BONNEX GR

Calcium with Gastro-Retentive Drug Delivery System

Prolonged Gastric Retention Time :
Released at a sustained rate over a period of 12 hours.
Better absorption and increases bioavailability therefore
minimum precipitation and no magma formation

Calcium Citrate	**596 mg**
Offering elemental Calcium of	**125 mg***
Vitamin D3	**50 IU**

**equal to 312.5 mg of Calcium in Calcium Carbonate*

Bonnex GR releases Calcium in optimal quantities over 12 hours
in the stomach for best absorption and safety

PARADIGM
PHARMA NUTRACEUTICALS

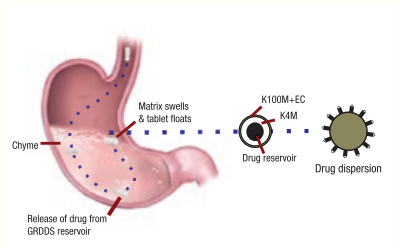
WHY GR Technology?

The stomach can absorb only a small amount of Calcium each time

"Dividing calcium intake over the course of a day results in a much more efficient absorption than ingesting the same total quantity in a single dose."

Calcium in human health. Humana Press

Gastro-Retentive Drug Delivery System : GRDDS



- Sustained drug delivery : continuously releasing the drug for a prolonged period of time (Prolonged Gastric Retention Time).
- Site specific drug delivery : Providing high drug concentrations at the absorption site (duodenum) for prolonged period of time resulting in efficient absorption.
- To reduced fluctuations of drug concentration
- Reduced frequency of dosing
- Minimized adverse activity at the colon
- Increases the oral bioavailability of calcium

GRDDS : Mechanisms of action

- **BONNEX GR** is coated with base substance (sodium bicarbonate), on ingestion when the tablet comes in contact with the gastric acid, as a result of acid base reaction tablet become porous and liberate CO2, which gets entrapped in the gellified hydrocolloid layer of K4M and K100M, thus making the matrix swell. The outer porous layer allows limited amount of acid to enter inside the tablet. This reaction decreases the specific gravity of the tablet, making it to float over chyme.
- **BONNEX GR** is formulated using a multipolymer matrix (MPM) of effervescent component (EC), K4M and K100M.
  - ***K100M*** osmotically swells and floats on the gastric content for 12 hours.
  - ***K4M*** allows BONNEX GR to swell and ensure optimum release of calcium at a desired rate for 12 hrs resulting in an increase in GRT and better control of calcium absorption at the duodenum.
- **BONNEX GR** is formulated using a gellified matrix. When gastric emptying occurs, the tablet sticks on the wall of the stomach due to the adhesive nature of the matrix. Hence gastric emptying time (of 2-3 hrs) does not affect the functioning of BONNEX GR

Floating GRDDS

- Designed using an effervescent component and swellable polymer matrix
- Has a bulk density less than that of gastric fluid
- Low density provided by the entrapment of air within polymer matrix
- Hence tablet remain buoyant in the stomach for prolonged period of time
- The drug is then released slowly at the desired rate near the absorption site (duodenum)

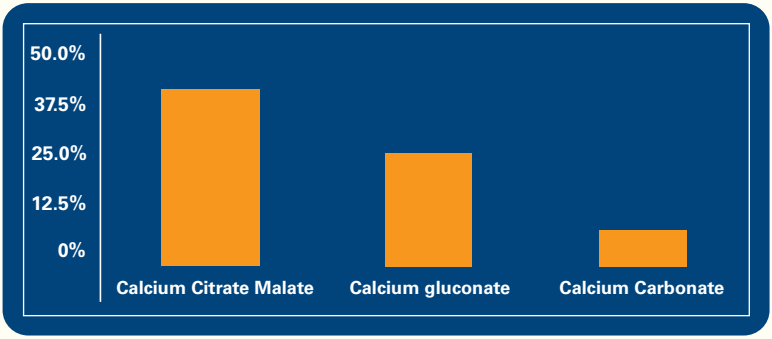
Better Absorption

Calcium Citrate is better absorbed than Calcium Carbonate

Source	Approximate Solubility mM/liter	Number of Subjects Tested	Fractional Absorption With a Meal	Fractional Absorption Without a Meal
Calcium oxalate	0.04	39	0.102 ± 0.040	
Hydroxyapatite	0.08	21		
Calcium carbonate	0.14	10/43	0.296 ± 0.054	0.235 ± 0.123
Tricalcium phosphate	0.97	10	0.252 ± 0.130	
Calcium citrate	7.3	7		0.242 ± 0.049
Calcium citrate malate	80	20	0.363 ± 0.076	
Bisglycinocalcium	1500	13		0.440 ± 0.104

Reference : Heany RP. et al, 1990. reprinted with permission

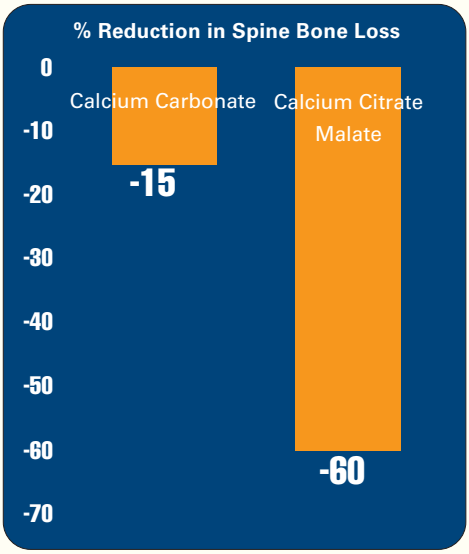
Absorption rates of commercially available calcium supplements vary



