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Commentary

Type of Magnesium Salt and Formulation Solubility Determines Bioavailability of Magnesium Food Supplements

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ABSTRACT

Magnesium (Mg^{2+}), an essential mineral and cofactor of more than 300 enzymatic processes, has a regulating role in energy metabolism, protein synthesis, muscle and nerve function, blood glucose and blood pressure control. The European Food Safety Authority (EFSA) proposes an Adequate Intake of 350 and 300 mg/day for men and women, respectively. Given deficiencies present in over 50% of the normal population, magnesium is currently a popular nutritional supplement. Based on the source of elemental magnesium, the supplements currently available on the market can be divided into 2 different categories: inorganic or organic salts of magnesium. Inorganic magnesium compounds are generally perceived as not as easily absorbable as organic magnesium compounds.

The aim of this study was to compare the efficacy of magnesium glycerophosphate and magnesium bisglycinate with different magnesium formulations previously tested by specific *in vitro* approaches that previously proved to provide a valid methodology to predict *in vivo* outcomes and effectiveness of magnesium supplements. Both in fasted and fed state the *in vitro* bioaccessibility, being a measure for the solubilization of the formulation during gastric incubation, was clearly higher for the organic salts of interest. Nevertheless it should be noted that poor solubility of a magnesium supplement, translating into poor dissolution, was a determining factor in bioaccessibility. Also in *in vitro* bioavailability, representing the absorption efficiency in the small intestine, the bisglycinate and glycerophosphate salts outperformed the inorganic magnesium oxide. Therefore we conclude that magnesium glycerophosphate and bisglycinate have a higher bioavailability compared to inorganic salts, when formulated in a highly soluble magnesium supplement.

Keywords: Magnesium; Bisglycinate; Bioaccessibility

INTRODUCTION

Magnesium (Mg^{2+}) is an essential mineral having a regulating role in energy metabolism, protein synthesis, muscle and nerve function, blood glucose and blood pressure control [1]. As a co-factor in more than 300 enzymatic reactions, which often depend on ATP, Mg^{2+} is involved in many biochemical pathways of key importance, including the degradation of macronutrients, oxidative phosphorylation, DNA and protein synthesis, neuro-muscular excitability, and regulation of parathyroid hormone (PTH) secretion. Intestinal Mg^{2+} absorption occurs predominantly in the small intestine via a paracellular pathway, and smaller amounts are absorbed in the colon, mainly via a transcellular pathway [2]. Mg^{2+} homeostasis depends on the collaborative actions of the intestine, responsible for Mg^{2+} uptake from food, the bone, which stores Mg^{2+} in its hydroxy-apatite form, and the kidneys, regulating urinary Mg^{2+} excretion [1].

The European Food Safety Authority (EFSA) recommends an Adequate Intake of 350 and 300 mg/day for men and women, respectively [3]. Overall magnesium content in various foods is declining from 25-80% compared with the levels before 1950 due to removal of magnesium during food processing as well as changes in soil conditions [4]. Supplementation has already demonstrated to be beneficial in a wide array of diseases in which magnesium plays a role. Amongst others a low Mg^{2+} status is associated with neurological diseases such as migraine, depression and epilepsy. Dietary Mg^{2+} intake has also been associated with lung function. Mg^{2+} plays a role in heart function by influencing myocardial metabolism, Ca^{2+} homeostasis, vascular tone, peripheral vascular resistance and cardiac output. Mg^{2+} exerts its effect on skeletal

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muscle function as Ca^{2+} antagonist on Ca^{2+}-permeable channels and Ca^{2+}-binding proteins. Mg^{2+}-deficient conditions result in hypercontractibility, which presents as muscle cramps and spasms in the clinic. Mg^{2+} has also been implicated in both endocrine and exocrine functioning of the pancreas [1]. Given the deficiencies present in over 50% of the normal population and the effects obtained using supplementation, magnesium is currently a popular nutritional supplement [5].

METHODOLOGY ADOPTED

Dietary Mg^{2+} uptake in the intestine varies within a broad range and depends on dose, food matrix, enhancing and inhibiting factors. Several studies have shown that the absorption of Mg^{2+} from food supplements under standard conditions is influenced by the type of Mg^{2+} salt [2]. The water solubility of a magnesium salt is of importance for the bioavailability. Studies demonstrate that organic salts of magnesium have a higher solubility than inorganic salts [6].

