**TECHNOLOGIES FOR THE PRODUCTION OF**

**PHARMACEUTICAL GRADE SODIUM CHLORIDE**

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**Abstract**

Sodium chloride for pharmaceutical applications must fulfill high purity requirements, as excipients or active pharmaceutical ingredients (API). In addition to the chemical purity, bacteriological limits must also be observed. The requirements are defined in pharmacopoeias (BP, Ch.P., JP, Ph.Eur., USP, KP, Ph.Rus.) and individually specified in quality agreements between salt producers and pharmaceutical companies.

Solar salts and rock salts cannot be used directly as pharmaceutical salt due to their insufficient purity and/or increased microbial content. The required purity can only be achieved by crystallizing vacuum salt. For this purpose, the methods single effect, multiple effect, MVR and recrystallization are available. The first three technologies require additionally the removal of mother liquor from the crystals by washing with purified water, usually per production campaign. The recrystallization process doesn’t require additional washing due to the low sulfate concentration in the process brine loop. The sulfate requirements for pharmaceutical salt will be automatically fulfilled. Generally, high bromide and potassium contents in the crude salt or in the crude brine make the production of pharmaceutical salt difficult or even impossible.

Several case studies from Europe, Asia and Africa confirm the recrystallization process as suitable for the production of pharmaceutical salt. The production of API sodium chloride requires compliance with GMP standards (FDA, EU-GMP). Pharmaceutical salt with extreme low sulfate limits, like in China, needs additional sulfate removal from the raw brine and/or double crystallization. Since anticaking agents or free-flow additives may not be used for pharmaceutical salt, special measures are required to prevent caking of the salt.

Granulation can be an additional process step. One possible application for granulation is the production of dry dialysis concentrates, where only the pharmaceutical grade vacuum salt is granulated or in mixture with other salts required for the dialysis. The preparation of pharmaceutical grade brine requires removal of undesirable ions, such as calcium, magnesium, and sulfate. This can be achieved by chemical precipitation, ion exchange and/or nanofiltration.

The main applications of pharmaceutical sodium chloride are hemodialysis and peritoneal dialysis. Further applications include IV (intravenous) solutions, oral rehydration salts and extraction of biological heparin. Due to the worldwide growing demand, this market segment might be of increasing interest for salt producers.

Keywords: Sodium chloride, vacuum salt, pharmaceutical salt, excipient, API, dialysis

1. **Supply and demand**

Pharmaceutical grade sodium chloride is required for dialysis solutions (hemodialysis, peritoneal dialysis, hemofiltration), intravenous (IV) injections, oral rehydration salts, channeling agents, osmotic agents, cleansing solutions, pharmaceutical formulations, nutrition (enteral, parenteral), extraction of biological heparin, and non-medical applications (corrosion testing, cosmetics, etc.).

Dialysis application dominates with a 50% share the global market due to the worldwide mounting kidney failure. The worldwide increasing wealth also drives the pharmaceutical grade sodium chloride market as spending in the healthcare sector are increasing. Dialysis is used as replacement for lost kidney functions, cleaning the blood from waste products through artificial means. Renal dialysis is vital to a growing number of patients around the world and the only alternative for many people, because kidney transplantation is precluded due to a shortage of donor organs. Sodium chloride is the major component of dry and liquid hemodialysis concentrates, as well as peritoneal dialysis solutions.

The second key application of pharmaceutical grade sodium chloride are IV solutions. These solutions have a wide range of applications which include regulation of blood pressure, hydration, electrolyte balance, medication and nutrition delivery, flushing, cleaning out IV lines and feed tubes, wound cleaning, renal dialysis and plasma collection.Urological and gynecological surgeries, and knee and hip replacements, may require up to 30 liters of solution for each treatment. Sodium chloride 0.9% injection bags are currently in shortage in the U.S. [1].

Most often, diarrhea kills children and elder people by dehydration. In order to replace the lost liquid, it is essential to feed extra drinks as soon as diarrhea starts. Oral rehydration therapy with oral rehydration salt (ORS) solutions is a cheap, simple and effective way to treat dehydration caused by diarrhea. It has substantially contributed to the dramatic global reduction in mortality from diarrheal disease. ORS is the name of a balanced glucose-electrolyte mixture, where each sachet with 20.5 grams contains 2.6 grams sodium chloride, 13.5 grams anhydrous glucose, 1.5 grams potassium chloride and 2.9 grams trisodium citrate, dihydrate [2].

