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Dedicated to Professor Emil Cordoș
on the occasion of his 80th anniversary

INFLUENCE OF TABLET FORMULATION ON *IN VITRO* RELEASE OF MAGNESIUM

CORINA MOISA[a], MARIA-ALEXANDRA HOAGHIA[b], DORINA SIMEDRU[b], OANA CADAR[b,*]

ABSTRACT. The transfer of active substances of pharmaceutical forms is influenced by several factors, among which the nature of the excipients used in compression. The objective of this study was to investigate the influence of cellulose and its derivatives (hydroxypropylcellulose, hydroxylpropylmethylcellulose, carboxymethylcellulose) on the release profile of magnesium from marketed tablets (T1-T4). *In vitro* release experiments were carried out using a dissolution apparatus, in ultrapure water and simulated intestinal fluid (pH=6.8). In selected formulations, the amount of magnesium released was determined using inductively coupled plasma optical emission spectrometry (ICP-OES). The magnesium dissolution profiles demonstrated complete dissolution for T1, even just after 5 min. Magnesium release rate decreased with the increase in cellulose and/or its derivatives proportion: T1<T3<T2<T4. An agitation speed of 50 rpm showed a more satisfactory magnesium release profile than 100 rpm.

Keywords: *magnesium release, in vitro, pH, matrix tablet*

INTRODUCTION

Magnesium is a macroelement mineral, the fourth most abundant cation in the human body and the second most abundant intracellular cation, after potassium [1, 2]. It takes part, as a cofactor, in more than 300

[a] *University of Oradea, Faculty of Medicine and Pharmacy, 29 Nicolae Jiga Street, RO-410028, Oradea, Romania*
[b] *Research Institute for Analytical Instrumentation, 67 Donath Street, RO-400293, Cluj-Napoca, Romania*
[*] *Corresponding author: oana.cadar@icia.ro*

enzymatic reactions included in the spectrum of the metabolic activity [3, 4]. Magnesium is essential both for the absorption and metabolism of calcium and vitamin D, and the calcium transport. Magnesium is important for muscle contraction by acting as a calcium antagonist, cellular proliferation, apoptosis, immune response, etc. Magnesium deficiency mobilizes calcium from bones, leading to abnormal calcifications in arteries and kidneys [5-7].

A low level of magnesium in the body is associated with significant cardiovascular conditions, including hypertension, heart rhythm disorders (arrhythmias), coronary artery disease (angina pectoris, myocardial infarction), hypercholesterolemia, hypertriglyceridemia, congestive heart failure and aggravation of pulmonary diseases [8]. Accidentally or not, the increasing incidence of cardiovascular disease in recent years corresponds to an increasingly lower magnesium intake [9-12]. Magnesium deficiency is associated with high levels of total cholesterol and triglyceride and low level of HDL cholesterol, respectively. In terms of insufficient dietary intake, administration of pharmaceutical forms of magnesium is increasingly used [9].

More than 90 % of drugs are orally administered. Solubility is one of the significant parameters to attain desired concentration of a drug in systemic circulation for pharmacological response to be shown [13]. Therapeutic effectiveness of a drug is directly related to the absorption and bioavailability of the drug after oral administration [14]. In the gastro intestinal tract, most absorption of oral drugs occurs in the small intestine due to its large surface area and high blood perfusion rate [15]. It is desirable that the oral tablet displays minimal drug release in the stomach and the small intestine (duodenum) and starts drug release in the tracts of the lower small intestine and colon.

The successful treatment of hypomagnesaemia depends on both the type of magnesium administered and the duration of the therapy. Magnesium efficient formulas are those in which magnesium is organically bound (acetate, bicitrate, methionate, ascorbate, gluconate, propionate or orotate). Magnesium mineral salts (chloride, sulphate) can't be absorbed, often having a laxative effect and thus reducing the therapeutic efficacy [16, 17]. *In vitro* dissolution study is an important aspect in the evaluation of the best formulation and also for understanding the possible risks like dose dumping, chemical contamination and drug interactions with food or other drugs [18-20].

