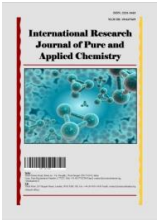

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A New Flame AAS Application for Magnesium Determination in Solid Pharmaceutical Preparations as an Active Ingredient and an Excipient

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Authors' contributions

This work was carried out in collaboration among all authors. Author AS performed the experiments and wrote the first draft of the manuscript. Author WA put the protocols for pharmaceutics and samples preparation, contributed to the interpretation of data and revised the manuscript. Author AAS managed the project in all stages and revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Objective: A new application of Atomic Absorption Spectroscopy (AAS) has been carried out to determine magnesium in its solid preparations (effervescent and uncoated compressed tablets) as an active ingredient and/or excipient.
Methodology: The linear range of magnesium was determined. A sample of magnesium effervescent tablets was analyzed. Magnesium stearate concentration was also indirectly determined in commercial paracetamol tablets using two digestion methods. Finally, a sample of drug-free tablets (only contain excipients) was analyzed to study the effect of talc on total magnesium content of the sample.
Results: Linear range was observed in concentrations between 0.08-0.40 ug/mL of magnesium. Effervescent tablets samples were recovered in the range between 98.66-103.00% which indicates that the product meets specifications. For paracetamol tablets, the content of magnesium stearate

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was in average of 0.2% and there is no differences between the two digestion methods (t=0.454). Our work on the drug-free sample proved a significant increase of magnesium concentrations in the presence of talc.

Conclusion: The AAS method is a simple and rapid technique that can be employed for the simultaneous estimation of magnesium in in-process and final products analyses.

Keywords: Flame atomic absorption; spectroscopy; magnesium; magnesium stearate; microwave digestion.

1. INTRODUCTION

Magnesium (Mg^{2+}) is an essential element in human biological system, as it has a vital role in bone and tissue metabolism. Some food like as milk, vegetables, nuts, and meat are natural sources of magnesium. Magnesium deficiency may occur as low consumption or as a complication of other diseases like alcoholism, diabetes, kidney failure and in some post-operative periods. Low magnesium intake can be treated by taking oral magnesium supplements or parenteral preparations [1]. Inhaled magnesium sulfate can be used to COVID-19 patients cause it leads to broncho-dilation by many mechanisms; while Mg^{2+} deficiency is related to more inflammatory response [2]. Several products are available in the market to manage magnesium deficiency. These products consist of different salts that, as a consequence, lead to different bioavailability profiles [3]. Other pharmaceutical ingredients such as vitamins and other minerals are usually added to magnesium supplements [1,4]. In addition to the use of magnesium as an active ingredient, other magnesium salts -like magnesium stearate- are used in pharmaceutical industry. Magnesium stearate is a commonly used excipient that can act as a lubricant in solid dosage forms at low concentrations [5]. Monitoring and controlling magnesium stearate concentration is of paramount importance in pharmaceutical industry. While lower levels of magnesium stearate accompany with tablets of poor quality and high susceptibility to mechanical stress, higher levels can lead to dissolution and bioavailability issues [6]. This give rise to the importance of providing a flexible analytical method that can selectively determine magnesium in high sensitivity and regardless of its salt form or other components in the product [1]. Many research showed that atomic absorption spectrometry (AAS) technique can be applied to detect trace levels of minerals in food [4], Catfish [7], geology [8] and Drugs [1,4,9,10]. Flame-AAS is an analytical technique that is frequently used to determine Mg^{2+} ions in raw material or as formulated preparations; alone or with other components [1] quantitatively and qualitatively [8]. To be employed, complex samples usually require pre-treatment steps to digest the matrix and present the metal to the instrument in a suitable form to be analyzed. For this purpose, acid-based wet digestion protocols are widely used [1]. This work aims to determine Mg^{2+} quantitatively as an Active Pharmaceutical Ingredient (API) in effervescent tablets as well as a lubricant in tablets by AAS using two different kinds of digestion methods and to compare these digestion methods.

2. METHODOLOGY

2.1 Instrumentation and Apparatus

A Phoenix 986 AAWin V2.1 Atomic absorption spectrometer with self-reversal background correction mode (SR lamp-BGC mode) has been used in this study. An Anton Paar Multiwave 3000 (Graz, Austria) with maximum pressure 86 bar and maximum temperature 220°C was used to digest powdered samples. A rotative Compression machine – pilot press 10 stations (knack technocrats, INDIA) was also used.

