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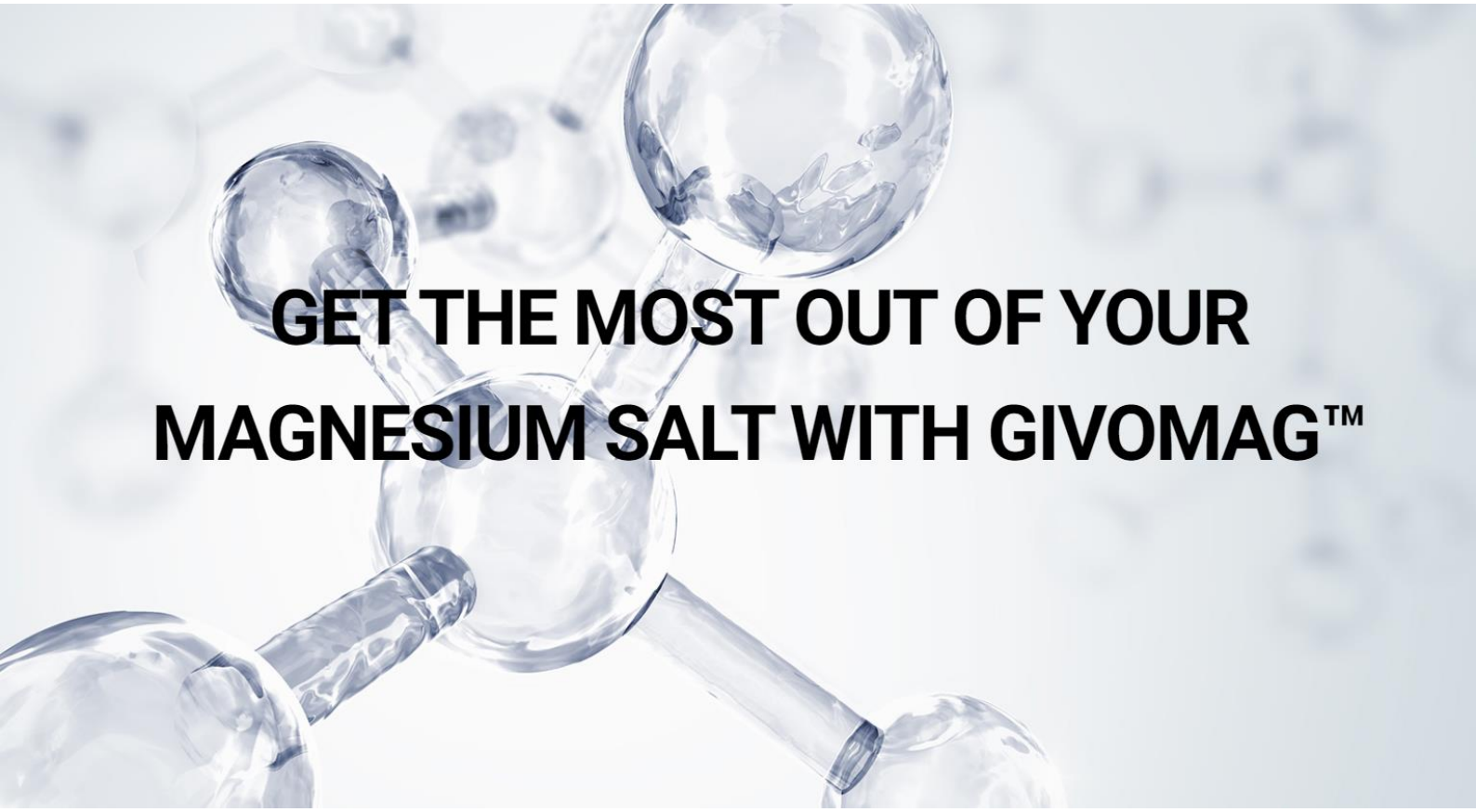
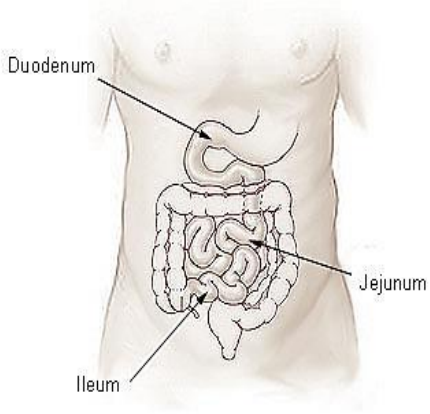


