DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE
A continuous publication, open access, peer-reviewed journal
ACCESS ONLINE

ORIGINAL RESEARCH

Clinical study of the tolerability of calcium carbonate–casein microcapsules as a dietary supplement in a group of postmenopausal women

Santiago Palacios PhD, MD, Marieta Ramirez MD, Mariella Lilue MD
Palacios Institute of Women´s Health, Calle Antonio Acuña, 9, CP. 28009, Madrid, España

Abstract

Background: Calcium is an essential macronutrient; however, currently supplements are often associated with gastrointestinal (GI) adverse events. The authors investigated the tolerability of a new delivery system for calcium supplementation, based on the functionalization of calcium carbonate ($CaCO_3$) particles by casein proteins, in a randomized, prospective, double-blind, active comparator clinical trial.

Methods: Around 208 postmenopausal women were enrolled and randomized 1:1:1:1 to one of the four calcium supplements, taken for 30 days: (1) microencapsulated $CaCO_3$ (micro$CaCO_3$) with a 90:10 mineral to protein ratio; (2) micro$CaCO_3$ with a 95:5 mineral to protein ratio; (3) conventional $CaCO_3$ tablets; and (4) calcium citrate tablets (CaCitr). The Gastrointestinal Symptom Rating Scale (GSRS) questionnaire was used to evaluate the GI tolerability and the Treatment Satisfaction Questionnaire for Medication (TSQM) to analyze the satisfaction of the participants with the use of the calcium supplements.

Results: The mean GSRS scores at baseline differed among the groups from 3.95 to 5.35 without statistical significance. After 1 month use of supplements, the group given micro$CaCO_3$ with a 90:10 mineral to protein ratio, showed the lowest mean GSRS score (6.07), while the group given conventional $CaCO_3$ showed the highest score (11.86). According to the completed TSQM questionnaire, the use of supplements was easier for both micro$CaCO_3$ groups in comparison with conventional supplements.

Conclusions: The micro$CaCO_3$ supplement has shown promising results in the context of GI tolerability and patient satisfaction in the use of supplements compared to conventional calcium supplements. The reduction of GI adverse events may increase the compliance to calcium supplements especially important among groups at risk of calcium deficiency.

Keywords: casein-functionalized calcium carbonate microcapsules, dietary calcium supplements, gastrointestinal adverse events, microencapsulated calcium carbonate, postmenopausal women.

Citation

Palacios S, Ramirez M, Lilue M. Clinical study of the tolerability of calcium carbonate–casein microcapsules as a dietary supplement in a group of postmenopausal women. Drugs in Context 2020; 9: 2020-1-4. DOI: 10.7573/dic.2020-1-4

Introduction

Calcium is an essential macronutrient required by humans that must be provided by the diet. It is a basic constituent of hydroxyapatite crystals, the mineral component of bones. Insufficient calcium accrual, leading to a suboptimal bone mass peak and low bone mineralization, is an important factor that leads to osteoporosis and fractures.[1] An important population group at risk for dietary calcium deficiency is postmenopausal women, whose estrogen deficiency impairs the bone turnover cycle, leading to a disproportionate increase in bone resorption compared with formation.[2] The average reduction in bone mass density (BMD) is about 10% during the menopausal transition period, with an average loss of 200 mg of daily calcium in the first 3–4 years.[3,4] Osteoporosis is the most prevalent disease in postmenopausal women, and is strongly associated with low quality of life. The International Osteoporosis Foundation estimated that approximately 30% of all postmenopausal women have osteoporosis in Europe and in the USA, and at least 40% of these women will experience one or more fragility fractures in their remaining lifetime.[5] The major goals of treatment for osteoporosis are the prevention of fractures and the maintenance or increase in BMD by consumption of an adequate amount of dietary calcium.[3] The recommended daily calcium intake for postmenopausal women is 1200 mg, and calcium supplementation is usually required to correct the deficiency and guarantee an appropriate daily intake of calcium.[3,6]

