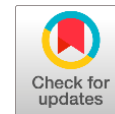


A comprehensive review of the use of Sodium Chloride (NaCl) in the development of the COVID-19 vaccine and medical applications



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Abstract Salt, specifically sodium chloride (NaCl), is the most common and essential salt used in chemical industries, food production and medical applications. This review extensively looked into the use of salt in medical applications and the development of vaccines, including the recently developed SARS-CoV-2 vaccine. This review also discussed several salt-producing systems to further understand the source of salt. This study focused on several main fields of medical use of salt: saline solution content, respiratory filtration, hyponatremia, ophthalmology, dermatology, and vaccine development studies. Several studies identified that NaCl could deactivate viruses as observed, NaCl is part of the COVID-19 vaccine excipient for Pfizer-BioNTech and AstraZeneca. Further applications of sodium chloride should be explored due to its various advantages in the medical field.

Keywords: salt, Sodium Chloride, NaCl, vaccine, SARS-CoV-2, COVID-19

1. Introduction

Hou et al (2017) defined the most common and basic salt as sodium chloride, represented by the symbol NaCl. Cirillo et al (1994) and Götzfried et al (2009) stated that it is necessary to note that different technologies for salt production are employed in other geographical areas of the world. Crystalline salt deposits (rock salt, solar salt in salt lakes) and dissolved salt are found in nature (seawater, salt lakes, natural brine), with seawater as the most common source of salt.

Further application of salt, in general, is described by Sedivy (2009), where the chemical industry consumes more than 60% of total production, making it the most important user of salt. This industry is largely concerned with the transformation of salt into chlorine, caustic soda, and soda ash, which are utilized in various applications such as petroleum refining, petrochemistry, organic synthesis, glass manufacture, and others. The human being is the second-largest user of salt, which is required to sustain physiological functioning and eating patterns, which account for around 30% of total salt production. Approximately 10% of the world's total salt production is needed for road de-icing, water treatment, cooling brine production, and several other smaller applications.

The history of salt's medicinal goes back hundreds of years, and it has been linked to many periods in human history. Cirillo et al (1994) revealed that seawater, mineral deposits, surface encrustations, salty lakes, and brine springs are all sources of salt. This approach resulted in significant deforestation in central Europe since wood was commonly utilized as a fire source to evaporate salt. Several regions' economies were heavily dependent on salt, which is reflected in the names of places. As salt was used as a basis for population censuses and taxation throughout the country, salt monopolies were commonplace. Other times, such as the French Revolution and the Indian Conflict of Independence, salt was blamed for the onset of war. Various cultural and spiritual meanings have been attached to salt over the centuries, dating back as far as the ancient Egyptians. Among the many benefits of salt in therapeutic applications include its ability to prevent putrefaction, reduce tissue swelling, and alleviate diarrhoea symptoms.

This comprehensive review study will look at medical uses as well as vaccine development. In addition, the contribution of sodium chloride (NaCl) in the recently discovered SARS-CoV-2 vaccine will be discussed. This paper's objective is to discuss sodium chloride (NaCl) and its role in the SARS-CoV-2 epidemic, as well as its manufacturing and medical applications. Sodium chloride will be evaluated in the context of medical applications, including saline solution, respiratory filters, hyponatremia, ophthalmology, dermatology, and vaccine development research, among other topics. As has been observed, sodium chloride (NaCl) has been found in several trials to be effective in treating viruses. NaCl is used as an excipient in the COVID-19 vaccine developed by Pfizer-BioNTech and AstraZeneca, which will be explored in greater depth in Section 5 of this paper.

2. Salt (Sodium Chloride, NaCl) and Production Technologies



Salt, specifically sodium chloride, is an ionic substance, while water is a molecular compound. A better understanding was described by Brown et al (2005) and supported by Atkins et al (2005), who explained that salt crystals, water molecules are composed of two hydrogen atoms joined together by polar covalent bonds to one central oxygen atom in the form of a two-atom molecule, each of which contains two hydrogen atoms. Oxygen in water molecules, which is electron-rich, has a partial negative charge, whereas the positive charge of hydrogen is predominant. The cation or sodium ion attracts the water molecule's partially negative end, while the anion or chloride ion attracts the water molecule's partially positive end. The ion in the solution is stabilized by the water molecules, which remove it from the sodium chloride lattice and completely surround it in a hydration sphere. Hydrated ions are dispersed uniformly throughout the solution due to their ease of movement through the water molecules. Crundwell (2019) illustrated the dissociation of salt in Figure 1, where sodium and chloride ions are simultaneously removed from the surface to produce hydrated ions in the solution (Crundwell 2019).