The rate of drug release is dependent on various factors such as the material matrix (composition, structure, swelling, degradation), the release medium (pH, temperature, ionic strength, enzymes) and the drug composition (solubility, stability, interaction with matrix) [21]. Cellulose and cellulose derivatives are commonly used in the formulation of dosage forms and healthcare products. Polymer content, molecular weight, concentration, degree of substitution and particle size have been shown to have an important effect

on drug release. However, the most significant factors that affect the drug release rate from cellulose matrices are the polymer concentration and drug/polymer ratio [22].

The aim of this study was to evaluate the magnesium release from marketed tablets containing cellulose and/or its derivatives, in two dissolution media: ultrapure water (UW) and simulated intestinal fluid (SIF, phosphate buffer, pH 6.8, enzyme free) at different time intervals.

RESULTS AND DISCUSSIONS

Magnesium supplements come in a variety of salts (e.g. citrate, oxide, gluconate, acetate, orotate) [23], however their bioavailability differs. Some studies reported the use of organic over inorganic forms: investigations of magnesium orotate, citrate and gluconate which demonstrated high solubility and bioavailability [24-26].

In vitro dissolution studies are important quality and stability tools for predicting *in vivo* performance. In this study, four marketed tablet brands containing the same active ingredient and different excipients, were studied for their *in vitro* magnesium dissolution behaviour in ultrapure water and simulated intestinal fluid (pH=6.8) for 5, 10, 30, 60 and 120 min time period, using USP reference dissolution apparatus. The content of cellulose and/or its derivatives in studied tablets was increasing in the following order: T1<T3<T2<T4. The magnesium release from the active ingredient itself was completely after 5 min. The obtained results for marketed tablets (T1-T4) are shown in Figures 1-4. The magnesium dissolution profiles demonstrated complete dissolution for T1, even just after 5 min.

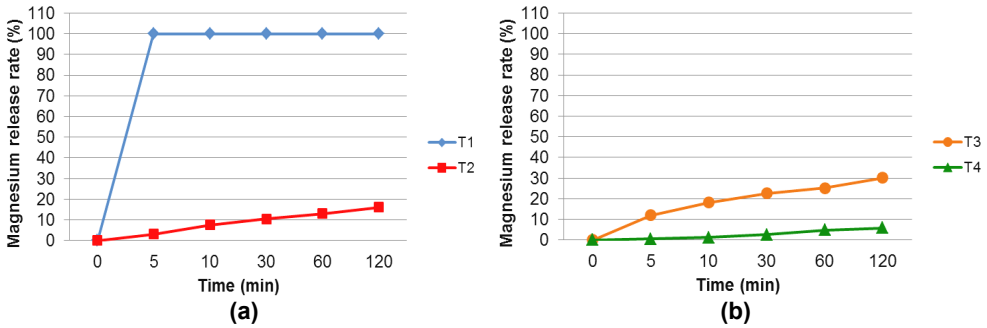

Figure 1. Release profile of magnesium from tablets of different excipients in UW, 50 rpm: a) T1, T2 and b) T3, T4.

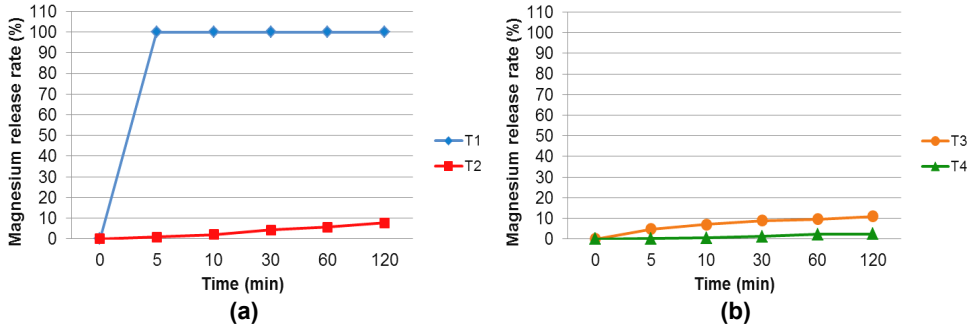

Figure 2. Release profile of magnesium from tablets of different excipients in SIF, 50 rpm: a) T1, T2 and b) T3, T4.

