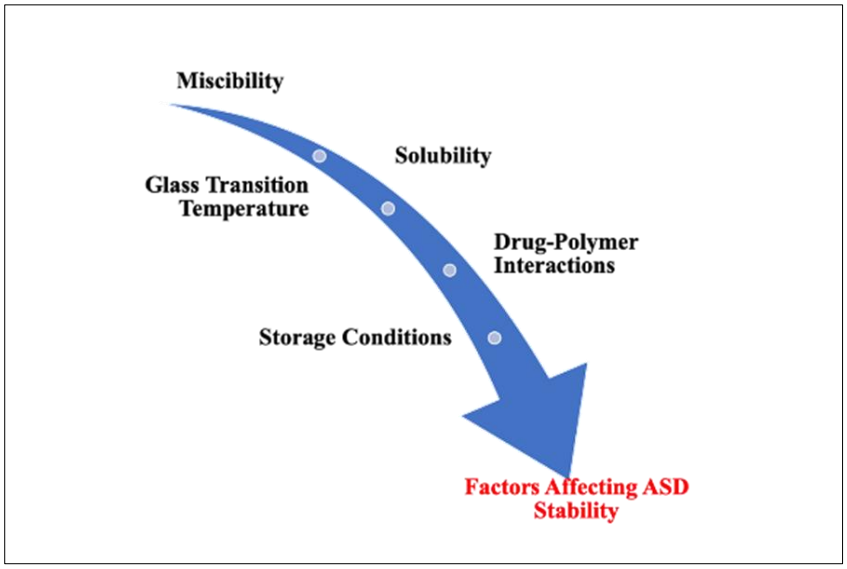

Figure 1 Factors influencing the stability of ASD systems

2.1. Role of surfactants

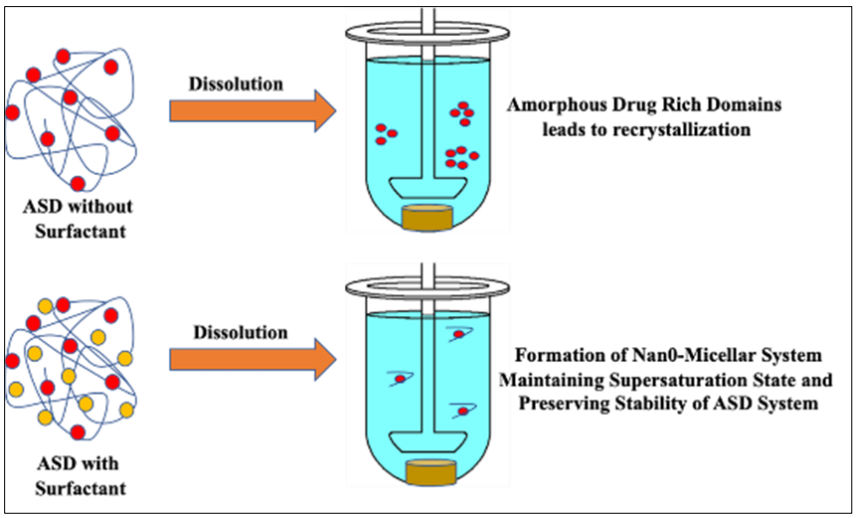

Figure 2 Schematic representation of the role of surfactant

The ASD systems are also prone to solution-mediated recrystallization of drugs when bought in contact with bulk dissolution media. When an ASD system is brought in contact with dissolution media, the drug might exist in a supersaturation state resulting in the recrystallization of the drug affecting the solubility and performance of the product. Thus incorporation of surfactant into the dissolution media or into the ASD system improves the stability and performance of the formulation. The surfactants, when added above the critical micellar concentration (CMC), result in the formation of the micellar system, thereby entrapping the amorphous drug and preventing recrystallization. The miscibility of the surfactant in the presence of drug and polymer needs to be evaluated for developing a robust formulation [69–80]. The miscibility can be evaluated by employing a thermal characterization technique, i.e.,

differential scanning calorimetry (DSC). The glass transition temperature of the ternary system (drug, polymer, and surfactant) needs to be monitored since the majority of the surfactants are low melting point materials and result in lower glass transition of the ASD systems. In addition, the surfactants will also help lower the processing temperatures, thereby exposing the formulation components to lower temperatures when processed by HME technology. A few case studies involving the investigation of the surfactant's role in preserving and improving the stability of ASD systems are discussed below.

3. Case studies

Shrawan Baghel et al. (2018) [81] investigated the role of surfactants in developing ASDs by spray drying. Dipyridamole and cinnarizine were selected as model drugs. Polyvinyl pyrrolidone K30 and hydroxypropyl methylcellulose K100 (HPMC) were selected as polymeric carriers. Sodium dodecyl sulfate (SDS) and poloxamer 188 were employed as surfactants. The formulations of drug-polymer; drug-polymer-polymer; drug-polymer-surfactant; and drug-polymer-polymer-surfactant were manufactured by spray drying approach by dissolving in a 1:1 ratio of dichloromethane and ethanol. The drug load was maintained at 20%w/w for all the investigated formulations, and the surfactant concentration was maintained at 5%w/w. The spray drying process was performed using a 0.2 mm size of nozzle at a 6 mL/min of flow rate by maintaining an inlet temperature of 80 °C. Upon investigating the developed formulations for *in vitro* drug release profiles, the formulations free of surfactant were able to maintain the supersaturation state of the drug compared with the surfactant-based formulations. The incorporation of surfactant has affected the drug-polymer interactions, thereby promoting the recrystallization of the drug. Thus drug-polymer interactions also need to be considered for developing stable ASD formulations.