GET THE MOST OUT OF YOUR MAGNESIUM SALT WITH GIVOMAG™

GIVOMAG



Gastrointestinal tract

1- Organic magnesium salts protect the mineral as it passes through the stomach

The stomach contents are highly acidic with a pH of 1.8 - 2.0.

Inorganic magnesium salts such as magnesium oxide and magnesium carbonate readily react in this highly acidic environment, the resulting reactions produce compounds that can cause flatulence and have a laxative effect.

Inorganic magnesium salts can also react with phytic acid contained in foods, binding the mineral resulting in suboptimal absorption.

Organic magnesium salts, for example those with a chelate structure (glycerophosphates) minimises the potential for these types of reactions.

2- Absorption of magnesium in the intestine (Ileum and Jejunum)

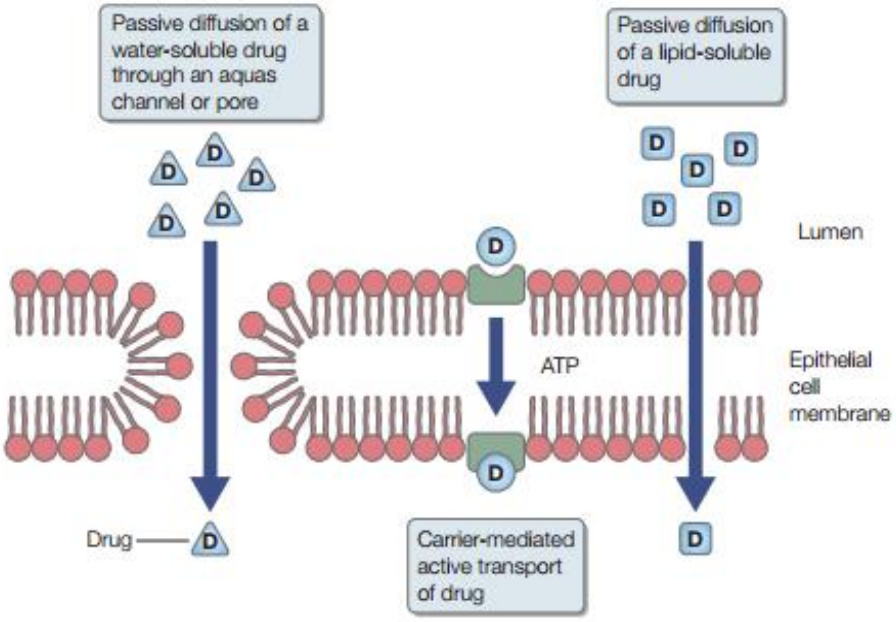
Magnesium has two mechanisms of transport:

Paracellular transport involves the absorption of Mg^{2+} through the small spaces between the epithelial cells and is a passive mechanism. It is responsible for **90%** of intestinal Mg^{2+}uptake.

Transcellular transport involves 2 processes :

The *active transport* of Mg^{2+} to the blood through the interior of the epithelial cell. This second type of Mg^{2+} transport is subject to tight regulation since the ions have to pass through two cell membranes [1].