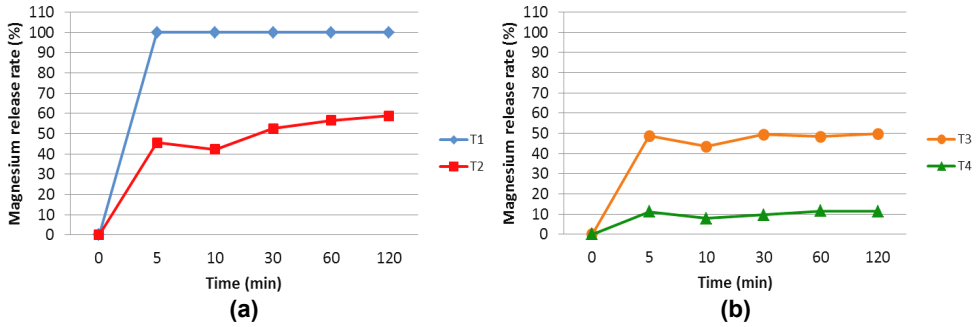

Figure 3. Release profile of magnesium from tablets of different excipients in UW, 100 rpm: a) T1, T2 and b) T3, T4.

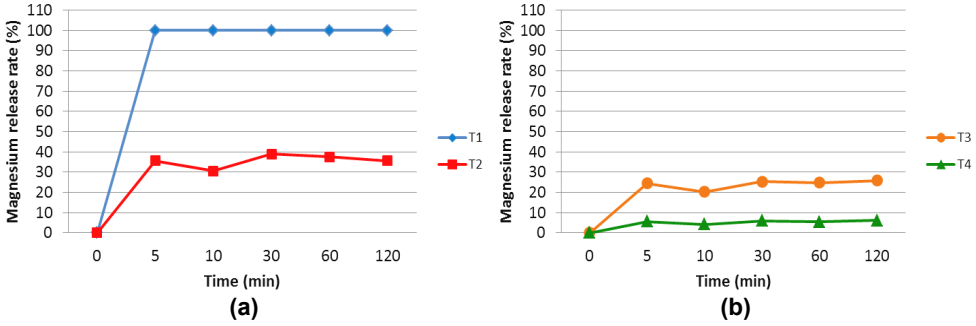

Figure 4. Release profile of magnesium from tablets of different excipients in SIF, 100 rpm: a) T1, T2 and b) T3, T4.

In vitro magnesium release behavior of investigated tablets was not affected by pH and dissolution media composition. The presence of cellulose derivatives in the composition of the tablets leaded to a delay in the release of

the magnesium from the tablet both in ultrapure water and simulated intestinal medium (phosphate buffer solution, pH 6.8). The tablet T1, containing no cellulose and/or its derivatives, exhibited better dissolution profile than tablets formulated with cellulose and/or its derivatives (T2-T4).

