https://doi.org/10.31925/farmacia.2023.5.23 **ORIGINAL ARTICLE**

THE PHARMACIST'S ROLE IN PROMOTING FOOD SUPPLEMENTS: CONSUMPTION OF MAGNESIUM SUPPLEMENTS IN WESTERN ROMANIA

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Manuscript received: May 2023

Abstract

Considering the significant role of Mg in the optimal functioning of the entire organism and the widespread consumption of Mg supplements, this study aim was to identify the main factors that influence the choice of Mg supplements by the population, how the consumption of Mg supplements evolved in the post-COVID-19 period compared to the COVID-19 period, but also the pharmacist's role in advising citizens and promoting Mg supplements. A comparative analysis regarding their consumption over two years, one during and one after the COVID-19 pandemic, was also carried out. For higher relevance of the study, pharmacies with higher consumption of Mg supplements from different county areas were chosen. Considering that most consumers purchase food supplements from pharmacies, the pharmacist's role is decisive in choosing these supplements; depending on the desired effect for each patient, the pharmacist indicated fast-acting or delayed-acting supplements. In this regard, the *in vitro* release of Mg at pH 1.2 and 6.8 from the most popular Mg supplements containing a variety of compounds, such as orotate, oxide, carbonate, lactate, citrate, and hydroxide was assessed. The obtained results indicate a higher consumption of dietary supplements containing both Mg and B group vitamins in the post- COVID-19 period. Also, the disaggregation of the tablets provides valuable information related to the time course of the therapeutic response and the amount of Mg compound released from the tablet.

Rezumat

Având în vedere rolul semnificativ al Mg în funcționarea optimă a întregului organism și consumul mare al suplimentelor de Mg, acest studiu a avut ca scop identificarea principalilor factori care influențează alegerea suplimentului cu Mg de către populație, modul în care a evoluat consumul suplimentelor cu Mg în perioada post-COVID-19 comparativ cu perioada COVID-19, dar și rolul farmacistului în consilierea populației și promovarea suplimentelor cu Mg. De asemenea, a fost efectuată o analiză comparativă privind consumul acestora pe parcursul a doi ani, în timpul și după pandemia COVID-19. Pentru o mai mare relevanță a studiului, au fost alese farmacii cu un consum mare de suplimente de Mg din diferite zone ale județului. Având în vedere că majoritatea consumatorilor achiziționează suplimente alimentare din farmacii, rolul farmacistului este decisiv în alegerea acestor suplimente; în funcție de efectul dorit pentru fiecare pacient, farmacistul indică suplimente cu acțiune rapidă sau cu acțiune întârziată. În acest sens, a fost evaluată eliberarea *in vitro* a Mg din comprimate la pH 1,2 și 6,8 din cele mai populare suplimente de Mg care conțin o varietate de compuși, cum ar fi orotat, oxid, carbonat, lactat, citrat și hidroxid. Rezultatele obținute indică un consum mai mare de suplimente alimentare care conțin Mg și vitamine din grupul B în perioada post-COVID-19. De asemenea, dezagregarea comprimatelor oferă informații valoroase legate de durata de timp a răspunsului terapeutic și cantitatea de compus Mg eliberat din comprimat.

Keywords: magnesium, consumption, pharmacist, release

Introduction

Food supplements are consumed daily by hundreds of millions of people for various reasons, the most used being vitamins and minerals. Magnesium (Mg) is an essential cation for the human body's proper functioning, encompassing its role as a cofactor for more than 300 enzymatic reactions [16, 19]. Clinical studies have demonstrated Mg's importance in preventing

of various diseases, such as cardiovascular pathologies, osteoporosis, diabetes, bronchial asthma and neurological diseases and overall health [1, 26, 46]. Moreover, Mg is important in regulating heart rate and blood pressure, intervening in peripheral vascular resistance and endothelial function by antagonizing the vaso-constrictor effect of calcium, bradykinin, angiotensin II and serotonin [7, 40]. In this regard, Mg influences the mechanisms affecting the neurotransmitters responsible for the response of nerve cells to stressful conditions that trigger peripheral vasoconstriction, increased blood pressure, etc. Moreover, Mg deficiency increases aldosterone synthesis, a process mediated by angiotensin II, and the production of thromboxane and vasoconstrictor prostaglandins. The conversion enzyme is also involved in the degradation of bradykinin [36].

Mg is an essential cofactor in converting vitamin D into its active form, contributing to combating rickets [12, 43]. Around 60% of the total Mg content of the human organism is found in the bones, constituting a significant part of the bone's mineral density and further reducing the risk of fractures [28, 45]. Moreover, Mg is an essential cofactor for enzymatic reactions constituting carbohydrate metabolism, involving insulin-dependent glucose absorption, with studies reporting that an Mg deficiency could increase the incidence of type 2 diabetes and lead to poor control of blood glucose in diabetic patients [15, 35, 36]. A series of studies have investigated the impact of Mg in asthma patients, concluding that by antagonizing the effect of calcium and influencing cyclic AMP (cAMP) at the intracellular level, Mg relieves symptoms due to bronchodilatation and bronchial muscle relaxation also mediates in the inhibition of N-methyl-D-aspartate (NMDA) receptors, regulating the level of calcium and, consequently, neuronal excitability [9, 18, 25].

Considering the complex role of Mg in the body, many studies have evaluated various conditions caused by the low Mg level in the body due to a Mg-deficient diet [8, 29]. Numerous studies associate Mg deficiency with an increased risk of cardiac arrhythmias by affecting the sodium–potassium adenosine triphosphatase (Na^+/K^+-ATPase), lowering intracellular potassium levels and increasing intracellular sodium levels [31]. Thus, variations in the Mg levels also reflect themselves in the electrocardiogram of the patients, with studies concluding that an Mg deficiency is correlated with an increased risk of developing atrial fibrillation. Low Mg levels also lead to endothelial dysfunction and increased morbidity and mortality due to myocardial ischemia and infarction [10].

Recent dietary surveys and epidemiologic studies revealed that around 50% of the general population has a Mg intake lower than the Recommend Daily Allowance (RDA) of 420 mg of Mg for men and 320 mg for women, considering 19 - 50 years as an age range [23, 41]. The low Mg level in the body is due mainly to a decreased intake, being correlated with a diet consisting of high quantities of processed foods, as well as vegetables or fruits, which have been grown using various substances that decrease mineral concentrations [30]. Other risk factors include smoking, alcohol consumption, stress, chronic fatigue and various renal and gastrointestinal disorders that negatively influence Mg reabsorption [14, 19, 44].

In order to combat Mg deficiency, it is recommended to use food supplements containing in various Mg compounds (*i.e.*, orotate, carbonate, oxide, lactate, citrate, hydroxide) in different concentrations. The bioavailability of Mg in these supplements is influenced by the type of Mg compound, the nature of the excipients used in the pharmaceutical formulation and the technological process specific to each manufacturer [32]. Thus, it is essential to supplement the Mg deficiency with supplements from which Mg is best absorbed.