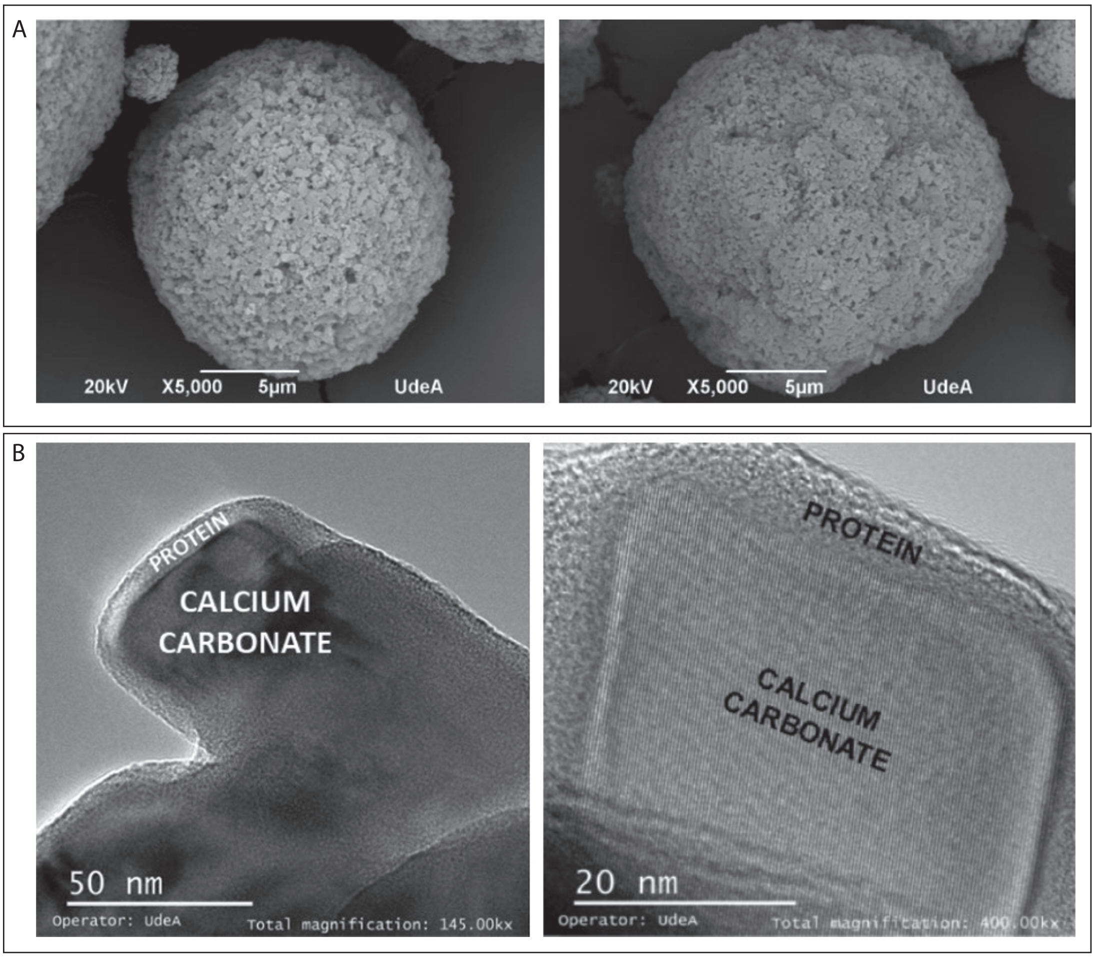
ISSN: 1740-4398

The currently most used calcium dietary supplements are calcium carbonate ($CaCO_3$) and calcium citrate (CaCitr), which are often associated with gastrointestinal (GI) adverse events such as constipation, excessive abdominal cramping, bloating, abdominal pain, or diarrhea.[7] Specifically, they are related to a high release rate of carbon dioxide when $CaCO_3$ particles are subjected to gastric acidic conditions.[8] The inconvenience and the frequency of such adverse events appear to contribute to low compliance.[9] Therefore, a new delivery system for calcium supplements is highly desirable to reduce $CaCO_3$ ionization in the stomach and the associated adverse events, which could increase the compliance to calcium supplements especially among the population at risk of calcium deficiency.

Controlled delivery systems, such as microcapsules, are promising candidates for encapsulating, delivering, and controllably releasing active ingredients including drugs and dietary supplements.[10–14] In the development of innovative controlled-release systems, the use of natural polymers derived from biological systems, including protein, DNA, lipids and polysaccharides, holds much promise as biocompatible and biodegradable options.[15–19] They have favorable pharmacokinetics and low toxicity.[10] Casein, the major milk protein, is an inexpensive, non-toxic, and highly stable biomolecule with structural and physicochemical properties, which facilitate its use as a natural polymer for controlled release.[20,21] Properties that facilitate the use of caseins as drug-delivery agents include binding to ions and small molecules, surface-active and stabilizing properties, self-assembly properties, and excellent gelation and water-binding capacities.[21]

The authors postulated that microencapsulation of $CaCO_3$ particles by a natural polymer such as casein protein should reduce and slow down the ionization of $CaCO_3$ under gastric acidic conditions, preventing the associated adverse GI symptoms, compared to bared $CaCO_3$ particles. Taking advantage of the suitable properties of the casein as a coating material, $CaCO_3$ particle surface was functionalized with sodium caseinate by an ionic gelation process followed by spray drying as described by Casanova and coworkers.[22] Two types of microcapsules, with different mineral to protein ratios, were studied (i.e. 95:5 and 90:10 ratios). Figure 1 shows

Figure 1. Electron microscope images of 95:5 (left) and 90:10 (right) systems. A. Scanning electron microscope images correspond to aggregates of primary particles (size: 3–15 µm). B. Transmission electron microscope images correspond to primary particles (size: 50–400 nm).