Although it is not an ideal method, since total serum magnesium concentration is not necessarily a good reflection of total body magnesium status, serum magnesium analysis is still the most widely used method [7]. Blancquaert et al. concluded that 6 h serum magnesium measurement following an acute single ingestion was a valid approach for comparing the *in vivo* bioavailability of two supplements. Their study provided a valid methodology to predict *in vivo* outcomes and effectiveness using two simple *in vitro* approaches: the Simulator of the Human Intestinal Microbial Ecosystem (SHIME®) and dissolution tests [8].

The aim of this study was to compare the efficacy of magnesium glycerophosphate and magnesium bisglycinate formulations with inorganic magnesium formulations previously tested by Blancquaert et al. [8], using the same *in vitro* methodology.

RESULTS

In addition to the formulations previously reported by Blancquaert et al., three additional Metagenics formulations were tested using the same *in vitro* testing methodology as described by Blancquaert et al. [8]. The SHIME® technology was applied to simulate the behavior of different formulations in the stomach and small intestine. Both in fasted and fed state the *in vitro* bioaccessibility, being a measure for the solubilization of the formulation during gastric incubation, was clearly higher for the organic salts of interest (Figures 1 and 2). The higher bioaccessibility of Mg Carbonate in the fed state compared to the fasted state can be attributed to the sampling time, being 120 min versus 45 min respectively. It should be noted that for some patients, e.g. post-bariatric surgery, the sampling time of 120 min is quite unrealistic, even in a fed condition.

Secondly the *in vitro* bioavailability, representing the absorption efficiency in the small intestine (% Mg^{2+} absorbed versus initial dose), was evaluated for all formulations in both fasted and fed conditions (Figures 3 and 4). The organic salt (magnesium glycerophosphate) and chelate (magnesium bisglycinate) showed a higher bioavailability and clearly outperformed the inorganic salts, in both fasted and fed state.

DISCUSSION

The present results further support the conclusions made before that the absorption of Mg^{2+} from food supplements is influenced by the type of Mg^{2+} salt and that the water solubility of a magnesium form (inorganic salt, organic salt, chelate, etc.) is an important factor, with a higher solubility correlating with an increased absorption [2,6]. It is important to note that the pH of the GI-tract can impact how soluble the magnesium form is, with a lower pH increasing magnesium solubility. It was shown previously that omeprazole suppressed passive magnesium absorption as the luminal acidity increased above the range (pH 5.5-6.5) in which

