A Comparison of DiMaCal™ to Calcium Carbonate

Introduction

According to the National Osteoporosis Foundation, osteoporosis is a major public health threat for an estimated 44 million Americans or 55 percent of the people 50 years of age and older. In the U.S. today, 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis. In 2005, osteoporosis-related fractures were responsible for an estimated $19 billion in costs. By 2025, experts predict that these costs will rise to approximately $25.3 billion (www.nof.org).

Adequate calcium intake is necessary for bone remodeling to take place in healthy individuals. In older adults adequate calcium intake can slow bone loss and lower the risk of fracture (Lin and Lane, Clin. Orthop. 425:126-134,2004). Furthermore, calcium supplementation is an important part of the medical management of osteoporosis in combination with various prescription medications.

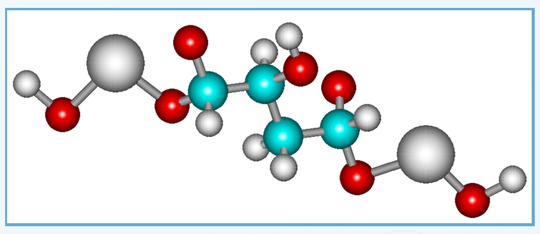
Calcium bioavailability is important when calcium intakes are low, or when an individual is growing or losing bone (Fairweather-Tait and Teucher, Nutr. Rev. 60:360-367,2002). Calcium absorption is dependent on many dietary and other environmental factors, including level of protein, sodium, caffeine, vitamin D, fructose and phosphorous in the body. Furthermore, one's genetic makeup, including the vitamin D receptor genotype, may also play a role in calcium absorption (Dawson-Hughes et al., J. Clin. Endocrinol. Metab. 80:3657-3661, 1995).

Supplementation with various calcium preparations is now the most common approach to increase calcium intake in individuals concerned with osteoporosis (Levenson and Bockman, Nutr. Rev.52:221-232,1994). However, it has been shown that the bioavailability of many commercial calcium preparations differs (Fairweather-Tait and Teucher, Nutr. Rev. 60:360-367,2002). The most common calcium supplement, calcium carbonate, is known to be generally well absorbed but other calcium forms, such as citrate, malate and amino acid chelate, have shown superior efficacy in some studies (Sakhaee K et al. Am J Ther. 6:313-21,1999, Heaney RP et al. Calcif Tissue Int 46:300–304, 1990).

DiMaCal™

DiMaCal™ is a patented form of calcium developed by Albion, leaders in bioavailable mineral nutrition. It is comprised of 2 moles of calcium bound to 1 mole of malic acid.

This product was developed to give manufacturers of dietary supplements a better alternative to calcium carbonate and other salt forms. DiMaCal has a much higher elemental calcium concentration (29% Ca) than other organic alternatives to calcium carbonate. DiMaCal has recently been granted GRAS (Generally Recognized As Safe) through self affirmation.



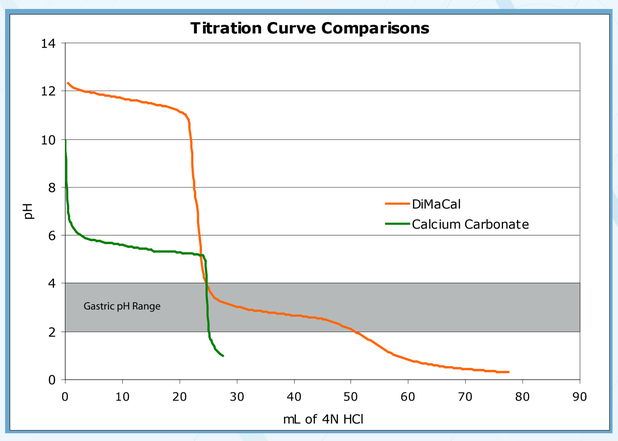
This poster presents the results of in vitro and in vivo trials to assess the bioavailability and physical properties of the product.

Buffering Capacity

One of the problems that can be encountered with calcium carbonate is the phenomenon of acid rebound and gas after a larger dose of this substance. To compare DiMaCal to calcium carbonate for this tendency, an in vitro test was performed.

Equal elemental amounts of calcium from DiMaCal and calcium carbonate were put into separate breakers and then equal amounts of simulated stomach acid was added to each beaker. The calcium carbonate foamed up forming gas bubbles, while the DiMaCal did not.