2.2 Materials and Reagents

All used chemicals were of analytical grade. Double distilled deionized water was used to prepare all solutions (conductivity $1\Omega^{\wedge-1}$/cm). All the glassware used were cleaned and rinsed with double distilled deionized water prior to use. Nitric acid (HNO_3) was supplied by (Panreac, Spain) and hydrogen peroxide (H_2O_2) by (Merck, Germany). An analytical grade magnesium chloride hexahydrate powder (Qualikems, India) was used to prepare magnesium standard solutions. Magnesium effervescent (Eff.) tablets (sunlife, Germany) Batch: L7292/7 and L8275/6. Commercial paracetamol tablets 500 mg. Talc (euro Minerals, Austria), Avicel (JRS pharma, Germany) and magnesium stearate (Peter Greven Asia SDN.BHD, Malaysia) were used to make drug-free tablets.

2.3 Methods

2.3.1 Calibration curve

First, a stock solution of Mg^{2+} (100.00 mg/L) was prepared from magnesium chloride hexahydrate powder. 25 mL of this stock solution was diluted to 250 mL in a volumetric flask with double distilled deionized water to obtain a (10.00 mg/L) Mg^{2+} standard solution. In order to obtain Mg^{2+} solutions (0.08–0.40 mg/L), appropriate volumes of the 10.00 mg/L Mg^{2+} standard solution were transferred into 100 mL volumetric flasks and completed to the target.

2.3.2 Sample preparation

2.3.2.1 Effervescent tablets

10 effervescent tablets were taken, grinded and mixed to obtain fine homogenous powder. Then 4.000 g (equivalent to the average weight of one tablet) was taken and dissolved using double distilled deionized water in 100 mL volumetric flask. The solution was sonicated for 10 minutes to ensure dissolution. After that, the solution was diluted 10000 fold, and measured by Flame AAS. A blank solution of double distilled deionized water was used.

2.3.2.2 Paracetamol tablets

10 paracetamol tablets were taken, grinded and mixed to obtain fine homogenous powder. Then 0.585 g (equivalent to the average weight of one tablet) was taken and digested by two protocols; wet digestion or microwave digestion.

Wet digestion was carried out using an oxidizing mixture consisted of (10 mL HNO_3 + 5 mL H_2O_2). The sample was transferred to a beaker and the oxidizing mixture added slowly with gentle hand mixing and set for 15 minutes at 60°C. Then, transferred to a volumetric flask of 25 mL and completed to volume by double distilled deionized water. 1 mL was transferred into 10 mL volumetric flask and completed with double distilled deionized water. Now, this solution could be measured by Flame AAS.

Microwave digestion was performed as follows: 0.585 g of commercial powdered paracetamol sample with 15 mL of oxidizing mixture were put in microwave refills. Then, refills were closed tightly and put in microwave and digested by microwave. The experimental digestion program parameters were fixed and given in Table 1.

After complete digestion, the content of refills was transferred to a volumetric flask of 25 mL and completed to volume by double distilled deionized water. 1 mL was transferred into 10 mL volumetric flask and completed with double distilled deionized water. Then measured by Flame AAS.

A blank digest solution was carried out for both digestion methods by the same way (for all the constituents without the sample).

2.3.2.3 Drug-free tablets

Three different prepared formulae were used to validate our method and investigate the influence of excipients on quantitative determination of Mg^{2+}. These in-lab prepared formulae are described in Table 2.

Each formula compressed to tablets using a rotative compression machine. Then 10 tablets from each formula were grinded. A sample equivalent to an average weight of one tablet was taken (0.504 g). A 15 mL of oxidizing mixture was added to each sample and put in microwave refills. Then, refills were closed tightly and put in microwave and digested by using the defined digestion program (Table 1). After complete digestion, the content of refills was transferred to a volumetric flask of 25 mL and completed to volume by double distilled deionized water. 1 mL was transferred into 10 mL volumetric flask and completed with double distilled deionized water (for F1), while for (F2 and F3) it was transferred into 25 mL volumetric flask. These solutions were next measured by AAS. A blank digest solution was carried out by the same way.

The AAS measurement parameters for all standard solutions and samples were as shown in Table 3.