Figure 1 The dissociation of salt to form chloride and sodium ions.
 Source: Crundwell (2019)

2.1. Technology in Salt production

2.1.1. Salt Production: Vacuum Crystallization

Vacuum salt requires the highest standards of quality. In its study, Sedivy (2009) described that solution mining is often used to extract brine from beneath the surface, which is subsequently chemically purified. Meanwhile, Kondorosy (2006) explained that these brines are nearly saturated, with a concentration of roughly 25% NaCl. Recrystallization is a well-known process in salt plants, although until now, it has been underutilized. This method can be used when the raw material is in solid form (rock- and solar salt). Recrystallization consumes a smaller amount of energy (steam, electricity) than other vacuum salt processes. The high vacuum salt quality, which can be achieved almost entirely without the addition of additives, is another noteworthy feature. A high-purity product can be made from raw salts that contain a considerable fraction of natural contaminants. Recrystallization is a type of adiabatic flash evaporation, including other processes. Flash crystallizers at varying pressures will be used to process a hot, saturated brine. Vacuum crystallizers achieve supersaturation via evaporation and adiabatic cooling of the brine feed simultaneously, and the crystallized salt production will begin as depicted in Figure 2.

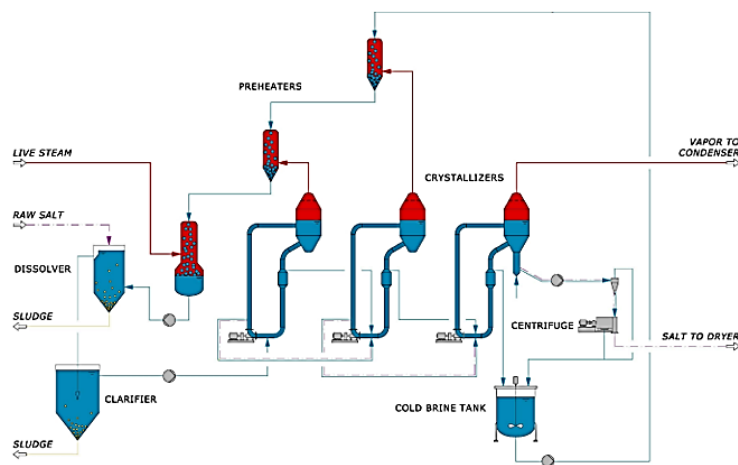


Figure 2 Mechanical Vapour Compression system.
 Source: Crundwell (2019)



Sediyy (2009) added that to crystallize 1 tonne of salt, 3 tonnes of water must be evaporated. A six-effect evaporation machine uses 0.62 tonnes of live steam six times. Steam condensation transfers 390 kWh t⁻¹ of salt heat at a pressure of 10 bar. In order to produce 1 tonne of salt, 450 kWh of primary energy is needed, assuming that the steam boiler works at 75 % efficiency.

2.1.2. Salt Production: Mechanical Vapour Compression

If electrical power is inexpensive, radial compressors can be employed to recompress vapour from the evaporator. Condenses in a heat exchanger against running brine and reaches boil due to the compressor raising the temperature of the vapour to that point. This technology utilizes about 160 kWh of electricity per tonne of salt. Assuming a 35% power generating efficiency, this system will consume around 450 kWh of primary energy per ton of salt. It is expensive to operate and maintain thermal evaporation units (vacuum plants) and vacuum salt. Because it is crystallized from brine containing up to 4% sulphate, vacuum salt always contains sodium sulphate, often 200-500 ppm or higher. Despite its low calcium and magnesium content (in the 1 - 10 ppm range), vacuum salt rarely achieves 99.95 % purity (Sedivy 2009; Kondorosy 2006).

Evans and Miller (2002) revealed that the evaporator heats the saline water to evaporate in the Mechanical Vapour Compression method. Compressing vapour raises both its temperature and pressure. The saline water supply is vaporized by steam after it has been heated. Condensation of water vapour and a steam jet generate enough heat to evaporate the saline feedwater that enters the reactor, as illustrated in Figure 3 (Evans and Miller 2002).

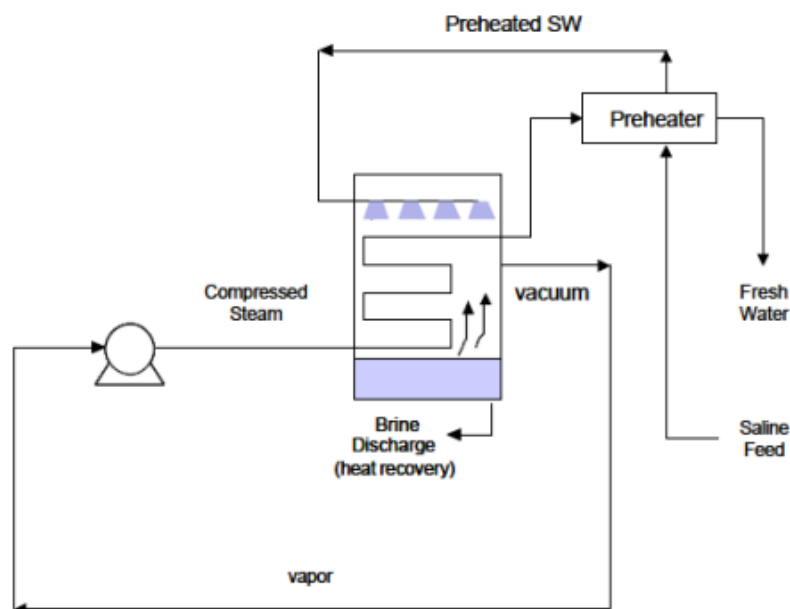


Figure 3 Mechanical vapour compression system.

