Journal of Pharmaceutical and Biomedical Analysis 49 (2009) 858–861

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

Short communication

Rapid quantitative analysis of magnesium stearate in pharmaceutical powders and solid dosage forms by atomic absorption: Method development and application in product manufacturing

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ARTICLE INFO

Article history:
Received 22 May 2008
Received in revised form 24 December 2008
Accepted 5 January 2009
Available online 9 January 2009

Keywords:
Magnesium stearate assay
Content uniformity
Atomic absorption
Process validation
Quick quantitation

ABSTRACT

The distribution of magnesium stearate (MgSt) in tablet granule has a significant impact on the compression process. A rapid quantitative method for evaluating magnesium stearate content by atomic absorption was established. The MgSt was extracted from the granule in 0.1 mol/L nitric acid and the resulting free magnesium ion quantitated by atomic absorption. The total analysis time was significantly shortened in comparison to the previously used sample ignition method.

This newly established method was evaluated with several drug products and several types of blender. The analytical method was also applied to tablets with poor compression (rough tablet surface). The MgSt content in these rough surface tablets was significantly lower than in tablets with smooth surfaces from the same batch.

From these results, this atomic absorption method is considered to be an accurate and useful method for evaluating MgSt distribution and can be applied to tablet manufacturing process validation.

1. Introduction

Magnesium stearate (MgSt) is widely used as a lubricant in tablet manufacturing. It is known that the distribution of MgSt in tablet granule has a significant impact on compression properties. A lack of MgSt uniformity in tablet granule due to insufficient mixing causes sticking or capping of the tablets during the compression process. On the other hand, over-mixing causes extended disintegration time and/or dissolution time as well as low tablet hardness due to the presence of a continuous hydrophobic film around the granule [1–6].

However, very few direct quantitative evaluation methods for MgSt distribution have been reported to date. A quantitative method using wet sample ignition has been employed but it is time consuming because the ignition process, usually takes several hours. Near-infrared spectroscopy (NIR) is now widely used for quantitative analysis in the pharmaceutical field. NIR can be applied to on-line monitoring of MgSt distribution during the mixing process [7] however, the establishment of the reference spectrum can be challenging and is highly influenced by the identity and concentration of the other ingredients. Recently, St-Onge et al. [8,10] and Green et al. [9] made a comparison of MgSt assay using laser-induced breakdown spectroscopy and the widely used NIR technique. They concluded that the laser-induced breakdown spectroscopy method is preferred for short-term investigations because fewer calibrations are required than that for NIR analysis. Also, Szalay et al. applied an energy dispersive X-ray fluorescence analyzer to the investigation of MgSt distribution in tablets [11]. These new analytical methods are able to evaluate the MgSt distribution in granules and tablets but the equipment is not available in most pharmaceutical laboratories.

The aim of this work was to establish a rapid quantitative method for evaluating the uniformity of MgSt distribution in tablet granule using flame atomic absorption spectroscopy (AAS) system which can be applied to process validation.

2. Materials and methods

2.1. Materials

The AA-6600 atomic absorption spectrophotometer (Shimadzu, Kyoto, Japan) was used in flame mode. For the extraction of MgSt in granules or tablets, AA grade nitric acid (Kanto Chemical, Tokyo, Japan) was used. Magnesium stearate (Taihei Chemical, Osaka,

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doi:10.1016/j.jpba.2009.01.004

Japan or Mallinckrodt Japan, Tokyo, Japan), lactose (DMV Japan, Tokyo, Japan), starch (Matsutani Chemical, Hyogo, Japan), povidone (ISP Japan, Tokyo, Japan), and microcrystalline cellulose (Asahi Kasei Chemicals, Tokyo, Japan) were used for the recovery tests and the method application studies. Magnesium standard solution (Wako Pure Chemical, Osaka, Japan) was used as the standard for the quantitation.

