IMPACT OF EXCIPIENTS ON SOLID-STATE FORM TRANSFORMATION OF INDOMETHACIN DURING LIQUID ANTISOLVENT (LAS) PRECIPITATION

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Background: 90% of new drug entities and 40% of approved drugs on the market have poor aqueous solubility which leads to unfavourable bioavailability. A variety of bottom-up and top-down methods exist to produce the crystalline particles. However, existing marketed formulations are generally produced by top-down technologies. These techniques are energy and time inefficient, limited in achievable crystal size, and exhibit lack of control over the resulting crystal structure. Product contamination and amorphization of the active pharmaceutical ingredients (API) during the process has also been reported.

As an alternative, a bottom-up approach can be applied, where particles of the desired size and polymorphic form are formed directly, in suspension. To become industrially viable, a scalable bottom-up technology should be developed that is able to produce a range of crystal suspensions from a large variety of challenging APIs.

Methods: Production of crystalline indomethacin suspensions via bottom-up (liquid antisolvent (LAS) precipitation) approach. The impact of excipients on the relative kinetics of nucleation, particle growth and stabilization of the suspensions after formation were investigated. In order to achieve the stable solid-state form, LAS precipitation was performed with seeding, at different concentrations, and before and after nucleation of the API.

Solid state characterisation, i.e. X-ray Powder Diffraction (XRPD), particle size determination, thermal analysis, FTIR spectroscopy, and Scanning Electron Microscopy (SEM), was conducted on the resulting suspensions.

Results: Particles of indomethacin of the aimed solid-state form were only obtained by using one of the two excipients studied. Additionally, it was only possible to obtain the stable solid state-form when seeds of the desired polymorphic form were added before nucleation. Different solid-state forms of the API were obtained by each technique, which may have a direct impact on dissolution rates.

The particle seeds had a size of approximately 17µm (D50), the particle size distribution (PSD) of the suspension was: 5-10µm, indicating that the size of the initial seeds may not be critical for the final PSD of the suspension.

Conclusions: An alternative, energy efficient bottom-up method for the production of drug microsuspensions with a reduced risk of contamination from milling equipment and fewer processing steps may prove to be comparable in terms of stability and PSD to the current industrially accepted top-down approaches.
Better control over chemical and physical properties of the suspension through selection of appropriate solvents, excipients and process parameters can be achieved via a bottom-up approach.