electron microscope images for both systems. Scanning electron microscope images indicate the formation of spherical aggregates of primary calcium carbonate particles sizing 3–15 µm (Figure 1A). The 95:5 system had an average particle size (d32) of 7.5 µm, whereas the 90:10 system showed a value of 9.0 µm. The transmission electron microscope image of both systems revealed the presence of a continuous milk protein layer covering the calcium carbonate particles with a thickness between 5 and 8 nm (Figure 1B). The dissolution study, following Method 701 USP, of $CaCO_3$ systems demonstrated that micro$CaCO_3$ particles 90:10 had the lowest solubilization grade (i.e. 63%) in comparison with the micro$CaCO_3$ particles 95:5 or the bared $CaCO_3$ particles, having values of 81 and 96%, respectively.

Herein, the authors report the use of this new calcium delivery system, used as a dietary supplement in a group of healthy postmenopausal women with a low intake of dietary calcium. The primary objective of the study was to evaluate the GI tolerability of micro$CaCO_3$. The secondary objectives comprised the comparison of the GI tolerability and the efficacy between micro$CaCO_3$ and the conventional supplements of $CaCO_3$ and CaCitr. In this work, the authors described the results related to the GI tolerability and patient satisfaction after 1-month usage of dietary calcium supplements.

Methods

Study design and study population

The study was a randomized, prospective, double-blind clinical trial (CALCIMIP, NCT03452696) that compared micro$CaCO_3$ with standardized $CaCO_3$, and CaCitr salts. A group of 208 healthy postmenopausal women was consecutively recruited for 6 months by a gynecologist from the medical center specialized in women health at the Instituto Palacios located in Madrid, Spain. The main inclusion criteria of the study consisted of postmenopausal females (postmenopausal criteria: older than 45 years with amenorrhea for at least 1 year) between 45 and 70 years old, low daily intake of dietary calcium (<900 mg/day),[23] and no presence of any pathologies that would prevent participation in the study according to the study protocol. Eligible participants were also required to be able to read and understand the informed consent form. Exclusion criteria included hypersensitivity to the active substances to test (i.e. calcium carbonate or calcium citrate) or to any of the excipients (i.e. milk proteins or added flavors), renal insufficiency, history of kidney or urinary stones, use in the last month of diuretics (furosemide, ethacrynic acid), aluminum salts, and/or thyroid hormones, or use of any other drug or experimental device during the 30 days prior to the selection.

The protocol was approved on April 20, 2018, by the Ethics Committee of clinical research of the Princess University Hospital, located in Madrid in Diego de León, 62 (CP: 28006). The study was performed in accordance with the Helsinki Declaration (1964) and subsequent amendments and with current Spanish regulations (Real Decreto 1090/2015, 4th December; Circular 07/2004 on research with health products), Good Clinical Practices standards and code of ethics. All participants volunteered for the study and signed an informed consent form. No personal data were recorded to guarantee the confidentiality of the participants' data.

Dietary supplements

Eligible participants were randomized to one of the four calcium supplements arms depicted in Table 1 in a 1:1:1:1 proportion.

Intervention procedures

Participants, who met the initial eligibility criteria and agreed to participate in the study, attended two visits. During Visit 1, inclusion and exclusion criteria were confirmed while participants were informed about all the aspects related to the study and signed the informed consent form. The medical history of the participants was gathered including any health conditions and current treatment. A physical exploration comprising

Table 1. Type of calcium supplements, their content, and the total daily intake of element calcium per treatment arm.

Treatment arm	Type of calcium supplement	Content per tablet	Tablets per day	Total daily intake of elemental calcium (mg)
Arm A	Micro$CaCO_3$ oral chewable tablet	• Protein: 10% • $CaCO_3$: 90% • Elemental calcium: 500 mg	2	1000
Arm B	Micro$CaCO_3$ oral chewable tablet	• Protein: 5% • $CaCO_3$: 95% • Elemental calcium: 500 mg	2	1000
Arm C	$CaCO_3$ oral chewable tablet	• Elemental calcium: 500 mg	2	1000
Arm D	CaCitr oral chewable tablet	• Elemental calcium: 315 mg	3	945

CaCitr, calcium citrate; $CaCO_3$, calcium carbonate; micro$CaCO_3$, microencapsulated calcium carbonate.

weight, height, blood pressure, and heart rate was performed together with the determination of vitamin D status. A vitamin D supplement was prescribed in case participants showed levels of vitamin D below 30 ng/mL. To evaluate GI tolerability, participants were asked to fill in the Spanish version of the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire. The scale is a disease-specific instrument of 15 items combined into 5 symptom clusters, such as reflux, abdominal pain, indigestion, diarrhea, and constipation. The GSRS has a 7-point graded Likert-type scale where 1 represents the absence of troublesome symptoms and 7 represents very troublesome symptoms. Its reliability and validity are well documented.[24]

After 30 days, physical exploration was performed during Visit 2. Data of adverse events and concomitant medication were also gathered. Participants filled in again the GSRS questionnaire, and their satisfaction with the calcium supplements was self-reported by completing the Spanish version of the Treatment Satisfaction Questionnaire for Medication (TSQM). This is a widely used generic measure of satisfaction with medication that has a Likert-type scale from 1 (extremely dissatisfied) to 7 (extremely satisfied).[25] Only the results obtained by both questionnaires related to the GI tolerability and the satisfaction with the use of calcium supplements are discussed subsequently.