2.2. Methods

2.2.1. Establishment of the analytical method and method validation

The extraction method followed the same principle as the identification test (1) for MgSt in the Japanese Pharmacopoeia. Tablet granule or one tablet was dispersed in diluted nitric acid and MgSt was hydrolyzed using sonication for 15–20 min and shaking for 15 min. After cooling, the solution was centrifuged at 3000 rpm for 10 min and the supernatant quantified by flame AAS at 285.21 nm.

2.2.2. Examples of method application

To evaluate MgSt distribution during mixing, samples of powder at each time point were taken from 6 to 10 locations within the mixing vessel and analyzed. A sample of the mixed powder equivalent to the weight of one tablet was used for the analysis at each individual sampling point for products A, C and D. A sample of tablet granule equivalent to one-fifth of the weight of the tablet was used to analyze product B because of the relatively high content of MgSt in this product formulation.

To evaluate the tablets with rough surfaces, six tablets were analyzed individually. Also, 10 tablets with smooth surfaces taken from the same manufacturing batch were analyzed at the same time as the control group.

3. Results and discussion

3.1. Establishment of the analytical method and its validation

3.1.1. Accuracy

Accuracy of the analytical method was investigated by recovery testing for magnesium in blank products A–D. The formula MgSt content in product A is 0.25 w/w%, in product B is 0.8 w/w%, in product C is 0.25 w/w%, and in product D is 0.22 w/w%. All of these products are either lactose (products A, C and D) or microcrystalline cellulose (product B) based formulations. Recovery tests were conducted from 10% to 200% of the formula MgSt concentration (e.g. for product A, 0.025–0.50 w/w% of MgSt was added). The results show around 100% recovery from 50% to 200% of the formula MgSt concentration. However, results at 10% of the formula MgSt concentration have some variation, with between 66% and 144% recovery (0.017–0.036 w/w%) because of the low concentration of MgSt. Based on the recovery, it was concluded that the method has sufficient accuracy for the evaluation of MgSt content uniformity in the formulation although the recovery of 10% was not consistent.

3.1.2. Precision

Precision results show low standard deviation, 0.1–0.7% for six separate measurements using solutions of each product. This is considered an appropriate precision for evaluating the distribution of MgSt in the sample.

3.1.3. Specificity

The AAS absorptions for several products without MgSt are shown in Table 1. This shows the background stemming from the other materials. The excipients in products A–D show some interference at the measurement wavelength. It is assumed that these absorptions have originated from a minor residue of Mg in the formulated materials. However, it was considered that these readings (from 2% to 9% of the formula MgSt concentration) are not detrimental to the evaluation of MgSt distribution.

This AAS method is not applicable to drug products containing magnesium in the excipients. Talc (magnesium silicate) or calcium carbonate has significant background absorption of magnesium thus the quantitation of MgSt with this method been impossible.

3.1.4. Limit of quantitation

The quantitation limit was determined through assessing the signal to noise (S/N) ratio (S/N = 10). Appropriate quantitation limits, around 4.5% of the formula MgSt content were observed on each product.

3.1.5. Linearity

Linearity was investigated using standard magnesium solutions of 10–200% of the formula MgSt content on each product. Good linearity ($r > 0.999$) was observed within the range studied.

3.2. Examples of method application

3.2.1. Influence of MgSt mixing time on tablet granule with different formulations

The influence of mixing time of MgSt in products with different formulations (products B and C) using the same blender (V60) and blending speeds was evaluated. The dispersion properties of MgSt in each product were different under the same mixing conditions (Fig. 1). For products B and C, there was no effect from over-mixing on the compression parameters or dissolution profile for up to 10 min of total blending time.

This kind of difference on the MgSt mixing has been observed experimentally (by test compression etc.), but the difference was not clearly evaluated by the analytical determination of MgSt distribution.

3.2.2. Influence of batch size and blender type on MgSt mixing

The influence of batch size (small scale: 5 kg, pilot scale: 30 kg and full scale: 200 kg) and blender type (V5, V60, and Bohle bin blender) on MgSt mixing time using product B was investigated. The results are shown in Fig. 2. It was confirmed that there was

Table 1
Specificity of the MgSt assay (interference from other materials).