Depending on the Mg level in the body, the patient's state of (pregnant women, athletes, treatments with drugs that lower the Mg level), a specific dose of Mg, and time are required for the expected therapeutic effect after treatment with Mg supplements. This information is specific to each patient; therefore, the choice of Mg supplement must be recommended by specialists (doctors, pharmacists, etc.). Therefore, this study aims to identify: (i) the supplements with the fastest Mg release after administration and (ii) the relationship between Mg release from the most marketed tablets and their consumption during and after the COVID-19 pandemic considering the neurological sequels in infected patients and the pharmacist's role in promoting food supplements. Even previous studies reported the bioavailability of Mg in the body, this study is important considering the differences between the countries considering the composition of Mg supplements, doses of the active substance, excipients on the release time of Mg from the pharmaceutical form and the absorption of Mg in the body [5, 39].

Materials and Methods

Study Design

The most consumed supplements containing Mg in the form of different compounds were chosen for the study according to the information we obtained from the pharmacy computer program. These data represent the quantities of Mg supplements (packs) released based on the medical prescription and the pharmacist's recommendation. The studied supplements (Table I) were purchased from 25 rural (RR) and 25 urban (UB) pharmacies in Bihor County, Romania and were within the validity period. Local rural and urban pharmacies provided the consumption of the analysed Mg supplements (P1 - P10).

We used the same pharmaceutical form for all samples (tablet). Depending on the excipient's nature, some

tablets are used for a faster effect after administration when the release occurs in the stomach, while for those with extended release, it occurs in the small intestine.

Table I

Composition of Mg supplements

Sample	mg Mg *per* tablet	Excipients	Mg compound	Mixture of active substances
P1	32.8	Silicon dioxide, croscarmellose sodium, cellulose, corn starch, povidone K30, lactose, talcum, Mg stearate	Orotate	-
P2	400	Cellulose, croscarmellose sodium, silicon dioxide, hydroxypropyl methylcellulose, titanium dioxide, shellac, palm oil	Oxide	Vitamin B1, B6, B12 and folic acid
P3	120	Cellulose, Mg salts of fatty acids, sodium carboxymethyl cellulose	Carbonate	Vitamin B6
P4	56.25	Cellulose, sorbitol, talcum, polyvinyl pyrrolidone, Mg salts of fatty acids	Carbonate	Vitamin B6
P5	155	Cellulose, silicon dioxide, Mg stearate, talcum, Mg stearate, hydroxypropyl cellulose, zinc, Mg, calcium gluconate, titanium dioxide	Oxide	Calcium, Zinc
P6	47.9	Sugar, calcium carbonate, titanium dioxide, talcum, gelatine, carnauba wax, lactose, corn starch, povidone K30, Mg stearate	Lactate	Vitamin B6
P7	100	Polyvinyl pyrrolidone, cellulose, corn starch, sodium carboxymethyl cellulose, silicon dioxide, hydroxypropyl methylcellulose, polyvinyl alcohol	Citrate	Vitamin B6
P8	48	Sugar, kaolin, gum arabic, carbopol, talcum, Mg stearate, carnauba wax	Lactate	Vitamin B6
P9	50	Sorbitol, cellulose, polyvinyl pyrrolidone, Mg stearate	Carbonate	Vitamin B6
P10	150	Stearic acid, silicon dioxide, Mg stearate, maltodextrin, corn starch	Hydroxide	Calcium, vitamin D, zinc

The disintegration speed of the tablet is an important factor in terms of the therapeutic effect; a faster release may maximize the therapeutic efficacy and minimize the side effects, *i.e.*, the irritation generated by the gastric retention time decreases. Other factors influencing bioavailability are related to solubility, considering that the active substance must reach the blood to exert its therapeutic effect. In this regard, we investigated the Mg release at pH = 1.2, the physiological level of the stomach prior to eating, and pH = 6.8 to determine the Mg release from samples containing retardation excipients. For the sample with fast Mg release under acidic conditions, the delay in Mg release at pH = 6.8 suggests that these supplements should be taken before a meal to achieve a faster Mg release and, consequently, a higher absorption rate at the cellular level. The disaggregation studies provide valuable information regarding the time of appearance of therapeutic effect after the administration of Mg supplement, as well as the amount of Mg released from the tablet at different time intervals.

In Vitro Release Study

In vitro release of Mg from the commercial tablets was performed using an DT126 dissolution tester type II (paddle method, 100 rpm, Erweka, Langen, Germany). Six tablets of every type were placed in sinkers to avoid flotation on the media's surface. The tablets were established in 900 mL of pH 1.2 acidic medium (0.1 M HCl) preheated at 37.0 ± 0.5°C for 120 min to simulate conditions in the gastric. 35 At 5 min time intervals, samples of 5 mL were withdrawn and immediately replaced with fresh medium with the same temperature and volume. Samples were filtered with a 0.45 μm membrane filter, and Mg concentrations were analysed using a Perkin Elmer Optima 5300 DV (Norwalk, CT, USA) inductively coupled plasma optical emission spectrometer (ICP-OES).

Statistical Analysis

The design of experiment (DOE) aimed to compare the consumption of Mg pharmaceutical products during the COVID-19 pandemic and one year after. Thus, two factors were considered: the COV19 Stat factor with Cov19 and postCov19 levels, and for different human-social settlements, the Location factor with for urban (UB) and rural (RR) areas levels. Pharmaceutical products (P1 - P10) consumption was counted for 25 different pharmacies (N = 25). Univariate statistical analysis consisted of a two-way analysis of variance (ANOVA, P = 0.05) with post-hoc multiple pairwise samples mean comparison test, Dunn-Sidakwith a confidence interval of 95% (P = 0.05). The Mg dosage data was subjected to non-linear regression for two values (pH = 1.2 and pH = 6.8). This statistical analysis was performed with GraphPad Prism v5.3 (GraphPad Software, 225 Franklin Street. Fl. 26, Boston, MA 02110, USA).

Multivariate statistical analysis considered as samples the interaction factor Cov19Stat*Location levels: Cov19_UB, Cov19_RR, postCov19_UB, postCov19_RR. The variables consisted of consumption values for all pharmaceutical products (P1 - P10) counted in the pharmacies (N = 25). The multivariate approach included several methods: Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA), multivariate ANOVA MANOVA (P = 0.05) and HCA (Hierarchical Cluster Analysis). All these methods calculate comparisons between multivariate data that consist of sample multivariate profiles. Each multi-

variate profile gathers sequentially all the parameter values for the sample. The multivariate analysis was calculated and graphically designed with a custom-made application based on standardized procedures from MATLAB 2022b CWL (The MathWorks Inc., 1 Apple Hill Drive, Natick, MA 01760-2098, USA) [3].

Results and Discussion

Mg consumption

The Mg consumption of the analysed samples during the COVID-19 and post-COVID-19 periods are presented in Table II and Figure 1. Only 2% of the total body Mg is located in the extracellular fluids, and it is difficult to determine the Mg levels in the human body [1, 38]. Therefore, we considered that *in vitro* studies on the Mg release rate from the pharmaceutical dosage form and the solubility of the Mg compounds are important indicators of Mg bioavailability [2, 33].

The obtained results indicate a high consumption of supplements among rural and urban populations, considering that we considered only the most used Mg supplements. An important aspect is the higher consumption of Mg supplements in the postCov19 period in both investigated areas. A higher increase is observed in supplements where Mg is associated with B vitamins [4, 37]. One possible explanation could be that following the COVID-19 infection, many people were left with sequels affecting the peripheral or central nervous system [22, 42, 47]. This fact is reflected in the higher number of medical prescriptions issued by neurologists, compared to the COVID-19 period when the number of medical prescriptions by cardiologists was higher. Regarding the ratio between Mg consumption to the number of prescriptions, a high percentage was prescript by cardiologists, neurologists and gynaecologists (pregnant women), followed by family physicians and pharmaceutical advice [13, 17, 27]. Another important aspect regarding the consumption of Mg supplements is the advertising on TV, in pharmacies and doctor's offices. There is a strong correlation between the consumption of supplements and these advertising as the results indicate that the most used supplements benefit from such commercials.