Calcium carbonate as low as 22 percent and calcium citrate malate as high as 42 percent (Intestinal Absorption)

Reference : Alternative Medicine Review Monographs; page 63

Better Efficacy



Significant reduction in loss of Bone Mass Density compared to calcium carbonate

Postmenopausal women were given either 500 mg calcium carbonate or calcium citrate malate for 2 years

Reference :
Dawson-Hughes B, Dallal G, Krall E. et al. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. N Engl J Med 1990;323: 878-883.

Higher Bioavailability

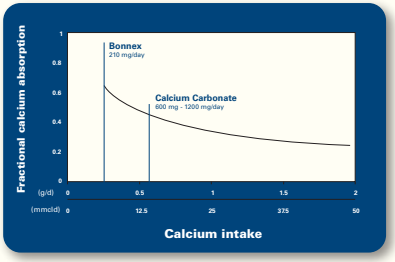
178 mg/dl for Citrate vs. 91 mg/dl for Carbonate in a study involving 1200 mg Calcium Citrate and Calcium Carbonate taken orally

	Placebo	Carbonate	Citrate
ΔC_{max} (mg/dl)	0.81 (0.58-1.05)	0.72 (0.56-0.89)	1.11 (0.94-1.29)
ΔC_{max} (%)	8.1 (5.8-10.4)	7.4 (5.6-9.2)	11.6 (9.5-13.6)
ΔAUC (mg-min/dl)	107 (59-154)	91 (58-125)	178 (141-214)

Reference : Robert P. Et al. Relative Bioavailability of calcium from calcium formate , calcium citrate and calcium carbonate, JPET June 2005 vol. 313 1217-1222

Optimum Quantity

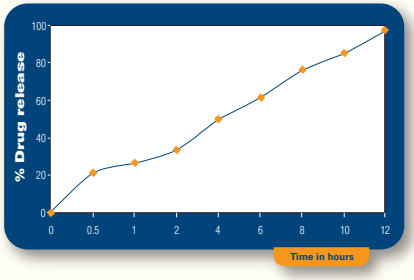
Optimum quantity of calcium for maximum absorption



- The amount of calcium consumed regulates the efficiency of intestinal calcium absorption.
- Calcium absorption efficiency increases when calcium intakes are low and decreases when calcium intakes are high
- Calcium supplement is best taken in small quantities, 1-2 times a day, depending upon need.
- The higher the amount in any one time, the less the body retains and absorbs.

Reference : Goodman & Gilman's Manual of pharmacology and therapeutics, 11th edition Pg 1059., Am J Clin Nutr. 2003;7 8:110–6.

BONNEX GR : Pharmacokinetics



Sustained release of calcium from BONNEX GR due to the Gastro Retentive Drug Delivery System ensures:

- Optimum calcium release at a desired rate from the multipolymer matrix (MPM) for efficient absorption
- Sustained availability of absorbable calcium at duodenum over 12 hrs
- Maximun calcium absorption ensures minimum precipitation and no magma formation

Safety Profile

- ✓ Calcium Citrate, known to be independent of risk of kidney stones
- ✓ Matrix's effervescent component (EC), sodium bicarbonate is a food additive safe in pregnancy
- ✓ US FDA and EU FDA approved semi-synthetic polymer HPMC used in the matrix, recognized as safe to humans including in pregnancy
- ✓ Thus all the components are free from toxicity and can be safely recommended in pregnancy

Calcium Citrate (Bonnex GR) is superior to Calcium Carbonate

1. **High solubility :** calcium citrate 7.3 mM/L, calcium citrate malate 80 mM/L, calcium carbonate 0.14 mM/L
2. **Better absorption :** calcium citrate 42%, calcium carbonate 22%
3. **Superior bioavailability :** 2.5 times more than calcium carbonate
4. **Better efficacy :** significant reduction in loss of Bone Mass Density (-60%) compared to calcium carbonate (-15%)
5. **Independent of gastric pH :** can take it at any time, even on an empty stomach, unlike the calcium carbonate form which is recommended with food
6. **Optimum quantity of calcium for maximum absorption**
7. **Safety :** reduced risk of oxalate stone formation
8. The best choice for people with inflammatory bowel disease and other conditions that hamper calcium absorption

(1) Alternative Medicines Review Monograph, pp 63;
(1) Barger-Lux MJ, et al. Calcium absorbability from milk products, an imitation milk, and calcium carbonate. Am J Clin Nutr 1988;47:93-95.
(2) Journal of Pharmacology and Experimental Therapeutic, June 2005, vol. 313
(3) Harvey JA, Zobitz MM, Pak CY. Calcium citrate: reduced propensity for the crystallization of calcium oxalate in urine resulting from induced hypercalciuria of calcium supplementation. J Clin Endocrinol Metab 1985;61:1223-1225.