Study outcomes and statistical analysis

The primary outcome was defined as the prevalence of patients who reported GI symptoms during the second visit per arm of treatment. The secondary outcome was defined as the prevalence of participants with GI symptoms in the A and B treatment arms compared with the C and D treatment arms in Visit 2. The scores of the questionnaire GSRS provided by the participants were analyzed to determine both outcomes. For the primary outcome, the scores of the GSRS of both visits were analyzed per arm treatment, while for the secondary outcome, the GSRS scores of the four treatment arms from the second visit were comparatively analyzed.

The satisfaction grade of the participants with the usage of calcium supplements was analyzed as an exploratory outcome. The scores of the questionnaire TSQM were analyzed to compare the results between the treatment arms.

Sample size and statistical analysis

The sample size calculation was based on a similar study.[26] The present randomized, double-blind clinical trial was powered considering a type I error (α) of 0.05 and type II error (β) of 0.20 (power was 80%). Additionally, 20% of dropouts were expected; therefore, more than 30 women in each group were recruited as a precaution. Data were analyzed using the analysis of variance (ANOVA) test to detect statistical differences. A *p*-value < 0.01 was considered statistically significant. The results were expressed as mean values ± standard deviation (SD) and calculated based on a per-protocol analysis.

Results

A total of 208 participants were recruited, and 177 finished the study. The age of the participants was between 45 and 72 years (59.5±6.6 years). The participants were randomized to one of the four treatment arms shown in Figure 2. In total, 31 women ceased participation in the study. In the group using micro$CaCO_3$ (arm A), 7 women discontinued because of the recommendation of their physician and none of them due to adverse events caused by the supplement. In the other three treatment arms, the main reason for discontinuation was GI symptoms and the difficulty of chewing the tablet. In total, 12 women interrupted the study because of GI adverse events taking micro$CaCO_3$ 95:5 (arm B: 6), $CaCO_3$ supplement (arm C: 4), or CaCitr (arm D: 2).

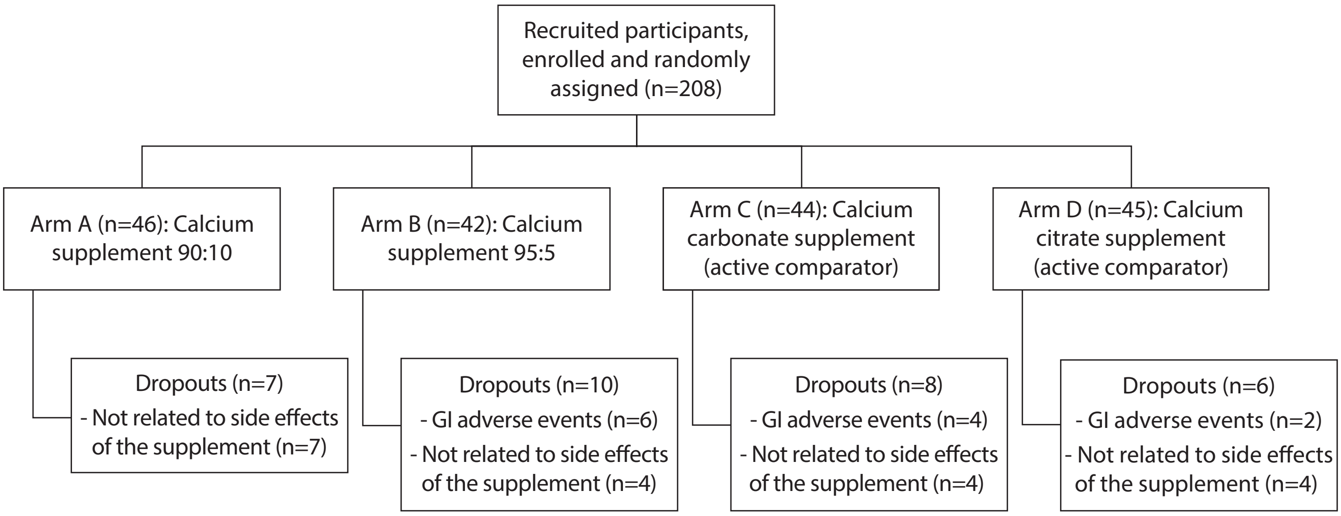
For all participants, age and clinical data including calcium intake, the mean arterial pressure (MAT), and the body mass index (BMI) were collected. In Table 2, the different variables are presented as an average per treatment group with no statistically significant differences between them ($p>0.01$) according to the ANOVA test. The women of arm A were on average the oldest participants (60.85 years), while the women in group B were the youngest (57.24 years). The lowest mean BMI corresponded to group D (26.77 kg/m^2), and was highest in group C (30.28 kg/m^2). MAT was overall the same in all the groups, at around 90 mmHg. Related to the dietary calcium intake, group D had the highest intake of calcium with an average of 701.4 mg/day, and group A the lowest with 638.61 mg/day.