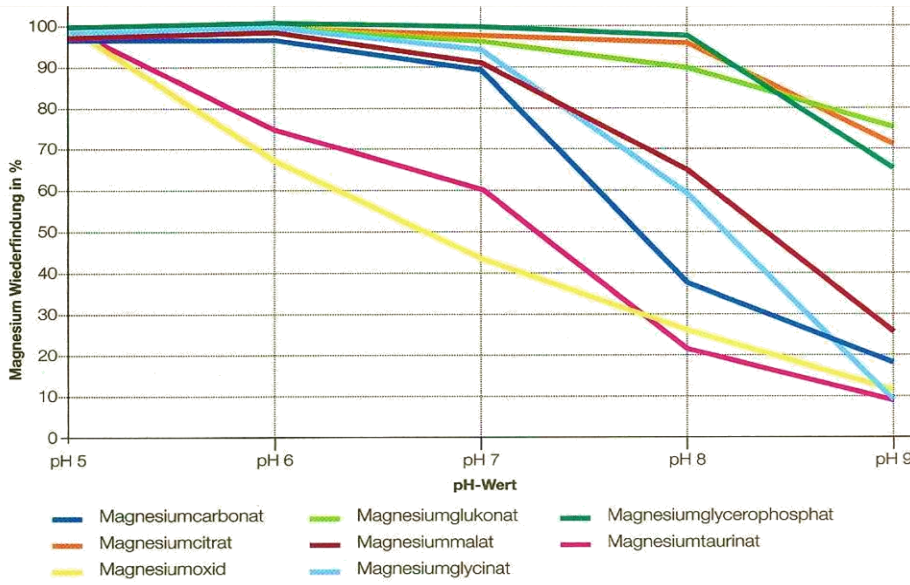
The *passive diffusion* of liposoluble particles, such as glycerol, across the cells.



It is important for magnesium salts to remain soluble in the alkaline (pH 7 - 8) environment of the intestine where absorption takes place.

Amongst the different types of magnesium salts, magnesium glycerophosphate (GIVOMAG™) has the ability to remain soluble at a pH of 7 - 8[2] meaning it is soluble in the intestine.

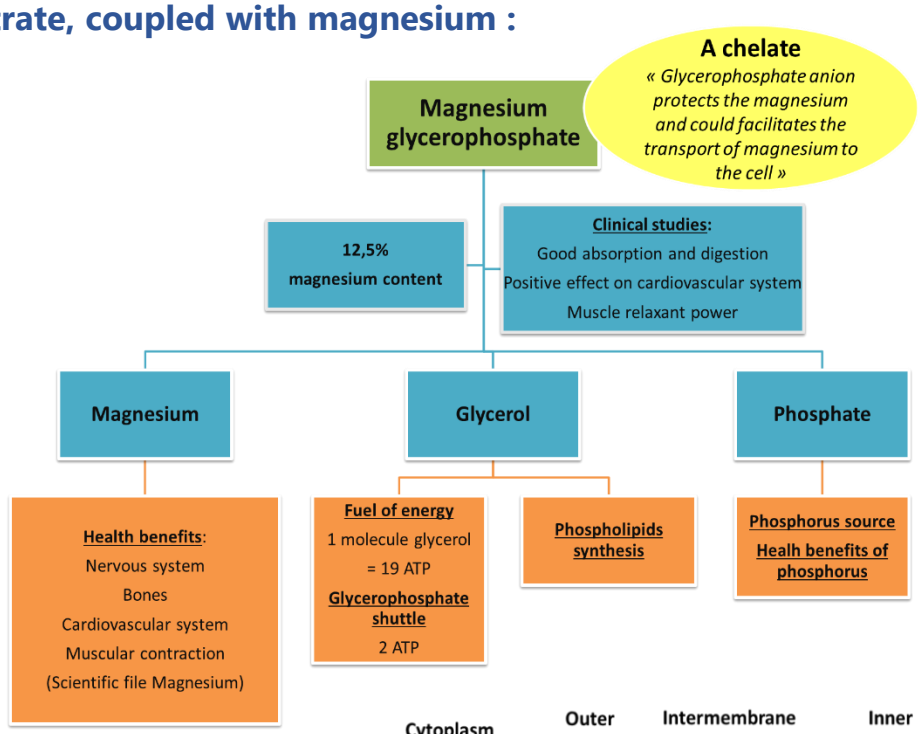
Glycinates, other amino acid chelates and oxides are relatively insoluble at alkaline pH, and as a consequence, are poorly absorbed. Furthermore, if magnesium salts are present in the form of Mg^{2+} ions they have a laxative effect by remaining in the colon and drawing water.



