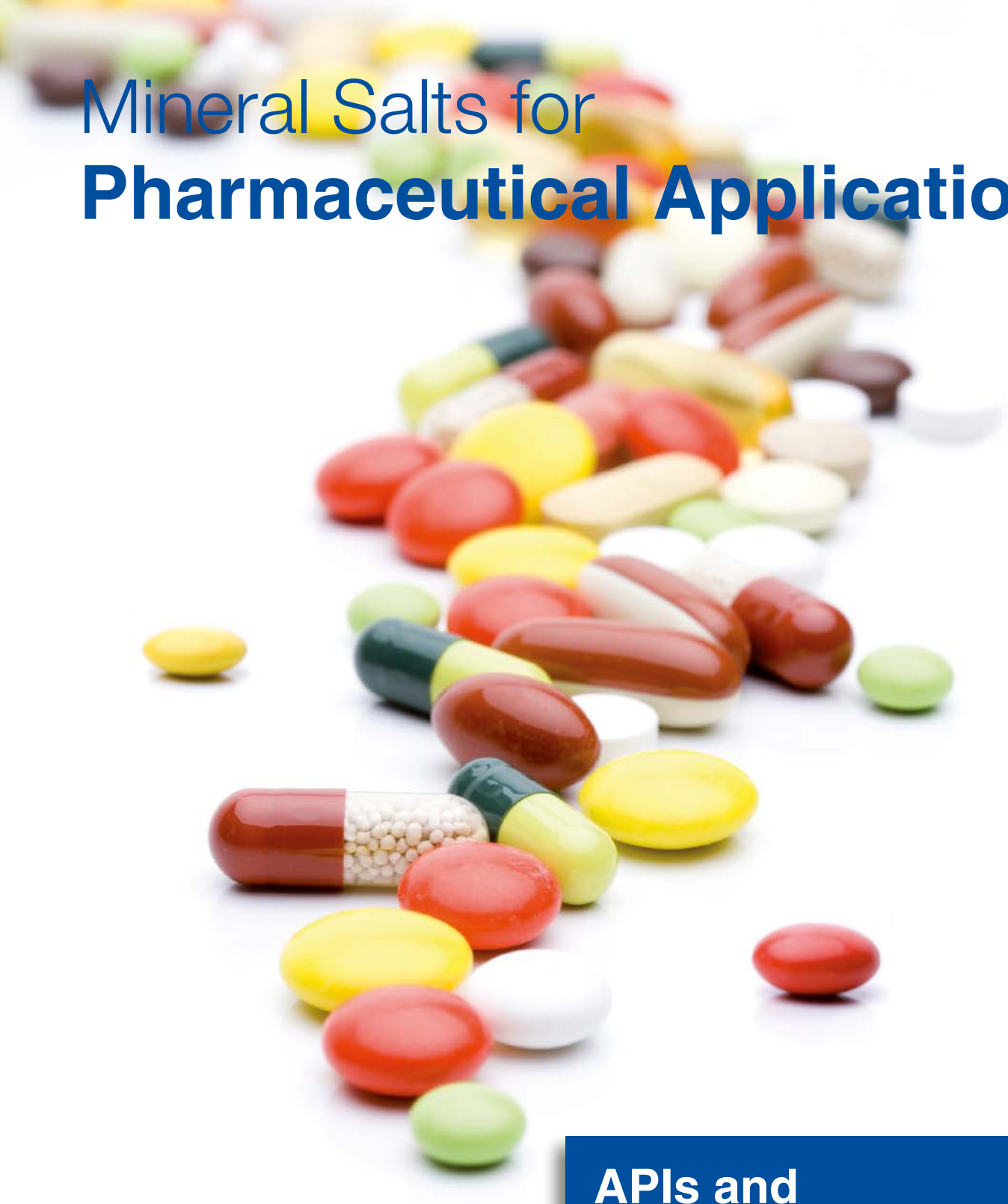
Mineral Salts for **Pharmaceutical Applications**



APIs and Excipients

Dr. Paul Lohmann®

High value mineral salts

The Competent Partner to the Pharma Industry

Dr. Paul Lohmann GmbH KG was founded in 1886 in Germany to produce reduced iron for the treatment of iron deficiencies. This original product was successfully followed by other Iron APIs, and later by other minerals, including: calcium, magnesium, zinc, potassium, copper etc.

