PHARMACEUTICAL ACTIVITY

Sepitrap™ 80, an innovative powdered dry excipient opening new prospects to formulate amorphous solid dispersions by HME process

A case study with Indomethacin

SEPPIC

SCIENCE THAT CARES

Introduction

Hot Melt Extrusion (HME) is a process in which heat and pressure are applied to melt one or several component(s) and force it through an orifice in a continuous process. HME is widely used in different sectors of application. This technology is also used in the pharmaceutical field, generally to formulate amorphous solid dispersions (ASDs) that improve the solubility of poorly soluble active ingredients. In order to stabilize the amorphous form of the active ingredient, a carrier is required, usually a polymer. However, when a polymer is used as a carrier, a step is added to the downstream process: the extrudates must be ground into granules. As well as prolonging the process, this grinding step often adds a risk of recrystallisation of the active substance, particularly when the ASD is exposed to moisture, thermal or mechanical stress [1, 2, 3, 4] .

Sepitrap™ Concept

Sepitrap™ is a micro-encapsulated solubilizer in powder form designed to simplify the manufacturing of solid oral form drugs. Sepitrap™ is an innovative concept proposed by Seppic that materializes as a surfactant in powder form to facilitate the direct compression drug manufacturing process while increasing the solubility of poorly soluble active ingredients. This patented concept is manufactured by adsorption of the solubilizer in liquid form onto a porous support (see figure 1).

Figure 1: Composition of Sepitrap™

New application possibilities with HME process

Sepitrap™ 80 offers new prospects for formulation and improving the bioavailability of active ingredients with low solubility regarding our latest publication [5].

The research was aimed to evaluate the use and compatibility of an innovative dry excipient, Sepitrap™ 80, in a HME process, to assess its ability to formulate ASDs for solubility enhancement of poorly water-soluble active ingredient while reducing the downstream process after HME by removing the grinding step. The API used as a model for this study is indomethacin, a BCS class II drug.

RESEARCH METHODOLOGY

- Characterization of the innovative excipient (Sepitrap™ 80 comprising 50wt% of liquid polysorbate 80 adsorbed onto a porous magnesium aluminosilicate) on its physical characteristics (particle morphology and size, specific surface area and volume of pores, crystallinity) and extrudability.
- Investigation of the impact of different drug loads (14.9%, 31.2%, 43.8%) on the innovative carrier.
- Production and characterization of carrier/IND extrudates at a high drug load (42-44%wt).

RESULTS

Good compatibility of Sepitrap™ 80 with HME

The passage of Sepitrap™ 80 through the extruder did not modify either its thermal properties, nor its surface properties (shape and size, confirmed by particle size and SEM analysis; see figure 2). Moreover, Sepitrap™ 80 presents a great adaptability to the HME technology thanks to its unique composition: the presence of polysorbate 80, in the pore and at the surface of the carrier, that probably acts as a lubricant against mechanical friction.

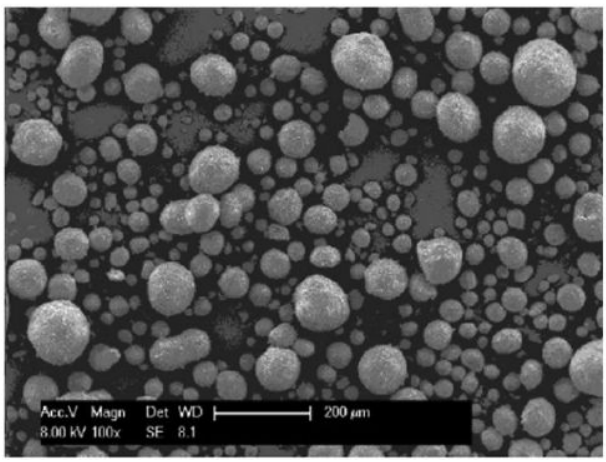

Figure 2: SEM image of Sepitrap™ 80 after extrusion (50wt% of polysorbate 80)

Improving API solubility and dissolution kinetics by obtaining an amorphous form

By extruding Sepitrap™ 80 (50wt% of surfactant) with a different loads of IND (14.9%, 31.2% and 43.8wt%), it was observed that IND was mainly present in amorphous form, confirming the formation of ASDs, which had a positive impact on the dissolution profiles and increased the solubility of API.

Improvement and acceleration of release profile, compared to commercial IND and physical blends, were observed within the first hour of dissolution for all the extrudates (14.9%, 31.2% and 43.8% load), and were directly proportional to the amount of Sepitrap™ 80 contained in the extrudates. After 5 minutes in the dissolution medium, the percentage of IND released increased by approximately 60% for an IND load of 14.9% compared to commercial IND. For all the different loads of IND, the dissolution profile obtained with the extrudates are in line with pharmacopoeial indications for immediate-release solid dosage forms (>80% API released in 30 min).

Apparent solubility of the different extrudates was 1.5 times greater than that of commercial IND, from the first hour of the experiment and remains stable over 24h. This improvement in solubility is due not only to the ASD form, but can also be attributed to the presence of surfactant.

A stability study was also performed which confirms that the ASDs obtained with Sepitrap™ 80 are relatively stable for 1 month despite extreme storage conditions (40°C/75%HR, open vials). Apparent solubility was also assessed after 1 month in these extreme conditions and also remained stable (less than 5% reduction in apparent solubility for extrudates with 43.8% IND).

Lastly, post-HME process, Sepitrap™ 80 clearly provided an advantage with the powdered formula to cut down the downstream process as compared to other polymers which require a grinding stage.

Conclusions

This study confirms, for the first time, that Sepitrap™ 80 has physical characteristics suitable for the extrusion process and shows good compatibility with HME process. In addition, according to this work, the HME process carried out with Sepitrap™ 80 enabled to transform the starting IND crystalline phase (commercial IND) into an amorphous form of the API. Obtaining an amorphous form of indomethacin made it possible to increase its solubility and dissolution rate. The evaluated innovative excipient opens up new opportunities for the formulation and improvement of bioavailability of poorly soluble active ingredients in the form of solid dispersions with a high drug load generated by hot melt extrusion. In addition, these amorphous solid dispersions obtained after HME are in powder form, which does not require shaping post-processing.

This represents a real advantage not only in terms of the process of producing amorphous solid dispersions, but also in terms of formulation stability. Thus, the carrier confirms to be an excellent choice of excipient for solubility enhancement by HME process.

Click here for the full technical paper

https://pubmed.ncbi.nlm.nih.gov/38235570/

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Sources

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