Global pharmaceutical grade sodium chloride consumption is estimated to reach 690 kt by 2019 [3]. The market is continuously growing, with North-America as the leading consumer, followed by the Asia-Pacific region and Europe. U.S., Germany and Japan are also among the world’s largest consumers. The Asia-Pacific region with China, India, Indonesia, Vietnam, etc. is the fastest growing market across the world, followed by North-America and Europe. By 2021, an annual growth rate of approximately 6% of the worldwide dialysis patients is expected. The overall pharmaceutical grade sodium chloride market will continue to grow with a compound annual growth rate (CAGR) of more than 5% in terms of volume. It is estimated to reach 1,000 kt by 2025, making the Asia-Pacific region, Africa, South-America, Eastern Europe, and the Russian Commonwealth particularly attractive for new capacities or capacity expansion.

At present, only around 30 companies out of hundreds of salt producers worldwide produce pharmaceutical grade sodium chloride. One reason for this is that pharmaceutical grade sodium chloride is a salt specialty with a market share of less than 1% of the total global salt demand. The major part goes to applications in the chemical industry, road de-icing, human and animal nutrition and water treatment.

In addition, pharmaceutical salt is only suitable in the form of vacuum salt, and specific measures in production, quality monitoring and documentation are necessary. Extra certifications and qualifications are also required.

1. **Quality requirements**

A distinction is made between two different pharmaceutical grade salt qualities: *Excipient* and *Active Pharmaceutical Ingredient* (API). Both qualities must correspond to the current sodium chloride monographs in the relevant pharmacopoeias, including Ph.Eur., USP, BP, JP, Ch.P., Ph.Rus., KP. The requirements of these monographs for sodium chloride are generally the same but must be examined in each case regarding the markets and customer specifications [4]. The most important are USP, JP, Ph.Eur., BP, and Ch.P. (Tab. 1).

Tab. 1: Current chemical requirements for pharmaceutical grade sodium chloride\*)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Pharmacopoeia** | **USP** | **JP** | **Ph.Eur.** | **BP** | **Ch.P** |
| NaCl % | 99.0-100.5 | 99.0-100.5 | 99.0-100.5 | 99.0-100.5 | 99.5-100.5 |
| Arsenic ppm | ≤ 1 | ≤ 2 | ≤ 1 | ≤ 1 | ≤ 0.4 |
| Iron ppm | ≤ 2 | ≤ 2 | ≤ 2 | ≤ 2 | ≤ 3 |
| Bromide ppm | ≤ 100 | ≤ 100 | ≤ 100 | ≤ 100 | ≤ 100 |
| Phosphate ppm | ≤ 25 | ≤ 25 | ≤ 25 | ≤ 25 | ≤ 25 |
| Potassium ppm  \*\*) \*\*\*) | ≤ 500 |  | ≤ 500 | ≤ 500 | ≤ 200 |
| Magnesium+Alkali-Earth Metals ppm | ≤ 100 (as Ca) | ≤ 100 (as Ca) | ≤ 100 (as Ca) | ≤ 100 (as Ca) |  |
| Magnesium ppm |  |  |  |  | 10 |
| Aluminium\*\*) ppm | ≤ 0.2 | ≤ 200 ppb | ≤ 0.2 | ≤ 0.2 | ≤ 0.2 |
| Sulfate ppm | ≤ 200 | ≤ 200 | ≤ 200 | ≤ 200 | ≤ 20 |
| Heavy Metals ppm | ≤ 5 | ≤ 3 | ≤ 5 | ≤ 5 | ≤ 2 |
| Loss on Drying % | ≤ 0.5 | ≤ 0.5 | ≤ 0.5 | ≤ 0.5 | ≤ 0.5 |

\*) Incomplete parameter list.

\*\*) If intended for use in the manufacture of peritoneal dialysis solutions, hemodialysis solutions, hemofiltration, or hemodiafiltration solutions.

\*\*\*) If intended for use in the manufacture of parenteral dosage forms.

