Foamed Hot Melt Extrusion for Solid Molecular Dispersions

By Tony Listro at Foster Delivery Science

Foamed hot melt extrusion (FHME) represents a second-generation HME technology to facilitate processing, improve milling efficiency and further increase the API release rate.

A significant number of new active pharmaceutical ingredients (APIs) are poorly water-soluble and cannot be formulated and processed with traditional aqueous methods. Hot melt extrusion (HME) has become an effective solubilisation tool in improving the dissolution rate of poorly water-soluble drugs to enhance their bioavailability after oral administration (1). These crystalline hydrophobic drugs can be dispersed in hydrophilic polymers using HME to manufacture amorphous solid dispersions.

Although relatively new to the pharmaceutical industry, melt extrusion is a widely-used technology in the plastics industry. It is a solvent-free process that achieves solid molecular dispersions by a melt-blending process, in which the API is dispersed and/or dissolved into a polymeric matrix. The resultant solid dispersion is extruded into strands and then cut or milled into a dense granular or pelletised form. While suitable for injection moulding tablets or extruding into film or fibre delivery forms, the granules or pellets often require additional milling prior to tablet pressing.

Initial studies indicated that adding foaming agents to the extrudate during the HME process could improve processing of high-melt viscosity materials, enhance milling of pellets for tablet manufacturing and, in some cases, increase API release rate.

Keywords

Hot melt extrusion (HME)
Foamed hot melt extrusion (FHME)
Solubilisation
Extrusion
Supercritical carbon dioxide
Nifedipine

HME Process and Analytical Methods

HME commonly utilises twin screw mechanical mixing of constituents to achieve dispersion of the API, polymers and excipients. Each formulation produced by HME has a 'process energy' comprising mechanical and thermal energies that ensure homogenous mixing without degradation of the API or excipients.

While mechanical energy influences the degree of mixing, thermal energy determines the amount of heat sustained by the formulation throughout the blending process. A number of variables are used to optimise the process formulation, including – but not limited to – barrel and screw designs. Extruder barrels are zoned in sections that are individually heated and cooled depending on the formulation process parameters. Extruder screws are individually constructed with components that assist in melting (via shear forces) and convey material through the barrel, while mixing and homogenising the formulation.

HME formulations are often characterised in a sequential fashion to ensure desired outcomes. Since dispersion of the API in the polymer matrix is critical, the first step is to assess dispersion quality using microscopy (light or scanning electron microscopy, SEM)) and thermal analysis methods (differential scanning calorimetry, DSC). Microscopy is used for a visual assessment of the dispersion to detect the presence of drug crystals on or within the dispersion, and is usually the most sensitive method to identify crystals. DSC is used to quantitatively confirm that the dispersion has a single glass transition temperature (T_g) and identify a value for the dry T_g.

This is followed by a complete analysis of dispersion quality using crystallinity determination methods (for example, x-ray powder diffraction (XRPD) or Raman spectroscopy) and evaluates performance using a non-sink dissolution test. XRPD or Raman can be used to identify the presence of crystals within the sample. The non-sink dissolution test evaluates each of the dispersions for enhancement and sustainability of supersaturation over the crystalline drug form.

Finally, the solid dose is evaluated for physical stability using DSC, and chemical stability by related substances. DSC can be used to analyse how the T_g

changes as a function of humidity. This test is used to assess formulations based on the value of the T_g at a constant equilibrated humidity, such that the highest T_g formulations would have the best predicted physical stability for miscible mixtures of drug and polymer. The related substance test is to evaluate that, under the processing conditions used to manufacture the dispersions, no chemical degradation of the drug substance occurred.

The APIs can be mixed with a variety of polymers at high temperatures to manufacture solid dispersions in different shapes (2). As such, polymer processing technologies – such as fibre and film extrusion, or injection moulding of shapes – can be employed for a variety of delivery forms. With appropriate post-extrusion processing equipment, such forms can be produced directly from the HME process.

Tablet forming, a common delivery form for oral dose pharmaceuticals, often requires additional milling of the extrudate to produce a powder suitable for forming tablets.

Foamed Hot Melt Extrusion

The pharmaceutical industry continues to investigate applications of HME technology in developing various drug delivery systems such as granules, pellets, tablets, transdermal systems and ophthalmic implants (3). Although HME is an attractive process for manufacturing pharmaceutical formulations, the processing of high-melting APIs and high glass-transition polymers is a challenge due to high melt viscosity. Permanent plasticisers such as triethyl citrate, tributyl citrate, dibutyl sebacate and surfactants have been investigated in order to reduce the melt viscosity during the HME process (4). Inclusion of these plasticisers, however, not only adds extra weight to the formulation but may also increase the possibility of crystallisation of amorphous APIs.

Recently, super-critical carbon dioxide (SC CO_2) is being used as a temporary plasticiser to reduce the glass transition of the polymers during HME, without being present in the final formulation. SC CO_2 acts as a molecular lubricant by increasing the free volume and reducing the chain entanglement after getting absorbed between the polymer chains (5). Further, such SC CO_2 induced foam HME product becomes more suitable for milling.

Foamed hot melt extrusion (FHME) has been considered a second-generation HME technology to facilitate processing, improve the milling efficiency of the extrudate and further increase the API release rate. In an initial investigation, the release rate of the poorly soluble drug nifedipine was improved by hydrophilic polymer Eudragit E PO using foam HME.