Table II

Factor Cov19Stat: average values of Mg consumptions

Cov19 Stat	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Cov19	$105.860^{b} \pm 82.45$	$14.580^{b} \pm 12.87$	$4.540^{b} \pm 5.34$	$1.000^{b} \pm 1.56$	$21.020^{b} \pm 20.90$	$26.660^{b} \pm 32.26$	$24.280^{a} \pm 122.46$	$123.460^{b} \pm 73.04$	$14.680^{b} \pm 15.93$	$57.780^{b} \pm 25.65$
Post-Cov19	$159.200^{a} \pm 77.64$	$32.220^{a} \pm 21.66$	$6.900^{a} \pm 7.49$	$2.020^{a} \pm 3.06$	$30.920^{a} \pm 24.43$	$43.820^{a} \pm 39.84$	$24.520^{a} \pm 121.99$	$162.580^{a} \pm 73.14$	$22.120^{a} \pm 20.98$	$85.200^{a} \pm 36.41$

Different letters, that accompanies mean values, describe statistically significant different mean values across the columns. The mean values comparisons were derived from ANOVA (P = 0.05) post-hoc test, Dunn-Sidak with a confidence interval of 95% (P = 0.05) (N = 25). Data expressed as mean values ± standard deviations.

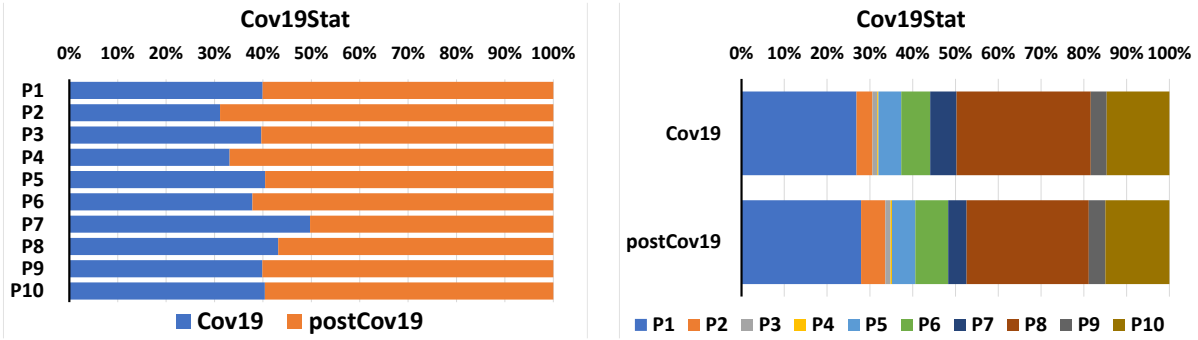

Figure 1.

The comparative consumption of Mg supplements during Cov19 and post Cov19 periods

Samples P1, P8 and P10 are the most commonly consumed supplements by the rural and urban populations during and postCov19 periods since they benefited from TV commercials and promotion in pharmacies and medical facilities. Consumption of samples 3 and 9 is significantly higher in rural areas than in urban areas, which may be related to their low price since they did not benefit from advertising on the Internet and in medical facilities. Consumption of sample P4 is reduced in both rural and urban areas, although the consumption of this supplement as well increased in the postCov19 period. In the case of sample P5, a similar consumption in rural and urban areas, but higher compared to the other samples, although this product was not advertised in the studied period. A plausible explanation could be that other products of the same brand are already familiar to the population. Sample P6 is a supplement with high consumption in both rural and urban areas, with a significant increase in the postCov19 period. In this case, these Mg supplements and other products of the same manufacturer widely used by the population mainly

for digestive disorders were advertised. The exclusive supplement of a specific pharmacy chain explains the high consumption of sample P7 in urban areas. Accordingly, the lack of consumption of this sample in rural areas is attributable to the absence of a pharmacy chain in these areas. The highest increase in the postCov19 period is observed in sample P2, both in rural and urban areas owing to high advertising on TV and in doctors' offices. Moreover, it has a complex composition associated with group B vitamins and Mg oxide. These results are also presented in Table III and Figure 2.

Table III

Factor Cov19 Stat Location: average values of Mg consumptions

Cov19 Stat* Location	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Cov19* RR	$81.010^{d} \pm 9.00$	$60.360^{a} \pm 7.77$	$29.193^{a} \pm 5.40$	$1.943^{a} \pm 1.39$	$63.490^{b} \pm 7.97$	$65.343^{a} \pm 8.08$	$0.000^{b} \pm 0.00$	$1285.043^{b} \pm 35.85$	$165.333^{c} \pm 12.86$	$586.690^{c} \pm 24.22$
Cov19* UB	$3480.440^{b} \pm 59.00$	$252.790^{b} \pm 15.90$	$5.833^{a} \pm 2.42$	$3.027^{a} \pm 1.74$	$822.477^{ab} \pm 28.68$	$1749.890^{a} \pm 41.83$	$29388.507^{ab} \pm 171.43$	$8759.907^{c} \pm 93.59$	$4.940^{bc} \pm 2.22$	$747.917^{bc} \pm 27.35$
Post-Cov19* RR	$692.073^{c} \pm 26.31$	$269.960^{a} \pm 16.43$	$53.573^{a} \pm 7.32$	$6.143^{a} \pm 2.48$	$137.917^{b} \pm 11.74$	$196.140^{a} \pm 14.00$	$0.000^{a} \pm 0.00$	$1826.177^{a} \pm 42.73$	$230.657^{a} \pm 15.19$	$1129.207^{ab} \pm 33.60$
Post-Cov19* UB	$3124.373^{a} \pm 55.90$	$645.543^{b} \pm 25.41$	$14.140^{a} \pm 3.76$	$12.740^{a} \pm 3.57$	$1080.873^{a} \pm 32.88$	$2577.083^{a} \pm 50.76$	$29129.290^{a} \pm 170.67$	$9075.657^{c} \pm 95.27$	$28.583^{ab} \pm 5.35$	$1560.823^{a} \pm 39.51$

Different letters, that accompanies mean values, describe statistically significant different mean values across the columns. The mean values comparisons were derived from ANOVA (P = 0.05) post-hoc test, Dunn-Sidak with a confidence interval of 95% (P = 0.05) (N = 50). Data expressed as mean values ± standard deviations.