Three generations later, much has changed in the family owned company, but one thing remains the same: the devotion to providing the highest quality minerals to the pharmaceutical industry worldwide.

After more than 125 years of producing and delivering mineral salts according to the highest standards, we have established ourselves as the leading supplier to the worldwide pharmaceutical industry. When it comes to mineral salts, Dr. Paul Lohmann is your reliable partner.

GMP Production and Quality Standards

Thanks to our long history as producer of APIs and excipients for the pharmaceutical industry, we are perfectly aware of the regulatory needs of our customers. Thus Dr. Paul Lohmann® was one of the first mineral salt producers to obtain a GMP Certificate.
This occurred in 1994 and this certification has been kept ever since.

At Dr. Paul Lohmann® we support our clients in regulatory aspects in many ways:

- GMP production of APIs and excipients in our two certified German factories.
- Product compliance with the most relevant pharmacopoeia (Ph. Eur., USP, BP), guaranteed by complete testing of all parameters.
- Full documentation of all processes to guarantee transparence and traceability.
- Qualification and monitoring of suppliers.
- Possibility of audits.
- Availability of diverse documentation.
- DIN EN ISO 9001:2008 certification

Thanks to these quality standards, our customers can be sure to comply with current pharma legislations and requirements when they use our products.

Certification and Documentation

To facilitate the registration of medicines containing our products, we have a growing number of **C**ertificates **o**f **S**uitability (**CoS/CEP**), **E**uropean **D**rug **M**aster **F**iles (**EDMF**) and **A**ctive **S**ubstance **M**aster **F**iles (**ASMF**) available.

SUBSTANCE	CEP NO.	VALID SINCE
Calcium Acetate, anhydrous	R0-CEP 2011-033-Rev 00	11/05/2012
Ferrous Gluconate	R1-CEP 2001-444-Rev 00	01/06/2010
Ferrous Fumarate	R1-CEP 2004-232-Rev 00	30/09/2010
Ferrous Sulfate, dried	R1-CEP 2007-368-Rev 01	19/12/2013
Ferrous Sulfate Heptahydrate	R1-CEP 2007-369-Rev 00	19/12/2013
Magnesium Carbonate, heavy	R1-CEP 2008-071-Rev 01	17/03/2014
Magnesium Carbonate, light	R0-CEP 2010-062-Rev 00	09/02/2011
Magnesium Citrate, anhydrous	R0-CEP 2009-017-Rev 00	05/11/2010
Magnesium Citrate, Nonahydrate	R0-CEP 2011-036-Rev 00	11/05/2012

Indication Fields of our Products

Thanks to our extensive product portfolio and flexibility in production, our products are used as APIs and excipients in the production of numerous medicines, nutritional supplements, clinical nutrition products, and OTCs all over the world for the treatment of the most diverse affections.

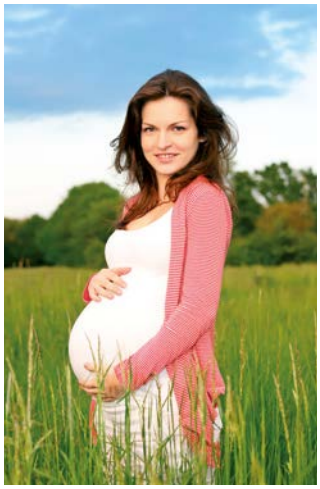
Iron Deficiency Anemia

It all began with iron and today it is still our most important product line. Many of our iron APIs are used worldwide to treat and prevent iron deficiency, anemia, and its consequences:

About 2 billion people suffer from anemia and an even larger number of people are affected by Iron deficiency (WHO, 2000).

Anemia affects all population groups, but pregnant women and young children are the most susceptible groups.

Dr. Paul Lohmann® produces many different Iron-APIs in its German factories to suit the different needs of its customers worldwide.