Nifedipine Initial Study

In an initial study, nifedipine was selected as a poorly water-soluble Biopharmaceutical Classification System (BCS) class II API (low solubility, high permeability) and poly(meth) acrylate, Evonik Industries' Eudragit® E PO grade (E PO), was chosen as a hydrophilic polymer. The drug was mixed with the polymer to prepare physical mixtures with following ratios:

- E PO 70: API 10: Talc 20
- E PO 89: API 10: Talc 1
- E PO 89: API 10: Foamed

These physical mixtures were extruded at 100 rpm, and SC CO_2 was injected into the extruder during extrusion. Temperature profiles along the screws were carefully set to ensure optimal mixing and prevent thermal degradation. An appropriate screw configuration was selected to avoid the high pressure CO_2 from escaping the extruder through the feeder.

Differential scanning calorimetry of milled HMEs was performed to confirm the transformation of crystalline API into its amorphous form. The samples were sealed in aluminum pans and heated to 200°C.

A dissolution study was performed using USP apparatus II at 37.5°C, and 50 rpm in 0.1N HCl for two hours.

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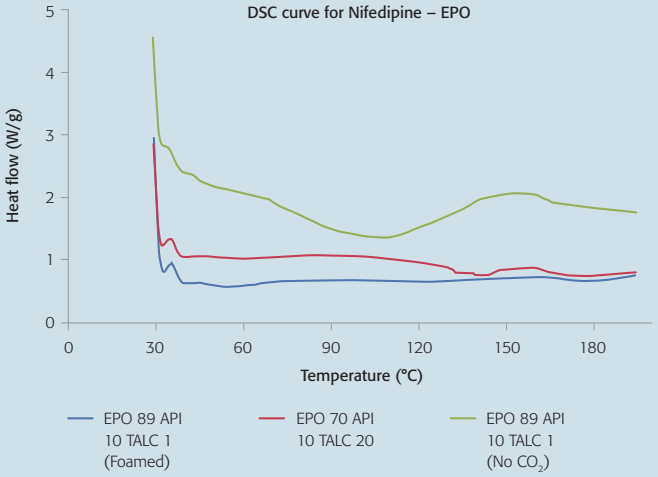


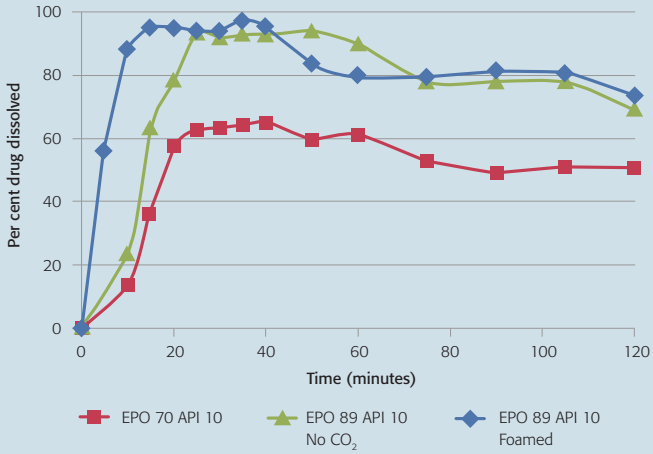


Figure 1: Differential scanning calorimetry of foamed drug loaded Eudragit E PO

Figure 2: Effect of foam extrusion on dissolution profiles of nifedipine HME product

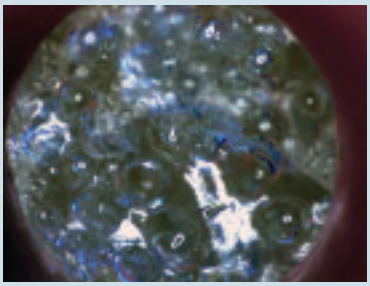
Results

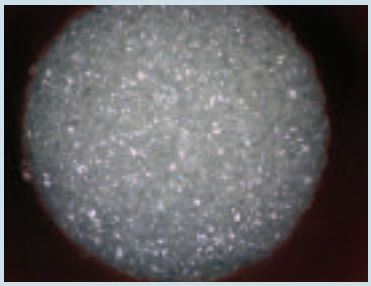
The melting endotherms of nifedipine were not detected in the HME samples that confirmed formation of amorphous solid dispersions of nifedipine in Eudragit E PO. Further, single glass transition temperatures were observed suggesting formation of molecular dispersions (see Figure 1).

The dissolution rate and supersaturation of nifedipine were significantly improved with the increase in polymer concentration as shown in Figure 2. Like un-foamed HME, nifedipine was entirely released within 20 minutes from the foamed HME. Moreover, the dissolution rate of foamed HME was faster than the un-foamed HME, given the same excipient:drug ratio (blue and green curves in Figure 2). Two foamed samples are significantly different in terms of dissolution rate and the final degree of supersaturation in dissolution medium (blue and red curves), which is probably due to the different excipient-drug ratio or addition of talc.

Figure 3 (below left): Optical micrograph of HME extrudate with no foam

Figure 4 (below right): Optical micrograph of HME extrudate with SC CO_2 foam





Conclusion

Super-critical carbon dioxide-induced foaming was successfully used to improve the processing of HME technology. The foamed HME molecular solid dispersions were found to be amorphous and the release rate of nifedipine could be tailored due to foaming. The study also demonstrated the unique advantages of using CO_2 as a plasticiser for HME.

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