Journal of Pharmaceutical Sciences xxx (2017) 1-8

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Selection of Solid-State Plasticizers as Processing Aids for Hot-Melt Extrusion

Dipen Desai [1,*], Harpreet Sandhu [1], Navnit Shah [1], Waseem Malick [2], Hossein Zia [2], Wantanee Phuapradit [1], Siva Ram Kiran Vaka [1]

[1] Kashiv Pharma LLC, 995 Route 202/206 Bridgewater, New Jersey 08807
[2] Independent Consultants

ARTICLE INFO

Article history:
Received 16 August 2017
Accepted 11 September 2017

Keywords:
hot-melt extrusion
binary mixtures
ternary mixtures
thermal analysis
rheology
solubility parameters
solid-state plasticizers
plasticization efficiency
empirical model
processing aid

ABSTRACT

The objective of the study was to select solid-state plasticizers for hot-melt extrusion (HME) process. The physical and mechanical properties of plasticizers, in selected binary (polymer:plasticizer) and ternary (active pharmaceutical ingredient:polymer:plasticizer) systems, were evaluated to assess their effectiveness as processing aids for HME process. Indomethacin and Eudragit® E PO were selected as model active pharmaceutical ingredient and polymer, respectively. Solubility parameters, thermal analysis, and rheological evaluation were used as assessment tools. Based on comparable solubility parameters, stearic acid, glyceryl behenate, and polyethylene glycol 8000 were selected as solid-state plasticizers. Binary and ternary physical mixtures were evaluated as a function of plasticizer concentration for thermal and rheological behavior. The thermal and rheological assessments also confirmed the miscibility predictions from solubility parameters. The understanding of thermal and rheological properties of the various mixtures helped in predicating plasticization efficiency of stearic acid, glyceryl behenate, and polyethylene glycol 8000. The evaluation also provided insight into the properties of the final product. An empirical model was also developed correlating rheological property of physical mixtures to actual HME process. Based on plasticizer efficiency, solid-state plasticizers and processing conditions can be selected for a HME process.

Introduction

Over the last 2 decades, hot-melt extrusion (HME) has been extensively evaluated as a promising technology in the medical device manufacturing and the development of pharmaceutical dosage forms. In addition to providing specific advantages for manufacturing modified release products, HME has been extensively applied for solubility enhancement for Biopharmaceutics Classification System class 2/4 compounds, transdermal drug delivery, and taste masking. Moreover, HME process can be adapted for conventional products and be exploited for continuous processing with high degree of process control/monitoring. A major advantage of HME is that several production steps can be consolidated into one continuous process. Other advantages of the HME technique include solvent-free processing, high degree of densification, and relatively easy and efficient scale up.[1]

A typical HME process involves embedment of active ingredient in a carrier matrix that can be comprised of one or more meltable substances such as polymeric materials,[2-7] low melting waxes,[8,9] lipid surfactants, or low melting actives or other functional excipients.[1] For the manufacturing of pharmaceutical solid dispersion and sustained release products, polymeric carriers frequently require incorporation of a plasticizer as a functional excipient. For HME process, plasticizers may help in lowering the processing temperatures or decrease the melt viscosity that may be critical for processing.[10] The use of plasticizers is a common practice to improve the processing and performance of certain high molecular weight polymers.[2-4,11] The choice of suitable plasticizers depends on several factors such as plasticizer-polymer miscibility and plasticizer stability.[1] Especially for amorphous solid dispersion formulation, miscibility of plasticizer with polymer is of paramount importance as it may impact the physical stability of dispersion system. Although commonly used pharmaceutical plasticizers such as triacetin,[4] citrate esters,[2,5] and lower molecular weight polyethylene glycols[2-4] have been investigated in hot-melt extruded systems, almost all of them are liquid. Nonuniform mixing of a polymer powder with a

* *Correspondence to:* Dipen Desai (Telephone: 908-895-1531; Fax: 908-707-9911).
E-mail address: dipend@kashivpharma.com (D. Desai).

https://doi.org/10.1016/j.xphs.2017.09.004
0022-3549/

liquid additive has been shown to result in an unstable mass flow when feeding the mixture into the extruder.[12] Such event may result in a nonhomogeneous product. To overcome such problem, McGinity et al. have demonstrated the need for preplasticized polymer in some instances.[13] Studies have also shown that evaporation and loss of plasticizer, during a high temperature process may lead to stability problems in the finished dosage forms.[14-16] To address these issues, researchers have demonstrated chlorpheniramine maleate and methylparaben as "nontraditional plasticizers" for HME process.[17,18] However, such components may have challenges with respect to compatibility and stability of the active ingredient in the product. Alternatively, supercritical fluids have been evaluated as temporary plasticizers for HME process, but such application may require special handling and equipment modifications.[19] Owing to aforementioned challenges with the liquid and nontraditional plasticizers, commonly used excipients that can act as plasticizers will not only provide consistent processing conditions and product but also better safety and compatibility profile.