Limits for bacterial endotoxins are only applicable to the sodium chloride to be used in parenteral preparations in cases where no further appropriate procedure for removal of bacterial endotoxins is foreseen. The European pharmacopoeia requires an endotoxin content of less than 5 I.U./g. It should also be noted that other customer-specific limit values or stricter limits may be required, e.g. instead of the usual bioburden of max. 100 CFU/g only max. 10 CFU/g.

In addition to the individual customer and monographs specifications, the following requirements are necessary: Certified QM-system ISO 9001, HACCP, traceability system with product labelling, regular audits by customers and experts. API quality is manufactured under GMP-conditions (ICH Q7, EU GMP) and in Europe supported by CEP documentation. This requires certifications with re-audits by the responsible pharmaceutical authorities.

The requirements for the downstream products can be found in international standards and guidelines (e.g. [2], [5]).

**3 Production technologies**

**3.1 Vacuum salt**

For use as a pharmaceutical grade sodium chloride, only the purest salt quality, namely vacuum salt, is suitable. The feed to vacuum salt installations can be saturated brine from solution mining operations, rock salt from dry mining, or solar salt from solar evaporation/crystallization ponds. The basic processes for vacuum salt production are brine purification, thermal evaporation and crystallization [6]. For the vacuum salt crystallization itself, different process types are in use:

* Single Effect Evaporation
* Multiple Effect Evaporation (MEE)
* Mechanical Vapor Recompression (MVR)
* Recrystallization

Due to the high sulfate content in the mother liquor, typically 20-40 g sulfate per liter, MEE and MVR plants produce vacuum salts with relative high sulfate contents of 250 ppm or more. In order to achieve the sulfate content required by the pharmacopoeia, the adherent mother liquor on the salt has to be removed in the centrifuge by washing with purified water. This washing process also reduces the bromide and potassium content in the salt. But these secondary minerals cannot be precipitated in the brine treatment ("Schweizerhalle" process). It is often useful to remove the salt slurry for the production of pharmaceutical salt from the first evaporator stages in the multi-stage MEE and MVR plants before the concentration of the secondary minerals such as sulfate, bromide and potassium becomes too high in the brine.

Recrystallization plants normally operate with a sulfate content of *ca.* 3 g/l in the brine loop. Therefore, the produced vacuum salt from impure rock salts or solar salts is low in sulfate, typically below 100 ppm. Consequently, a salt washing on the centrifuge is not required [7]. The only necessary measure for quality assurance is the removal of very fine-grained salt (<0.2 mm) by sieving. This fine-grained salt shows increased contents of secondary minerals, mainly sulfate. The separated fine salt can be used for other applications. These “quality-by-design” installations produce pharmaceutical grade sodium chloride continuously over the year (Tab. 2).

Tab. 2: Typical analysis for pharmaceutical grade sodium chloride from recrystallization process

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Unit** | **Content** | **Parameter** | **Unit** | **Content** |
| Identification |  | Passes test | Phosphates | ppm | <1 |
| Appearance of solution |  | Passes test | Magnesium+  Alkaline Earth Metals | ppm | 30 |
| Acidity (0.01 M NaOH) or Alkalinity (0.01 M HCl) | ml | ≤0.5 | Iron | ppm | 0.03 |
| Loss on Drying | % | <0.1 | Sulfate | ppm | 86 |
| Arsenic | ppm | <0.5 | Ferrocyanides |  | Passes test |
| Barium | ppm | 0.07 | Assay | % | 99.9 |
| Heavy Metals (as Pb) | ppm | <3 | Potassium | ppm | 22 |
| Bromides | ppm | 26 | Aluminium | ppm | 0.05 |
| Iodides |  | Passes test | Bioburden | CFU/g | 1 |
| Nitrites |  | Passes test | Endotoxins | I.U./g | <0.8 |

The Chinese pharmacopoeia requires a very low limit of max. 20 ppm sulfate for pharmaceutical grade sodium chloride. There are two possibilities to produce salt of this quality: Firstly, sulfate removal from the brine by means of adding of barium salts such as barium chloride or barium carbonate. Consequently, low soluble barium sulfate will be formed and can be precipitated as solid sludge. Secondly, relative pure vacuum salt can be re-dissolved in water and can be re-crystallized again. The disadvantages of barium addition are the relatively high costs for the chemicals, the difficult disposal of barium sludges, and the risk of excess dosing of barium into the brine. The safe way is the twofold crystallization of vacuum salt. Of course, with the disadvantage of additional operational costs for producing pharmaceutical grade sodium chloride.