OUR MOST POPULAR IRON APIs

Ferrous Sulfate, dried or 7-hydrate
- Highly bioavailable
- High iron content
- Economical
- CEP available

Available as Powder and Micro2

Ferrous Fumarate
- Highly bioavailable
- High iron content
- CEP available
- Very stable

Available as:
- **Powder**
- **Micronized powder**
- **DC Granules**
- **Microencapsulated granules**

Ferric Ammonium Citrate green or brown
- Good solubility for syrups and drops
- Non oxidant
- Very stable

Ferric Pyrophosphate
- Very stable iron salt
- Good taste
- Non oxidant

Available as Micronized Powder and Micro2

Ferrous Gluconate
- Highly bioavailable
- Good solubility
- Different particle sizes available
- CEP available

Ferrous Bisglycinate
- Highly bioavailable
- Well tolerated
- Mild taste

Osteoporosis

Current long life expectations are leading to an increase in age related illnesses. One of them, especially affecting (but not only) women, is osteoporosis. One of the preferred options to prevent and treat osteoporosis is the use of Calcium supplements, either as prescription or as OTC products.

Dr. Paul Lohmann® offers several different Calcium Salts that can be used for the treatment of osteoporosis.

Since calcium absorption is also influenced by magnesium, Combined Calcium + Magnesium supplements can also be an interesting option. For this purpose we also offer a wide range of magnesium salts.

Strontium Salts are also becoming an interesting choice for the treatment of osteoporosis, due to their beneficial effects on bone density and bone formation. We currently offer the following strontium salts:

- Strontium Acetate
- Strontium Citrate
- Strontium Lactate

INTERESTING CALCIUM SALTS

Calcium Carbonate
- The most popular calcium salt
- Natural origin
- Very high calcium content

Also available as DC Grade

Tricalcium Citrate
- High bioavailable
- Neutral taste
- High calcium content

Available as:
- **Powder**
- **Micronized powder for optimal taste**
- **Granules for direct compression**

Calcium Pidolate
- Highly bioavailable for optimal calcium absorption
- Highly soluble

Calcium Lactate Gluconate
- Higly soluble calcium salt
- Neutral taste

Other Mineral Deficiencies – From A to Z

Many factors, such as stress, sports, pregnancy, a growth phase or diverse illnesses are some of the factors that can lead to mineral deficiencies.
In order to restore the mineral balance, nutritional supplements with different minerals may be used: With options from A like ammonium to Z like zinc, Dr. Paul Lohmann® can provide the entire range of your mineral needs.

Recommended nutritional values for minerals: [1, 2]

MINERAL SALT	US CURRENT RDI (REFERENCE DAILY INTAKE)	EU RDA (RECOMMENDED DAILY ALLOWANCE)
Calcium	1000 mg	800 mg
Magnesium	400 mg	375 mg
Potassium	-	2000 mg
Iron	18 mg	14 mg
Zinc	15 mg	10 mg
Manganese	2 mg	2 mg
Copper	2 mg	1 mg
Selenium	70 µg	55 µg
Iodine	150 µg	150 µg
Chromium	120 µg	40 µg
Molybdenum	75 µg	50 µg
Fluorine	-	3.5 mg
Phosphorus	1000 mg	700 mg
Chloride	3400 mg	800 mg

The Reference Daily Intake (RDI) is the value established by the US Food and Drug Administration (FDA) for use in nutrition labeling (Daily Value (DV) in %).
Recommended Daily Allowances (RDA) according to Regulation 2008/100/EC on nutrition labeling for foodstuffs.

Antacids

Antacids are preparations indicated to prevent and relieve the pain of gastric hyperacidity and dyspepsia. They normally consist of basic compounds that neutralize the hydrochloric acid in the stomach.

PRODUCTS FOR THIS INDICATION
Calcium Carbonate
Magnesium Carbonate
Magnesium Hydroxide
Magnesium Oxide
Magnesium Trisilicate

Laxatives

Saline laxatives attract and retain water in the intestinal lumen, increasing intraluminal pressure and thus softening the stool. They may alter a patient's fluid and electrolyte balance.

Our actives with laxative effect can be divided into two groups:

Magnesium salts
Most Magnesium salts in high doses have laxative effects (osmotic laxatives) and are therefore used in oral OTC products to treat constipation.

