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Hot melt extrusion is a powerful processing technology for the production of pharmaceutical solid dosage forms that can provide time-controlled and targeted drug delivery, improved taste and/or improved bioavailability of poorly soluble drugs.

Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization

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Over the past few decades hot melt extrusion (HME) has emerged as a powerful processing technology for the production of pharmaceutical solid dosage forms in which an active pharmaceutical ingredient (API) is dispersed into polymer matrices. It has been shown that formulations using HME can provide time-controlled, sustained and targeted drug delivery, and improved bioavailability of poorly soluble drugs. In this review, the basic principles of the HME process are described together with an overview of some of the most common biodegradable and nonbiodegradable polymers used for the preparation of different formulations for this method. Further, the applications of HME in drug delivery and analytical techniques employed to characterize HME products are addressed.

Introduction

Q2 Since the 1930s, hot melt extrusion (HME) has found its place as an established process in the plastics and food industries. In the 1980s, HME was used for the first time in the formulation of pharmaceuticals [1]. From that time on, this technique has emerged as a potent processing technology for the development of solid dosage forms, in which the active pharmaceutical ingredient (API) is dispersed into polymer matrices. It has been demonstrated that formulations using HME can provide time-controlled, extended and targeted drug delivery, and improved bioavailability of poorly soluble drugs. Several aspects of HME techniques have been extensively reviewed [2–6]. Further, the number of HME-based patents has been growing in the past decades.

HME technology offers numerous advantages over the traditional emulsification-based microencapsulation methods: fewer processing steps, reduced process time, continuous operation, absence of solvents or water during processing and superior mixing [3]. Additionally, although HME is often used as a batch process, it can be adapted for continuous manufacturing [7,8]. Moreover, the range of innovative applications using this technique is expanding. Recently, HME has been successfully used to encapsulate and homogeneously disperse nanocrystals from the

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Professor Henderik W. Frijlink received his PhD degree from the University of Groningen (The Netherlands). He was head of the Pharmaceutical Development Department of Solvay Pharmaceuticals. Since 1998, Dr Frijlink is Professor and Chairman of the Department of Pharmaceutical Technology and Biopharmacy at the University of Groningen. The main interests of his current research are technical and biopharmaceutical aspects of pulmonary drug delivery, stabilization of biopharmaceuticals by sugar glass technology and gastrointestinal targeting strategies for oral drugs and the application of nanotechnology for oral products. He is (co-)author of more than 180 peer-reviewed papers and (co-)inventor of 12 patents.

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1359-6446/© 2015 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.drudis.2015.01.012

Please cite this article in press as: Stanković, M. et al. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.01.012

liquid phase into the polymer melt as a one-step process [9]. By contrast, HME is a thermal process, which might compromise the integrity of the API or the polymer stability; especially when these are heat- and/or shear-sensitive molecules. The process requires high energy input coming from the used shear forces combined with high temperatures and, additionally, it requires sufficient material flow properties for processing. These requirements limit the process to a restricted number of available polymers [10]. Taken together, HME is achieving an important and challenging role in formulation science.

This review appraises the role of HME in formulation development and provides an overview of some of the most-used biodegradable and nonbiodegradable polymers in preparation of various formulations by HME, the application of HME in drug delivery and characterization techniques employed in evaluation of the HME products.

HME process

HME is a process in which material melts or softens under elevated temperatures and is further forced through a dye, usually with the help of one or two conveyer screws in a barrel. The process itself can be divided into several steps, involving heating of the material, feeding, mixing and conveying, flow through the dye and downstream processing of material. Each of these steps can be controlled and affect the final properties of the product.

