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Original Research Paper

Impact of process parameters on Mg–St content and tablet surface wettability in the external lubrication method for a rotary tablet press

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ABSTRACT

External lubrication is a new alternative used in compression processes of the pharmaceutical industry to minimize the negative effect of lubricant and to resolve sticking problems. This method can also prevent the deterioration of tablet properties; e.g., reduced tensile strength and a retarded rate of drug dissolution. The current study prepared tablets using the external lubrication method with varying potential critical process parameters and clarified the process of external lubrication via statistical analysis. In accordance with past results, tablets prepared using the external lubrication method had better tablet properties (higher hardness and more rapid disintegration) than those prepared using the internal lubrication method. Quantitative analyses of the magnesium stearate content and contact angle showed that the wettability of the tablet surface increased with the magnesium stearate content. Analysis of variance showed that all potential critical parameters are influential for the magnesium stearate content, but not for the disintegration of tablets. In addition, predictions of the magnesium stearate content and disintegration time of tablets made using a model equation correlated well with observed values. The external lubrication method can thus be applied by identifying the critical process parameters in the compression process during the development and manufacture of pharmaceutical products.

1. Introduction

Lubricants such as magnesium stearate (Mg–St) are essential additives for the formulation of tablets in the pharmaceutical industry. The main reason for adding lubricants to pharmaceutical ingredients is to improve the powder flowability and to prevent tableting problems associated with sticking, picking, capping and lamination. Although Mg–St is usually blended with a powder or granules, immediately prior to compression at a concentration ranging from 0.25% to 1.5% [1,2], an excessive amount or excessive mixing time of Mg–St has been reported to deteriorate the tablet quality in terms of delayed tablet disintegration, slower drug dissolution and reduced tablet hardness [1,3,4]. This deterioration in quality might be explained by the surface coverage of a hydrophobic film of Mg–St on the powder or granules, which can reduce the wettability and water permeability of the material while weakening the binding interactions between particles [5–8]. In addition, the physicochemical properties of Mg–St can differ from batch to batch [9], and the blending conditions and concentration of the lubricant should thus be carefully determined during the development of pharmaceutical formulation and manufacturing processes to ensure consistent product quality and a high level of process understanding.

As an alternative to the internal Mg–St lubrication method, an external lubrication method using Mg–St has attracted attention because it reduces the manufacturing time by omitting lubricant blending, minimizes the negative effect of the lubricant and resolves sticking problems. A lubricant is mixed with compressed air at a constant rate and is continuously sprayed onto the surfaces of the punches and dies via a dedicated nozzle during the time interval between the discharge of tablets and the filling of the dies with powdered materials [2,10–12]. Any excess lubricant is removed using a vacuum dust collector near the spraying nozzle. The important advantage of the external lubrication method is that the concentration of lubricant incorporated into each tablet is less than that when using the internal Mg–St lubrication method

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[10,11]. In fact, a thin layer of lubricant on the tablets has been reported to form when implementing the external lubrication method, thus preventing the sticking problem [11]. In addition, the external lubrication method has been demonstrated to reduce the capping tendency to a level comparable with that achieved with the internal lubrication method at a typical Mg–St concentration by determining the residual and maximum die wall pressures of a single punch tablet press [13]. However, previous studies using a rotary tablet press determined only relationships between a manufacturing condition and/or Mg–St content in the tablets and the tablet property. Thus, very little information is available regarding the quantitative analysis and practicality of the external lubrication method, and our overall level of process understanding therefore remains limited. Furthermore, no quantitative information on the wettability of the tablet surface subjected to the external lubrication system is available, although wettability studies are often conducted to evaluate the lubrication property of a tablet surface in the case of the internal lubrication method. Such studies would shed light on the mechanism of the external lubrication method compared with that of the internal method.