Sodium Sulfate used for whole bowel irrigation, a process designed to prepare the bowel for surgery or colonoscopy and to treat certain types of poisoning. [3, 4]

PRODUCTS FOR THIS INDICATION
Magnesium Carbonate
Magnesium Citrate
Magnesium Hydroxide (for Milk of Magnesia)
Magnesium Sulfate
Sodium Sulfate

Kidney Stones / Cystitis

Kidney stones, also known as renal calculi, are solid aggregates formed in the kidneys.

If stones grow to a certain size they can cause very painful obstructions of the ureter.

Chelating agents, such as citrates, inhibit the nucleation, growth, and aggregation of those crystals.

Sodium, Potassium and Magnesium Citrates or combinations thereof are used to relieve discomfort in urinary tract infections, such as cystitis and to reduce the acidosis seen in distal renal tubular acidosis.

PRODUCTS FOR THIS INDICATION
Magnesium Citrates
Potassium Citrates
Sodium Citrates
Sodium Potassium Citrate
Magnesium Potassium Citrate

Phosphate Binders for Hyperphosphatemia

Hyperphosphatemia is an electrolyte disturbance in which the level of phosphate in blood is abnormally elevated. It is primarily due to chronic renal failure, but can also be caused by hypoparathyrodism or osteomalacia. Often, calcium levels are lowered (hypocalcemia) due to precipitation of phosphate with the calcium in tissues.

Hyperphosphatemia is treated with phosphate binders and by dietary restriction of phosphate.

The preferred phosphate binders for the treatment of hyperphosphatemia in patients with renal insufficiencies are calcium acetate and calcium formate.

PRODUCTS USED AS PHOSPHATE BINDERS	
Calcium Acetate	**CEP and DMF available!**
Calcium Formate	
Calcium Carbonate	
Calcium Citrate	

Lithium Salts for Bipolar Disorder and Manic Depression

Lithium salts have been used as a first-line treatment for bipolar disorder for many years. The therapeutic effect of lithium salts appears to be entirely due to the lithium ion, Li^+. Lithium is also noted for reducing the risk of suicide.[5]

PRODUCTS FOR THIS INDICATION [6]
Lithium Citrate
Lithium Gluconate
Lithium Sulfate

Zinc for Common Colds

It is generally known, that zinc has a beneficial effect on the immune system. Some scientific research shows that zinc lozenges and tablets, when taken at the onset of a cold, can shorten its duration.

Zinc Gluconate and Zinc Acetate are used in lozenges and tablets for the effective treatment of colds and to support the immune system.

Topical Agents

OTITIS

Aluminium Hydroxide Acetate & Aluminium Acetotartrate are used in ear-drops to reduce oedema and inflammation of the ear. They cause an acidic environment, hostile to pathogenic bacteria.

BLEEDING GUMS

Aluminium Lactate is used in mouth rinses and Toothpastes to stop gums bleeding.

DERMATITIS

Lithium Gluconate is effective in the treatment of seborrhoeic dermatitis.

ACNE

Aluminium Lactate is used in anti-acne lotions because of its astringency.
Zinc acetate is used due to its light antibacterial effect.

DRY SKIN

Ammonium Lactate is a potent humectant used in the treatment of dry scaly conditions of the skin, including ichtiosis vulgaris.

PRURITUS AND ITCHING

Calamine is a traditional astringent and anti-pruritic used in powders, creams, lotions and ointments for the treatment of a variety of skin conditions.

BREAST FISURES

Copper and Manganese Gluconates are used in the treatment of breast fisures during and after breast feeding.

CANKER SORES

Milk of magnesia is useful against canker sores (aphthous ulcer) when used topically. [7]

Acid-Base Balance

The body's acid-base balance is normally tightly regulated, keeping the arterial blood pH between 7.38 and 7.42. [8] Acid-base imbalance occurs when the blood pH shifts out of the normal range. [8] Modern lifestyle, characterized by high meat diets, fast food consumption, smoking, alcohol, sports, and the pressure for high performance, can all cause an acidification of the body (acidosis).

