Hydrophilic polymers in spray dried amorphous dispersions: Exploring polyvinyl alcohol

Giovanni Raspantini, Lena Müller, Thomas Kipping, Laura Halstenberg, Nicole Di Gallo

Purpose

A crucial factor influencing dissolution and bioavailability is the solubility of the Active Pharmaceutical Ingredient (API). The Biopharmaceutical Classification System (BCS) arranges APIs into four classes by means of solubility and permeability. In classes II and IV, APIs are prone to solubility issues that can lead to challenges in formulation development. At this moment, around 40% of marketed drugs exhibit solubility issues with an increasing trend: estimations show a rise of solubility issues for New Chemical Entities reaching values of 90%.[1] This number indicates that formulation strategies that address solubility issues will gain increasing importance. The amorphous state is a higher energy form, which, on the one hand shows higher solubility but, on the other hand is less stable. This state can be obtained by disruption of the crystalline lattice of the API and generated by dissolving and rapid drying with auxiliary materials added for further stabilization. Therefore, polymers are widely used to introduce a matrix in which the amorphous state can be stabilized for manufacturing of an amorphous solid dispersion (ASD).[2] This kind of product may be obtained by spray drying the respective API with one or more fitting polymers, where the pool of polymers to choose from is vast.[3]

Objectives

Polyvinyl alcohol (PVA) is a polymer that is known to significantly increase solubility of poorly soluble APIs and inhibit their re-crystallization tendency and has been intensively studied in Hot Melt Extrusion and Vacuum compression molding processes.[4] Here we would like to show the applicability of PVA in spray drying applications. For this, indomethacin (IND), a BCS II API, is used. A dedicated three-fluid nozzle technology is evaluated to allow the creation of ASDs using rather hydrophilic polymers. This enables a new method of manufacturing and extends available polymers applicable to the process.

Methods

Spray drying

Spray drying is performed using a Buchi B295 (Buchi Labortechnik AG, Switzerland) with Nitrogen as the spraying gas (670 L/min), an inlet temperature of 90 °C and outlet of 50 °C with 35 m³/h at 100% Aspirator rate. The drug loading is 30% w/w, respectively.

Parteck® MXP 3-82, Parteck® MXP 4-88, PVP K30, and a PCL-PVAc-PEG grafted co-polymer (grafted co-polymer): Indomethacin (IND) is dissolved in acetone and deionized water in a ratio of 7:3. The polymers are dissolved in water. A three-fluid nozzle is used, the inner feed forwarding IND solution, the outer feed forwarding the polymer solution.

HPMC-AS: IND and HMPC-AS are dissolved in acetone and deionized water in a ratio of 7:3. The solution is sprayed using a two-fluid nozzle.

Dissolution

Dissolution of 25 mg IND is performed on a SOTAX AT7 smart (SOTAX AG, Germany) in 900 mL SGF at 75 rpm and 37 °C; UV detection at 318 nm.

XRPD

Diffractograms of powders are measured using an Miniflex 600 X-ray diffractometer (Rigaku, Japan) with CuKα radiation (λ = 1.54 Å). Samples were scanned in reflectance mode from 3° to 50° 2θ (deg), with a scan speed of 10° 2θ (deg)/min and a step size of 0.020° 2θ (deg). The acceleration voltage and current are 45 kV and 15 mA.

Results

Dissolution measurements

Dissolution data in simulated gastric fluid (SFG) is presented in Figure 1. The release of crystalline IND is severely limited. Only 0.7 mg/L of IND are found in the dissolution medium after 120 minutes whereas the spray dried dispersion using PVA 3-82 shows a tenfold increase in release at the final timepoint followed by PVA 4-88. The maximum peak of drug release from the ASD using PVA 3-82 is reached after 15 minutes with dissolution of 15 mg/L that only gradually decreases over time.

