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Scale-up and blender change model for the pharmaceutical lubricated mixing process

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ABSTRACT

In the pharmaceutical lubricant mixing process, lubricity of granules after mixing was evaluated by measuring the contact angle with water and tablet hardness. The granules were prepared using three different types of popular tumble mixers; V-blender (effective volumetric capacity: 70 L), Container blender (36 L) and Bin blender (20 L) with different powder loading rates (10–88%), blender rotation speeds (18–37 rpm) and mixing times (5–120 min) for model placebo formulation. Contact angle measurement and tablet hardness are useful as alternative characteristics for evaluation of granule lubricity. Based on the experimental data, mixing performance index (MPI), which is an empirical equation including blender type, powder loading ratio, mixing rotation speed and batch size as functional parameters, was developed. Mixing ability (MA) was defined by the combination of MPI and mixing time. Calculated MA exhibited good correlation with tablet hardness (correlation coefficient is 0.89) in all datasets. MA was verified by nine different drug product data with different manufacturing scales, to enable the MA model to support the formulation researcher to set mixing process parameters when the batch size or blender type changes.

1. Introduction

In general, the tablet manufacturing process consists of a granulation/drying process, an external excipient (e.g. additional disintegrants or diluents) mixing process, a lubricated mixing process and a tableting process. In the tablet manufacturing process, the tablet is manufactured by using two punches and a die. Sticking or die friction trouble occurs in the tableting process if there is no lubricant in the formulation, therefore a lubricated mixing process is needed to prevent these issues. The lubricated mixing process is very important in tablet manufacturing because the lubricated mixing quality is influenced by granule properties (e.g. particle size distribution, specific volume) resulting from the previous granulation/drying process, which also affects the tablet properties (e.g. tablet hardness and disintegration) in the tableting process. The lubricity of lubricated mixing granules is changed by changing the mixing conditions like mixing time, rotation speed and so on.

The manufacturing scale of drug products becomes bigger with the progress of a drug product development stage. Also, the type of manufacturing equipment may be replaced due to the changes to the manufacturing site. In these cases, some issues have occasionally been observed because there are few perfect scale-up rules or few appropriate compatibility models between different types of equipment. For the lubricated mixing process, there are several blenders with different types and sizes in the laboratories and commercial plants. Many changes regarding not only batch size but also blender type occur in the scale-up study or as post approval changes. In the scale-up study, it was difficult to set appropriate process parameters for a newly installed blender, therefore, some issues, such as sticking in the tableting process or breaking of a tablet in the material handling process, occasionally occurred naturally or due to excess lubricity in the lubricated mixing process.

In the process parameter setting, a trial-and-error approach may be employed as a conventional method on a product by product basis. Therefore, we often require some time for the scale-up study until the process parameters are optimized.

To adjust the Froude number between different sized blenders requires one of the scale-up methods defined by the mixing scale and mixing speed with the same type of blender. The Froude number can be utilized for setting the mixing rotation speed of different scale mixers based on experimental conditions. However, the Froude number cannot be applied for parameter prediction in the case where the powder filling ratio or blender type has been changed.

The coefficient of mixing rate defined by the powder filling ratio, rotation speed, blender scale and powder properties was proposed for quantitative mixing uniformity [1]. The coefficient of mixing rate

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focuses on binary mixing and mixing uniformity. Therefore, it is necessary to modify these in order to apply the lubricated mixing because the powder lubricity will change despite the constant mixing uniformity. Another quantitative method was proposed using coloring particles in a tumble mixer [2–4] to evaluate the influence of the powder filling ratio and the number of revolutions. However, these studies also focused on mixing uniformity.

In the lubricated mixing process, it is necessary to consider not only mixing uniformity but also lubricity of granules simultaneously. There are many reports about the characteristics of some blenders for lubricity, however, there are few reports about the scale-up model or process parameter prediction model for lubricity [5–9]. Recently, an in-line lubricity monitoring study using near infrared reflectance (NIR) or Raman spectroscopy has been widely reported and process control technologies are progressing significantly [10–12]. On the other hand, in the process controls using spectroscopic analysis, we require a large amount of experimental data and human resources for developing control models. Additionally, a large amount of data for the maintenance of the PAT (Process Analytical Technology) model is also required.