3 – What about glycerophosphate substrate, coupled with magnesium :

In addition to its ability to maintain a high solubility in the intestine, unlike other magnesium chelates (such as bisglycinates or taurinates), the glycerophosphate is a source of **glycerol** and **phosphorous.**

The glycerophosphate fuels the body with lipophilic Magnesium, well know for its high diffusion across the body and throughout the blood brain barrier.

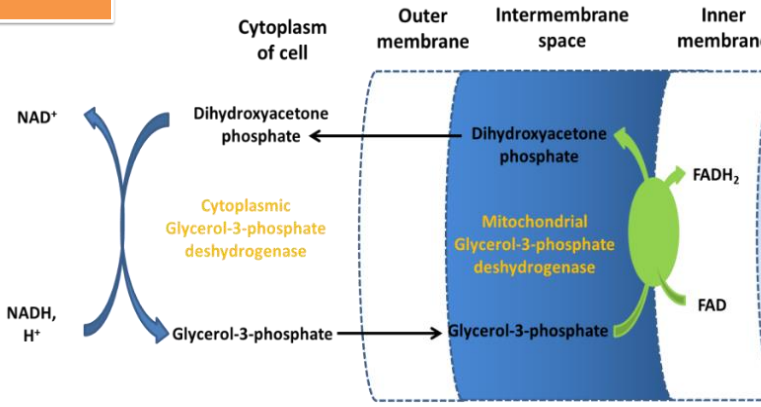


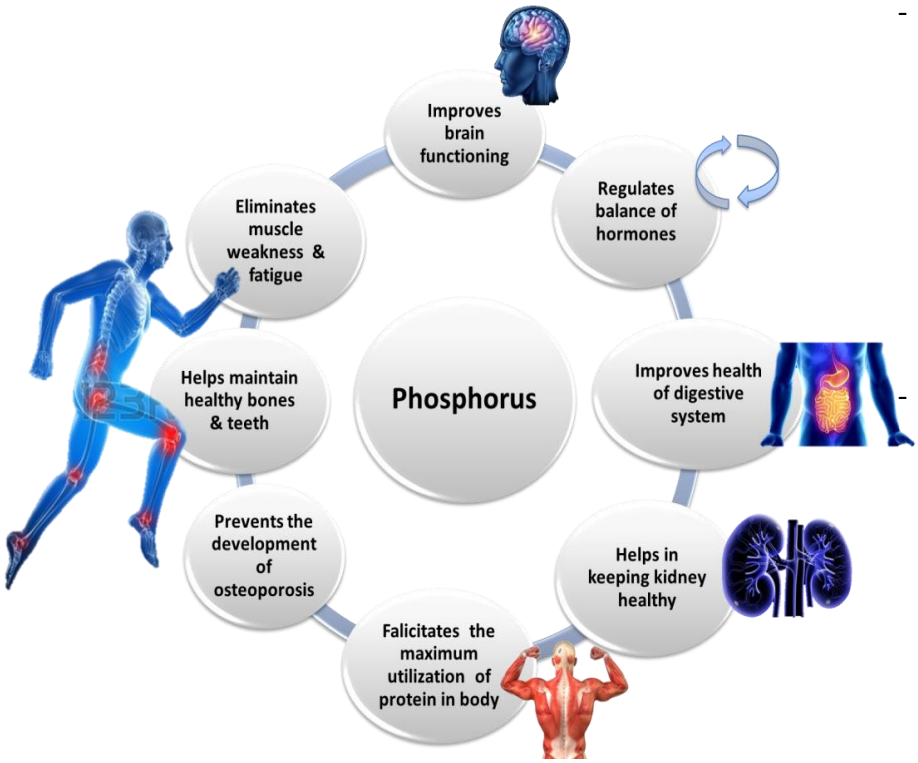
Glycerol is participating to :

- ATP production: coenzymes produced into the cytoplasm (NADH from glycolysis) are oxidized inside the mitochondria and thereby participate to the respiratory chain which generates energy (ATP)[3].