Chokshi et al.[20] have demonstrated the capability of HME to improve the dissolution rate of a poorly water-soluble active pharmaceutical ingredient (API) by converting it to the amorphous form in the presence of suitable polymers. The high molecular weight acrylic polymers used in the study required high processing temperature and resulted in elevated mechanical torque (% motor load) during the extrusion. Although various studies have demonstrated the effect of plasticizers on HME process and product performance,[21-25] no single study has investigated the systematic approach for selecting a suitable plasticizer. Since predictive tools such as solubility parameters, thermal analysis, and rheological evaluation are commonly used to assess the processibility and performance of products, such techniques can also be applied for the selection of suitable plasticizers.

The primary objective of the current investigation was to evaluate physical and mechanical properties of plasticizers in selected binary (polymer:plasticizer) and ternary (API:polymer:plasticizer) systems to assess their effectiveness for HME process. Solubility parameters, thermal analysis, and rheological evaluation were used as assessment tools. In addition, the key thermal and mechanical properties were correlated with the actual HME process parameters.

Materials and Methods

Materials

Form I crystalline (γ) indomethacin (INM) (Ria International) and Eudragit E PO (EPO) (Evonik, Marl, Germany) were selected as model API and polymer, respectively. Stearic acid (SA) (Mallinckrodt) glyceryl behenate (GB) (Gattefossé, Saint-Priest, France), and polyethylene glycol (PEG 8000) (Dow-Union Carbide) were selected as solid-state plasticizers to be investigated. All other reagents were of analytical grade.

Methods

Preparation of Physical Mixtures

Binary (polymer:plasticizer) and ternary (API:polymer:plasticizer) physical mixtures were prepared in the ratio of 95:05, 90:10, and 85:15 and 50:45:05, 50:40:10, and 50:35:15, respectively. The API, polymer, and plasticizer were mixed in a mortar with pestle, and blends were passed through a 60-mesh screen. These blends were further mixed using turbula mixer for additional 15 min.

Calculation of Solubility Parameters

The solubility parameter (δ) is the most common approach to quantify cohesive energy of a material.[26,27] The cohesive energy corresponds to the total attractive forces within a condensed state of a material and can be defined as the amount of energy needed to separate the atom of a solid or liquid to a distance where no interactions occur between atoms.[28] For this study, the group contribution method was used to calculate the solubility parameters for binary and ternary mixtures. The solubility parameters were calculated using Van Krevelen[29] and Fedors[30] group contribution methods.

As per Van Krevelen method[29]

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$$

$$\delta_d = \frac{\sum F_{di}}{V}; \delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V}; \delta_h = \sqrt{\frac{\sum E_{hi}}{V}};$$

where δ, total solubility parameter; δ_d, contribution from dispersion forces; δ_p, contribution from polar forces; δ_h, contribution of hydrogen bonding; F_{di}, molar attraction constant due to dispersion component; F_{pi}, molar attraction constant due to polar component; E_{hi}, hydrogen bonding energy; V, molar volume.

As per Fedors method[30]

$$\delta = \frac{\sum \Delta e_i}{\sum \Delta V}$$

δ, solubility parameter; Δe_i, energy of vaporization; V, molar volume.

For various groups, the values of F_{di}, F_{pi}, E_{hi}, Δe_i, and V (molar volume) are given in the literature.[29,30] Compounds with similar values of δ are likely to be miscible, because the energy of mixing released by interactions within the components is balanced by the energy released by interaction between the components. Researchers have classified excipients based on the difference between the solubility parameters of excipients and APIs (Δδ). It has been shown that the compounds with a $\Delta\delta < 7.0$ $MPa^{½}$ are likely to be miscible; however, the compounds with $\Delta\delta > 10.0$ $MPa^{½}$ are likely to be immiscible with each other.[31]

Thermal Analysis

Miscibility of the API with polymer is based on the shift in melting endotherm or glass transition temperature (T_g) of the API.[32,33] Based on Gordon–Taylor equation (GT equation), if components are miscible then the mixture will show a single T_g that ranges between the T_g of pure components and would depend on the relative proportion of each component. The T_g of mixtures can be predicted using GT equation.[34]

$$T_{g(mix)} = \frac{w_1 \cdot T_{g_1} + K_1 \cdot w_2 \cdot T_{g_2}}{w_1 + K_1 \cdot w_2}$$

For ternary systems, modified GT equation can be used to predict the T_g of the system.[35]

$$T_{g(mix)} = \frac{w_1 \cdot T_{g_1} + K_1 \cdot w_2 \cdot T_{g_2} + K_2 \cdot w_3 \cdot T_{g_3}}{w_1 + K_1 \cdot w_2 + K_2 \cdot w_3}; K_1 = \frac{T_{g_1} \cdot \rho_1}{T_{g_2} \cdot \rho_2}; K_2 = \frac{T_{g_2} \cdot \rho_2}{T_{g_3} \cdot \rho_3};$$

where T_g is the glass transition temperature, w_1, w_2, and w_3 are the weight fractions of components, and K is calculated from the densities (ρ) and T_g of the amorphous components.

Thermal analysis was carried out using SII 5200 differential scanning calorimeter (Perkin-Elmer®, Shelton, CT), equipped with a liquid nitrogen cooling accessory. Samples (5-10 mg) were