Source: Evans and Miller (2002)

2.1.3. Salt production: Solar Evaporation (Seawater)

The seawater salt production process begins with stabilization, removing large particles from seawater and serving as a feed reservoir. This is followed by evaporation, concentration, crystallization, and finally, harvesting the final salt product, as mentioned by Santosa (2015).

Further understanding of solar evaporation salt production is described by Sulistyaningsih and Alighiri (2018) with seawater pumped into ponds to collect salt, as depicted in Figure 4, where it steadily builds up over time. In these ponds, seawater was evaporated by solar evaporation, which was then used to control the salt content of the water. The Bunker, which serves as a storage facility for the water, is where the old water is stored. The crystallization process took place in the crystallization table. Evaporation begins after going through seawater settling and evaporation ponds. After the salt crystallizes, it is harvested. After collecting the salt, the crystallized salt was also washed. In addition, as the land was being drained of salt, the harvested salt was moved from the salt table to a mound. For additional processing, it was shipped to a warehouse.

As much as 90% of the water must evaporate before NaCl crystals begin to form. Another 6.16 percent is evaporated before the brine (bitterns), which includes 8.37 kg NaCl per m³ of original seawater, is discarded. The sun's evaporation can recover 21.72 kg of NaCl from a cubic meter of salt water. Saturated salt brine thermal evaporation requires 43.74 kg, whereas virtually saturated brine requires 3 kilograms of water to evaporate 1 kg of NaCl crystals. The good news is that solar energy is completely free (Sedivy 2009).

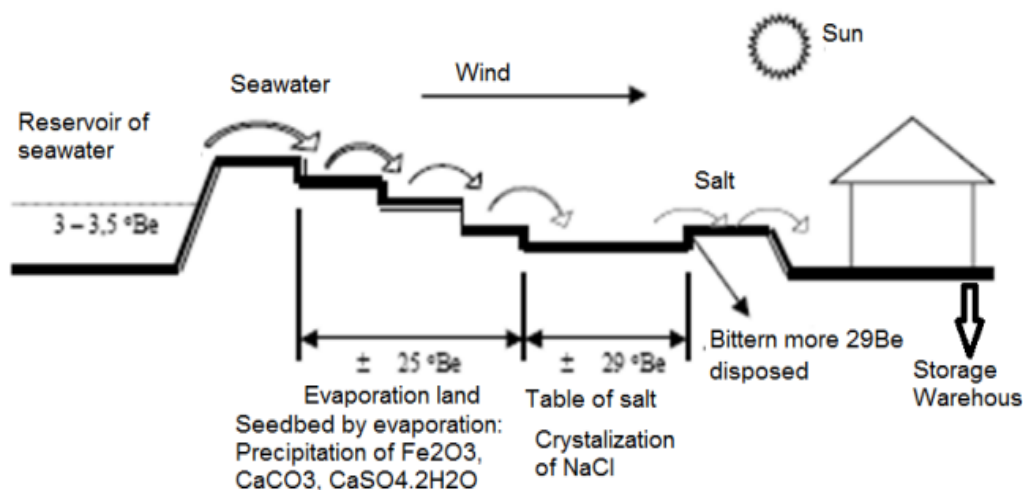


Figure 4 Process of evaporation used to produce salt.

Source: Sulistyarningsih and Alighiri (2018).

2.1.4. Salt production: Solar Evaporation (Seawater)

Desalination is becoming increasingly popular as a freshwater alternative due to the increasing demand caused by human population growth and industrial activity. A huge amount of saline water is treated to produce freshwater during the desalination process, and a concentrated brine is returned to the environment. The desalination chemicals and salt concentrations in the concentrated brine are very high. Various efforts have been made to limit, treat, or reuse rejected brine due to the detrimental environmental effects of wrong brine treatment and stricter pollution control legislation. Brine reuse is one of the most promising approaches to brine treatment in terms of both ecological and salt conservation. By combining desalination with salt production, waste brine can be recycled and valuable salts recovered. Total desalination expenses can be reduced by attaining zero liquid discharge, boosting water recovery, and producing profitable salt through integrated processes (Wenten et al 2017).

Wenten et al (2017) defined desalination as the method of purifying salty water, such as brackish water or saltwater, by eliminating the salts in domestic and industrial usage. A two-stream separation of the saline water is achieved using this procedure. Water in the first stream is fresh and has relatively low salt content, whereas water in the second is brine and has a relatively high salt content. Thermal and membrane desalination methods are the two main types of desalination processes, as mentioned by Al-Karaghoul, and Kazmerskic [31]. The most common seawater desalination processes include multi-effect distillation (MED), multi-stage flash (MSF), and vapour compression (VC) (Wenten et al 2017; Al-Karaghoul and Kazmerski 2013).

Membrane-based desalination systems use a permeable membrane to remove salts from water. Due to the membrane's selectivity, one component can only be accessed by the other (Wenten 2002; Wenten et al 2017). Reverse osmosis (RO), nanofiltration (NF), forward osmosis (FO), and membrane distillation (MD) are membrane desalination technologies. In the meantime, electrodialysis (ED), electrodeionization (EDI), and microbial desalination cells (MDC) can produce freshwater by allowing salts or ions to pass across a membrane (Wenten et al 2017).