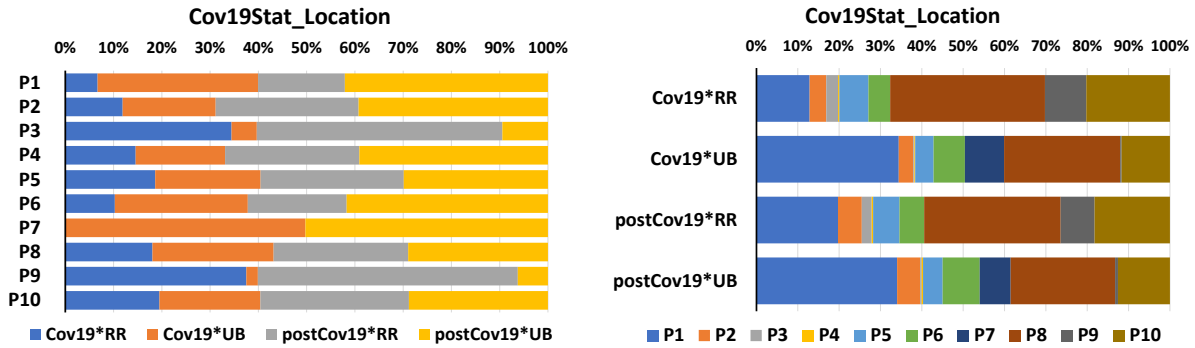

Figure 2.

The comparative consumption of Mg supplements during COVID-19 and post-COVID-19 periods in RR and UB areas

Multivariate Analysis

The design of experiment (DOE) was used to compare the Mg pharmaceutical products consumption in the Cov19 pandemic period and one year after (*i.e.*, the Cov19Stat factor levels) and for different human-social areas (*i.e.*, the Location factor levels). The main objective of the multivariate analysis is to determine the sample clusters, and for each sample which are the pharmaceutical products with dominant consumption. From the mentioned multivariate analysis sequence, only the MANOVA has statistically significant results (P = 0.05), this method giving 95% accuracy to the overall sample clustering process.

The results of PCA are presented in Table IV and Figures 3, 4, 5 and 6. According to the Kaiser-Guttman rule [20, 24], considering only the principal components with eigenvalues greater than 1, we explained cumulative variance value is 75.32%, which only implies PC1 to PC4. A total explained variance higher than 95% (that can assure high accuracy) is achieved by considering at least the first eight principal components (PC1 - PC8 gives 96.73% of the explained cumulative variance, Table IV). This situation forced the use of LDA in conjunction with MANOVA (P = 0.05) method to generate the correct number and content of sample clusters and, finally, the graphical verification with the HCA method.

Table IV

Principal component analysis (PCA) statistical results

PC	Eigenvalue	Variance (%)	Cumulative variance (%)
1	2.827	28.27	28.27
2	2.270	22.70	50.97
3	1.370	13.70	64.67
4	1.065	10.66	75.32
5	0.820	8.20	83.52
6	0.659	6.59	90.11
7	0.414	4.14	94.25

PC	Eigenvalue	Variance (%)	Cumulative variance (%)
8	0.249	2.49	96.73
9	0.175	1.75	98.48
10	0.152	1.52	100.00

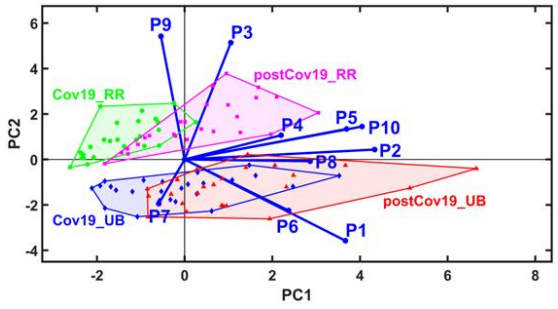

Figure 3.
Principal component analysis (PCA) biplot representation with principal axes PC1 and PC2

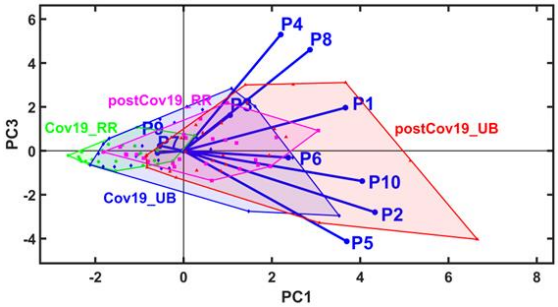

Figure 4.
Principal component analysis (PCA) biplot representation with principal axes PC1 and PC3

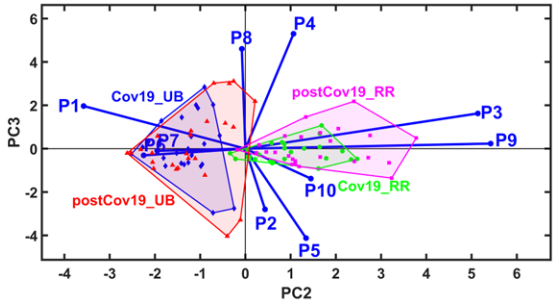

Figure 5.
Principal component analysis (PCA) biplot representation with principal axes PC2 and PC3

Figures 3, 4, 5 and 6 are the PCA bi-plots overlaying the sample groups with principal coordinates with the variable vectors. The variable vectors start in the biplot origin and point out the areas that prescribe the highest levels of the corresponding variable (*i.e.*, pharmaceutical product). Accordingly, the neighbouring areas have the lowest levels of the corresponding variable in the opposite direction of the vectors. Accordingly, the PCA method generates a qualitative relative comparison between the samples. Also, it provides information about the dominant variables that characterize the samples.

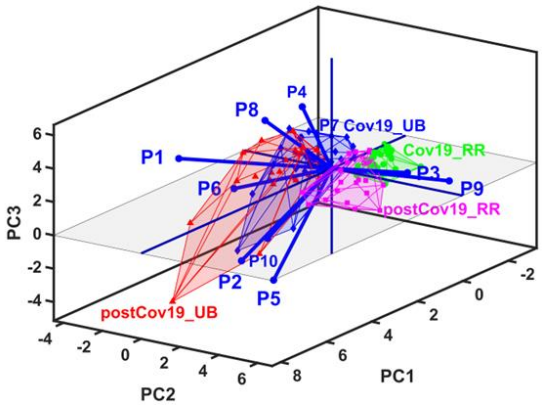

Figure 6.
Principal component analysis (PCA) 3D biplot representation with principal axes PC1, PC2 and PC3

Figure 6 shows variable grouping based on their correlation (in principal coordinates) prescribed graphically by small solid angles between their corresponding vectors. In way, the variable groups are: P2, P5 and P10; P3 and P9; P4 and P8; P1 and P6; and singletons P1 and P7. Samples Cov_19_UB with postCov19_UB are partially overlapping but are totally discriminated from Cov_19_RR and postCov19_RR, which also are partially overlapped. The variables that discriminate the Cov_19_UB and postCov19_UB samples from Cov_19_RR and postCov19_RR samples, are P1, P3, P6, P7 and P9. Variables P3 and P9 are dominant only for Cov_19_RR and postCov19_RR samples; on the other hand, variables P1, P6 and P7 are dominant only for Cov_19_UB and postCov19_UB. Variables P2, P4, P5, P8, and P10 are dominant mostly for postCov19_RR, postCov19_UB samples and partially for Cov19_UB sample.

Clustering information was generated by considering the sample principal coordinates (*i.e.*, PCA scores) as input data for LDA, MANOVA (P = 0.05) and HCA.

Linear discriminant analysis generates canonical coordinates for the samples (*i.e.*, LDA scores) and variable vectors (PC1 - PC10) *(i.e.*, LDA loadings). This multivariate method calculates the canonical coordinates to maximize the relative distances between samples; thus, it is expected to generate the proper sample clusters. LDA biplots (Figures 7, 8, 9 and 10) show small overlapping parts of Cov_19_RR and postCov19_RR samples, but large overlapping parts of Cov_19_UB and postCov19_UB samples. This fact emphasizes the possible three clusters: Cov_19_UB with postCov19_UB as a cluster and two singleton clusters: Cov_19_RR and postCov19_RR.