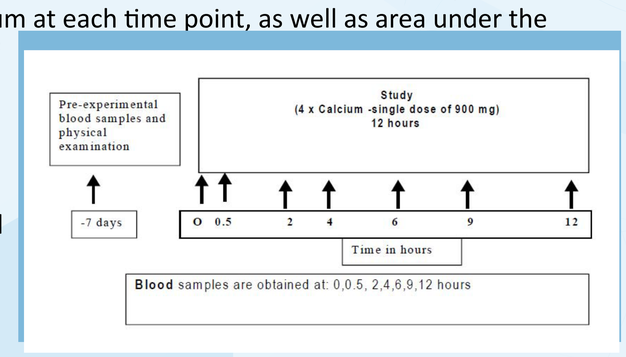
In addition, titrations of calcium carbonate and DiMaCal were carried out in the laboratory. The experiments were carried out by titrating 100 mL of 0.05 M solutions of either DiMaCal or calcium carbonate with 4N HCl. The pH of each solution was measured with each 0.05 mL addition of HCl. A comparison of the two titration curves demonstrates that DiMaCal has buffering capacity in the gastric pH range; whereas, calcium carbonate has little to no buffering capacity in the gastric pH range. From these in vitro tests, it could be concluded that DiMaCal would not have the gastric problems seen with calcium carbonate. The data may also indicate that there are release rates for each of the calcium atoms.



Clinical Bioavailability

Two separate clinical trials have been conducted to assess the bioavailability of DiMaCal A schematic representation of the protocol can be seen in figure 1.in comparison to calcium carbonate. In trial one, a high dose of elemental Ca, 900 mg, was evaluated. In trial two, a moderate dose of elemental Ca, 300 mg, was evaluated. In both studies, several healthy adults were blindly and randomly given one dose of each product, with a minimum of 1 week washout between supplements, under similar dietary conditions. Blood was taken immediately before supplement administration and at 0.5, 2, 4, 6, 9 and 12 hours after the dose. The pharmacokinetic measures were the determination of calcium at each time point, as well as area under the concentration-time curve (AUC0-12h), half life, time at maximum concentration (Tmax) and maximum plasma concentration (Cmax) for calcium.

A schematic representation of the protocol can be seen in figure 1



In the high dose study, it was observed that DiMaCal was significantly better absorbed than calcium carbonate. The serum level of Ca was also found to be elevated for a much longer time. This indicates a longer half life which could be a reflection of the higher presence of the calcium in an absorbable form for a longer period, relating to the chemistry of this patented form of calcium. The Cmax was also higher for the DiMaCal than the calcium carbonate.

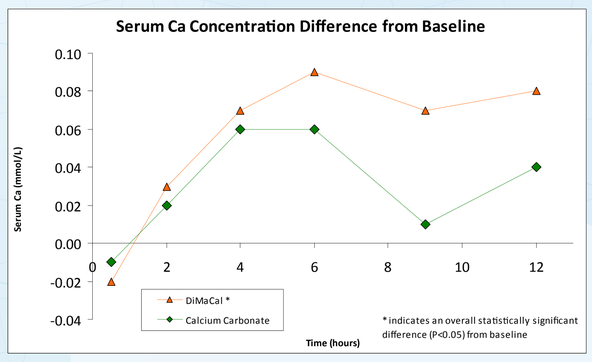
Absorption Data for High Dose Trial:

Difference from Baseline within DiMaCal Treated Group.

Time Points (hr)	Serum Ca (mmol/L)	SD	*P value <0.05
0	2.30	0.09	
0.5	2.29	0.08	-
2	2.34	0.09	-
4	2.37	0.10	*
6	2.40	0.08	*
9	2.37	0.09	*
12	2.38	0.12	*

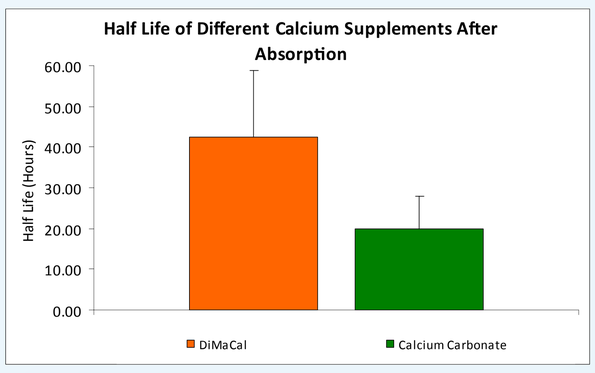
Difference from Baseline within Calcium Carbonate Treated Group.