In this study, we aimed to develop a model for scale-up and blender type changes to set appropriate mixing process parameters with no additional work for formulation researchers. At the experimental stage, the influence of blender types (V-blender, Container blender and Bin blender) and process parameters (powder filling ratio, rotation speed of blender and mixing time) on lubricity were evaluated by the contact angle and tablet hardness measurement using a placebo formulation. Based on these results, we developed an empirical equation including the Froude number, powder filling ratio and blender types as parameters. The equation is the index of mixing performance under given mixing conditions, known as mixing performance index (MPI). Mixing ability (MA) was developed as a model for scale-up of the lubricated mixing process and blender type/size change. MA can be used with the combination of MPI and the mixing time for the prediction of mixing process parameters. MPI fitting parameters were validated using nine formulations and 1 to 500 kg scales' experimental results so that the MA model can be widely used for pharmaceutical lubricated mixing processes.

2. Materials and methods

2.1. Blenders

TCV-30 (V-blender), TB-36L (Container blender) and MC-20 (Bin blender) were used. These three types of blenders are popular as tumble mixers classified as diffusion mixers in SUPAC-IR Equipment Classifications [13]. The container volume and rotation radius of each blender used are shown in Table 1.

2.2. Materials

D-Mannitol (Pearlitol® 50C, Roquette), pregelatinized starch (PCS® PC-10, Asahi-Kasei Chemicals), crospovidone (Polyplasdone™ INF-10, ISP), and hydroxypropylcellulose (HPC-L, Nippon Soda) were purchased from each vender. Granules consisting of these materials are manufactured using a fluidized bed granulator (GPCG-15, Powrex). Magnesium stearate (Magnesium Stearate NF Kosher Passover HyQual®, Mallinckrodt) was used as a lubricant. Granule properties and magnesium stearate particle sizes used in these experiments are shown in Table 2.

Table 1
Information of types and sizes of blenders used.

Container type (blender type)	SUPAC subclass	Container volume	Rotation radius
TCV-30 (V type)	V-blender	70 L	0.300 m
TB-36L (Tote type)	Bin blender	36 L	0.280 m
MC20 (Bohle type)	Bin blender	20 L	0.313 m

Table 2
Characteristics (specific volume and particle size) of placebo granules and particle size of magnesium stearate.

Properties	TCV-30	TB-36L	MC20
Bulk specific volume [cm^3/g]	2.9	2.8	2.9
Granules particle size (×50) [μm]	158	167	180
Mg-St particle size (×50) [μm]	7	7	7

2.3. Lubricated mixing experiment

Experimental conditions in this study are shown in Table 3. The granules were loaded into the blenders at the given filling ratio and the blenders were rotated under a set speed. The granules were sampled with a pencil-type powder sampler at each specified mixing time. Mixing was continued up to the final sampling point (120 min).

2.4. Contact angle measurement

A Contact Angle System OCA15 Plus (DataPhysics Instruments GmbH, Filderstadt) was used for contact angle measurement. The granules mixed with lubricant were placed on a slide with an adhesive tape and flattened into a uniform layer with the thickness of about 300 μm. A water droplet was placed on the uniform layer using a microsyringe automatically moving at a constant speed. Photographs of the water droplet were taken with a CCD camera and the contact angle was measured from these pictures.

2.5. Tableting and tablet hardness measurement

The tablets were prepared using an Autograph AG-I 20 kN (SHIMADZU) which is able to compress powder or granules into tablets with a constant speed. The reason why an Autograph was used instead of an actual tableting machine was to remove the tableting condition effect on the tablet hardness. The punches used were flat shaped with a 10 mm diameter, compression force was applied at 1200 kgf, compression rate was 10 mm/min and tablet weight was 300 mg. Tablet hardness was measured by a TBH20 tablet hardness tester (Erweka, Heusenstamm, Germany).

3. Results

3.1. Impact of mixing time on granule contact angle

It is known that magnesium stearate has a hydrophobicity property, and that it spreads on the surface of the granules after becoming attached to granules as the mixing process progresses [14]. In order to

Table 3
Mixing conditions of MPI development.

Blender type	V-blender	Tote blender	Bohle blender
Filling ratio	10, 20, 35, 50, 70, 85%	10, 20, 35, 50, 70, 83%	10, 21, 36, 52, 72, 88%
Mixing time		5, 10, 20, 30, 60, 90, 120 min	
Rotation speed[a]	37 rpm	29 rpm	18 rpm

[a] Rotation speed was set up so that the Froude number was the same as the commercial plant production machine.