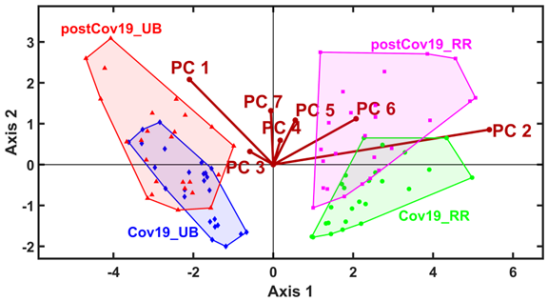

Figure 7.
Linear discriminant analysis (LDA) biplot representation with canonical axes Axis1 and Axis2

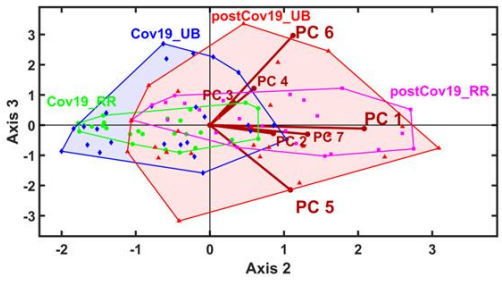

Figure 9.
Linear discriminant analysis (LDA) biplot representation with canonical axes Axis2 and Axis3

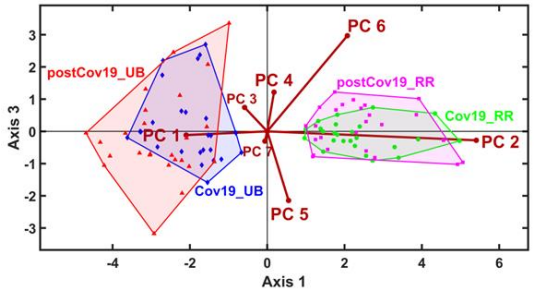

Figure 8.
Linear discriminant analysis (LDA) biplot representation with canonical axes Axis1 and Axis3

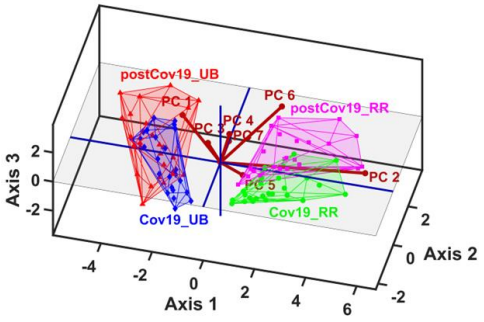

Figure 10.
Principal component analysis (LDA) 3D biplot representation with canonical axes Axis1, Axis2 and Axis3

Table V

Statistical significance values calculated with MANOVA (P = 0.05) multivariate method, from multiple pairwise comparisons of the samples (*i.e.*, the Cov19Stat factor levels) with Bonferroni correction

MANOVA, p-values	Cov19_UB	postCov19_UB	Cov19_RR	postCov19_RR
Cov19_UB	–	–	–	–
postCov19_UB	0.116	–	–	–
Cov19_RR	< 0.0001	< 0.0001	–	–
postCov19_RR	< 0.0001	< 0.0001	0.026	–

The canonical coordinates are also used by MANOVA (P = 0.05) method to generate the pairwise sample comparisons. Table V presents the statistical significances (p-values) of the pairwise sample comparisons.

The results from the *in vitro* Mg release studies showed a good correlation between the supplement with a high rate of consumption in the selected pharmacies in both rural and urban areas – Mg orotate, and the supplement with the best release rate at both pH values – Mg orotate (sample P1). The next position in terms of consumption in the urban area, but with the highest consumption rate in the rural area, is occupied by sample 8 – Mg lactate, showing a good release of Mg at pH = 6.8. For the following samples, there is no longer a good correlation between the level of consumption and the release time of Mg, which cannot be considered a positive aspect. The Mg release from the pharmaceutical dosage forms occurs as quickly as possible after administration in order to reduce irritation of the gastric mucosa and achieve the therapeutic effect in the shortest possible time after administration in patients with Mg deficiency.

The release time of Mg from the tablets depends on the excipient's nature, which explains the high differences in Mg release from samples 6 and 8, even if the Mg compound is the Mg lactate in both cases. The same result is remarked in samples P3, P4 and P9 containing Mg carbonate. So, the solubility of the Mg compound and the excipient's nature strongly affect the Mg bioavailability. The presence of certain excipients in the composition of the tablets ensures a delayed Mg release from the pharmaceutical dosage form (delaying excipients, binder, and disintegrant). In tablet manufacturing, the compression pressure force is an important factor that strongly influences mechanical properties and releases properties. Since all studied samples are in the form of tablets, the differences affecting disintegration are the nature of the Mg compound, compression excipients and the equipment used in tablet manufacturing. The results reveal significant differences in terms of Mg release at both pH = 1.2 and pH = 6.8 (Tables VI, VII, VIII, IX and X, Figures 11 and 12).

Table VI

Non-linear regressions of Mg dosage (mg) at pH = 1.2

pH = 1.2	Allosteric sigmoidal, Y = Vmax * X^h/(Khalf^h + X^h)					
	P2	**P5**	**P6**	**P8**	**P9**	**P10**
Best-fit values						
Vmax	131.5	161.7	55.76	159.5	62.26	165.7
h	2.088	2.542	2.139	1.171	1.493	2.18
Khalf	39.75	13.64	6.442	123.4	21.08	19.86
Kprime	2186	767.2	53.79	280.7	94.63	674.9
Std. Error						
Vmax	4.032	2.65	3.584	69.73	6.974	4.711
h	0.1191	0.1192	0.2804	0.1175	0.2373	0.1239
Khalf	1.885	0.29	0.4879	73.9	3.756	0.6858
Kprime	784.3	225.9	20.85	52.18	49.14	218.7
95% Confidence Intervals						
Vmax	123.2 to 139.9	156.2 to 167.3	46.99 to 64.53	13.03 to 306.0	47.61 to 76.92	155.8 to 175.5
h	1.842 to 2.334	2.292 to 2.793	1.453 to 2.825	0.9237 to 1.418	0.9941 to 1.991	1.919 to 2.440
Khalf	35.86 to 43.64	13.03 to 14.25	5.249 to 7.636	0.0 to 278.7	13.19 to 28.97	18.42 to 21.30
Kprime	567.0 to 3804	292.6 to 1242	2.777 to 104.8	171.1 to 390.4	-8.608 to 197.9	215.5 to 1134
Goodness of Fit						
Degrees of Freedom	24	18	6	18	18	18
R square	0.9944	0.9942	0.992	0.9918	0.9442	0.9922
Adjusted R square	0.9939	0.9936	0.9894	0.9909	0.938	0.9913
Sy.x	3.464	3.95	1.265	1.332	3.586	4.376

Due to variable maximum Mg dosage time stamp, there were compared two regression functions: allosteric sigmoidal and linear.
The preferred regression model was chosen based on extra sum-of-squares F test (P = 0.05).