Clara E Correa Soto et al. (2022) [82] have investigated the role of various surfactants (cationic, anionic, and non-ionic) on the stability and release profiles of ASDs developed by rotaflash evaporation technique. The formulations were developed with drug load ranging between 40-60 %w/w, and the surfactant concentration was maintained identically at 5 %w/w for all the investigated formulations. The formulation components were dissolved in methanol and subjected to rotaflash evaporation by maintaining a water batch temperature of 50 °C. Clopidogrel was selected as a model hydrophobic drug candidate, and Kollidon VA 64 was employed as a polymeric carrier. A wide variety of surfactants such as SDS, cetyltrimethylammonium bromide (CTAB), Tween 80, and tocopherol polyethylene glycol 1000 succinate (TPGS) have been investigated. Among all the investigated formulations, SDS at 5 %w/w of concentration was able to maintain the stability and supersaturation state up to a drug loading of 50 %w/w. This shows the importance of screening suitable type of surfactant for developing ASD systems.

Tanvi M Deshpande et al. (2018) [83] investigated the role of sodium lauryl sulfate (SLS) and TPGS in improving the stability of itraconazole-based ASDs developed by the spray drying approach. Various polymers HPMC E50 LV, PVP K30, Kollidon VA 64, Soluplus, HPMCAS-HF, Eudragit L100-55, and PEG 4000, have been invest8gated for developing ASDs. All the formulations were investigated for a drug load of 50 %w/w, and the drug solution was prepared for a solid content of 10% in a 2:1 ratio of methylene chloride and methanol. The process of spray drying was performed at 80 °C of inlet temperature and 12 mL/min of feed rate. Among all the investigated formulations, the binary ASDs of the drug and HPMCAS-HF were found to be stable and able to maintain the supersaturation state of the drug with no recrystallization. The formulations of ternary ASD dispersions were found to be unstable, attributing to the competition between drug and surfactant for the binding sites of the polymer. Thus incorporation of surfactant into the binary ASD system will not improve the stability of the formulations in all cases.

Schittny A et al., (2020) [84] investigated the role of surfactants in combination when employed in the ASD system. Efavirenz was selected as a model drug, and the ASDs were developed for a drug load of 20-30 %w/w using hydroxypropyl methylcellulose phthalate (HPMCP) HP50 and HP55 as base polymer by HME process. Upon investigation of the developed formulations, the ASDs with a combination of sucrose palmitate and polysorbate 80 as surfactants have influenced the drug release kinetics and maintained the supersaturation state of the drug. The *in vivo* characterization of the formulations in rates has resulted in improved bioavailability when compared with the pure drug and binary ASD system with drug and polymer. This shows the importance of surfactants in maintaining stability and improving the *in vivo* performance when administered orally.

Anura S Indulkar et al., (2022) [85] investigated the roles of various surfactants on the release profiles and stability of ASDs developed for ritonavir drug using copovidone as a polymeric carrier by rotaflash evaporation. Span 85, TPGS, Span 20, Tween 80, and SDS were selected as polymeric carriers. The formulations were investigated for a drug load of 30 %w/w and 5 %w/w of surfactant. The solutions for rotaflash evaporation are prepared by dissolving the physical mixtures in dichloromethane and methanol (1:1 ratio). Among all the formulations, the ternary ASD systems consisting of drug, polymer, and surfactant have resulted in improved release profiles. However, the ability of the surfactants to

maintain the stability of the formulations varied across the surfactants. The formulations with span 85 and TPGS have resulted in the complete release of the drug with no recrystallization. The formulations with span 20 and Tween 80 have resulted in incomplete release profiles and induced crystallization of the drug. The formulations with SDS have resulted in around 80% of drug release with no recrystallization. Among all the investigated surfactants, span 20 and TPGS have resulted in smaller particle sizes of 1 micron. Overall, span 85 has resulted in stable formulation with complete drug release profiles. No correlation was observed between the properties of the surfactants and the crystallization of the drug.

Sugandha Saboo et al., (2021) [86] investigated the effect of surfactants on the release profiles and stability of ASDs developed by rotaflash evaporation. The solution of physical mixtures is prepared in a 1:1 ratio of dichloromethane and methanol. Felodipine was selected as a model drug, and Kollidon VA 64 was selected as a polymeric carrier. The concentration of surfactant (TPGS) was maintained identical at 5 %w/w for all the formulations. Upon investigation of formulations for in vitro drug release profiles, the binary formulations consisting of drug and polymer have resulted in faster release profiles of only up to 20% of drug loading. Whereas incorporation of surfactant has resulted in improved kinetics of release profiles up to a concentration of 35% drug loading. The size of the ASD nanoparticles was found to be ranging between 200 - 300 nm. The presence of surfactant has prevented recrystallization of the drug, and the formulations of ternary mixtures consisting of drug, polymer, and surfactant were found to be stable for 12 hours when exposed to 100 %RH conditions. This shows the role of surfactant in aiding the release kinetics and stability of supersaturated drug solution.

4. Conclusion

In recent years ASDs have been most widely investigated for improving the solubility of poorly water-soluble drug substances. Various manufacturing strategies such as HME, spray drying, kinetisol are being employed for developing ASD systems. However, the stability of the amorphous drug remains to be a major challenge for developing ASD systems. The poor stability of amorphous drugs limits the drug loading resulting in an increased volume of the dosage form affecting patient compliance. Various factors, such as poor miscibility, drug-polymer interactions, and storage conditions, play a crucial affecting the stability of ASDs. Apart from the physical stability of ASDs, the recrystallization of drugs when present in a supersaturated state is another challenge affecting the performance of ASD formulations. In recent years, the incorporation of surfactant into binary mixtures of drug and polymer is being most widely investigated to prevent the solution-mediated recrystallization of drugs. However, still, a lot of research is warranted to establish the selection criteria of the surfactants.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declare that they have no conflict of interest.

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