**3.2 Prevention of caking**

In order to prevent caking of the pharmaceutical grade sodium chloride during storage and transport, free-flow (silicates, silicon dioxide, carbonates) or anticaking agents (ferrocyanides) may not be used. To achieve a sufficient caking resistance, it is very important that the salt crystals from the crystallizers come with an enclosed brine content as small as possible (moisture content at 420°C <0.1%). The centrifuged salt is subsequently dried with hot air to a minimum residual moisture (moisture content at 110°C <<0.05%). Before storage, packaging and loading, the salt must be cooled down very well. It is recommended to circulate the salt stored in large silos pneumatically or with mechanical conveying equipment.

**3.3 Granulation**

A good technical solution for preventing hardening is the mechanical particle size enlargement by granulation and tableting. Sodium chloride in granular form is well known and used for different applications, such as for food industry and for water softening in dishwashers. Granulation of pharmaceutical grade sodium chloride by compaction of dry salt (size distribution 0.2-0.8 mm) with roller presses alongside crushing results in a product (size distribution 0.2-8 mm) which sustainably keeps its free-flowing property for a long time. At the same time, it can be assured that the dissolving of this coarse salt to be used in the preparation of aqueous solutions, e.g. dialysis solutions, works well. The experience shows that the production of large granule crystals coming from an Oslo growth-type crystallizer is not economical enough.

It is generally recommended that as little time as possible is spent between production, transport and processing of pharmaceutical grade salt. This is especially important when the salt is transported as bulk material or packaged in big flexible intermediate bulk container (FIBC) bags. If necessary, hardened salt can be crushed with lump breakers and milling machines into a small-grained, free-flowing product again.

**3.4 Pharmaceutical brine**

The “Schweizerhalle” process treats a raw rock salt brine into a purified brine with very low calcium and magnesium content. To meet the specification of a pharmaceutical grade brine, the sulfate content has to be reduced by adding of barium chloride and precipitation of barium sulfate and/or nanofiltration. But it is a precondition that the entering raw brine has already a low bromide and potassium content. A pharmaceutical grade brine can be used as a raw material in the pharmaceutical industry without an expensive additional crystallization step, e.g. for the production of IV solutions and dialysis concentrates (Tab. 3).

* 1. **Various important aspects**

The decision on the most feasible process for the production of pharmaceutical grade salt has to be taken on the specific circumstances such as available raw material, production rate and energy considerations. Beside of these aspects, high attention has to be paid on the correct selection of the materials of construction, quality of the used utilities etc. A supplementary contamination of the purified brine respectively of the pure salt has to be avoided.

Tab. 3: Specification for pharmaceutical grade brine (derived from the monographs for sodium chloride in the pharmacopoeias)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Unit** | **Content** | **Parameter** | **Unit** | **Content** |
| Identification |  | It responds to the tests for sodium and chloride | Phosphates | mg/l | ≤5 |
| Appearance |  | The solution is clear and colorless | Mg+Alkaline Earth Metals | mg/l | ≤25 |
| pH |  | 4.5-7.0 | Iron | mg/l | ≤0.5 |
| Particulate matter |  | Meets the requirements | Sulfate | mg/l | ≤65 |
| Arsenic | mg/l | ≤0.2 | Ferrocyanides |  | Free (passes test) |
| Barium | mg/l | ≤0.5 | Assay | % | Not less than 95.0% of the labeled content |
| Heavy Metals (as Pb) | mg/l | ≤1 | Potassium | mg/l | ≤125 |
| Bromides | mg/l | ≤25 | Aluminium | mg/l | ≤0.2 |
| Iodides |  | Free (passes test) | Bioburden | CFU/ml | ≤10 |
| Nitrites |  | Free (passes test) | Endotoxins | I.U./ml | ≤3 |