The ICH Q8 document (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Pharmaceutical Development) recommends that critical process parameters (CPPs) be specified and appropriately controlled according to the results of multivariate experiments. In this way, it is possible to understand the drug products and manufacturing processes according to a systematically associated functional understanding of the material properties and process parameters in terms of the critical quality attributes of the drug products [14]. We previously evaluated six process parameters for controlling the concentration of lubricant added by the external lubrication system and demonstrated that the spray rate of the lubricant, air volume of the dust collector, and rotation speed of the rotary press were potential CPPs [15]. In the present study, we investigated the criticalities of these potential CPPs for the external lubrication method in terms of the characteristics of the resulting tablet products by evaluating the relationships between the wettability of the tablet surface, disintegration property or hardness and the lubricant concentration of the whole tablet. Furthermore, a simple model equation that predicts the amount of lubricant in tablets was established from the results of statistical analyses.

2. Material and method

2.1. Reagents and chemicals

Mg–St of normal grade was purchased from Taihei Chemical Industrial Co. Ltd. (Osaka, Japan). Lactose monohydrate (Di-lactose® R) was purchased from Freund Corp. (Tokyo, Japan), and microcrystalline cellulose (Ceolus™ PH-101) was purchased from Asahi Kasei Chemicals Corp. (Tokyo, Japan). Nitric acid (60%; specific gravity, 1.38) and a standard solution of magnesium (Mg1000) were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan).

2.2. Overview of the external lubrication system

Mg–St was dispersed into the external lubrication system (EXTALUB, Hata Iron Works, Kyoto, Japan) using compressed air, and the resulting material was transferred via a tube to a dedicated spraying nozzle ready to be sprayed onto the punches and dies used in the rotary tablet press (HT-X20, Hata Iron Works). The spray rate (g/min), which is the weight of lubricant consumed by the feeding of the nozzle per unit time, was measured using standard weighing equipment.

2.3. Monitoring of the degree of dispersion and concentration of lubricant

The degree of dispersion of the lubricant was monitored using a laser sensor located at the point where the lubricant was dispersed into compressed air in the external lubrication system. The degree of dispersion can be expressed as $100 \times (1 - I/I_0)(\%)$, where I is the intensity of the light transmitted by the lubricant-dispersed air and I_0 is the intensity of the incident light. The light path length was 100 mm. The concentration of lubricant (mg/L) in the air flow was calculated from the spray rate (g/min) and the inlet dispersion air volume (L/min).

2.4. Preparation of tablets using the external lubrication method

The powder for compression was prepared by blending a 4:1 (w/w) mixture of lactose monohydrate with microcrystalline cellulose using a diffusion mixer (container mixer PM200, L.B. Bohle, Ennigerloh, Germany). The tablets were prepared using a rotary tablet press and the external lubrication system. The rotary tablet press HT-X20 used in this study had 20 stations, and its maximum rotation speed was 70 rpm. All 20 stations were used for preparation of tablets using the external lubrication method. The gravity feeder was used for providing the powder for compression on the turntable. The diameter and curvature radius of the punches used in the present study were 8.0 and 12.0 mm, respectively. The powder was compressed to form tablets of 180 mg in weight and 3.3 mm in thickness. The spray rate, flow air volume of the dust collector and rotation speed of the rotary tablet press were selected as variable parameters from the parameters of the external lubrication system and rotary tablet press, because these have been previously demonstrated to affect the amount of Mg–St in the tablets [15]. Their values are given in Table 1. For all samples, the tablets analyzed were those manufactured 10 min after initiating the compression process.

2.5. Preparation of tablets using the internal lubrication method

The mixed powder (99 wt%) described above containing lactose monohydrate and microcrystalline cellulose was blended with 1 wt% of Mg–St for 10 min at 20 min^{-1} using a 20-L diffusion mixer (container mixer LM20, L.B. Bohle, Ennigerloh, Germany). The resulting blend was used to evaluate the compression process of the conventional internal lubrication method. Tablets were

Table 1
Experimental settings of the external lubrication system.

Sample No.	A1	A2	A3	A4	A5	A6	A7	A8
Spray rate of Mg–St (g/min)[a]	1.0	1.0	1.0	1.0	2.0	2.0	2.0	2.0
Flow air volume of dust collector (m^3/min)	0.4	0.2	0.4	0.2	0.4	0.2	0.4	0.2
Rotation speed of rotary tablet press (min^{-1})	40	40	20	20	40	40	20	20

[a] Spray rates were 0.97–1.03 g/min or 1.97–2.03 g/min, which were determined by the calculation of 3 min' moving average including the sampling point.