2.1.5. Salt Production: Double Fortification Salt (DFS)

A double fortification salt (DFS) containing iodine and iron has been proposed as a means of mass prevention of iron deficiency anaemia. Iron reactions were a major concern in the early stages of DFS manufacturing. Later, DFS is produced as an iron formulation stabilized to prevent adverse reactions between iron and iodine. DFS can now be made by mixing iron into iodized salt and letting it sit for a while. Iodizing salt is a simple technique involving combining an iodine solution, either potassium iodate or potassium iodide, with the salt. Most countries have set a minimum iodine retention criterion for iodized salt. Washing and drying salt before iodization is possible to produce refined salt with a NaCl content of >98%, however, this is optional to suit customer demand for whiter salt and is not needed to iodize (Shields and Ansari 2021).

Adding iron to salt that has already been iodized is simple and requires only the dry mixing of the iron formulation with the salt. Figure 5 depicts an overview of the DFS manufacturing process. As part of the two-step procedure to make DFS (with Ferrous Sulphate, SHMP, and Salt), a premix was first made of salt with FS and SHMP, blended with salt and then dried. For the production of DFS (with encapsulated ferrous fumarate), the ferrous fumarate is mixed with iodized salt in a 1:10 ratio. A ribbon blender or screw mixer is used to generate the final DFS product, which is then combined with any remaining bulk iodized salt and blended (Shields and Ansari 2021).

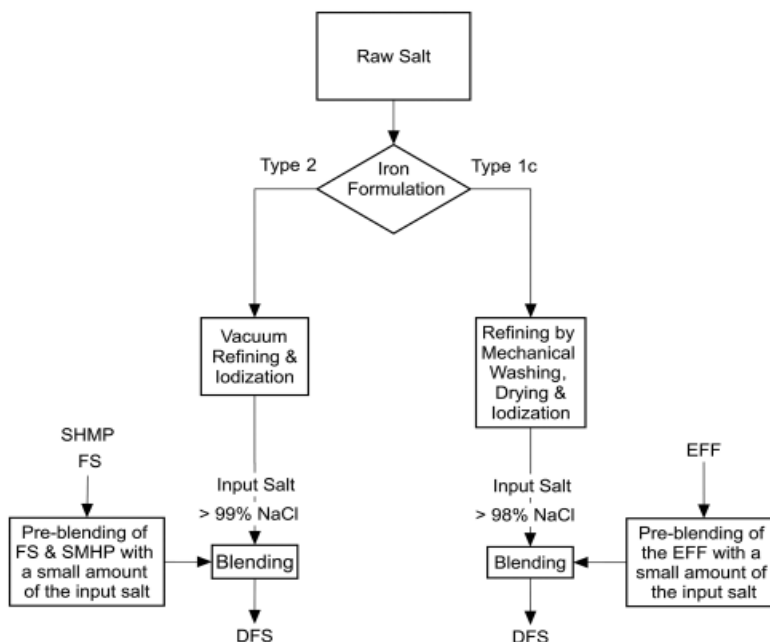


Figure 5 The overview manufacturing process for DFS.

Source: Shields and Ansari (2021).

2.1.6. Salt Production: Pharmaceutical Grade Sodium Chloride

Sodium chloride must meet strict purity standards as a pharmaceutical excipient or active pharmaceutical ingredient (API). The bacteriological limitations must also be respected in addition to the chemical purity. Due to the lack of purity and/or increased microbial content, solar salts and rock salts cannot be used as medicinal salts. Crystallization of vacuum salt is the only way to reach the desired level of purity (Kondorosy and Evatherm 2018).

One of the methods being defined by Kondorosy and Evatherm (2018) is single-effect evaporation which shows how "off-spec" salt from a vacuum salt mill can be used and converted into pharma salt. The wet scrubber or the dryer's exhaust air cyclone may be the source of "off-spec" salt. Because these thin crystals are so small, they can be dissolved in pure water, usually the condensate of their vapour. To make pharmaceutical salt, a special "booster crystallizer" must be used to process this exceptionally pure and saturated salt brine (Figure 6) (Kondorosy and Evatherm 2018).

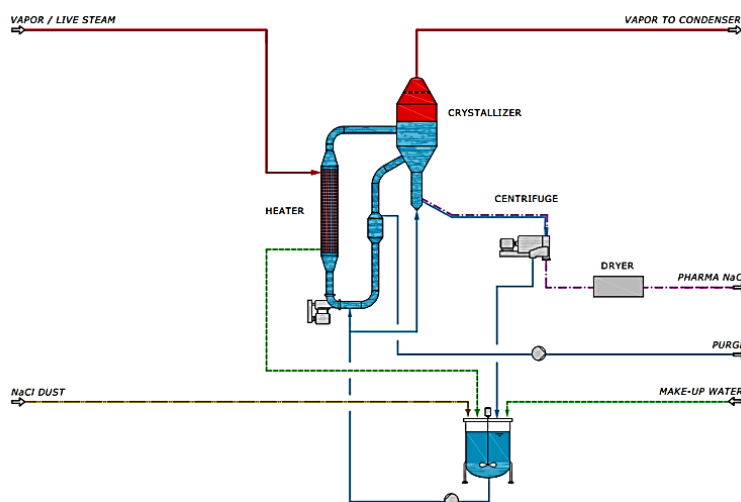


Figure 6 Schematic diagram of single effect evaporation.