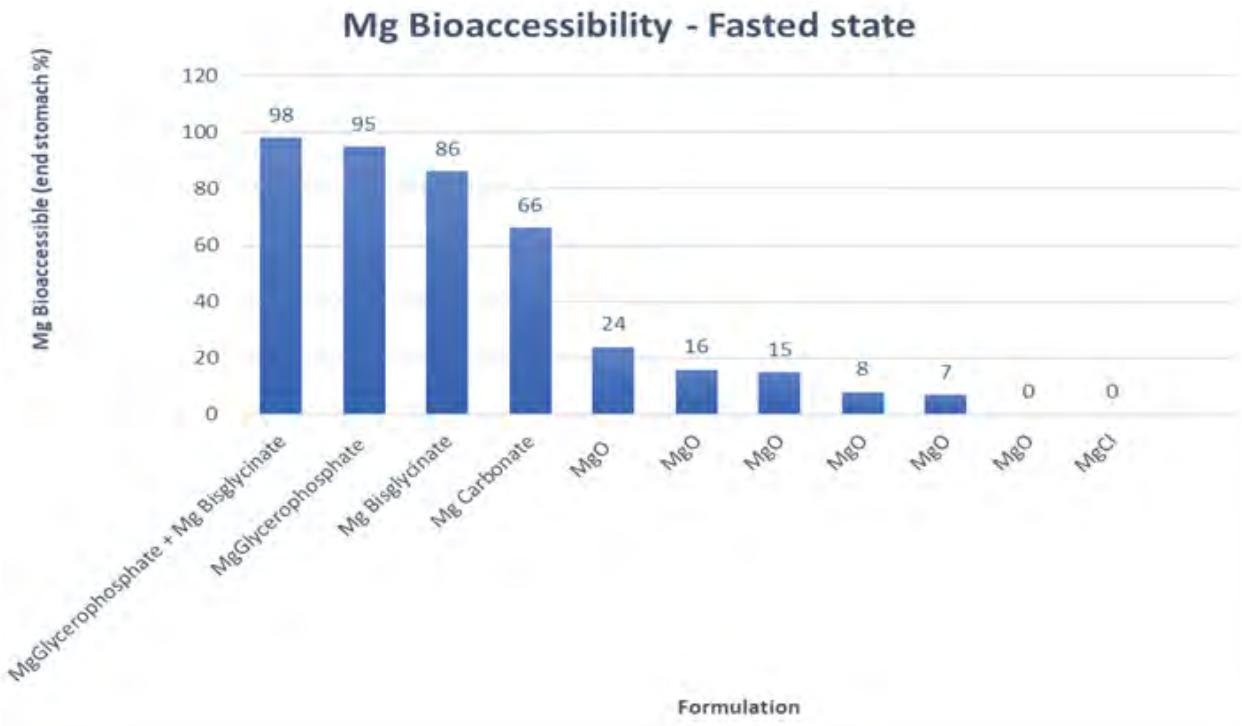

Figure 1: Relative (%) Mg^{2+} release during the stomach incubation upon simulated ingestion of Mg-containing formulations under fasted conditions Adapted from Blancquaert et al. 2019 [8].

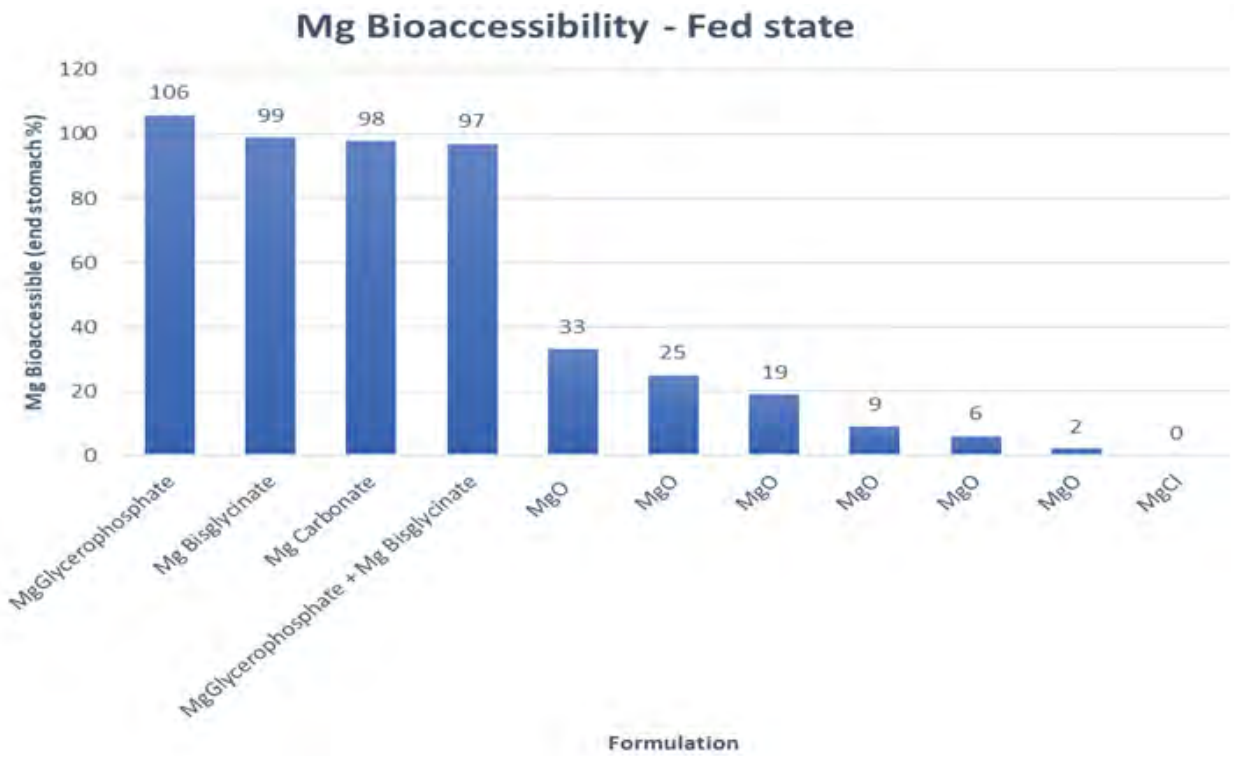

Figure 2: Relative (%) Mg^{2+} release during the stomach incubation upon simulated ingestion of Mg-containing formulations under fed conditions Adapted from Blancquaert et al. 2019 [8].