Table VII

Non-linear regressions of Mg dosage (mg) at pH = 6.8

pH = 6.8	Allosteric sigmoidal, Y = Vmax * X^h/(Khalf^h + X^h)							
	P2	**P3**	**P4**	**P5**	**P6**	**P7**	**P9**	**P10**
Best-fit values								
Vmax	342.9	136.8	69.43	160.3	66.86	99.8	54.74	163
H	1.63	1.805	1.39	2.231	1.54	2.316	1.861	1.44
Khalf	28.39	18.89	21.01	26.79	32.18	19.23	23.94	19.96
Kprime	233.8	201.4	68.96	1534	209.6	941	369	74.51
Std. Error								
Vmax	8.871	4.12	2.973	5.179	6.134	2.061	1.065	5.5
H	0.08861	0.09679	0.08057	0.1731	0.1417	0.1429	0.0794	0.09607
Khalf	1.308	0.7943	1.514	1.188	4.383	0.5435	0.7026	1.202
Kprime	55.79	47.08	11.54	763.3	64.67	372.9	78.79	16.93
95% Confidence Intervals								
Vmax	324.6 to 361.3	128.2 to 145.5	63.18 to 75.67	149.5 to 171.0	53.97 to 79.74	95.51 to 104.1	52.53 to 56.96	151.5 to 174.4
H	1.447 to 1.813	1.602 to 2.009	1.221 to 1.560	1.871 to 2.591	1.242 to 1.837	2.019 to 2.613	1.696 to 2.027	1.240 to 1.640
Khalf	25.69 to 31.09	17.22 to 20.56	17.83 to 24.19	24.31 to 29.26	22.97 to 41.39	18.10 to 20.36	22.48 to 25.40	17.46 to 22.46
Kprime	118.6 to 348.9	102.5 to 300.3	44.72 to 93.20	-53.42 to 3122	73.74 to 345.5	165.4 to 1717	205.2 to 532.9	39.30 to 109.7
Goodness of Fit								
Degrees of Freedom	24	18	18	21	18	21	21	21
R square	0.9938	0.9928	0.9925	0.9884	0.986	0.9895	0.996	0.9885
Adjusted R square	0.9932	0.992	0.9917	0.9873	0.9845	0.9885	0.9957	0.9874
Sy.x	8.487	3.155	1.382	5.715	1.747	3.393	1.071	4.677

Due to variable maximum Mg dosage time stamp, there were compared two regression functions: allosteric sigmoidal and linear.
The preferred regression model was chosen based on extra sum-of-squares F test (P = 0.05).

Table VIII

Preferred regression model of Mg dosage (mg) at different pH levels

pH = 1.2	Straight line P7	pH = 6.8	Straight line P8
Best-fit values		**Best-fit values**	
YIntercept	56	**YIntercept**	-5
Slope	4.4	**Slope**	5.3
Std. Error		**Std. Error**	
YIntercept	2.347	**YIntercept**	0.7303
Slope	0.2968	**Slope**	0.09238
95% Confidence Intervals		**95% Confidence Intervals**	
YIntercept	49.49 to 62.51	**YIntercept**	-7.027 to -2.973
Slope	3.576 to 5.224	**Slope**	5.044 to 5.556
Goodness of Fit		**Goodness of Fit**	
Degrees of Freedom	4	**Degrees of Freedom**	4
R square	0.9821	**R square**	0.9988
Adjusted R square	0.9777	**Adjusted R square**	0.9985
Sy.x	1.818	**Sy.x**	0.5657

Table IX

Results of Mg dosage at pH = 1.2 for all time stamps

t (min)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
5	32.80^{g} ± 0.17	1.96 ± 0.07	120.00^{c} ± 4.36	56.25^{e} ± 4.39	18.00 ± 1.10	20.50 ± 1.41	78.00 ± 1.39	3.47 ± 0.49	8.70 ± 0.99	12.70 ± 0.82
10	–	2.50 ± 0.10	–	–	48.30 ± 0.82	40.10 ± 1.43	100.00^{d} ± 2.17	7.83 ± 1.31	15.60 ± 0.76	32.80 ± 1.83
15	–	15.60 ± 0.74	–	–	88.30 ± 1.18	47.90^{f} ± 0.87	–	12.11 ± 1.10	22.00 ± 3.77	55.00 ± 2.11
20	–	21.30 ± 1.39	–	–	119.00 ± 2.02	–	–	18.60 ± 1.01	28.00 ± 1.30	78.00 ± 1.30
25	–	38.00 ± 1.20	–	–	132.50 ± 0.62	–	–	20.19 ± 1.21	32.10 ± 0.80	107.00 ± 1.80
30	–	52.00 ± 0.92	–	–	147.00 ± 1.25	–	–	25.60 ± 1.59	45.60 ± 1.31	121.50 ± 1.32
60	–	88.50 ± 2.78	–	–	155.00^{b} ± 2.71	–	–	48.00^{f} ± 1.20	$50.00^{e,f}$ ± 1.14	150.00^{b} ± 1.57
90	–	111.00 ± 0.75	–	–	–	–	–	–	–	–
120	–	121.50^{c} ± 2.29	–	–	–	–	–	–	–	–

Data is expressed as mean ± standard deviation. Pairwise means comparisons were done only for the maximum values of the dosages; one way ANOVA (P = 0.05; N = 3). Different letters designate significant statistically different means.

Table X

Results of Mg dosage at pH = 6.8 for all time stamps

t (min)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
5	32.80^{g} ± 0.17	17.50 ± 0.78	15.70 ± 0.82	9.90 ± 0.10	10.90 ± 1.05	5.60 ± 0.40	9.30 ± 0.79	21.50 ± 0.66	2.10 ± 0.40	18.70 ± 0.44
10	–	52.00 ± 0.95	33.00 ± 1.44	15.70 ± 0.85	15.67 ± 1.46	9.80 ± 0.26	17.80 ± 0.30	48.00f ± 0.46	9.30 ± 0.53	47.50 ± 0.60
15	–	88.70 ± 0.78	51.00 ± 0.26	28.00 ± 0.26	32.00 ± 0.44	15.00 ± 0.52	32.50 ± 1.04	–	17.50 ± 0.95	61.00 ± 0.44
20	–	121.50 ± 0.52	69.30 ± 0.44	33.70 ± 0.20	51.30 ± 0.52	18.80 ± 0.26	52.00 ± 0.44	–	21.50 ± 0.66	78.30 ± 0.35
25	–	153.00 ± 0.98	88.00 ± 0.17	39.00 ± 0.36	73.60 ± 0.26	28.60 ± 0.26	67.00 ± 0.35	–	28.00 ± 0.62	96.00 ± 0.44
30	–	187.00 ± 0.36	98.70 ± 0.26	43.00 ± 0.26	98.00 ± 0.35	33.00 ± 0.26	75.20 ± 0.36	–	33.50 ± 0.79	111.30 ± 0.36
60	–	265.30 ± 0.46	120.00c ± 0.26	56.25^{e} ± 0.39	129.30 ± 0.35	47.90^{f} ± 0.36	88.30 ± 0.44	–	47.00 ± 0.17	128.00 ± 0.35
90	–	280.00 ± 1.73	–	–	155.00^{b} ± 2.65	–	100.00^{d} ± 1.30	–	$50.00^{e,f}$ ± 1.18	150.00^{b} ± 1.11

t (min)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
120	–	326.70[a] ± 2.95	–	–	–	–	–	–	–	–

Data is expressed as mean ± standard deviation. Pairwise means comparisons were done only for the maximum values of the dosages; one way ANOVA (P = 0.05; N = 3). Different letters designate significant statistically different means.

