International Journal of Pharmaceutics 529 (2017) 543–556

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Direct compaction: An update of materials, trouble-shooting, and application

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ARTICLE INFO

Article history:
Received 17 April 2017
Received in revised form 8 July 2017
Accepted 10 July 2017
Available online 16 July 2017

Keywords:
Directly compressible materials
Content uniformity
Sticking
Capping
Application

ABSTRACT

Direct compaction (DC) is the preferred choice for tablet manufacturing; however, only less than 20% of active pharmaceutical ingredients could be compacted via DC as its high requirement for functional properties of materials. Materials with improper functionalities could lead to serious troubles during DC manufacturing, such as content non-uniformity, sticking, and capping, all of which profoundly affect the properties of final products and, thus, severely restrict the practical application of DC. With undoubted importance, these seem to be unexpectedly ignored by reviewers but not researchers in terms of many original research articles published recently. Therefore, as an informative supplement and update, this review mainly focused on trouble-shooting and application situation of DC, together with several newly reported materials.

Contents

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http://dx.doi.org/10.1016/j.ijpharm.2017.07.035
0378-5173/

1. Introduction

Direct compaction (DC), one of the three basic methods for tablet manufacturing, has developed steadily over the years. It's now the preferred choice for tableting in terms of its multifarious merits, e.g., simplicity, continuous nature, cost and time effectiveness, and elimination of heat and moisture effects (Mangal et al., 2015; Garg et al., 2015; Järvinen et al., 2013b). However, its application is still limited, and only less than 20% of APIs could be compacted via DC as the high requirement for the functional properties of materials, e.g., excellent flowability, compactibility, etc (Mirani et al., 2011; Vanhoorne et al., 2014). Researchers often chose to modify particle structures or to prepare composite particles via co-processing to obtain materials for DC (Yuan et al., 2013; Okhuelegbe et al., 2015). Simultaneously, specific technologies and processes, e.g., spay drying and freeze-drying, were also utilized to improve the functionalities of a material itself (Littringer et al., 2012; Kaialy et al., 2016). Furthermore, novel excipients were being discovered and developed to promote the production of DC (Builders et al., 2013).

Unreasonable choice of materials, instruments and equipments, and process conditions during DC manufacturing will lead to serious problems, such as content non-uniformity, sticking, capping, etc., all of which profoundly restrict the application and development of DC (Mao et al., 2013; Bunker et al., 2011; Nakamura et al., 2011). Besides modifying the properties of materials, efforts to solve these problems are generally classified into three major groups: (i) studying and illuminating the mechanism of these problems (Akseli et al., 2014); (ii) monitoring and analyzing online, and predicting before scale-up with the help of advanced detection technologies (Nakamura et al., 2016; Akseli et al., 2013; Sulub et al., 2011); (iii) developing novel instruments and equipments to decrease their occurrence (Paul et al., 2017a; Ervasti et al., 2015). In addition, the SeDeM diagram system is often utilized as formulation problem solver, since it can solve pre-formulation and formulation problems of DC tablets effectively (Saurí et al., 2014; Bhavsar et al., 2015; Scholtz et al., 2017).

DC has been widely utilized in production of various tablets. Besides conventional tablets, it's also employed to manufacture controlled-release tablets, oral dispersible tablets, and sublingual tablets, etc (Wlodarski et al., 2016; Jayasree et al., 2014; Pawar and Jadhav, 2015; Rachid et al., 2012). Both formulation and processing of DC have significant influences on tablet quality; thus, more attention should be paid to summarize the excipients and process parameters that had been utilized for DC successfully. This will provide useful information for the development of new DC production, and promote more extensive application of DC.

Recent literatures about DC mainly focus on the following four aspects: (i) the performance evaluation of commercially available DC materials (Komersová et al., 2016; Haware et al., 2015), (ii) the development of multifunctional DC materials via co-processing (Wlodarski et al., 2016; Garg et al., 2015; Coucke et al., 2009), (iii) solutions to the problems appeared in DC (Yousaf et al., 2014; Järvinen et al., 2013a; Shi et al., 2016; Paul et al., 2017b; Akseli et al., 2014; Suñé-Negre et al., 2014), and (iv) the application cases of DC (Okhuelegbe et al., 2015; Aodah et al., 2016; Tung et al., 2017; Shehata et al., 2015). Several excellent reviews have been published in this field (Mirani et al., 2011; Rojas et al., 2012; Thoorens et al., 2014; Mangal et al., 2015; Li et al., 2017a,b). For example, some reviews were written from the view of the role of material science in co-processing, methods and technologies of co-processing of excipients, and merits of various commercially available and investigational co-processed excipients (Rojas et al., 2012; Mirani et al., 2011; Sauer et al., 2013; Osei-Yeboah and Sun, 2015; Maghsoodi, 2012). Rashid et al. (2013) outlined a comprehensive understanding on the physicochemical and compactible properties of multifunctional starch-based excipients designed for DC. Some researchers reviewed from the perspective of pharmaceutical DC applications of materials, e.g., microcrystalline cellulose (MCC) (Thoorens et al., 2014), chitin and chitosan (Badwan et al., 2015), etc. From the view of material properties, Mangal et al., 2015 reviewed the achieved understanding of the relationship between fundamental properties and functionality of materials for DC. In our recent review (Li et al., 2017a,b), the improved functionalities of composite materials were summarized and discussed from the perspective of structural characteristics of particles based on particle engineering. However, all the reviews mainly involved the above aspects (i) and (ii) but rarely the aspects (iii) and (iv). With undoubted importance, the aspects (iii) and (iv) seem to be unexpectedly ignored by reviewers, but not researchers, since there are indeed many original research articles published recently on them. Therefore, as an informative supplement and update (mainly based on researches published in recent five years), this review mainly focused on trouble-shooting and application cases of DC, together with a concise introduction of several DC-graded single or composite materials that were not included in the previous reviews.

2. An update of DC-graded materials

In our recent report (Li et al., 2017a,b), the DC materials based on composite API and/or excipient powders were summarized and discussed from the perspective of structural characteristics of particles. Several excellent reviews have also been published in this field (Mirani et al., 2011; Rojas et al., 2012; Mangal et al., 2015). Nevertheless, two single materials and a recently reported composite material for DC weren't included. Therefore, as a necessary update and supplement, they were first reviewed in this section.

2.1. Hypromellose (HPMC)

HPMC is widely used in various pharmaceutical formulations with diversified functions, e.g., tablet binder, coating agent, and sustained-release matrix (Rowe et al., 2006). This can be attributed to its widely optional viscosity, sparing cost, safety, stability, and relatively low hygroscopicity (Rowe et al., 2006; Grdešič et al., 2016). Traditionally used several grades of HPMC provide different viscosity and extent of substitution; but none of them are suitable for DC.