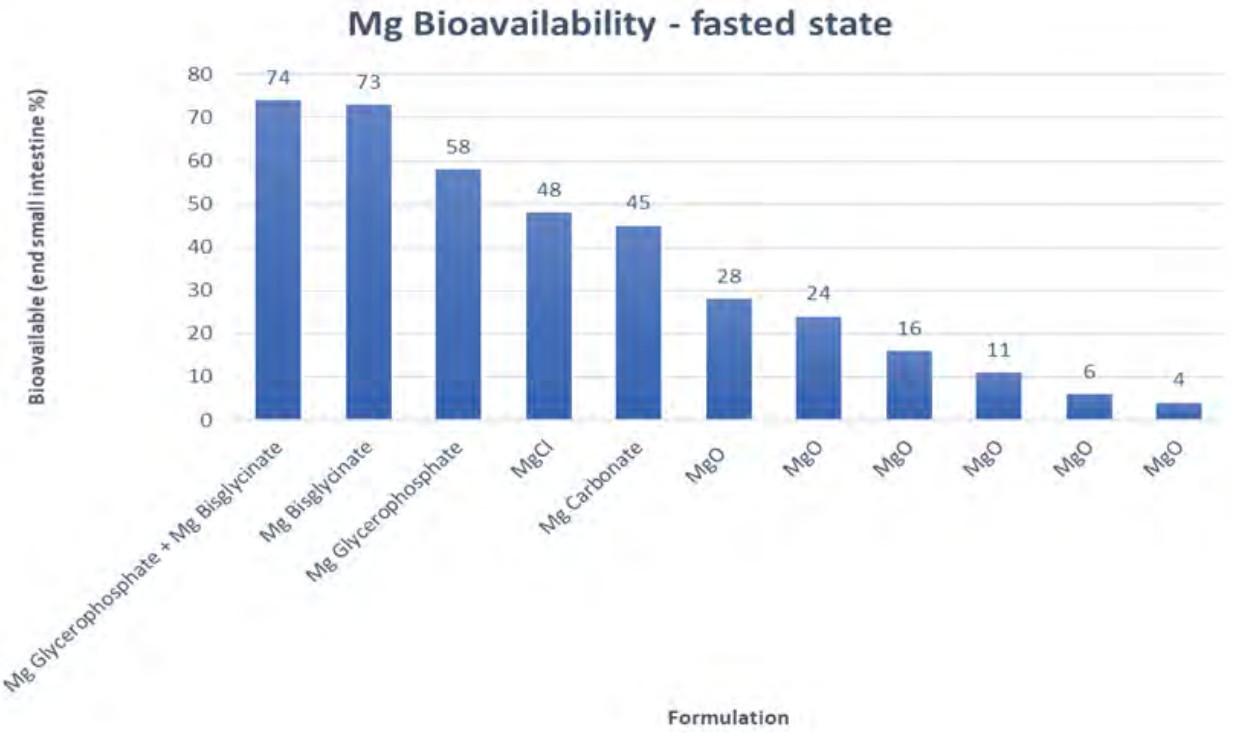

Figure 3: Relative (%) Mg^{2+} release during the small intestinal incubation upon simulated ingestion of Mg-containing formulations under fasted conditions Adapted from Blancquaert et al. 2019 [8].

claudin 7 and 12 expression is optimized, magnesium hydration shell stripping is most effective, and electrostatic coupling between magnesium and the transporter takes place [9]. The dissolution tests performed in this study confirmed these observations and the conclusion that the solubility of the magnesium supplement is of the utmost importance for bioavailability.