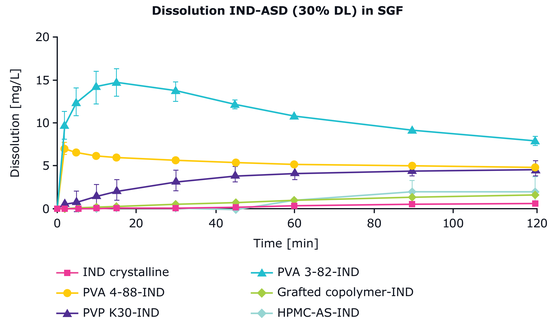

Figure 1.
ASDs with 30% DL IND. 25 mg IND in Simulated Gastric Fluid (SGF) pH 1.2. Apparatus 2, paddle, 37 °C, 75 rpm. UV Vis detection at 318 nm.

X-ray powder diffraction (XRPD) measurements

Using x-ray powder diffraction, the amorphous state of IND in the generated ASDs is determined and compared to the diffractogram of the crystalline substance as seen in Figure 2. While dominant peaks at 19.6, 21.8 and 29.5° 2θ indicate the crystalline state, these sharp signals are not present in the spray dried drug-polymer samples using PVA 3-82, PVA 4-88, grafted co-polymer and HPMC-AS demonstrating the amorphous state. Only the PVP K30 sample shows an incomplete transition from the crystalline to the amorphous state.

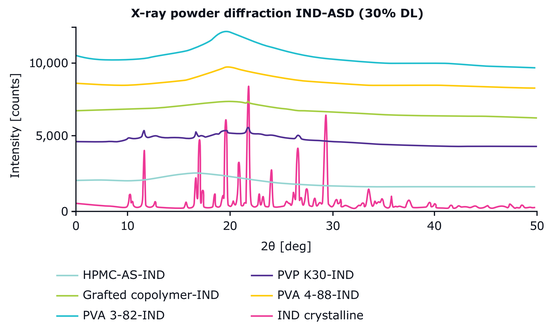

Figure 2.
X-ray powder diffraction of ASDs and crude IND. CuKα radiation (λ = 1.54 Å), reflectance mode from 3° to 50° 2θ (deg), scan speed of 10° 2θ (deg)/min, step size of 0.020° 2θ (deg). Acceleration voltage 45 kV and current 15 mA.

Conclusions

In this study the poorly soluble compound IND was investigated in ASDs with a 30% drug loading stabilized by different polymers. It is shown how the hydrophilic polymer, polyvinyl alcohol, can be used as an excipient for the creation of spray dried amorphous solid dispersions. PVA 3-82 was able to enhance dissolution, showing a fast onset as well as ensuring high release values of IND over the time of 120 minutes. This highlights the application for prolonging the supersaturated state of low soluble compounds in solution and their precipitation inhibition.

References

1. Loftsson, T. and Brewster, M.E. Pharmaceutical applications of cyclodextrins: basic science and product development. J Pharm Pharmacol, 62 (11), 1607–1621 (2010).
2. Bhujbal, S.V., Mitra, B., Jain, U., Gong, Y., Agrawal, A., Karki, S., Taylor, L.S., Kumar, S., Zhou, Q. Pharmaceutical amorphous dispersion: A review of manufacturing strategies. Acta Pharm. Sin B, 11 (8), 2505–2536 (2021).
3. Ziaee, A., Albadarin, A.B., Padrela, L., Femmer, T., O'Reilly, E., Walter, G. Spray drying of pharmaceuticals and biopharmaceuticals: critical parameters and experimental process optimization approaches, 127, 300–318 (2019).
4. Shadambikar, G., Kipping, T., Di-Gallo, N., Elia, A.G., Knuettel, A.N., Treffer, D., Repka, M.A. Vacuum Copression Molding as Screening Tool to Investigate Carrier Suitability for Hot-Melt Extrusion Formulations. Pharmaceutics, 12 1019 (2020).

Contact details: lena.mueller@sigmaaldrich.com

Lit. No. MK_PS12781EN 09/2023

SAFC®
Pharma & Biopharma Raw Material Solutions