N	MgSt concentration (w/w%)			
	Product A (0.25 w/w%)[a]	Product B (0.8 w/w%)[a]	Product C (0.25 w/w%)[a]	Product D (0.22 w/w%)[a]
1	0.0034	0.0728	0.0235	0.0121
2	0.0035	0.0776	0.0235	0.0117
3	0.0035	0.0440	0.0223	0.0114
Mean	0.0035	0.0648	0.0231	0.0117
S.D.	0.00006	0.01817	0.00012	0.00035
Interference with the assay value (%)[b]	2.8	8.1	9.2	5.5

[a] Theoretical MgSt content of each product.
[b] Calculated against the theoretical contents (formula MgSt content).

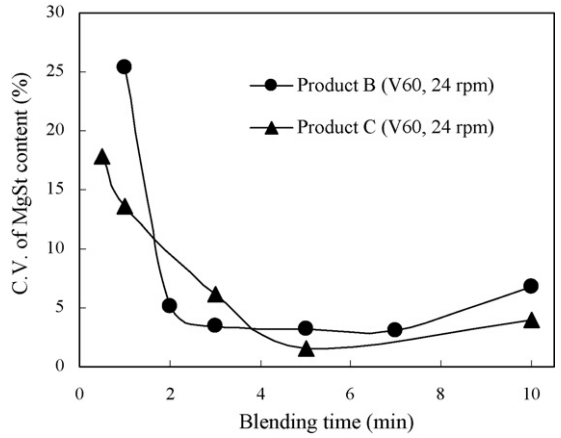

Fig. 1. Influence of granule formulation on mixing time of MgSt under the same mixing conditions. The *Y*-axis is expressed as the coefficient of variation (C.V., %) of MgSt content from 10 samples taken at each mixing time.

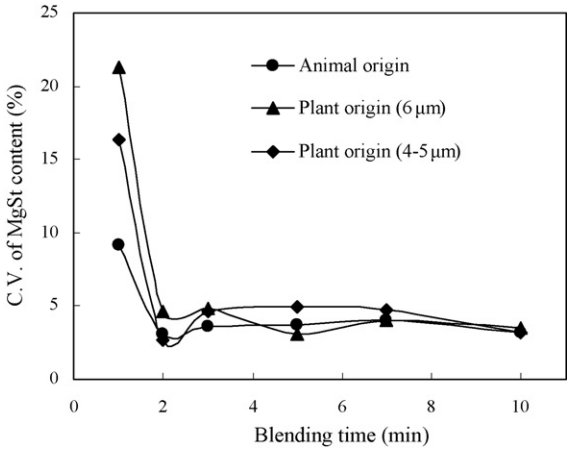

Fig. 3. Influence of the origin of MgSt on the mixing time of MgSt using the same blending conditions (product B, 5 kg, Bohle blender). The *Y*-axis is expressed as the coefficient of variation (C.V.) of MgSt content from 10 sampling points at each time point. Note that there was no difference in the uniformity of MgSt from animal and plant after 2 min of mixing.

no significant influence on the mixing time when the batch size or the blender type were changed as studied for product B using this analytical method.

Usually, when the scale up of mixing processes is investigated, the rotation speed of the blender is calculated in order to ensure that the tangential speed of the mixer is equivalent in the two mixing processes when the blenders are using the same mixing system (e.g. V5 and V60 blender). However, this calculation cannot be applied to blenders using different systems (e.g. V60 and Bohle bin blenders).

This result is an example which suggests that tangential speed calculations can be applied for the scale up of product B when blenders are using the same mixing systems, although application of the theory is not effective in all cases. Therefore, the analytical method for evaluating the mixing profile of MgSt is useful where the blender systems are different.

