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Downstream processing of amorphous solid dispersions into tablets

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Abstract

Amorphous solid dispersions have gained tremendous attention as a commercially viable solubility enhancement technique for poorly water-soluble drugs. However, poor drug loading associated with poor drug-polymer miscibility is a major challenge in the downstream processing of ASDs. While many downstream techniques are available for converting ASDs into final dosage forms, oral solids remain the most commercially viable. The type of excipients used in the conversion of ASDs into tablets are very similar to the excipients used in conventional tablets. For example, the binders used in conventional tablets are widely used as polymeric carriers in case of ASDs. The physical properties of ASDs manufactured using spray drying or hot melt extrusion pose major challenge in converting ASDs into oral tablets. The current review focuses on various challenges associated with converting ASDs into tablets and provide a comprehensive review on various excipients used in manufacturing tablets using ASDs.

Keywords: Amorphous Solid Dispersions; Hot Melt Extrusion; Spray Drying; Tablets

1. Introduction

Poor aqueous solubility of APIs is one of the most challenging issues in the pharmaceutical industry. Various solubility enhancement techniques have been developed to improve the aqueous solubility of BCS class II and IV drugs (1, 2). One such technique is the conversion of the poorly water-soluble crystalline drug into highly soluble amorphous drugs using solid dispersion technique. A solid dispersion can be defined as a dispersion of drug particles in a polymeric carrier matrix. There are various types of solid dispersions depending on the physical state of the drug in the polymeric matrix. When the drug particles are molecularly dispersed in the polymeric matrix, the solid dispersions are referred to as amorphous solid dispersions (ASDs) (3). ASDs are the most popular type of solid dispersions due to their ability for rapid solubilization in the bio-relevant media. This is essential when spring and parachute dissolution profile is required. There are various techniques for the preparation of ASDs. In the early days, solvent based techniques like rota evaporator, spray drying were widely used for preparing ASDs. Gradually, solvent free techniques like melt quenching, hot melt extrusion, KinetiSol etc. gained popularity (4, 5). Out of all these techniques, spray drying, and hot melt extrusion are the most popular and commercially viable techniques for the manufacturing of ASDs. The three main aspects in the formulation of successful ASDs are the selection of ideal excipients, selection of ideal manufacturing technique and downstream processing to manufacture tablets or capsules (6). Selection of ideal excipients requires thorough knowledge of the physical properties of the drug. An ideal ASD formulation should be stable throughout the shelf life, should not recrystallize during *in vitro* dissolution and show spring and parachute effect (7). The second aspect is the selection of an ideal processing technique which depends on the properties of the drugs (8). HME is usually avoided for thermolabile drugs. Spray drying becomes challenging if the drug and polymer is not soluble in any common solvent. These considerations should be taken while selecting an ideal processing technique for manufacturing of ASDs (9). Once the ASDs are prepared, the need to undergo downstream processing to get converted to a final dosage form. The most popular dosage forms for ASDs are tablets and capsules (10). Usually, ASDs with high drug lodging sufficient

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for a single dose are milled and combined with filler then finally filled into capsules. If the dose is high, then the ASDs are combined with suitable excipients and compressed into tablets. Most of the times when the ASDs have poor compressibility, roller compaction will be performed to improve the compressibility. The present review summarizes various excipients used in the downstream processing in converting ASDs into tablets.