Commercially available extruders normally consist of a feeder and optionally a side feeder, a conveyer barrel with one or two screws and a dye that shapes the melt pumped through the extruder to provide the desired dimensions at a specific throughput rate [11] (Fig. 1). The barrel of commercially available extruders is usually divided in sections, which are clamped together. Accessories can comprise a heating or cooling device for barrels, degassing unit, a caterpillar with conveyer belt for stretching and cooling the product and a solvent delivery pump. In addition, extruders are sometimes equipped with an inline laser to measure the strand diameter [11]. The downstream processing equipment can be coupled to the extrusion dye and can form either the final dosage form (injection molding, shaping calendar) or intermediate product for further processing (strand cutting, film extrusion, cooling calendar, dye-face pelletizing) [8]. In many extrusion processes, co-extrusion is used to process two or more materials that flow through different channels but are fed through the same dye to produce a multilayered product, where each layer has specific properties. Co-extrusion can optimize product performance by combining multiple carriers with different properties [12].

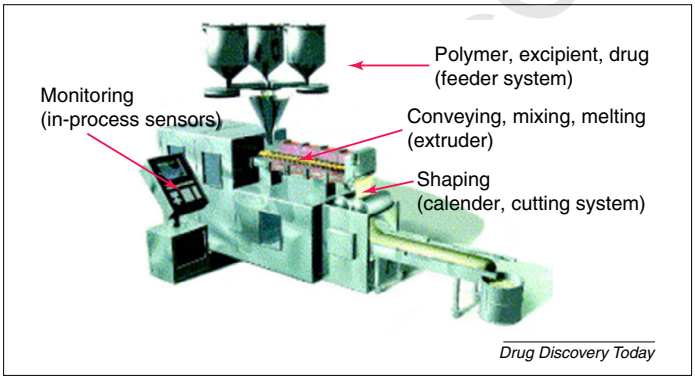

FIGURE 1

Schematic representation of a pharmaceutical hot melt extruder; feeding system, extruder body with screws, shaping and cutting system and monitoring system.
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The extruder can have one or two screws. The twin-screw extruder has become the preferred device owing to its better mixing capability. The twin-screw extruder utilizes two intermeshing screws and allows a number of different configurations to be obtained in all zones, from the feeder until the dye. Screws can rotate in the same (co-rotating) or in the opposite (counter rotating, used when the high shear forces are required) direction. The friction between the barrel, mixture and rotating screws provides the driving force for the material to reach the dye.

Depending on the extruder design, the material can be fed at different locations. For example additives can be added to the melt at several downstream locations, using a side feeder. Liquids can also be introduced using a liquid pump and liquid injection system [11]. After the material enters the transition zone it melts or fuses as a result of the increased temperature in the barrel. The material further blends with the API with the help of screws and it moves along the barrel toward the dye. When the material reaches the metering zone in the form of a homogenous melt or dispersion, it is delivered through the dye cavity and sized to obtain its final shape. The material extruded from the dye in the form of, for example, a strand will be further referred to as an 'extrudate' in this review.

The cooling of an extrudate can be done by air, water or by a contact with a cold surface. Semi-crystalline polymers have a very sharp melting point and consequently a very sharp solidification temperature. Choosing the cooling rates is important when extruding semi-crystalline polymers to obtain a product with the required crystallinity; rapid cooling would lead to the formation of small crystals and a relatively low overall crystallinity, whereas annealing would result in additional crystal growth and higher overall crystallinity. Thus, when a high crystallinity is preferred, the extrudate should be cooled slowly, with a rate determined by throughput rate and the temperature of the cooling medium (air, roll temperature of caterpillar) [11]. Amorphous polymers do not have a distinct temperature below which they solidify, rather a transition that extends over a certain temperature range. The midpoint of the transition is usually referred to as the glass transition temperature (*Tg*). For more information about the crystalline versus amorphous polymers, the readers are referred to [11].

The quality of the product from the extrusion process is affected by different parameters, such as the viscosity of the material, the interrelation of the viscosity with shear rate and temperature and the elasticity. Therefore, requirements on reproducibility demand close monitoring of various process conditions. Today, extruders allow inline monitoring and control of the process parameters such as temperature, melt pressure, screw speed, torque, feed rate, and so on. Besides monitoring of various extrusion process conditions, various modeling approaches that can improve the understanding of the mechanisms behind the HME process and thus decrease trial and error efforts have been investigated [13,14]. The melt pressure largely depends on the temperature, feed rate, screw speed, polymer viscosity and miscibility of polymer, drug and other excipients [2]. Additionally, factors such as ambient

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