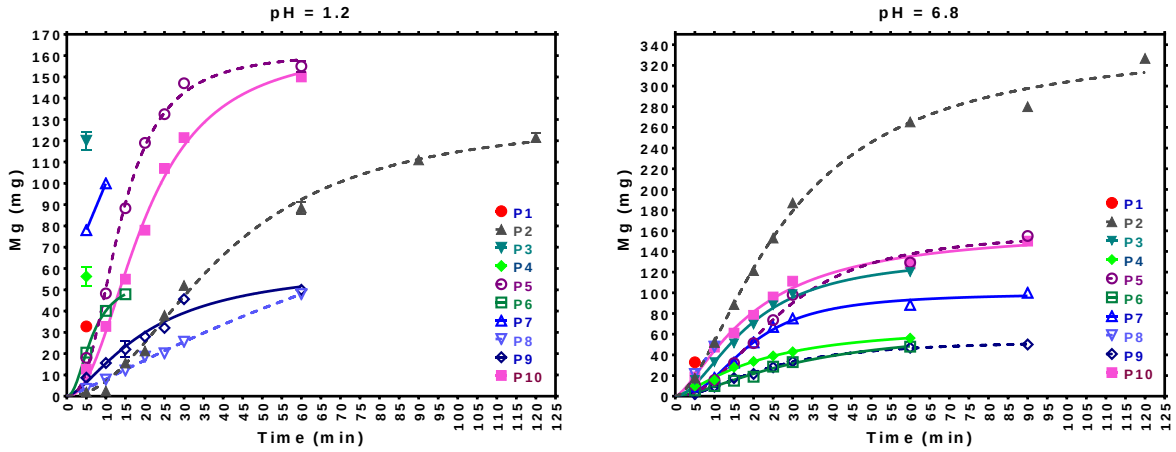

Figure 11.
Mg release from the samples P1 - P10

For sample P1, both the nature of the excipients chosen for compression and the nature of the active compound (Mg orotate) favour good Mg release at both pH values. Moreover, the Mg orotate is the supplement with the highest consumption rate in the pharmacies included in our study. This supplement also benefits from good promotion in doctor' offices, pharmacies and on media. Compared to the other studied supplements, Mg orotate is the most prescribed Mg compound by medical specialists, especially cardiologists. The positive results in improving patient outcomes who took this medicine on doctors' and pharmacists' advice led to its high consumption. The short disintegration time of the tablet from the moment of administration ensures good Mg absorption and rapid improvement of the symptoms caused by low Mg levels in the body [2, 33].

The release of Mg from sample P2 is low at both pH values, a possible explanation being related to the nature of excipients that ensure a prolonged release of the active substance (Mg oxide) from the tablet. In this case, this medical formulation is usually used for maintenance therapy and not necessarily in the acute phase when rapid restoration of the Mg level in the human body is required.

Samples P3, P4, and P9 have the same Mg compound in their composition, *e.g.*, Mg carbonate, without any excipient that delays the release of the active substance; however, there are differences in the choice of excipients used to produce the tablets. Samples 3 and 4 show an excellent Mg release from the tablet at both pH values shortly after administration. Sample P9 shows good Mg release at pH = 1.2 and low Mg release at pH = 6.8. A possible explanation for the significant difference in Mg release time from the tablets is related to the technological variables considering the same Mg compound (Mg carbonate) present in all three samples.

The excipients used for sample P5 delay the Mg release; however, a better release is observed at pH = 1.2. Similar to sample P2, these supplements are recommended in maintenance therapy, after reaching the optimal Mg level in the body and for people who do not get enough Mg by eating Mg-rich foods.

Samples P6 and P8 contain the Mg lactate and have similar or common excipients in their composition, the nature of the excipients should not significantly affect the Mg release. Sample P6 shows a good Mg release at pH = 1.2, while sample P8 shows a better release at pH = 6.8. Therefore, a possible explanation for the differences in the Mg release could be the technological variables.

Generally, the samples show good Mg release at pH = 1.2 and less satisfactory at pH = 6.8. These supplements contain water-soluble polymers that ensure the release of Mg citrate from the tablets in a relatively short time after administration at the stomach level. In the case of sample 10, we observe a long disintegration time of the tablet at both pH values, but better at gastric pH. The nature of the excipients has no adverse effect on the Mg release, a possible explanation for the delayed Mg release being the technological variables.

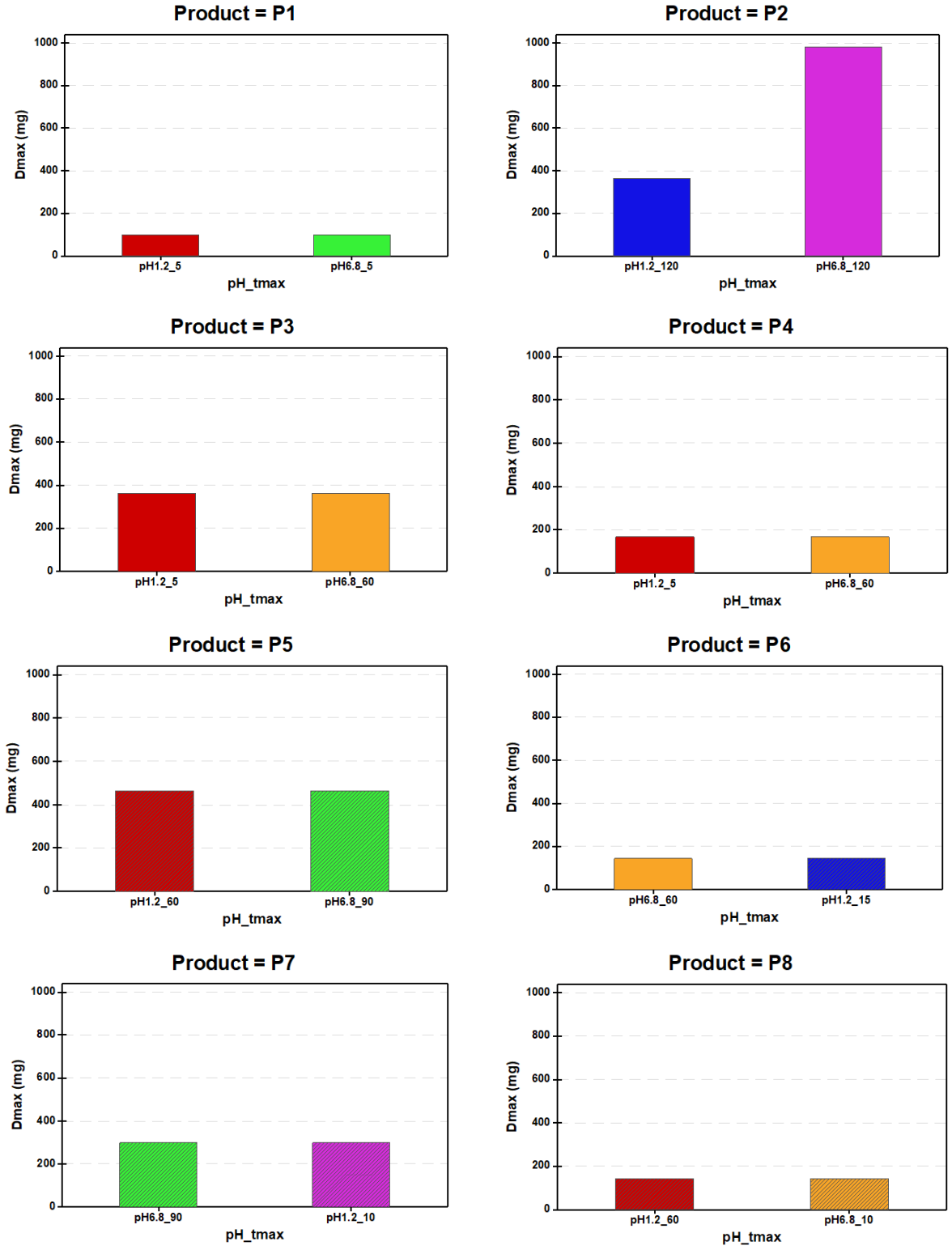

Figure 12.