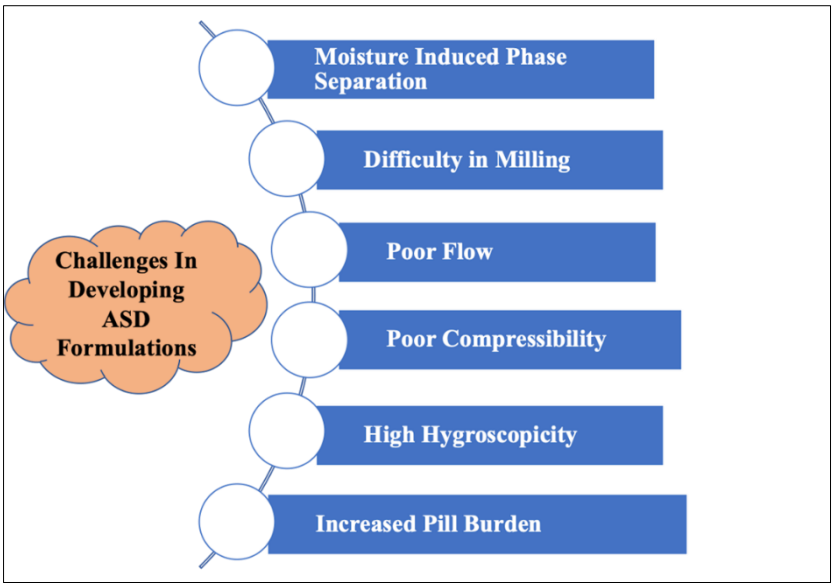

Figure 1 Various challenges associated with tableting of ASDs

2. Various Excipients for Tableting of ASDs

To overcome various challenges associated with tableting of ASDs, several excipients are used either as part of ASDs or as tableting components. Several researchers studied the impact of formulation components and commonly used tableting excipients on the mechanical properties of tablets. The impact of microcrystalline cellulose, lactose, and a model drug on the ASDs prepared using two polymeric carriers, HPMC-AS and copovidone was studied (11). The authors have prepared ASDs using spray drying and HME and studied the tensile strength, compression pressure, elastic modulus, dynamic hardness as indicators of compaction properties. The properties of excipients before and after processing were compared and concluded that the compaction properties had the capability to identify and quantify the compression characteristics of excipients used in tableting.

3. Co-processed Excipients

Various publications have demonstrate that co-processed excipients are better compared to conventional excipients for tabletting of ASDs (12, 13) . Co-processed excipients are physically modified for better flow, diluent potential, low fill variation and compressibility without changing their chemical structure. In one of the reported studies, three mannitol based co-processed excipients, Pearlitol Flash, Pharmaburst and Ludiflash were used to prepare orodispersable tablets of carvedilol and Soluplus ASDs (14). The results showed that tablets with Pearlitor Flash (co-processed mannitol and starch) showed lower disintegration time of 36.5 sec and faster drug release of 94.46% after 30 min. On the other hand, the powder blends with Pharmaburst displayed better compressibility and flowability and a disintegration time of 47 s and a drug release of 94.2% after 30 min.

3.1. Use of binders in ASDs

In conventional tablets, binders like PVP K30, PVP K90, cellulose derivatives etc. are used at lower concentrations to increase the hardness of the tablets. In case of ASDs, most of the conventional binders are used as carriers to stabilize the amorphous drug. Often, they are used at higher concentrations, resulting in harder tablets. This in turn hinders rapid disintegration, which often means that additional excipients are required to maintain tablet performance. To put that into perspective, to make a tablet containing 100 mg of drug with 20% drug loaded ASDs, the total weight of the tablet will be 500 mg, excluding the additional excipients required for disintegration and flow improvement. It is suggested to use at least 10% of the blend should contain disintegrating agent to compensate for high amounts of binders. It results in increased pill burden which causes patient compliance issues (15). Even if the pill size is within the limit, the use of

large amounts of disintegrating agents causes serious problems during storage and coating due to absorption of water by the disintegrating leading to swelling of the tablet and a decrease of tablet hardness. Absorption of water also causes phase separation and result in recrystallization. This will in turn effect the dissolution performance. When five different binders, PVP, acacia, gelatin, sodium CMC and ethyl cellulose were investigated at different concentrations for their effect on hardness and disintegration time of ASD tablets, it was observed that increase in the amount of binder increased the hardness and disintegration time. The tablets containing gelatin were harder compared to other tablets. The tablets containing PVP disintegrated faster due to water solubility of PVP. However, increasing the amount of PVP decreased the drug release since the tablets became too hard (16).

The primary role of binders in ASDs is to prevent the phase separation and recrystallization of amorphous drug throughout the life cycle of the product. Therefore, it is essential for the amorphous drug to be miscible with the binder to remain stable. This becomes a challenge at higher drug loading since higher amounts of binder is required for the drug to be completely miscible. There are various studied that demonstrate various theoretical and experimental methods for the determination of miscibility of drug in binders. All these studied have a common conclusion that higher the amount of binder used, higher will be the amount of amorphous drug in ASDs. However, it is not always ideal to use larger amounts of binders. In case of ASDs prepared using PVP K12, higher concentrations of binders reduce the drug release. This is due to the formation of a boundary layer around the drug molecules by PVP K12. This reduces the total available surface area for dissolution and reduces the rate of dissolution. Polyethylene glycol (PEG) is one of the versatile and commonly used binders/ carriers in formulation of ASDs. It also acts as a surfactant, which increases the drug release by increasing the saturated solubility of poorly water-soluble drugs. ASDs of PEG 6000 and diazepam were prepared and compressed them into tablets using direct compression and wet granulation. They have reported that the disintegration time of the tablets has increased but interestingly, the t50% and t85% were significantly shorter due to the improved aqueous solubility of diazepam as a function of the increasing PEG6000 concentration.