- Phospholipid production: Phospholipids are the main constituent of the biological membranes of major organs (heart, brain, etc.). Most phospholipids are phosphoglycerides, whose head is organized around a glycerol-3-phosphate residue. The two hydroxyl functional groups are esterified by a fatty acid, constituting two aliphatic tails[4].

- Blood Brain Barrier: The glycerol-3-phosphate shuttle is often assumed to be important in the brain[5] and glycerol shuttles





Phosphorous :

- Health benefits: phosphorus is integrated to diverse functions ranging from the transfer of genetic information to energy utilization. Phosphorus forms the backbone of DNA and RNA and is an essential component of phospholipids that constitute all lipid bilayer membranes. Phosphorus is an integral component of the body's key energy source, adenosine triphosphate, ATP

- Storage of Mg in the bones: More than 60% of the Mg is located in the bones. In an *in vitro* study, authors [6] investigated the effect of incorporating magnesium glycerophosphate in the enzymatic process of platelet-rich fibrin (PRF) mineralization, for **bone regeneration** applications. The incubation with magnesium glycerophosphate increase the storage of magnesium and the **proliferation of osteoblasts**.

4 - GivoMag : third generation of chelated magnesium, with a unique protection

A **monochelated magnesium** :

Several chelated forms of magnesium have been developed over the past years in the market:

- Mono chelates as for example : glycerophosphate, EDTA
- Bis/Di chelates : gluconates, lactates, glycinates, aspartates

As we have previously seen, the chelation is protecting the mineral through its way in the gastrointestinal tract. However, the mineral needs to be "deprotected" by the chelate to reach its final targets. Thus, the chelation strength of the complex, represented by the stability constant (Log K), should exist but not be too high. Monochelates are having one log K value, whereas bi-chelates are separated in 2 times and thus have 2 log K constants.
In this context, the mineral deprotection requires less energy with a mono-chelation than in the case of a bi-chelation.

It is well admitted that stability constants (log K values [7]) should be comprised between : **1 <Log K< 4**

A too strongly bonded Mg will be poorly used by the body. It's often the case with 'Mg N' ionic bonds, such as amino acids and EDTA, difficult to break.

		1 ligand		2 ligands				
		Glycerophosphates	EDTAs	Gluconates	Citrates	Lactates	Aspartates	Glycinates
Mg	chemical formula	$C_3H_7O_6MgP$	$C_{10}H_{12}MgN_2Na_2O_8$	$Mg(C_6H_6O_7)_2$	$Mg_3(C_6H_5O_7)_2$	$Mg(C_3H_5O_2)_2$	$Mg(C4H6O4N1)_2$	$Mg(C2H_4O_2N)_2$
	Log K (Lange's Handbook)	2,5	10,41	0,70 / ?	3,29 / ?	1,37 / ?	? / ?	3,44 / 6,46
	Log K (NIST database)	?	8,69	1,16 / ?	2,8 / ?	0,93 / ?	2,43 / ?	3,45 / ?

Magnesium glycerophosphate is the perfect chelated form of magnesium with a Log K value of 2,5.