Source: Kondorosy and Evatherm (2018).

This process example is easy to implement and may have a thermal energy consumption comparable to that of this process. Many of the older MVR systems may have a surplus of heat that might be used to power this "booster crystallizer". A parallel connection between the 2nd and 3rd effect, for example, can help improve energy efficiency in MEE installations. An optional Thermal Vapor Recompression (TVR) system is available for a bigger production capacity (Kondorosy and Evatherm 2018).



Hemodialysis and peritoneal dialysis are two of the most common uses of pharmaceutical sodium chloride. IV (intravenous) solutions, oral rehydration salts, and the extraction of biological heparin are just a few examples of further applications. A pharmaceutical grade brine must be prepared by removing undesired ions, such as calcium, magnesium, and sulfate. Granulation can be an additional stage in the manufacturing process. Granulation could be used to produce dry dialysis concentrates (Kondorosy and Evatherm 2018).

3. Sodium Chloride (NaCl) in Medical Applications

3.1. Salt Production: Pharmaceutical Grade Sodium Chloride

Meng et al (2018) conducted a study to compare the effects of hypertonic saline solutions containing 3% sodium chloride injections in peripheral IV catheters to routine-care solutions (RCSs). Adult inpatients were examined to determine the frequency of patient and catheter phlebitis in this study, which concluded that patient and catheter phlebitis rates were not significantly different between infusions of % sodium chloride injection and infusions of routine-care solutions (RCSs) through separate PIV catheters. On the other hand, Dillon et al (2018) performed the same investigation on the % sodium chloride delivered via peripheral venous injection on hyponatremia patients treated in the neurosurgical ICU and found it comparable to other hyperosmotic medicines for Infusion-related adverse events (IRAEs).

In addition, Smart et al (2019) studied the potential of hypertonic saline to prevent shedding of the endothelial glycocalyx (EG) and inflammation after fluid resuscitation. In this study, hypertonic saline was compared to isotonic saline in patients with suspected sepsis in the emergency room to see if it affected EG shedding and inflammation signs. Compared to individuals given isotonic saline, Smart et al (2019) also indicate that a single bolus of hypertonic saline potentially increased blood osmolality but observed no effect on markers of epidermal growth factor (EG) shedding or inflammation. In a post-hoc review of data from the Edinburgh and Lothians Viral Intervention Study (ELVIS) pilot randomized controlled trial (RCT), Ramalingam et al (2020) reported that NaCl also has an antiviral action in vitro that is effective against a wide range of viruses, and conducting hypertonic saline nasal irrigation and gargling (HSNIG) reduced the coronavirus upper respiratory tract duration infection (URTI) by an average of two and a half days. Chatterjee et al (2021) supported Ramalingam et al (2020) statement and added that SARS could also be removed from the nasal cavity and throat using a normal saline nasal spray and gargle (NSNSG). Mullaguri et al (2020) also identified the administration of fludrocortisone, salt pills, and a 3 % buffered hypertonic saline solution to maintain euvolemia and treat hyponatremia. Application of 0.9% salt solutions on higher-risk patients studied by Jo et al (2017) and this study taken into the possibility of contrast-induced acute kidney injury (CI-AKI) following contrast-enhanced computed tomography (CE-CT), where it was found that the risk of CI-AKI was the same following administration of a balanced salt solution.

3.2. Sodium Chloride in Respiratory Filter Development

Quan et al (2017) indicate that increasing osmotic pressure and crystallizing salts on salt-coating can improve virus adsorption on filter fibres and inactivate viruses. Quan et al (2017) have developed a reusable viral deactivation approach for surgical mask main fiber filtering units using sodium chloride salt. Rocky et al (2020) conducted a similar study where salt coating on the fiber surface dissolves and then recrystallizes during drying, killing pathogens exposed to virus aerosols. Compared to a normal mask filtration layer, salt-coated filters had a much higher filtering efficacy, and mice infected with virus penetrated via salt-coated filters had a 100% survival rate. If a respiratory virus outbreak or pandemic occurs, salt-coated filters could be employed to produce a broad-spectrum airborne pathogen prevention device (Quan et al 2017).

On the other hand, Rubino et al (2021) created salt-based formulations to coat membrane fibers in the manufacture of antimicrobial filters. Salt recrystallization effectively matched the H1N1 influenza virus and *Klebsiella* bacteria's inactivation kinetics. The pathogen inactivation capability of the salt coatings was maintained even in extreme environmental conditions Rubino et al (2020).

Filtration rather than destroying viruses is how the filtering facepiece successfully eliminates viruses. For centuries, sodium chloride (NaCl) has been used to prevent infections in various conditions. The hygroscopic salt crystals on the filtering facepiece attract harmful organisms if it reach the surface. Antiviral medications and filtration might be included in the masks, making them far better both in use and against cross-infection after they are thrown away. Nano dry salt (NDS) particles were created using NaCl solution in Park et al (2021) investigations, eliminating the necessity for the chemical immersion approach seen in Figure 7. In terms of aerosol filtration testing, this method is comparable to the standard roll-to-roll method (Jia et al 2020; Khandavalli et al 2018). HCoV-OC43 and 229E strains were used as SARS-CoV-2 surrogates and standard filtration test particles to verify the material's efficiency in deactivating coronavirus Park et al (2021).