For the study of the evolution of the GSRS questionnaire between the treatments, the two-way ANOVA test was performed on two factors (time and supplement) with repeated measures in one of them (supplement). The results showed a significant effect on GSRS score before and after the use of the supplements, independently of the treatment ($F=40.76$; $p<0.001$). The interaction between the type of treatment and the changes in the GSRS score was also significant ($F=4.03$; $p=0.008$), indicating the influence of the type of supplement on the evolution of the GSRS score.

The tolerability of the calcium supplements was evaluated by comparison of the mean score of the GSRS survey from Visit 1 and Visit 2 per treatment arm (Table 3). In Visit 1, the overall score in all arms was between 3.95 and 5.35, while in the Visit 2, higher scores were reported in the B, C, and D groups. The highest score was reported in the group treated with conventional $CaCO_3$ (arm C: 11.86). The groups treated with micro$CaCO_3$ 95:5 or CaCitr had a score of 9.5, while group A had the lowest score (6.07) with an insignificant increase of the mean GSRS score of −0.72 ($p=0.628$) between the two visits. In the other treatment groups, the absolute difference of GSRS score between Visit 2 and 1 was >5 points, with arm C being the highest difference of −7.91 ($p<0.001$; Table 3).

The difference in mean GSRS score among treatment arms before the use of supplements was minimal ($p=1$). However, after 30 days of supplement consumption, the difference of mean GSRS

Figure 2. Participants in the randomized, double-blind clinical trial, the number of dropouts, and the reasons for dropout in each of the treatment arms.



GI, gastrointestinal.

Table 2. Age and clinical data of the 177 participants gathered during Visit 1.

	Treatment arm, mean (SD)				*F*(3;173)	*p*-value
	A	**B**	**C**	**D**		
Age, y	60.85 (7.02)	57.24 (6.77)	60.27 (5.8)	59.47 (6.3)	2.568	0.056
Calcium intake, mg/day	638.61 (185.23)	650.93 (181.4)	664.7 (158.18)	701.4 (139.54)	1.193	0.314
MAP, mmHg	89.98 (13.34)	90.62 (6.61)	91.91 (6.48)	91.24 (5.24)	0.416	0.742
BMI, kg/m^2	28.73 (10.05)	27.07 (4.39)	30.28 (16.15)	26.77 (5.12)	1.137	0.336

Treatments arms definition: A, micro$CaCO_3$ 90:10; B, micro$CaCO_3$ 95:5; C, $CaCO_3$; D, CaCitr.
BMI, body mass index; MAP, mean arterial pressure; SD: standard deviation; y = years.

Table 3. Mean GSRS score in Visit 1 and Visit 2 and differences between them per treatment arm.

GSRS	Mean score (SD)			
	Visit 1, Mean (SD)	**Visit 2, Mean (SD)**	**Difference Visit 1–Visit 2**	***p*-value**
Treatment arm				
A	5.35 (7.06)	6.07 (7.03)	−0.72	0.628
B	4.29 (5.52)	9.57 (9.57)	−5.29	0.001
C	3.95 (5.63)	11.86 (11.85)	−7.91	<0.001
D	4.20 (4.68)	9.51 (9.00)	−5.23	<0.001
Total	4.46 (5.77)	9.21 (9.64)		

Treatment arms definition: A, micro$CaCO_3$ 90:10; B, Micro$CaCO_3$ 95:5; C, $CaCO_3$; D, CaCitr.
GSRS, Gastrointestinal Symptom Rating Scale; SD, standard deviation.

Table 4. Mean TSQM scores of the most relevant questions per treatment arm.