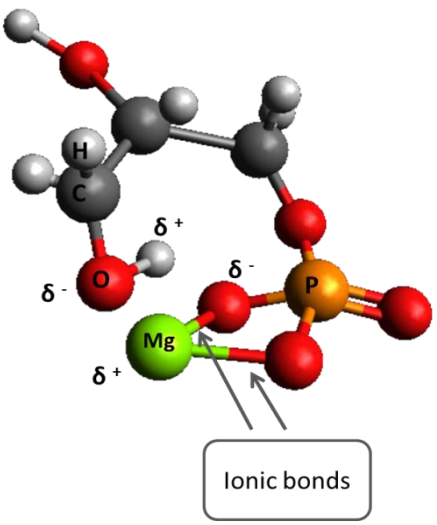
2 ionic bonds

between glycerophosphate and magnesium

2 electrostatic bonds

- O#Mg
- O#H

IDEAL CHELATION STRENGTH



5- A clinical study about potential side effects of Magnesium glycerophosphate

Aim **:** investigation of the diarrhea incidence as a side effect of daily oral magnesium consumption.

Subjects **:** 20 volunteers with latent magnesium deficiency (42 to 75 years old).

Since magnesium mineral is distributed almost everywhere in the human body (muscles, brain, bones…), it is impossible to compare magnesium bioavailability from several forms of magnesium with a simple blood analysis. Thus, the only relevant studies about magnesium bioavailability are related to the difference of excreted mineral amounts.

In this clinical study, eleven different forms of magnesium compounds were tested along with a placebo (maze flower) during 28 days to compare diarrhea incidence.
This study demonstrates that magnesium glycerophosphate is having as low influence on diarrhea than a placebo.
Knowing that diarrhea is caused by ionized mineral which becomes excreted from the metabolism (laxative effect) and thus not absorbed, we can consider that magnesium is better absorbed when ingested in the form of glycerophosphate than any other form.

Tab. 2: Incidence of diarrhea (%) in 20 volunteers upon the oral use of different magnesium compounds in the amount of 400 mg Mg during 28 days.

Mg compound	Incidence
Sulfate	96
Chloride	78
Oxide	47
Hydroxide	45
Carbonate	40
Hydroxycarbonate	37
Lactate	32
Gluconate	27
Phosphate	20
Glycerophosphate	7
Glucose-1-phosphate	7
Placebo	7

Tab. 3: Incidence of diarrhea (%) in 20 volunteers upon the oral use of 1 : 1 mixtures (by weight) of magnesium glycerophosphate hydrate with different magnesium salts in the amount of 400 mg Mg during 28 days.

Mg-glycerophosphate 1 : 1 with	Incidence
Mg oxide	15
Mg hydroxide	12
Mg carbonate	8
Mg hydroxycarbonate	7
Mg lactate	7
Mg gluconate	7
Placebo	7

With the best absorption and tolerance incidence, the magnesium glycerophosphate has the ability to avoid side effects unlike other forms of magnesium showing a laxative effect.

Mixtures of magnesium with glycerophosphate with other forms can be considered too, as shown in the second table.

It is particularly important for sensitive human groups such as babies, children, 50+ aged persons, persons suffering from allergies or under medical nutrition…to consume well tolerated and highly bioavailable forms of minerals, and GIVOMAG is part of them.

6 – A new medicine based on magnesium glycerophosphate – NEOMAG

Context : the MHRA (Medicines & Healthcare product Regulatory Agency – UK) decided to replace an injectable Mg - Magnesium Sulphate IV injection 10% (Martindale Pharmaceuticals Ltd, UK) – by **Neomag**, a chewable tablet of magnesium glycerophosphate (4mmol – 97mg of Mg).

In this context, an open label, randomised, crossover comparative study has been performed to determine the bioavailability of the Neomag oral tablets (containing magnesium glycerophosphate), versus intravenous magnesium sulphate after administration to health adults under fasting conditions.

The conclusion of the study shows improved absorption of magnesium in the form of orally administered magnesium glycerophosphate, compared to intravenously administered magnesium sulfate.

This clinical trial was pivotal gaining approval for Neomag as a superior and safer way to improve magnesium status.

CLINICALLY STUDIED
BIOAVAILABILITY

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9. UK License number : PL 36116/003