According to Machado et al (2020), modified nonwoven sheets showed significant inactivation of airborne human coronaviruses (surrogates of SARS-CoV-2) while retaining their original filtration capabilities. These coated sheets inhibited aerosol filtering with pressure drop even during saliva droplet and dust exposures. Precertification face masks may be required to undergo valve leak DOP, NaCl, and inhalation/exhalation testing to meet NIOSH guidelines (Respirator Precertification). One of the most effective techniques for assessing whether face respirators meet the NIOSH protocol

requirements is the sodium chloride (NaCl) aerosol method (Rengasamy et al 2018; Forouzandeh et al 2021). The ability of a mask to filter sodium chloride (NaCl) aerosols determines whether or not it is approved under British Standard BS EN 149:2001+A1:2009. These aerosols have a sub-micrometer particle size, making it possible to compare their effectiveness against viruses that may be killed during the aerosolization process to NaCl filtration (Zone et al 2020; Pascoe et al 2020). NaCl particles smaller than 500 nm were used by Mallakpour et al (2021) to test the filtration ability of a full-face mask. This investigation collected pressure drops, quality factors, and resistance to disinfection (70% ethanol).

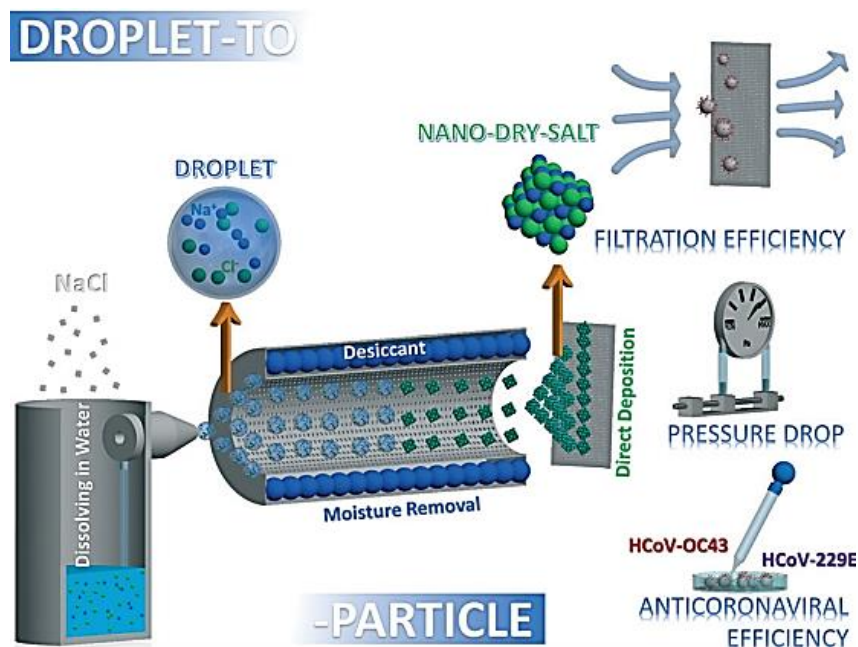


Figure 7 Nano dry salt generation and direct deposition on an electret nonwoven sheet.

Source: Park et al (2021).

3.3. Sodium Chloride in Hyponatraemia

Hyponatremia is frequently induced by a vasopressin axis imbalance. It is also common to use oral sodium chloride as the mainstay of treatment to improve serum sodium levels (Jacob et al 2019). Several studies indicated that the most effective treatment for hyponatremia symptoms is using 3% sodium chloride (3% NaCl) (Metheny and Moritz 2021; Shah et al 2022). Patients with severe hyponatremic encephalopathy, traumatic brain injury, and cerebral edema may benefit from this treatment. With the hyperosmolar drug, infusion responses were either rare or no more prevalent than with normal solutions (Metheny and Moritz 2021). A study made by Constantinou et al (2021) using oral sodium chloride (Slow Sodium[®]) as hyponatraemia prophylaxis in patients with Grade 1 and Grade 2 aneurysmal subarachnoid haemorrhage (aSAH), according to the World Federation of Neurosurgical Societies (WFNS) observed that prophylactic treatment for hyponatraemia with this drug was found to be effective and safe, resulting in less hyponatraemia, fewer hospital days and better long-term neurological outcomes. Woodward et al (2018) indicate in their study that continuing treatment for high sodium concentrations may be necessary if there is no underlying reversible cause such as medicine or infection. Reducing fluid intake, increasing urine volume (thus allowing for less severe liquid restriction), or using vaptans (a solute such as sodium chloride or urea) to promote aquaresis are all viable options. When antidiuretic hormone (ADH) levels are consistently elevated, solutes such as sodium chloride can be given to patients to increase urine volume. Meanwhile, in the pharmacy of children's hospitals, prescriptions of 3% NaCl is often administered following established policy or practice guidelines. Peripheral intravenous (IV) administration in a non-intensive care unit is permitted in a small percentage only of overall children's hospital pharmacies as per surveyed conducted by Shah et al (2022).