Time Points (hr)	Serum Ca (mmol/L)	SD	*P value <0.05
0	2.38	0.08	
0.5	2.38	0.10	-
2	2.40	0.08	-
4	2.45	0.10	-
6	2.45	0.10	-
9	2.40	0.07	-
12	2.43	0.09	-



Half Life Data for High Dose Trial:

Supplement	Mean (Hour)	SD	P value
DiMaCal	42.48	16.25	
Calcium Carbonate	20.00	8.04	0.001



In the moderate dose study, the DiMaCal demonstrated a statistically significant serum calcium increase at 2 and 4 hours, where no corresponding significant increase was seen with the calcium carbonate. Unfortunately, because of problems in the lab, no half life data was collected for the moderate dose study.

Absorption Data for Moderate Dose Trial

Statistical Differences of Ca Serum Concentration over time for calcium carbonate

Time Points (hr)	Serum Ca (mmol/L)	SD	P values
0	2.32	0.09	
0.5	2.29	0.10	-
2	2.32	0.06	-
4	2.36	0.09	-
6	2.31	0.07	-
9	2.32	0.07	-
12	2.36	0.06	-

Statistical Differences of Ca Serum Concentration over time for calcium carbonate

Time Points (hr)	Serum Ca (mmol/L)	SD	P values
0	2.32	0.09	
0.5	2.29	0.10	-
2	2.32	0.06	-
4	2.36	0.09	-
6	2.31	0.07	-
9	2.32	0.07	-
12	2.36	0.06	-

The other pharmacokinetic parameters indicated no statistical significant differences between DiMaCal and calcium carbonate. In both studies there were no adverse events directly linked to the treatment, including gastric upset. The summary for all data from the two clinical trials can be found in the following table.

900 mg Study	**AUC**		**Cmax**		**Tmax**		**Half Life**	
Treatment	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Calcium Carbonate	27.99	2.67	2.52	0.08	5.15	3.21	20	8.04
DiMaCal	27.81	1.61	2.44	0.08	7.23	3.6	42.48	16.25
P Value	p=0.957 (t test) for DiMaCal vs. CaCO3		p=0.006 for DiMaCal vs. CaCO3		p=0.45 between groups		p=0.001 for DiMaCal vs. CaCO3	
300 mg Study	**AUC**		**Cmax**		**Tmax**		**Half Life**	
Treatment	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Calcium Carbonate	27.98	0.72	2.41	0.07	4.09	4.66	na	na
DiMaCal	27.88	0.92	2.39	0.07	4.79	2.78	na	na
P Value	p=0.650 between groups		P=0.431 between groups		between groups		na	

Summary

The measurement of AUC does not yield absolute bioavailability values, but is well suited for comparison of two (or more) preparations. It has a low signal to noise ratio, because unlike drugs, the studied substance (calcium) has a normal serum presence prior to dosing, and it is a tightly regulated value. Due to this, the absorption increments tend to be a small fraction of what is already present and the body's homeostatic forces actively dampen the absorptive rise (Heaney R, Journal of Nutrition; 131:1344S-1348S). This helps explain why the 900mg dose study exhibited a larger apparent margin in absorption in favor of the DiMaCal over calcium carbonate than what was seen in the 300 mg dosage study.

DiMaCal appears to be a high calcium containing ingredient that is better absorbed and potentially better tolerated than calcium carbonate. It is of note that the gap in absorption between DiMaCal over calcium carbonate was larger at the 900mg does than at the 300mg dose. Previous calcium absorption studies have indicated that as you increase the dose of calcium, the relative absorption of the calcium decreases in terms of percentage of absorption. For DiMaCal, this effect is not as evident as it is for calcium carbonate.

It may very well be that the release of the calcium from the DiMaCal molecule takes place at different rates for each of the calcium, thus decreasing the tendency for the calcium to saturate the absorption sites and transfer mechanism for calcium absorption, and allowing for more efficient calcium absorption at higher doses.

In conclusion, DiMaCal is a unique, patented form of calcium, which contains 2 moles of calcium bound to one mole of malic acid. The compound has a high calcium content, high bioavailabilty, and is safe and effective. The product is GRAS through self affirmation providing an effective organic source of calcium.