	Mean score (SD)				*F*(3;173)	*p*-value
	A	B	C	D		
TSQM_Q9	4.87 (1.48)	4.93 (1.33)	3.91 (1.41)	3.42 (1.37)	12.328	<0.001
TSQM_Q10	4.96 (1.38)	5.07 (1.18)	4.32 (1.44)	4.07 (1.27)	5.990	0.001
TSQM_Q14	5.02 (1.24)	5.24 (0.91)	4.64 (0.97)	4.27 (1.51)	5.744	0.001

Treatment arms definition: A, micro$CaCO_3$ 90:10; B, Micro$CaCO_3$ 95:5; C, $CaCO_3$; D, CaCitr.
TSQM_Q9: How easy or difficult is it to use the medication in its current form?; TSQM_Q10: How easy or difficult is it to plan when you will use the medication each time?; TSQM_Q14: Taking all things into account, how satisfied or dissatisfied are you with this medication?
Answers for TSQM: extremely difficult 1, very difficult 2, difficult 3, somewhat easy 4, easy 5, very easy 6, extremely easy 7.
TSQM, Treatment Satisfaction Questionnaire for Medication.

score of arms A and B compared with arms C and D were more pronounced. The comparison of GSRS scores of micro$CaCO_3$ 90:10 (arm A) with the rest of supplements showed the most remarkable differences, being the highest when arm A was compared to conventional $CaCO_3$ (–5.80; $p=0.025$). Mean difference between arms A and B was –3.51 and between arms A and D was –3.45. Mean differences in GSRS score between women using micro$CaCO_3$ 95:5 (arm B) and conventional supplements (i.e. arms C and D) were smaller (–2.29 and 0.06, respectively).

As an exploratory outcome, the results of the TSQM questionnaire were compared. This survey, generally, is designed for patients with chronic diseases who take medication to control the disease and its symptoms. In this case, the participants only answered three relevant questions related to the use of dietary supplements. The questions, referred in Table 4, were: Question 9: "How easy or difficult is it to use the medication in its current form?" Question 10: "How easy or difficult is it to plan when you will use the medication each time?" and Question 14: "Taking all things into account, how satisfied or dissatisfied are you with this medication?" For the three questions, statistically significant differences were found between the treatment arms (Table 4). Overall, the best mean score (SD) in TSQM was observed in treatment groups using a micro$CaCO_3$ supplement. While arms A and B had the best results, arm D was the lowest score in this questionnaire. As an average, participants taking micro$CaCO_3$ (arms A and B) considered that it was easy (4.87 [1.48] and 4.93 [1.33], respectively) to take the supplements in comparison with the participants taking $CaCO_3$ and CaCitr, which answered that using the supplement was only somewhat easy (3.91 [1.41]) and difficult (3.42 [1.37]), respectively. The participants treated with micro$CaCO_3$ supplement agreed that it was easy (4.96 [1.38] and 5.07 [1.18]) to plan to use the supplement, while the women treated with $CaCO_3$ or CaCitr agreed that it was only somewhat easy (4.32 [1.44] and 4.07 [1.27]). The answers for the general question about overall satisfaction with the supplements (Q14) showed smaller differences: CaCitr supplement had the lowest mean score, somewhat satisfied (4.27 [1.51]) compared to satisfied (5.02 [1.24], 5.24 [0.91], and 4.64 [0.97]) in the other three treatment arms (Table 4).

The comparison of TSQM scores of arm A with other supplement arms provided relevant insight into the satisfaction in the use of the new formulation of calcium supplement. For question 9, the mean difference of the score between the micro$CaCO_3$ supplement (arm A) and conventional $CaCO_3$ (arm C) was 0.96 ($p=0.008$) and with CaCitr, it was 1.45 ($p<0.001$). For question 10, a mean score difference of 0.64 ($p=0.105$) for $CaCO_3$ and of 0.89 ($p=0.009$) for CaCitr compared to arm A was calculated. Question 14 also showed a significant difference in the overall satisfaction between groups A and D (0.76; $p=0.015$). Between the two types of micro$CaCO_3$ supplements, there were no significant differences in any of the questions ($p \sim 1$).

Discussion

The authors evaluated the GI tolerability profile of micro$CaCO_3$ with a 90:10 mineral to protein ratio and 95:5 mineral to protein ratio in postmenopausal women compared with conventional $CaCO_3$ and CaCitr. Their findings showed that supplementation with micro$CaCO_3$, after 30 days, produced fewer GI adverse events compared to conventional calcium supplements. Therefore, the microencapsulation of $CaCO_3$ particles by casein protein helps to reduce the formation of carbon dioxide in the stomach and prevent the associated adverse GI symptoms. Between the two types of microcapsules with different mineral to protein ratios, the GSRS score was lower among the women using micro$CaCO_3$ 90:10. These results are, also, in concordance with the dissolution test results that indicated the lowest solubilization grade under acidic conditions for the micro$CaCO_3$ 90:10 in comparison with the micro$CaCO_3$ 95:5 system.