3.4. Sodium Chloride in Ophthalmology

Sodium (Na⁺) and chloride (Cl⁻) ions, which are key electrolytes in blood plasma and tears, were the topic of a study by Badugu et al (2020). According to this study, fluorescent contact lenses can be used to monitor the concentrations of Na⁺ and Cl⁻ ions in tears. To connect non-covalently to silicone hydrogel (SiHG) contact lenses, fluorescent dyes sensitive to Na⁺ and Cl⁻ were derivatized. As depicted in Figure 8, low-polarity and non-polar regions and interface regions may be present in macromolecular structures. There is a light pink water or tear fluid channel, and a blue silicone region is seen. Green spots on the lens surface indicate ionic species. The water-silicone interface is a binding site for sodium and chloride fluorophores.

According to the study's findings, NaCl-lens could be used to identify rapid, non-invasive whole-body hydration and other linked illnesses or infections (Badugu et al 2020).

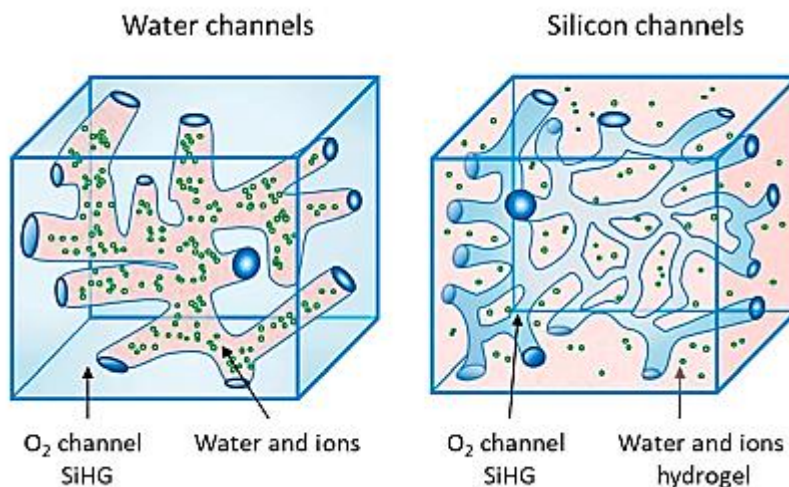


Figure 8 Contact lens semi-interpenetrating polymer networks.
 Source: Badugu et al (2020).

In a study by Carracedo et al (2018), a viscous artificial tear improved patient comfort and reduced corneal staining during the orthokeratology lens fitting process compared to saline solution. To determine whether or not using hypertonic saline solution following cataract surgery is safe and effective. To expedite satisfactory visual outcomes, especially in substantial postoperative corneal necrosis, the administration of 5% hypertonic solution has been demonstrated to be safe and beneficial in managing postoperative corneal edema (Tzamalidis et al 2020). It was found that the use of autologous serum-based eye drops for treating severe dry eye and a chronic corneal epithelial defect was safe and effective in the study by Shtein et al (2020). In most cases, the serum is obtained through specialized serum-separating tubes during regular blood draws. Blood is separated into serum and other solid components by centrifugation after being allowed to clot. After that, the serum can be taken out and diluted to the required concentration with an eye-compatible solution, such as balanced salt solution or preservative-free normal saline, or another sterile, preservative-free, eye-compatible solution.

3.5. Sodium Chloride in Dermatology

A study conducted by El-Amawy and Sarsik (2021) defined that dilution of intralesional injections of steroids with saline was utilized to lessen the risk of atrophy caused by the steroids. Saline has also been used to treat atrophic scarring following surgery to treat leishmaniasis, granulomas, and the therapy of acne scars. Intralesional steroid injections can be made more effective by diluting the steroids with saline, commonly used in dermatology. All types of atrophic scars were significantly improved by saline injection, but mild to moderate scars showed the most improvement (El-Amawy and Sarsik 2021). For 12 weeks, Khan et al (2020) injected an intra-dermal isotonic saline solution into the skin of individuals with post-acne atrophic scars under local anaesthesia. All wounds responded well to saline injections, although mild to moderate scars responded the best. Intradermal injections of normal saline into atrophic facial scars are safe and effective, according to Asghar et al (2019). Another study by Pravangasuk et al (2021) showed that injecting normal saline with a pneumatic injector helped cure acne scars. As a result of the lower risk of side effects, injectors are more commonly used for acne scar treatment than hypodermic needles.

4. Sodium Chloride in Various Vaccine Study

Several studies identified that a virus could be rendered inactive by applying NaCl (Wieringa et al 2011; Quan et al 2017; Luo et al 2017; Tatzber et al 2020; Gupta 2020). According to Bishop et al (1976), it was shown that incubating reticuloendotheliosis virus (REV) cells for 24 hours in conditions with a lower concentration of sodium chloride hindered viral growth in vaccine development (NaCl). At the same time, increasing the amount of suppression was associated with a decrease in salt concentration in the medium (Bishop et al 1976). In the study, Ramalingam et al (2018) also remarked that bleach's core component, HOCl, is antibacterial and antiviral and added myeloperoxidase is essential for the generation of HOCl in non-myeloid cells. Increased access to sodium chloride (NaCl) can improve antiviral activity against many different types of viruses (Ramalingam et al 2018).