In the presence of water, the cellulose derivatives modify their properties, their main property being swelling, which leads to the formation of a gel that prevents the release of magnesium. The obtained results indicate that cellulose and/or its derivatives could retard the magnesium release in both simulated intestinal fluid and ultrapure water, but at different levels. Results revealed a significant difference in magnesium release behavior between the tablets with lactose and those with cellulose and its derivatives. A very rapid release of magnesium from lactose tablets was found (5 min) in both UW and SIF, whereas tablets containing cellulose and/or its derivatives showed the retardation of magnesium release. This was due to the high water solubility of lactose; therefore, water easily penetrates into tablets and magnesium ions are rapidly released. Cellulose and its derivatives are less soluble in water than lactose; consequently, the water penetration into the tablet matrix is more difficult. This leads to the delay of magnesium release. The amount of cellulose derivatives in the composition of the tablets influences the magnesium's time release from the tablet. Therefore, in tablets containing low quantity of cellulose derivatives, the magnesium dissolves faster in the dissolution medium compared to tablets containing cellulose derivatives. Similar results were obtained by Enayatifard [27], which showed that the release rate decreased as the concentration of hydroxypropylmethylcellulose increased.

The immediate-release tablets (T1) are entirely available immediately for absorption following oral ingestion, providing a faster therapeutic effect. In contrast, the market tablets (T2-T4), with slower magnesium release, are appropriate for maintenance treatment.

Mild agitation conditions should be maintained during dissolution experiments to allow maximum discriminatory power. Generally, the dissolution apparatus tends to become less discriminating when operates at faster speeds, resulting in a flatter drug release profile [28]. For our study, it can be concluded that the magnesium release profile at 50 rpm detected small changes in tablet composition (Figure 1 and 2), while, at 100 rpm, dissolution proceeded to quickly (Figure 3 and 4). Therefore, the satisfactory magnesium release profile was observed at 50 rpm. This result was in agreement with the finding of Soni et *al.* [29].

The pH of the dissolution medium was measured before and after the dissolution test (Figure 5 and 6). The pH slowly changes during the dissolution test due to the solubility of the drug substance or the excipients [30].

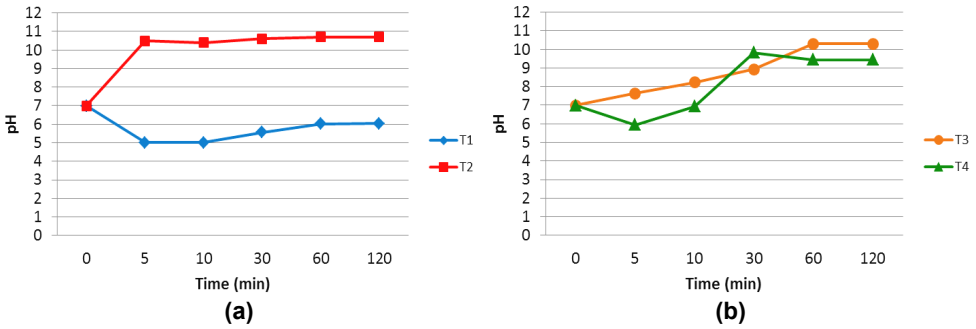

Figure 5. Changes in pH after immersion of different tablet brands in UW, 50 rpm: a) T1, T2 and b) T3, T4.

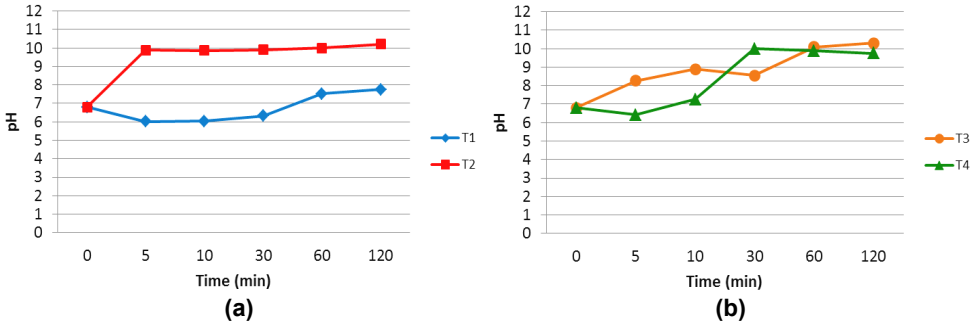

Figure 6. Changes in pH after immersion of different tablet brands in SIF, 50 rpm: a) T1, T2 and b) T3, T4.