Different mineral salt combinations, which can bind and neutralize the excess acid may be used to help restore the normal acid-base balance of the body. The most popular minerals for this purpose are:

CITRATES
Trisodium Citrate
Tricalcium Citrate
Tripotassium Citrate
Trimagnesium Dicitrate
CARBONATES
Calcium Carbonate
Magnesium Carbonate
Sodium Bicarbonate
Potassium Bicarbonate

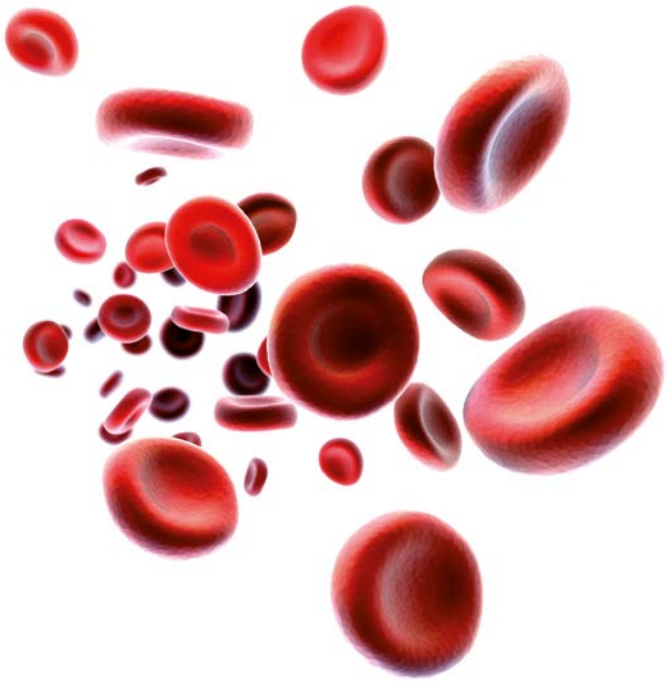
Blood Treatment

Sodium Citrate as Anticoagulant

Buffered sodium citrate is used in clinical laboratories and blood banks as an effective anti-coagulant, usually in a ratio of 1:9 sodium citrate/blood. The citrate chelates the calcium of the blood by forming calcium citrate and thus disrupts the blood clotting mechanism. It is used today in blood collection tubes and for the preservation of blood in blood banks.

Sodium Acetate for Plasma Fractionation

As the conjugate base of a weak acid, a solution of sodium acetate and acetic acid can act as a buffer to keep a relatively constant pH. This is useful especially in biochemical applications where reactions are pH dependent. Sodium acetate is used to prepare the elution solution used during the fractionation of blood plasma to obtain immunoglobulins (IgG) for the treatment of diverse diseases.



Excipients

Besides the use as APIs, many of our products are also widely used as excipients.

In addition to our own products, we also offer additional products to complete this product range.

Your advantage:

- Warranty of quality (we qualify the producer and control every lot of the incoming material)
- Transparency in the supply chain
- Reduced number of suppliers
- Cost saving due to combining excipient deliveries with APIs

OUR PORTFOLIO OF EXCIPIENTS

Buffering Agents

- Sodium Citrate
- Sodium Acetate
- Potassium Citrate

Emulsifiers

- Sodium Citrate

Antimicrobial Preservatives

- Potassium Benzoate
- Sodium Benzoate

Also available as micronized powder

- Sodium Propionate

Lubricants

- Sodium Benzoate

Also available as micronized powder

- Calcium Stearate
- Magnesium Stearate
- Zinc Stearate

Anticaking Agents

- Magnesium Carbonate
- Calcium Carbonate
- Tricalcium Phosphate
- Magnesium Trisilicate

Carrier for Tablets and Capsules

- Calcium Carbonate
- Tricalcium Phosphate
- Magnesium Carbonate
- Magnesium Oxide

Glidants

- Tricalcium Phosphate
- Magnesium Trisilicate

Alkalizing Agent

- Sodium Citrate
- Sodium Bicarbonate
- Potasium Bicarbonate

Special Product lines – the right material for the right medicine

Over time, we have developed different product lines, optimized to meet the needs of customers producing specific galenic forms:

DC Granulates for the Direct Compression of Tablets

Our DC Granulates were developed to allow the fast and economical production of tablets by direct compression. Some of them contain additional excipients to optimize the results.