**4 Case studies**

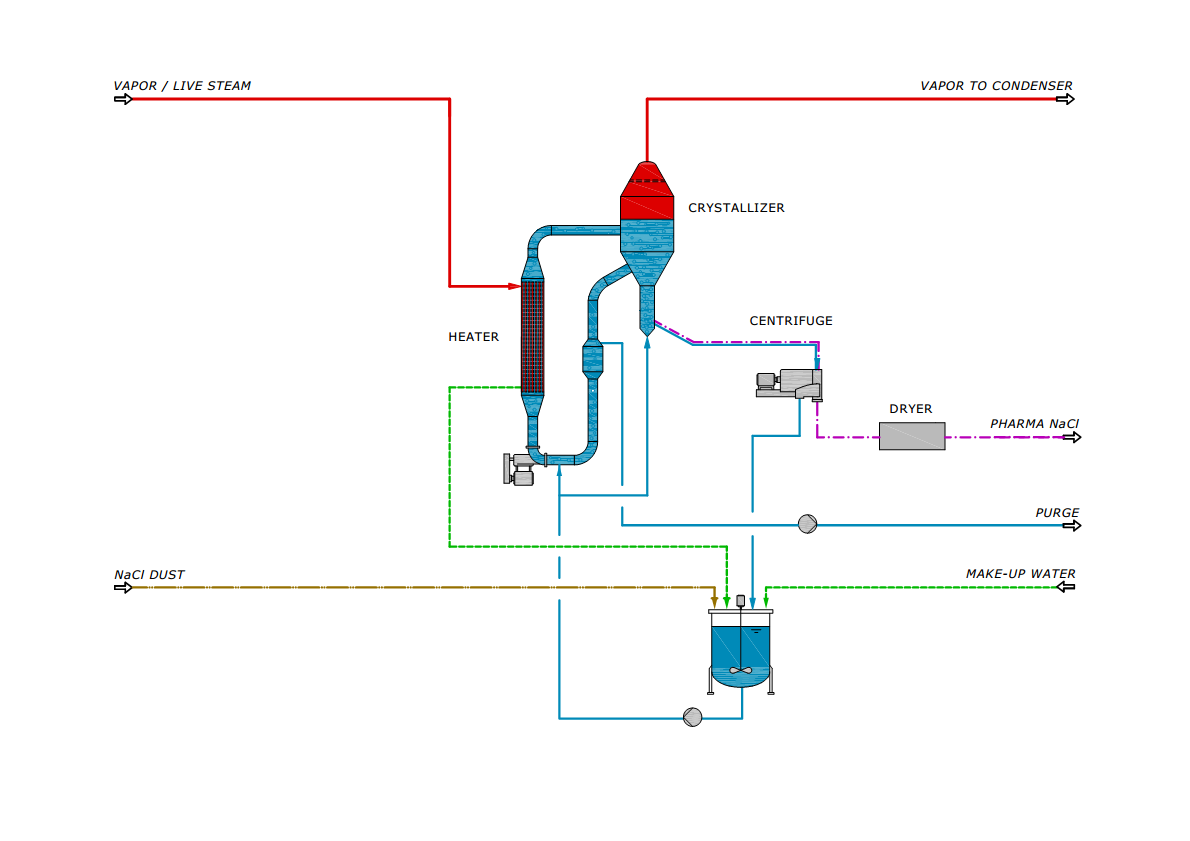
As previously mentioned above, there are various technologies available to produce pharmaceutical salts from different raw materials. The following section shall give a brief overview about typical realization possibilities.

**4.1 Pharma salt production from salt dust**

The first case shows a simple example how “off-spec” salt from a vacuum salt plant can be reutilized and be upgraded into pharma salt. “Off-spec” salt can come for instance from the wet scrubber or from the exhaust air cyclone of the dryer. Instead of dissolving or screening out of these fine crystals, they can be dissolved again in pure water, which can be in most cases the own vapor condensate. This extraordinary pure and saturated salt brine can be fed into a separate single “booster crystallizer” only for the production of pharmaceutical salt (Fig. 1).