3.2.3. *Influence of the origin of the MgSt on the mixing properties*

The influence of the origin of MgSt on the mixing time was investigated using an animal origin and the two plant origin materials in granule of product B (5 kg scale, Bohle bin blender). The results show a difference on the mixing effectiveness among three different origins at the beginning of the mixing process (Fig. 3). However, after the first 2 min of mixing, the uniformity of MgSt distribution was considered equivalent under the conditions used.

Recently, widely used animal origin MgSt has been substituted by material of plant origin because of concern over bovine spongiform encephalopathy (BSE) and it has been reported that the functionality of plant origin MgSt is different from the animal origin material [12]. Differences in the blending properties were only obvious at the beginning of the mixing process and there was no noticeable difference after 2 min of mixing. However, the mixing speed of MgSt in granules was affected by the properties of the granules to which the MgSt was added. This trend may therefore differ when using other granules and/or different blenders. Further investigations are necessary to understand any differences in the dispersion properties of animal and plant origin MgSt in other products.

3.2.4. *Relationship between MgSt mixing time and dissolution speed of tablet*

The influence of the MgSt mixing time on the dissolution speed (dissolution profile) was investigated using product A in a pilot scale (24 kg, V60 blender) with plant origin MgSt.

After the compression of the tablets at each MgSt mixing time, the dissolution profiles of the tablets were investigated. As shown in Fig. 4, the MgSt distribution reached a steady state after 1 min of mixing and no segregation was observed for up to 7 min (left figure). However, significant dissolution delay ($p < 0.01$, Student's *T*-test) at the 10 min time point of the dissolution profile was observed for tablets at 7 min mixing (right figure). No influence of over-mixing

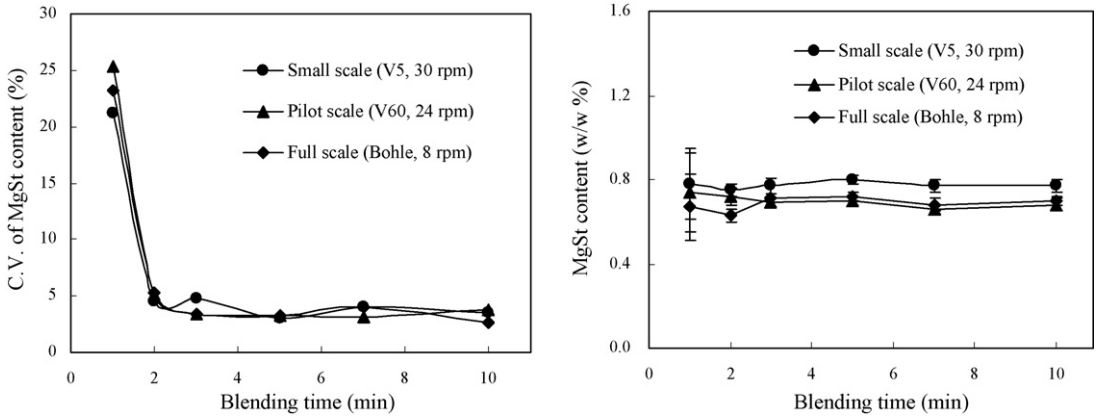

Fig. 2. Influence of batch size and blender type on MgSt mixing of product B (small scale: 5 kg, pilot scale: 30 kg and full scale: 200 kg). The figure of the left shows the relationship between the blending time and the coefficient of variation of MgSt and the figure on the right shows the mean content of MgSt at the same time points (the target MgSt content is 0.8 w/w%).