PRODUCTS	BENEFITS OF DC GRANULATES
Calcium Carbonate DC	• Optimal Tablet properties • Cost savings due to - More economical production of tablets - Less needs of binding agents - Less losses of raw material due to good flowability and low dusting • Easier dosing
Tricalcium Citrate DC	
Calcium Phosphate DC	
Ferrous Fumarate DC	
Magnesium Carbonate DC	
Trimagnesium Dicitrate DC	
Magnesium Hydroxide DC	
Magnesium Lactate DC	
Magnesium Trisilicate DC	

Granulates for optimal Sachets and Sticks

Thanks to their granular form and exceptional flowability, our granulated and microencapsulated products allow for the easy handling and filling of sachets and stick packs. Additionally, our micro-encapsulated products offer a mild taste and low reactivity, which allows for the development of exceptionally good tasting finished products.

GRANULATES FOR STICKS AND SACHETS
Ferrous Sulfate, dried Micro2
Ferrous Fumarate, microencapsulated
Ferric Pyrophosphate Micro2
Magnesium L-Aspartate
Magnesium Citrate
Zinc Oxide, microencapsulated

Special grades for Soft Gelatine Capsules and for Chewable Tablets

An homogeneous and smooth distribution of the APIs in the oil is essential for the production of appealing soft gelatin capsules. This may be difficult with some common grades of many minerals. To help with this, Dr. Paul Lohmann® offers a range of minerals with the right particle size to achieve optimal soft gelatine capsules.

Avoiding the bad taste of some mineral salts is always a challenge when developing chewable products. Dr. Paul Lohmann® offers a range of minerals salts, which allow for the production of good tasting chewable products.

OUR PRODUCTS
Tricalcium Citrate 4-hydrate
Ferrous Fumarate
Ferrous Gluconate
Ferric Pyrophosphate
Ferrous Sulfate dried
Trimagnesium Dicitrate, anhydrous
Trimagnesium Dicitrate 9-hydrate
Magnesium Glycerophosphate
Magnesium Lactate 2-hydrate
Magnesium Oxide
Zinc Citrate 3-hydrate
Zinc Sulfate 1-hydrate

Mineral Salts Low in Endotoxins for Injectables

The manufacture of products for parenteral administration requires particular caution: it is subject to special requirements [11] and is regulated by Chapters 2.6.8 and 2.6.14 of the European Pharmacopoeia (Ph.Eur.). [12]

For this very special kind of pharmaceutical products Dr. Paul Lohmann® offers a range of mineral salts with very low levels of endotoxins (< 6.0 EU/g), used to facilitate the production of parenteral products, such as injectables and dialysis solutions.

Endotoxins* or pyrogens are generated, for example, when gram-negative bacteria decompose. [9]

Quantities of these lipopolysaccharides as low as 0.1 ng per kilogram of bodyweight can cause fever reactions in humans and animals [10] if they get into the bloodstream.

OUR PRODUCTS
Calcium Acetate
Magnesium Acetate 4-hydrate
Magnesium DL-Aspartate 4-hydrate
Magnesium Oxide light
Magnesium Sulfate
Potassium Acetate
Potassium DL-Aspartate 0.5-hydrate
Sodium Acetate 3-hydrate
Monosodium Citrate anhydrous
Trisodium Citrate 2-hydrate
Sodium Glycerophosphate
Sodium Lactate Solution

* Endotoxins are organic molecules with a mass of 10 to 20 kDa. They can exist as larger aggregates with a mass of up to 1000 kDa.

Overview of our Other Competencies

Micronized mineral salts

Micronization is a process by which particles are reduced to a size below 10 µm. Thus, dispersion behavior in suspensions is improved, the specific product surface increases (potential enhancement of bioavailability) and soluble mineral salts dissolve even better. Insoluble mineral salts of such fine particle structure are no longer perceivable in the mouth (no grittiness).

Microencapsulated products

In microencapsulation, the individual mineral salt particles are encased with a protective layer of vegetable fat. As a result, the mineral salts and the surrounding product are separated from each other in order to prevent chemical reactions or alterations in taste.

Micro2

The two positive characteristics of micronization and microencapsulation are combined in our Micro2 products. As such, they offer considerable benefits when used in food, dietary supplements and pharmaceutical products.

Research & Development (R&D)

Every day we deal with new challenges in application science and technology. That is why we also develop products and procedures in close collaboration with our customers.

Our R&D labs offer a wide variety of possibilities to develop products and applications. You can take the opportunity to work on your application together with us at our plant in Emmerthal/Germany.

References

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