CONCLUSIONS

In this study, *in vitro* magnesium dissolution behaviour from the same drug, belonging to different brands, in ultrapure water and simulated intestinal medium was tested at periodic time intervals. The magnesium release in buffer solution and ultrapure water was independent of the pH and dissolution media composition. Furthermore, it was shown that higher amount of cellulose and/or its derivatives in formulations caused a decrease in magnesium release rates. Increase in agitation speed from 50 to 100 rpm increased "*in vitro*" magnesium release rate from tablets. pH of the dissolution medium changes as the dissolution of active ingredient and drug components occurs.

EXPERIMENTAL SECTION

Materials

To perform the study, both magnesium and magnesium/calcium tablets of four different manufacturers, with a range of nine commonly used excipients in pharmaceutical formulations: microcrystalline cellulose, hydroxypropyl-methylcellulose, carboxymethylcellulose, hydroxypropyl-methylcellulose, lactose monohydrate, magnesium stearate, gelatin, titanium dioxide and talcum were used. Five blister packs were purchased from a local pharmacy shop. The market tablets belong to four different brands. The labelled shelf life of all tablets was 2-4 years after production date and was taken for evaluation before one year of the labelled expiry date. After purchasing, the tablets were coded separated as pair of magnesium and magnesium/calcium: T1 and T2 for magnesium tablets and T3 and T4 for magnesium/calcium tablets (Table 1). The total cellulose (derivatives) content of the tablet weight was: T1 (0%) < T3 (10%) < T2 (25%) < T4 (35%). All reagents were of analytical grade, purchased from Merck (Germany) and used without further purification.

Table 1. Details of magnesium and calcium/magnesium market tablet formulations.

Crt. No.	Formulation code	Type	Cellulose and its derivatives
1	R (reference/active ingredient)	Mg	-
2	T1	Mg	-
3	T2	Mg	Microcrystalline Cellulose Hydroxypropylcellulose Hydroxypropylmethylcellulose Carboxymethylcellulose
4	T3	Ca/Mg	Microcrystalline Cellulose Hydroxypropylmethylcellulose
5	T4	Ca/Mg	Hydroxypropylmethylcellulose

Magnesium ion release study

The dissolution tests were carried out to determine magnesium release pattern in a dissolution apparatus (Electrolab, TDT-08L Plus) following the USP paddle method, at 37 ± 0.5º C, 50 and 100 rpm rotation speed. The experiments were performed in 900 ml dissolution media: (*i*) ultrapure water (pH=6.998) and (*ii*) simulated intestinal fluid (pH 6.8, buffer solution containing K_2HPO_4-NaOH), respectively, during a specific period of time (5, 10, 30, 60 and 120 min). The amount of magnesium was equivalent to 200 mg. Also, the magnesium release from the active substance was studied. A 5 ml sample

was collected at predetermined time point, filtered through a 0.45 µm pore size filter and analyzed for magnesium content using inductively coupled plasma optical emission spectrometer (ICP-OES) Optima 5300 DV (Perkin Elmer, USA). The limit of detection (LOD=0.01 mg/L) was calculated on the basis of the equation $LOD=3s_b/m$, where s_b was the standard deviation of 10 successive measurements of blank and m was the slope of calibration curve [7]. The possible interference with phosphorous, potassium and sodium related interference were not observed at the magnesium emission line (285 nm). The pH was measured with a 350i multiparameter (WTW, Weilheim, Germany). Each experiment was repeated in triplicate. All dilutions were prepared using deionized water (18.2 MΩ/cm) obtained from a Millipore Direct-Q3 UV Ultrapure water system (Millipore, Molsheim, France). All PTFE and glass vessels were soaked in 10% (v/v) HNO_3 overnight and rinsed with Milli-Q water prior to use.

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