The chain length and molecular weight of the fillers can also affect the drug release and tableting properties of ASD tablets. The release of ketoprofen from tablets was affected significantly when two different grades of HPC was used (17, 18). The EF grade of HPC showed slightly slower release than ELF grade. However, the ELF grade exhibited better tabletability behavior during compression. In the same study, the authors have demonstrated that the use of highly water-soluble fillers like mannitol has significantly increased the dissolution rate. The choice of processing conditions also effects the performance of the fillers. The choice of filler also impacts the crushing strength of the tablets. PVPVA64 based tablets possessed significantly better crushing strength than those prepared with HPMC. Cellulose based fillers like HPMC forms a gelling matrix and allows the drug to dissolve incrementally. On the other hand, water soluble polymers like PVPVA64 tablets were found to show better disintegration time compared with HPMC. To prevent the formation of gelling layer, inorganic salts like potassium carbonate, potassium bicarbonate etc. were incorporated into the tablets. The results showed faster dissolution with inorganic salts compared to the tablets without inorganic salts (19). If the particle size of the ASDs is small, then gelation of the carriers does not make a significant impact on the drug release since the tablet will disintegrate into smaller particles. However, the size of the individual particles will define the dissolution rate in that case. Therefore, it is important to control the particle size distribution after milling of ASDs, in case of HME. Along with that, the influence of compression force, the type of the filler and its particle size distribution should be confirmed during formulation development if immediate release is required.

3.2. Fillers for ASDs

Fillers are the excipients used to improve the wettability of tablets and to make up the required tablet weight (20). In ASD-containing tablets, water-soluble fillers like mannitol or lactose are mostly commonly used in combination with microcrystalline cellulose (MCC). Although fillers increase the pill size and result in pill burden, they are very essential for stability of ASDs. When used at right concentrations, fillers act as spacers in between the ASD particles which contain high molecular weight binders and prevent the increase in the particle size of ASDs during storage. When smaller particle size MCC grades were used for making ASD tablets, the internal porosity of the tablets was found to be higher, resulting in faster disintegration, and higher supersaturation. On the other hand, when higher particle size grades are used, gelling could be observed on the tablet surface, resulting in slower dissolution. The excellent lubrication and compaction properties of MCC makes it an ideal filler in formulating ASD and liquid-solid tablets (21). The use of MCC in the powder blend improves the compressibility, which is often a challenge for ASDs (22). The use of elastic materials like sodium starch glycolate can potentially lower the tensile strength of the tablets due to reduce in the bonding area. However, beyond a certain level of a highly compressible plastic material, a slight decrease in hardness can occur (23). Co-processed excipients like spray dried lactose coated with sodium caseinate or gelatin was shown to have excellent compaction properties (24, 25). These coating additives accumulate on the surface of droplets during the spray-drying process and increase the bulk density, flowability and reduce the wetting time of powders. The use of sodium caseinate, gelatin and HPMC as coating on the spray dried lactose increased the particle size, but also significantly enhanced

flowability. ASDs of ibipinabant with PVP as a carrier was prepared using spray-drying technique (15, 26). The spray dried ASDs were mixed with different fillers like lactose, mannitol and MCC and their effects on the physical stability of the API were assessed. It was reported that in tablets containing MCC as a filler, only 13% of amorphous drug converted into crystalline form after 3 months of storage at accelerated conditions (40 °C/75% RH). On the other hand, tablets containing mannitol showed around 92% recrystallization of the amorphous drug under same conditions. These results were found to be in line with the dissolution data where tablets containing MCC showed more than 90% drug release. The rationale for higher recrystallization induced by mannitol is due to the fact that mannitol is crystalline in nature which can potentially induce secondary nucleation and crystal growth of the API. Another hypothesis is the use of higher compression pressures for mannitol-based tablets due to poor compressibility as compared to MCC based tablets which are highly compressible.