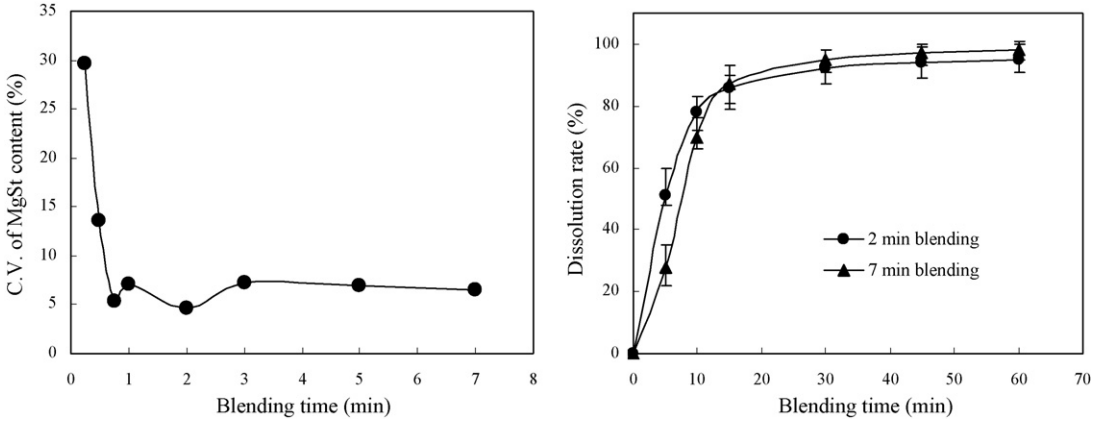

Fig. 4. The influence of MgSt mixing time on the dissolution profile of product A. The left figure shows the time course of the MgSt distribution during mixing and the right figure shows the dissolution profile of product A tablets at mixing times of 2 min and 7 min.

Table 2
Comparison of the MgSt content in rough surface tablets and smooth surface tablets.

	MgSt content (w/w%) in the tablets[a] (range)
Rough surface tablets ($n = 6$)	0.10[b] (0.09–0.12)
Smooth surface tablets ($n = 10$)	0.26 (0.25–0.26)

[a] The target MgSt content is 0.25 w/w%.
[b] p 0.01 = 33.631 > 2.977 (Student's T-test).

MgSt on the dissolution rate beyond the 10 min time point was observed for this product.

The test results suggest that the optimum MgSt mixing time for product A is around 2 min. Product A shows a relatively rapid dissolution profile, thus the influence of MgSt over-mixing was not large but it is speculated that the influence of over-mixing could be significant for products with slower dissolution properties.

3.2.5. Relationship between rough surface tablets and MgSt content

A comparison of the MgSt content in tablets with rough and smooth (normal) surfaces in one full scale batch of product C was conducted using the analytical method. As shown in Table 2, the MgSt content of tablets with rough surfaces is significantly lower than that of the smooth surface tablets.

Further investigation revealed that the uniformity of MgSt after the mixing process was poor in this batch (C.V. 41.7%). Therefore, the mixing time of MgSt was extended from 2 min to 3 min and it was found that the uniformity of the MgSt content was improved to approximately 20% (C.V. 14.3%, 23.9%) on two batches. After this improvement, the compression problem seen with product C was solved.

4. Conclusion

The rapid quantitative method for evaluating the uniformity of MgSt distribution in tablet granule or tablets using a conventional AAS system was established and validated. The method can measure the MgSt contents in granules or tablets in about 30–40 min for 10 samples once the AAS system has been set up. With this quick method, the uniformity of MgSt distribution in the tablet granule can be evaluated without delay to the manufacturing process. Moreover, this method uses standard analytical equipment. Therefore it can be conducted in most pharmaceutical laboratories equipped with a conventional flame AAS system.

This AAS method could not be applied to formulations which contain magnesium. Other modern evaluation methods such as laser-induced breakdown spectroscopy and energy dispersive X-ray fluorescence analyzer target magnesium therefore have the same limitation. If the product contains magnesium, then another approach like NIR or delivertized HPLC method [13], which can quantify the stearic acid in MgSt, must be considered.

The test results using several different drug products clearly demonstrate the value of this new analytical method in the investigation of the relationship between the tabletting process and MgSt distribution in the formulation. This analytical method will be a useful tool in the detailed investigation of tablet compression issues related to MgSt distribution in formulations.

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