Table 1. Microwave program for digestion of commercial paracetamol samples

Phase	Initial temperature (◦C)	Final temperature (◦C)	Rate (◦C/min)	hold (min)
1	25	150	25	5
2	150	150	-	8

Table 2. Formulae of drug-free tablets

Formula	Avicel %	Magnesium stearate %	Talc %	Average weight of 1 tablet (mg)
1	99.8	0.2	-	504.0
2	98.5	0.5	1.0	
3	99.0	1.0	-	

Table 3. Analytical parameters for the measurement of magnesium by AAS

Light source	Magnesium hollow lamp
Wavelength (nm)	285.2
Work lamp current (mA)	2.0
Slit width (nm)	0.4
Negative high voltage (V)	300.0
Power supply (mA)	4.0
Flame flow (mL/min)	1500.0
Flame height (mm)	6.0

3. RESULTS AND DISCUSSION

In this study, magnesium was determined in standard solutions and pharmaceutical preparations by flame AAS.

3.1 Calibration Curve

Linearity of response was studied by using Mg^{2+} standard solutions containing 0.08, 0.10, 0.15, 0.20, 0.30, 0.35, and 0.40 µg/mL using AAS. Determination of magnesium was carried out using air–acetylene flame by plotting absorbance for each solution versus its magnesium concentration. Equation of the calibration straight line was (y = 0.172x + 0.0008) and correlation coefficient after least squares analysis was r = 0.9994, which indicates a strong relation. As shown in Fig. 1.

3.2 Limit of Detection and Limit of Quantification

The limit of detection (LOD) is the least concentration of an analyte in a sample that can be detected reliably and gives an instrument signal different from the blank. The limit of quantification (LOQ) is the lowest amount of analyte in a sample that can be quantitatively determined with adequate accuracy and precision [1]. LOD and LOQ were determined by 3.3*SD/m and 10*SD/m, respectively. Where SD is the standard deviation of blank absorbance measures and m is the slope of the calibration curve equation. LOD value was 0.0155 µg/mL and LOQ 0.0471 µg/mL. Previous research [4] reported AAS technique with better sensitivity in terms of LOD and LOQ values, but ICP-MS detector was employed in their study which explains the higher sensitivity characteristic. Nonetheless, pharmaceutical preparations studied in our work contain relatively higher magnesium content, and thus our work showed sufficient sensitivity to quantitatively determine magnesium in these preparations without using the highly demanding ICP-based detector.

3.3 Magnesium Content of Magnesium Effervescent Tablets

Three samples were tested for their Mg^{2+} content and the results are shown in Table 4.

No specifications were reported for magnesium effervescent tablets analysis in USP-38. Therefore, pharmacopoeial limits of magnesium oral solution [90-110%] [11] were used for comparisons. Our results comply to these limits which proves that the analyzed product meets the required specifications

3.4 Magnesium Content of Commercial Paracetamol Tablets

Two different digestion methods were utilized for samples preparation of commercial paracetamol tablets. Results are shown in Table 5.

Paracetamol is a class III on BCS (Biopharmaceutical Classification System) categorizing [12]. It is the most commonly used antipyretic and analgesic and quick action is usually preferred, so factors affecting

bioavailability must be determined. Choosing an appropriate portion of lubricants has a major role determining the bioavailability. Magnesium stearate can be used as a lubricant (at concentrations between 0.25% and 5.00% w/w) [5]. Issues like decrease in drug release (extent and rate) are common when using high concentrations of hydrophobic lubricants [13], delayed dissolution and decreased bioavailability. Therefore, it is necessary to accurately determine the amount of magnesium stearate.

In this work we used Mg^{2+} amount to refer to magnesium stearate using equation: Each 591.3mg magnesium stearate is equivalent to 24.305mg Mg^{2+}(F).

The previously mentioned equation can be used to determine magnesium stearate concentration unless talc is found in the formula [10]; because it contains a mixture of silicate, one of which is magnesium silicate [5]. However, the formula of the commercially tablets analyzed in our work do not contain talc and magnesium stearate concentration was in the minimum acceptable range. Even so, analyzed tablets revealed good mechanical characteristics, which means that this low concentration of magnesium stearate was sufficient to provide appropriate lubrication effect or the manufacturer used a combination of hydrophilic (like PEG 4000) and hydrophobic lubricants (magnesium stearate) in the formula [6]. This allows controlled dissolution profile and quick onset of drug release.