3.3. Lubricants for ASDs

Lubricants are the excipients used to reduce the contact area between the powder particles and the die wall surface and punch surfaces. As a results, the tablets will not stick to the die wall or the punch surface. The effective surface area of the particles plays a major role in the determination of the lubricant efficacy. In case of ASDs, based on the type of technology used, the particle size is mainly under 100μm. Along with that ASDs contain large concentrations of polymeric carriers/ binders which are sticky in nature (27, 28). Therefore, higher concentration of lubricants is needed than in conventional tablets. This comes with a downside of reduction in wettability due to presence of more lubricant. This should be an important consideration which optimizing the formulations for ASDs. Also, due to the poor bonding strength of the lubricants and their elastic nature, use of higher concentrations of lubricants can significantly reduce the tensile strength of the tablets.

3.4. Glidants for ASDs

If ASDs are prepared using HME technique, the filaments are milled to obtain desired particle size around 100 microns. In case of ASDs prepared using spray drying or electrospinning, the process parameters usually determine the particle size of ASDs. Irrespective of the technique used, reduced particle size of ASD powders usually results in poor flowability coupled with increased interparticle frictional and cohesive forces. Therefore, glidants are essential to improve the flow of ASD powders. There are only a handful of articles in the literature discussing the effects of glidants on the tableting of ASDs. The most frequently used glidants in solid oral dosage forms are the colloidal silicon dioxide derivatives like Neusilin, Cab-O-Sil etc. Various types of hydrophilic and hydrophobic colloidal silicon dioxides were evaluated for their effect on improving the flow characteristics of MCC (29). The results suggested that hydrophobic silicon dioxide decreased the inter particulate forces to a greater extent as compared to hydrophilic materials. The mixing speed was also evaluated in the same study and the authors have concluded that aggressive mixing can results in lower inter particulate forces and better flowability. There is still a need for extensive research to study the effect of glidants on the flowability of various ASDs.

Table 1 List of excipients used in compression of ASDs into tablets

Excipient	Function	Examples
Fillers	Provide bulk and enable accurate dosing of potent ingredients	Lactose, Sorbitol, Micro crystalline cellulose (MCC), dicalcium phosphate (DCP), sugar alcohols
Binders/ Carriers	Maintains the amorphous nature of the drug by kinetic hinderance.	HPMCAS, PVP, PVPVA64, Soluplus, Eudragit
Disintegrants	Aid dispersion of the tablet in the gastrointestinal tract, releasing the active ingredient and increasing the surface area for dissolution	Starch, Cellulose derivatives (HPC), Crospovidone
Glidants	Improve the flow of powders during tablet manufacturing by reducing friction and adhesion between particles. Also used as anti-caking agents.	Colloidal anhydrous silicon and other silica compounds
Lubricants	Similar action to glidants, however, they may slow disintegration and dissolution. The properties of glidants and lubricants differ, although some compounds, such as starch and talc, have both actions.	Stearic acid and its salts (e.g. magnesium stearate)