Another key element linked to solubility is the fact that the strong attraction of water to magnesium ions is responsible for the common side effect of diarrhoea in response to magnesium supplementation. In respect to this mechanism, the benefit of magnesium bisglycinate is two-fold. Firstly, in the chelated state the magnesium ion is neutral and does not add osmotic pressure to the intestinal electrolyte status. Too many ions in the intestine would increase the osmotic pressure which would cause a flow of water into the intestinal lumen to dilute these ions and to lower their concentration, forming loose stools or developing diarrhoea. Secondly, the reduction in pH, caused by glycine's buffering

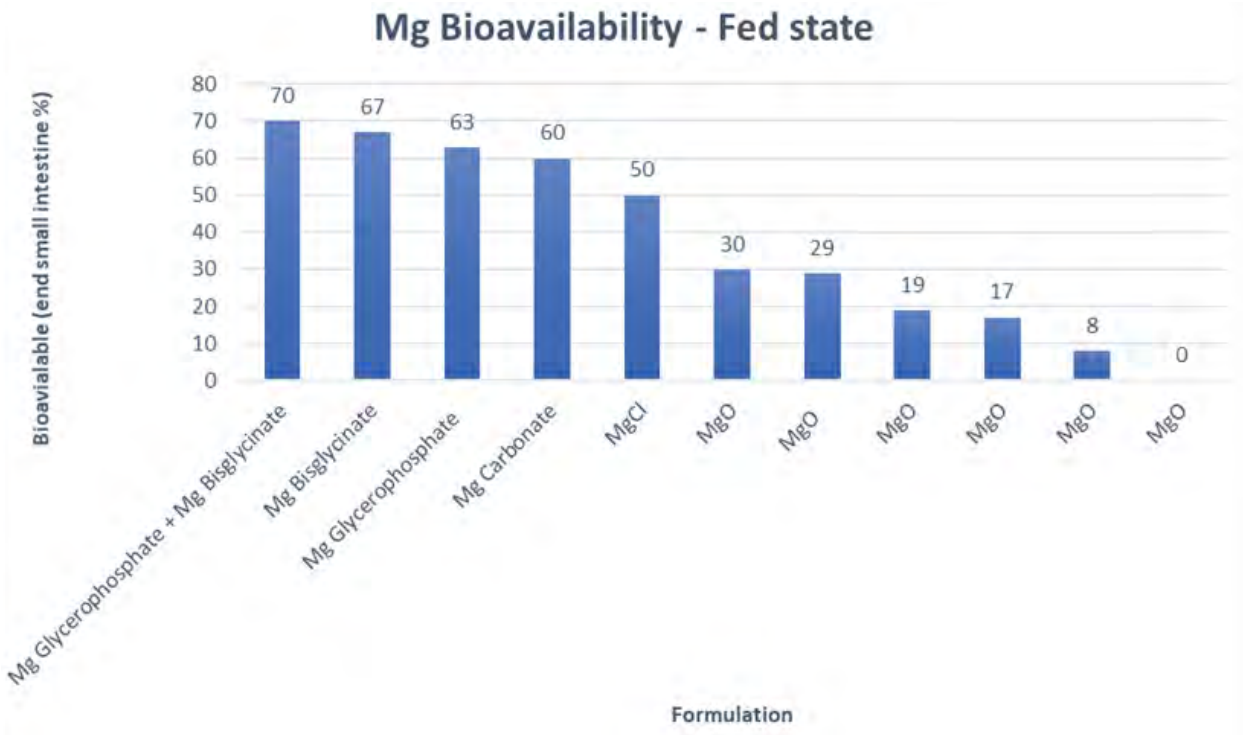

Figure 4: Relative (%) Mg^{2+} release during the small intestinal incubation upon simulated ingestion of Mg-containing formulations under fed conditions Adapted from Blancquaert et al. 2019 [8].

capacity, improves the dehydration and therefore absorption of magnesium. This minimizes laxation and improves the tolerability of magnesium bisglycinate [9].

CONCLUSION

In conclusion from this study, using the valid methodology described by Blancquaert et al. to predict *in vivo* outcomes and effectiveness by the combination of *in vitro* SHIME® and dissolution tests, we can state that magnesium glycerophosphate and bisglycinate have a higher bioavailability compared to inorganic salts like magnesium oxide and magnesium chloride, under the condition that the magnesium salt is formulated in a highly soluble magnesium supplement.

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