The GI adverse events associated with calcium supplements impact negatively on long-term compliance, which may limit their effectiveness.[9] The better GI tolerability observed with the use of this new delivery system may contribute to successful compliance in target groups, especially in those with health problems where the GI symptoms could worsen their clinical conditions.[27,28] In chronic asymptomatic diseases as osteoporosis, overcoming non-adherence presents a challenge. According to recent studies concerning the treatment of osteoporosis, adherence to long-term calcium and vitamin D supplementation varies between 30 and 75%.[29] Beyond side effects, convenience and satisfaction in the use of supplementation are key aspects in order to increase compliance. The results from the TSQM questionnaire revealed that the micro$CaCO_3$ 90:10 delivery system was easy and satisfactory to use compared to conventional supplements. Those two factors may be important for successful adherence to calcium supplements in postmenopausal women and therefore to reduce their risk of fractures.[30]

The principal limitation of this study was the lack of gathered clinical data related to the presence or absence of GI adverse events after the use of supplements, beyond the patient-reported outcomes via the GSRS questionnaire. Moreover, the study was performed with a small sample and for a short period of time. In order to confirm the good GI tolerability of the micro$CaCO_3$ supplement, a long-term study with a bigger sample size should be performed.

The positive result of the micro$CaCO_3$ supplement in postmenopausal women could encourage a study using this type of delivery system in different risk groups with additional calcium requirements, such as individuals over 50 years to prevent fractures and bone loss[28] or individuals with high risk of cancer in the digestive system, especially colorectal cancer.[6,31]

Conclusions

The micro$CaCO_3$ delivery system showed promising results in both questionnaires, GSRS and TSQM, compared with the conventional supplements, $CaCO_3$ and CaCitr. The participants who took micro$CaCO_3$ supplement reported fewer GI adverse events and were more satisfied than those using calcium supplements. The fewer GI adverse events associated especially with the use of micro$CaCO_3$, with a mineral to protein ratio 90:10, might facilitate increased adherence to calcium supplementation, especially important among the groups at risk of calcium deficiency as postmenopausal women.

Contributions: All authors contributed extensively to the work presented in this paper. All authors have contributed significantly to the conception, design, or acquisition of data, or analysis and interpretation of data. All authors have participated in in drafting, reviewing, and/or revising the manuscript and have approved its submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: This work was supported by Nexentia S.A.S. The authors have no other conflict of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at https://www.drugsincontext.com/wp-content/uploads/2020/03/dic.2020-1-4-COI.pdf

Acknowledgements: The authors would like to thank to Dr Herley Casanova and Msc Jorge Jaimes (Colloids Group, University of Antioquia, Medellín, Colombia) for providing SEM and TEM images and relevant physicohemical properties of calcium carbonate microcapsules. Writing and editorial assistance was provided by Content Ed Net (Madrid, Spain).

Funding declaration: This work was supported by Colciencias-Sumicol S.A., University of Antioquia Grant 1115-562-38446 Cto 0162-2014 and Nexentia S.A.S. Writing and editorial assistance was funded by Nexentia S.A.S.

Article URL: https://www.drugsincontext.com/clinical-study-of-the-tolerability-of-calcium-carbonate-casein-microcapsules-as-a-dietary-supplement-in-a-group-of-postmenopausal-women

Correspondence: Santiago Palacios, Palacios Institute of Women´s Health, Calle Antonio Acuña, 9, CP. 28009, Madrid, Spain. spalacios@institutopalacios.com

Provenance: submitted; externally peer reviewed.