This process example is simple in operation and realization and from an energetic point of view might have a comparable low thermal energy consumption. Many of the elder MVR installations might have a certain heat excess, which could be perfectly used to drive this “booster crystallizer”. In case of MEE installations, this unit can connected parallel between the 2nd and 3rd effect for instance, which helps to increase to energy efficiency. For larger production capacities, the unit can be equipped with a Thermal Vapor Recompression ( TVR) system as well.

Typical production capacities for such kind of installation lies between 300-600 kg/hr. Several such units are actually in the feasibility and/or execution phase already.

Fig. 1: Production of pharmaceutical grade sodium chloride from vacuum salt dust using single effect evaporation

**4.2 Pharma salt production from low quality solar salt**

As previously discussed, recrystallization plants may produce “automatically“ pharmaceutical grade sodium chloride salts, assuming the crude salt quality is within reasonable limits. This example of application shows how even very low crude salt qualities can be converted into high grade salts in an economical way. Given by the natural circumstances, the available solar salt in Bangladesh represents actually the biggest challenge in the production of pure vacuum salt. In the past years there was in Bangladesh a continuous conversion from the so called “black crude salt” (harvested from natural solar ponds) into “white crude salt”, which comes from solar ponds with polyethylene layers. Although the productivity of the solar ponds could be increased, the crude salt quality still remains challenging such as NaCl ~ 75%, MgCl2 ~3%, MgSO4 ~2.1%, CaSO4 ~3.4% and insolubles around 4%. Especially the high Mg content represents a difficulty to achieve the pharmaceutical grade quality. This latest development demonstrates a possibility to reduce efficiently the Mg- and the insoluble content in the raw material. By means of an additional cold leaching process, a significant part of the Mg content can be “leached out” by a partially unsaturated counter current brine flow. As a welcome secondary effect, also the insoluble particles will be removed as much as possible. Due to a smart overall water balance management, the salt losses can be kept on a minimum level. The upgraded raw salt can be fed directly into a conventional recrystallization plant without any additional treatment (Fig. 2).

Typical capacities lie between 5,000-30,000 kg/h.