Comparisons of Mg dosage for all products at maximum time stamps (tmax) at pH = 1.2 and pH = 6.8
In order to facilitate the interpretations, graphs are built up on pH tmax values

The highest increase was remarked in the case of samples P1 (169%), P2 (149%) and P6 (99%) in the rural area and P9 (161%), P4 (110%) and P2 (103%) in the urban area. During the COVID-19 and post-COVID-19 periods, the most consumed Mg supplements were sample P1 in urban and P8 in rural areas, respectively. In the case of sample P7, there is a high consumption in the urban area and a total lack of consumption of this supplement in the rural environment because it is an exclusive supplement for a chain of pharmacies that does not have pharmaceutical units in the rural environment. A good disaggregation

(approximately 5 min) of the Mg supplements was found for samples P1, P3 and P4 at pH = 1.2, which indicates a rapid therapeutic effect after oral administration and allows their use in acute treatment for the rapid restoration of Mg level in the body. The obtained results at pH = 6.8 indicate a good disaggregation for samples P1 and P8 (approximately 10 min).

At pH = 1.2, the samples with the fastest Mg release are P1 (orotate), P3 (carbonate) and P4 (carbonate) (5 min) followed by P7 (citrate) (10 min) and P6 (lactate) (15 min). These Mg supplements are recommended for an immediate effect because their absorption is appropriate at this pH value. The samples P5 (oxide), P8 (lactate), P9 (carbonate) and P10 (hydroxide) release Mg 60 min after the administration, while sample P2 (oxide) after 120 min. These Mg supplements are recommended for delayed action because the Mg release occurs later. At pH = 6.8, the samples with the fastest Mg release are P1(orotate) (5 min) and P8 (lactate) (10 min). In this case, the therapeutic effect appears quickly, these Mg supplements being indicated for an immediate effect. For a lasting effect at pH = 6.8, the samples P3 (carbonate), P4 (carbonate), P6 (lactate) (60 min), P5 (oxide), P7 (citrate), P9 (carbonate), P10 (hydroxide) (90 min) and P2 (oxide) (120 min) are recommended. Thus, concerning the pH value, the sample P1 (orotate) is the most indicated Mg supplement for an immediate effect, while the sample P2 (oxide) containing the largest amount of Mg, where the Mg release is the slowest, is indicated in the chronic treatment of the Mg deficiency in the body.

Our previous study on different mice tissue, using different Mg compounds (orotate, sulphate, oxide, chloride, carbonate, citrate) administrated by oral gavage indicates an intracellular Mg absorption differs from the results obtained *in vitro* with the same Mg compounds, but in the form of tablets and not the pure substance [34]. These results indicate that it is enough to use a compound with good intracellular absorption if it is included in an appropriate pharmaceutical dosage form, from which it can be released in a reasonable time interval to achieve the therapeutic effect [11].

The choice of Mg supplements is influenced considerably by the pharmacist's recommendation, the promotions of the producing companies, and the price. The pharmacist's recommendation is essential for people who need help deciding what to choose and those who have doubts about the best choice or have no previous experience. The friendliness and promptness of the pharmacist are factors that influence the choice of supplements by the population. As a specialist in medicine, the pharmacist recommends the Mg supplement depending on its composition and the bioavailability of each supplement, depending on the needs of the patient who addresses him. All studied Mg supplements are appropriate to be used in therapy, the difference consisting in the release of the active substance, the price and the Mg concentration in each tablet.

The *in vitro* studies on the studied Mg supplements provide valuable data related to the therapeutic effect following their administration. Since the studied supplements were produced by various manufacturers and contained different Mg compounds in various concentrations, the results delivered valuable information that medical specialists can use to attain optimal results in treating patients who need Mg supplementation. Besides, the pharmacist's knowledge regarding the excipient's nature and type of Mg compound is essential since it definitively influences the therapeutic effect and possible adverse reactions related to gastric irritation, overdose and under dosage following the administration of Mg supplements. Therefore, the pharmacist's role becomes crucial due to its unique position to help patients, considering that some use supplements without a medical prescription. In addition, pharmacists should check patient understanding, counsel efficacy, prevent non-conforming use, avoid toxicity and encourage patients to be informed about their use of food supplements [6, 21].

Even if there are studies on the Mg bioavailability from pharmaceutical forms, it is imperative to continue these studies considering that food supplements are not subject to rigorous controls as in the case of drugs. Moreover, it is important to point out the aspects related to the factors that influence bioavailability to help patients benefit from the most suitable dietary supplements.

Conclusions

The important role in the function of the human body of Mg and the factors that lead to lower Mg levels generate a high consumption of supplements containing various Mg compounds among the urban and rural populations, which are higher in the urban areas. In the post-COVID-19 period, an increase in the consumption of Mg supplements both in rural and urban areas was observed. Analysing the consumption of Mg supplements in all the pharmacies studied, high consumption is found in the case of samples P1, P8 and P10 in both the COVID-19 and post-COVID-19 periods. Depending on the excipients used to obtain the tablets, the disaggregation time increases, some supplements being used in chronic therapy to maintain the Mg level in the human body in the case of people who fail to ensure the optimal Mg level from food or who suffer from various pathologies that prevent the Mg absorption. Accordingly, only in the case of sample P1 a good disaggregation at pH = 1.2, and pH = 6.8 was remarked, accompanied by the highest consumption in the urban area. Sample P8 is the most consumed supplement in the rural area and the

second most consumed in the urban area. The rapid disaggregation of the sample P8 at pH = 6.8 makes this product frequently used to maintain the Mg level in the human body. The pharmacist's role is to recommend the Mg supplement that is most suitable for the patient according to the body's needs at the time. The choice of Mg supplement is important to make a medical specialist because many factors influence the bioavailability of Mg. Therefore, not only a specific Mg supplement is suitable because the causes a low Mg levels are different from one patient to another and often vary over time, even in the same patient. The specialists in the medical field know these aspects and the factors that positively influence the bioavailability of Mg and can recommend the best Mg supplement for each patient. Regarding the role of Mg in the body, further studies on the factors that influence the Mg absorption in the body, as well as the level of Mg in various foods considering the increasing pollution associated with the lowering of minerals in soil are required.

Acknowledgement

This work was carried out through the Core Program within the National Research Development and Innovation Plan 2022-2027, carried out with the support of MCID, project no. PN 23 05 (O.C.).

Conflict of interest

The authors declare no conflict of interest.

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