Submitted: 31 January 2020; **Peer review comments to author:** 20 February 2020; **Revised manuscript received:** 19 March 2020; **Accepted:** 20 March 2020; **Publication date:** 23 April 2020.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editor-in-Chief gordon.mallarkey@bioexcelpublishing.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Cano A, Chedraui P, Goulis DG, et al. Calcium in the prevention of postmenopausal osteoporosis: EMAS clinical guide. *Maturitas* 2018;107:7–12. https://doi.org/10.1016/j.maturitas.2017.10.004
2. Beto JA. The role of calcium in human aging. *Clin Nutr Res*. 2015;4:1–8. https://doi.org/10.7762/cnr.2015.4.1.1
3. Tella SH, Gallagher JC. Prevention and treatment of postmenopausal osteoporosis. *J Steroid Biochem Mol Biol*. 2014;142:155–170. https://doi.org/10.1016/j.jsbmb.2013.09.008
4. Ji M-X, Yu Q. Primary osteoporosis in postmenopausal women. *Chronic Dis Transl Med*. 2015;1:9–13. https://doi.org/10.1016/j.cdtm.2015.02.006
5. IOF. Epidemiology. International Osteoporosis Foundation. *Epidemiology* 2015. https://www.iofbonehealth.org/epidemiology. Accessed April 2020.
6. Cho E, Smith-Warner SA, Spiegelman D, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. https://doi.org/10.1093/jnci/djh185
7. Lewis JR, Zhu K, Prince RL. Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. *J Bone Miner Res*. 2012;27:719–722. https://doi.org/10.1002/jbmr.1484
8. Weerapol Y, Cheewatanakornkool K, Sriamornsak P. Impact of gastric pH and dietary fiber on calcium availability of various calcium salts. *Sci Tech J*. 2010;4(1):15-23.
9. Reid IR, Mason B, Horne A, et al. Randomized controlled trial of calcium in healthy older women. *Am J Med*. 2006;119:777–785. https://doi.org/10.1016/j.amjmed.2006.02.038
10. Zhang Y, Chan HF, Leong KW. Advanced materials and processing for drug delivery: the past and the future. *Adv Drug Deliv Rev*. 2013;65(1):104-120. https://doi.org/10.1016/j.addr.2012.10.003
11. Glowka E, Stasiak J, Lulek J, et al. Drug delivery systems for Vitamin D supplementation and therapy. *Pharmaceutics* 2019;11:347. https://doi.org/10.3390/pharmaceutics11070347
12. Wells AJ, Hoffman JR, Gonzalez AM, et al. Effects of 28-days ingestion of a slow-release energy supplement versus placebo on hematological and cardiovascular measures of health. *J Int Soc Sports Nutr*. 2014;11:59. https://doi.org/10.1186/S12970-014-0059-2
13. Sarao LK, Arora M. Probiotics, prebiotics, and microencapsulation: a review. *Crit Rev Food Sci Nutr*. 2017;57:344–371. https://doi.org/10.1080/10408398.2014.887055
14. Jampilek J, Kos J, Kralova K. Potential of nanomaterial applications in dietary supplements and foods for special medical purposes. *Nanomater (Basel, Switzerland)* 2019;9. https://doi.org/10.3390/nano9020296
15. Yingchoncharoen P, Kalinowski DS, Richardson DR. Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come. *Pharmacol Rev*. 2016;68:701–787. https://doi.org/10.1124/pr.115.012070
16. Zhang Y, Sun T, Jiang C. Biomacromolecules as carriers in drug delivery and tissue engineering. *Acta Pharm Sin B*. 2018;8:34–50. https://doi.org/10.1016/j.apsb.2017.11.005
17. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. *Chem Rev*. 2016;116:2602–2663. https://doi.org/10.1021/acs.chemrev.5b00346
18. Lohcharoenkal W, Wang L, Chen YC, Rojanasakul Y. Protein nanoparticles as drug delivery carriers for cancer therapy. *Biomed Res Int*. 2014;2014:1–12. https://doi.org/10.1155/2014/180549
19. Kaczmarek B, Sionkowska A. Drug release from porous matrixes based on natural polymers. *Curr Pharm Biotechnol*. 2017;18: 721–729. https://doi.org/10.2174/1389201018666171103141347
20. Livney YD. Milk proteins as vehicles for bioactives. *Curr Opin Colloid Interface Sci*. 2010;15:73–83. https://doi.org/10.1016/J.COCIS.2009.11.002
21. Elzoghby AO, Abo El-Fotoh WS, Elgindy NA. Casein-based formulations as promising controlled release drug delivery systems. *J Control Release*. 2011;153(3):206–216. https://doi.org/10.1016/j.jconrel.2011.02.010.
22. Casanova HF, Perez Zapata C, Restrepo C, Arango JD. Ionic gelation on solids. US20160271071A1. October 2, 2018.
23. Cormick G, Belizán JM. Calcium intake and health. *Nutrients* 2019;11(7):1606. https://doi.org/10.3390/nu11071606
24. Kulich KR, Madisch A, Pacini F, et al. Reliability and validity of the Gastrointestinal Symptom Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire in dyspepsia: a six-country study. *Health Qual Life Outcomes* 2008;6:12. https://doi.org/10.1186/1477-7525-6-12
25. Candia V, Ríos-Castillo I, Carrera-Gil F, et al. Effect of various calcium salts on non-heme iron bioavailability in fasted women of childbearing age. *J Trace Elem Med Biol*. 2018;49:8–12. https://doi.org/10.1016/j.jtemb.2018.04.029
26. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes*. 2004;2:12. https://doi.org/10.1186/1477-7525-2-12

27. Heaney RP. Calcium supplements: practical considerations. *Osteoporos Int*. 1991;1:65–71. https://doi.org/10.1007/BF01880445
28. Tang BM, Eslick GD, Nowson C, et al. Use of calcium or calcium in combination with Vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007;370:657–666. https://doi.org/10.1016/S0140-6736(07)61342-7
29. Touskova T, Vytrisalova M, Palicka V, et al. Patterns of non-adherence to supplementation with calcium and Vitamin D in persistent postmenopausal women are similar at start and 1 year later: a qualitative longitudinal study. *Front Pharmacol*. 2016;7. https://doi.org/10.3389/fphar.2016.00339
30. Spangler M, Phillips BB, Ross MB, Moores KG. Calcium supplementation in postmenopausal women to reduce the risk of osteoporotic fractures. *Am J Health Syst Pharm*. 2011;68:309–318. https://doi.org/10.2146/ajhp070175
31. Park Y, Leitzmann MF, Subar AF, et al. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med*. 2009;169(4):391–401. https://doi.org/10.1001/archinternmed.2008.578