3.5. Disintegrants for ASDs

The primary role of disintegration is to enhance the surface area of the drug exposed to the aqueous environment thus facilitating and accelerating dissolution. In some instances, variations in peak plasma levels were more correlated with differences in disintegration time than dissolution rate. Since in case of ASDs the main aim is usually to enhance the dissolution rate, rapid disintegration is desired to form an immediately dissolving tablet. Hirasawa et al. (2004) prepared nilvadipine containing ASD granules with a high-speed agitation granulator which were subsequently compressed into tablets. A combination of crospovidone and methylcellulose, both widely used disintegrants, was applied as the ASD carrier. An additional portion of methylcellulose and low substitution hydroxypropylcellulose was used as the binder and disintegrant during compression, respectively (5, 7). The effects of particle size of crospovidone and viscosity of the disintegrant and methylcellulose, were assessed. An increase was found in tablet hardness and apparent solubility as the particle size of crospovidone decreased while dissolution rate slowed with finer particles as the disintegration time increased. Increased hardness and disintegration time with finer particles could be attributed to an increase of the number of contact points amongst the particles (30). On the other hand, hardness and dissolution rate increased and apparent solubility did not change when higher viscosity grade of methylcellulose was applied. The higher viscosity grade (MC25) tended to act more as a binding than a disintegrating agent compared to the lower viscosity material (MC15). The compression of melt extruded ASD granules with different grades of disintegrants was studied (5, 31). They observed that in case of Kollidon CL (particle size: 110–130mm) and CL-SF (particle size: 10–30mm), that with Kollidon CL-SF the tablet exhibited faster disintegration at each concentration and compaction force than with Kollidon CL. It was suggested that Cl-SF possessed a higher water uptake capacity (7.5–8.5 g water/g polymer) than CL (3.5–5.5 g water/g polymer). Disintegration time as well as the formation of a GPN depended on several factors. In the case of Polyplasdone XL (particle size: 100–130mm) and XL-10 (particle size: 30–50mm), results were complex to interpret. At low concentrations, XL-10 seems to be more effective, but the reverse observation was noted at high concentrations. The explanation for these phenomena may be related to the mechanism of the disintegrants. Polyplasdone grades function mainly by wicking (32, 33). At elevated concentrations XL-10 grade with small particle size can form a coherent network upon compression that interferes with disintegration while larger particles of the XL grade may provide capillaries through which wicking can more efficiently occur. It would be of interest to investigate the effect of the ratio of particle size of ASD and the disintegrant as a function of the action of the latters as a spacer. Design of experiments seems to be an effective way to determine the appropriate amount of a disintegrant, as well as other excipients (e.g., lubricants or binders) (34). The optimized level of a disintegrant should be determined such that an appropriate disintegration occurs but without swelling due to the ambient moisture. Based on the literature, a concentration of 10% is usually targeted but other examples have also been reported. ASD were prepared by freeze-drying and converted to tablets by direct compression from this dispersion that had satisfactory hardness and disintegration time with 30% load of the disintegrants (15% crospovidone and 15% calcium silicate) (35).

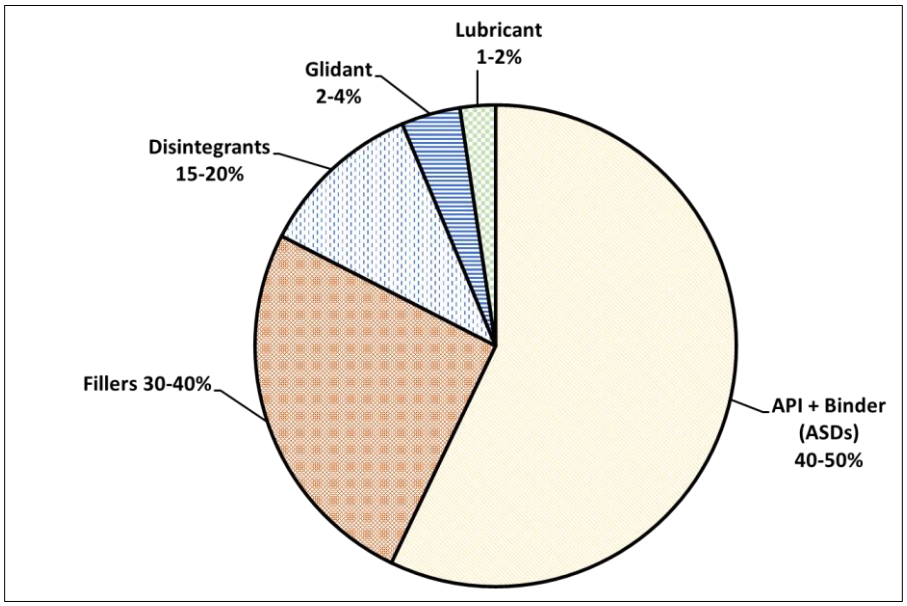

Figure 2 Typical concentrations of excipients used in formulation of tablets using ASDs

4. Conclusion

Amorphous solid dispersions have a tremendous potential to be used as the most commercially viable technique for solubility enhancement of poorly water-soluble drugs. The two major techniques used in the preparation of ASDs are hot melt extrusion and spray drying. Depending on the manufacturing technique used, the physical properties of the amorphous solid dispersions change significantly. In case of spray dried dispersions, the bulk density is low, and the powder is poorly flowing. In case of ASDs prepared using HME, the powder has high bulk density but extremely difficult to mill. The selection of the polymeric carrier plays a major role in the downstream processing of ASDs. ASDs prepared using polymers with good compressibility are easy for downstream processing. Therefore, it is essential to select the polymeric carriers with good miscibility as well as good compressibility and less hygroscopicity to form tablets that can sustain accelerated storage conditions.

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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