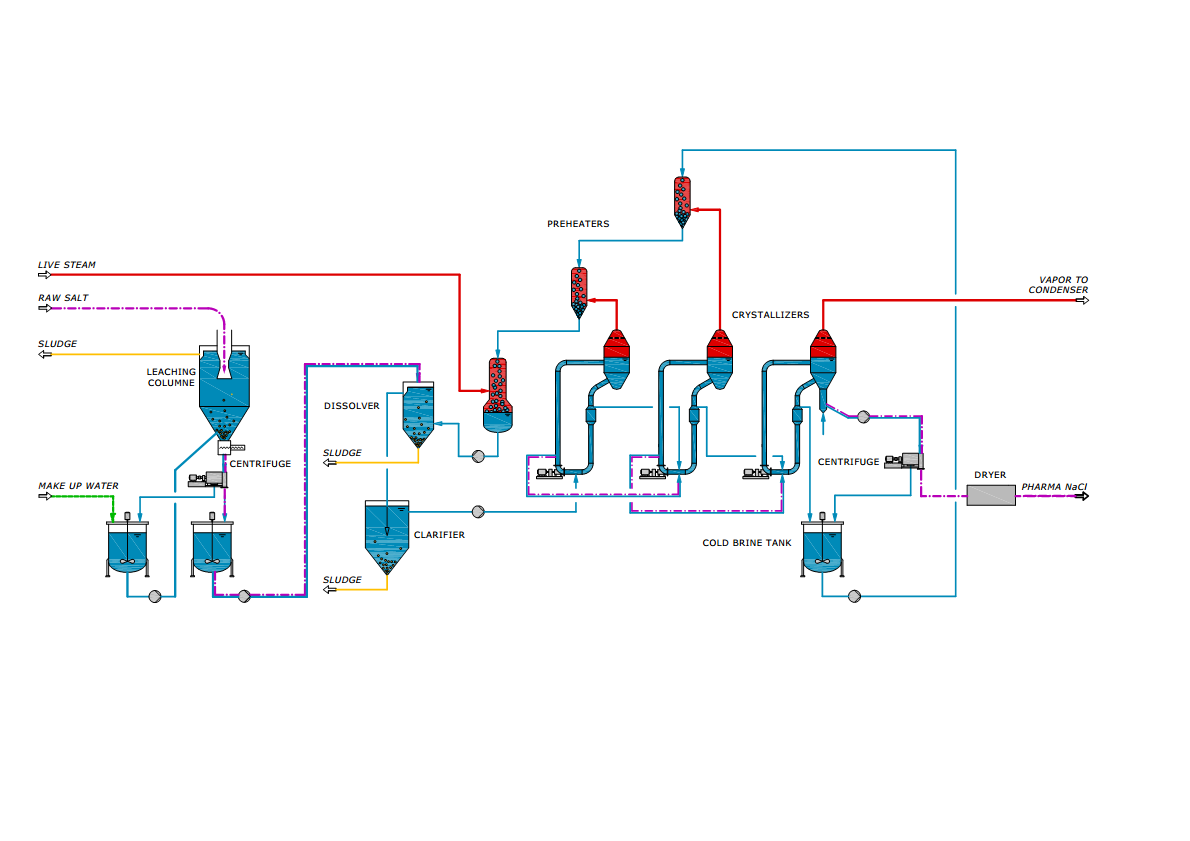


Fig. 2: Production of pharmaceutical grade sodium chloride from solar salt using three-effect recrystallization process (Bangladesh)

**4.3 Pharma salt production from rock salt**

As only a minor part of the total salt production is dedicated to the pharmaceutical industry, the question may arise how to split the production of a single salt plant into food and into pharmaceutical grade salt. The example of ENASEL, Algeria (Entreprise National de Sel) shows an interesting and economical solution. The available rock composition is around NaCl~89%, MgCl2~1%, MgSO4~5.7% and CaSO4~1%. A conventional recrystallization process would have been predestined for this kind of raw material, but the availability of the required utilities made a MVR process the most suitable solution. As widely known, the requirements for premium food grade salt are less stringent as the same for pharmaceutical salt.

For the production of the food grade salt, a so called “CaSO4 seeding process” is foreseen. The rock salt enters firstly into a cold leaching unit as described above in order to reduce the Mg content as much as possible. After dissolving the rock salt, the raw brine is led into a one-stage chemical reactor, where, by dosing of lime and/or caustic soda, the remaining Mg salts are precipitated. Only the CaSO4 content remain dissolved in the so-called semi treated brine. During the subsequent evaporation/crystallization process, beside the NaCl, CaSO4 is also crystallized. By means of an elutriation column, also called salt leg, the CaSO4 can be separated from the NaCl crystals and by additional washing in the centrifuge, a sodium chloride purity of approx. 99.95%wt will be achieved, which corresponds to a premium food grade salt quality.

The purge of this process together with the CaSO4 crystals is collected in an intermediate storage tank, from which a “Schweizerhalle brine treatment process” is fed. The MVR plant can be operated on demand with this fully treated brine and subsequently pharmaceutical grade salt can be produced (Fig. 3).

Typical feasible capacities are in the range of 10,000-40,000 kg/h. The share of pharma salt of this production capacity can be chosen more or less individually with the restriction, that the pharma production run should last at least 24 continuous hours.

1. **Conclusions**

For the production of pharmaceutical grade sodium chloride, brine, rock salt or solar salt and vacuum salt can be used as raw material. With the available technical standard processes for vacuum salt production, only a few additional measures are necessary to achieve the high quality pharmaceutical salt.

Granulation of pharmaceutical salt is an excellent way to keep the product free-flowing over a longer period. The production of pharmaceutical grade brine offers additionally new business opportunities.

The worldwide increasing demand for pharmaceutical salts is attributable to global population growth and increasing life expectancy. Investments in capacity extension in existing saltworks and in new green field installations might be economical. New installations should be preferably set up in proximity to the main users in the dialysis and IV solution industry.