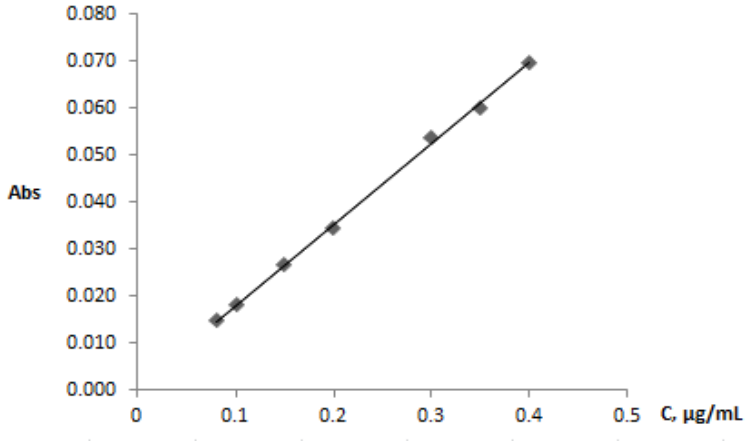

Fig. 1. Calibration curve of magnesium standard solutions
Each absorbance is the mean of six replicates

Table 4. Magnesium amount in magnesium effervescent tablets

Sample NO.	Mg^{2+} * (mg/tab.) ± SD	Labeled amount of magnesium (mg/tablet)	Assay%
1	206.00 ± 0.000433	200	103.00%
2	199.00 ± 0.000433		99.50%
3	197.33 ± 0.000566		98.66%

**: mean of 3 measurements*

Table 5. Magnesium amount in paracetamol tablets by two digestion methods

	Mg^{2+}		Mg.Stearate		
Sample NO.	**Amount per tablet (µg)**	**SD**	**Amount per tablet (mg)**	**% in tablet**	**%Average**
1: wet digestion	59.750	14.238	1.453	0.248	0.220
	63.000		1.532	0.261	
	36.875		0.897	0.153	
2: microwave digestion	52.500	3.125	1.277	0.218	0.205
	46.250		1.125	0.192	
	49.400		1.201	0.205	

Table 6. Magnesium amount of drug-free tablets for F1 and F3 formulae

Sample NO.	Mg^{2+} (µg/tab.)	Mg.Stearate content (mg/tab)	Average weight of 1 tablet (mg)	Mg.Stearate% in tablet	Accepted range% [14]	Recovery%
F.1	40	0.9731	504	0.1930%	95-105	96.50
	41	0.9974		0.1978%		98.90
	43	1.0461		0.2075%		103.75
F.3	205	4.9873		0.9895%	97-103	98.95
	207	5.0359		0.9991%		99.91
	210	5.1089		1.0136%		101.36

t-test study was performed to compare two digestion methods and the result was: $t_{calculated}$ = 0.454 < $t_{tabulated}$ = 4.30 which means that there is no differences between two methods. Despite of the result, microwave digestion is preferred because it is more rapid, greener, flexible; parameters can be adjusted (pressure and temperature) which may decrease the amount of chemicals used, and gives more repeatable results. While wet digestion is associated with longer time, need more amounts of acids, less repeatability (high SD as shown in Table 5), and more importantly that sample may pollute because the system is open.

3.5 Magnesium Content of Drug-free Tablets

Three formulae containing different percentages of magnesium stearate, avicel, and talc were prepared to determine their magnesium content and to investigate the influence of talc presence on Mg^{2+} quantitative determination. Results obtained from F1 and F3 formulae are shown in Table 6.

Both F1 and F3 results were within the accepted range as shown in Table 6. However, F2 needed more dilution steps to be measured and contained 491.25 µgMg^{2+}/tablet (higher than F3 content) which represents total Mg^{2+} amount coming from both magnesium stearate and talc. This result agrees with Keiichi Sugisawa et al. [10] findings who recommended not to use AAS when talc is used in formula.

4. CONCLUSION

A rapid and highly sensitive AAS method for the determination of magnesium was applied. It can quantify magnesium in Eff.tablets preparation to ensure that it is within accepted limits. And more over, to determine magnesium embedded in excipients such as magnesium stearate which contributes to dissolution profiles and bioavailability. This method could be used to determine total magnesium coming from excipients, but cannot differentiate between Mg^{2+} coming from talc or magnesium stearate.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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