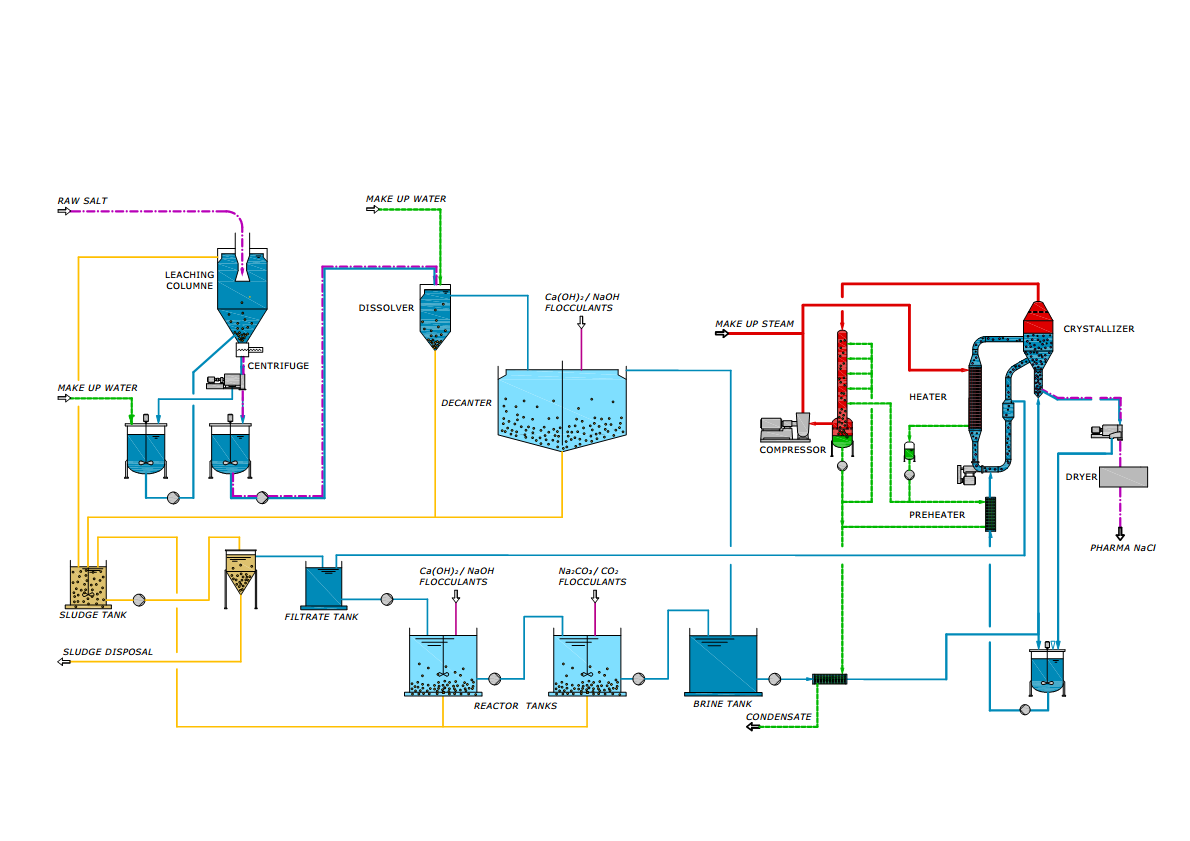


Fig. 3: Production of pharmaceutical grade sodium chloride from rock salt using MVR (ENASEL, Algeria)

**Literature**

[1] FDA Drug Shortages: Sodium chloride 0.9% Injection Bags. <https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Sodium%20Chloride%200.9per%20Injection%20Bags&st=c> (accessed 19 July 2017).

[2] World Health Organization, UNICEF: ORAL REHYDRATION SALTS - Production of the new ORS. Geneva, Switzerland, 2006.

[3] MarketsandMarkets: Pharmaceutical Grade Sodium Chloride Market, Global Trends & Forecast to 2019. Report Code: CH 3339, 2015.

[4] Goetzfried, F.: Presentation “Global Trends in Salt Quality”. International Salt Summit, NIRMA University, Ahmedabad (India), 2010.

[5] ISO 13958:2014-04: Concentrates for hemodialysis and related therapies.

[6] Kondorosy, E.: Vacuum salt production by using various processes. In: Proceedings of the International Conference on Salt, pp 40-45, Ahmedabad (India), 2006.

[7] Goetzfried, F; Kondorosy, E.: Recrystallization process for the upgrading of rock- and solar salts. In Proceedings of the 9th International Symposium on Salt, pp 700-711, Beijing (China), 2009 (edited by Sha Zuoliang, Gold Wall Press, Beijing).