It has been hypothesized that high NaCl concentrations affect immune responses in various ways. Type I interferon generation and signalling appear to be significantly influenced by high salt levels, as shown by these data, which adds to our

understanding of how innate immune responses are controlled, as indicated by Zhang et al (2018). Luo et al (2017) also defined that simply changing the NaCl content in vaccines has the potential to greatly enhance the vaccine's adjuvant effects, which are safe, quick to make, and inexpensive. When tested in vitro on the E.G7-OVA tumor model, the OVA/Al/high salt formulation significantly reduced tumor growth (Luo et al 2017).

A method studied by Yang et al (2020) using liquid phase extraction to measure residual VPA in influenza vaccine showed significantly improved by using a saturated NaCl solution to salt out the analyte from the vaccine medicament component. The Dole extraction process was further enhanced by Yang et al (2020) by adding saturated sodium chloride (NaCl) solution to the vaccine sample to salt out valproic acid (VPA) in the flu vaccine. While for the influenza vaccine, Santos et al (2018) used solubility reduction at high salt concentrations to extract organic compounds by salting out and revealed that influenza vaccine NTC7482-41H-VA2 HA purification also uses low-salt purification, which is cost-effective, ecologically safe, and efficient (Santos et al 2018). The adsorption of antigens can enhance the immunostimulatory effects of vaccines onto aluminium hydroxide (AH) adjuvants. The function of antigen adsorption on aluminium hydroxide (AH) adjuvants was to boost vaccination immunostimulatory potency (Art et al 2017). However, Art et al (2017) identified that NaCl affects the structure of AH adjuvants, leading to vaccine formulation changes and misinterpretation of antigen adsorption on adjuvant particles. Art et al (2017) also demonstrate that the surface chemical composition of commercial AH adjuvant particles suspensions is not affected by ionic strength (*I*) adjustment with NaCl nor by deposition on gold surfaces. Meanwhile, another study conducted by Crommelin et al (2021) included sodium chloride in the viral vector vaccine components for the Zaire Ebola virus.

5. Sodium Chloride Applications during SARS-CoV-2 pandemic

5.1. Sodium Chloride in SARS-CoV-2 Treatment and Immunization

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), a new virus, has caused a global health crisis that is unprecedented. Aerosol droplets from the mouth or nose travel from one infected patient to another through a direct aerosol attack, the size of which varies depending on the type of the encounter, such as talking, coughing, or sneezing. As depicted in Figure 9, respiratory viruses can commonly enter the body through the nose, mouth, and eyes (Rocky et al 2020). In an environment where most of the population lacks antibodies to this new virus, an infection can spread quickly and cause serious illness (Khandavalli et al 2018). A hypertonic saline solution was tested to determine if it could limit virus replication. The plasma membrane is depolarized by NaCl, resulting in a low energy state without affecting mitochondrial activity (Machado et al 2021). According to Machado et al (2021), a hypertonic saline solution containing 260 mM NaCl (1.5%) inhibits SARS-CoV-2 replication. In various stages of COVID-19 treatment, this discovery could lead to simple, safe and low-cost therapeutics. Pandemic costs could be reduced, and the health of infected people could be improved in the long run.

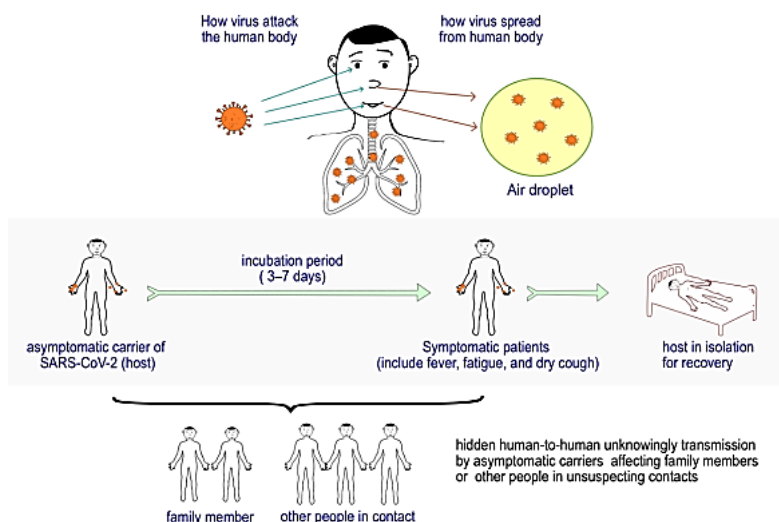


Figure 9 Infection route of COVID-19 in the human body.

Source: Rocky et al (2020).

As a result of the SARS-CoV-2 outbreak, widespread immunization is now necessary, but there are not enough resources to do it. Ramalingam et al (2019) state that the ability of sodium chloride to increase local chloride ions (NaCl) in the upper respiratory tract stimulates the production of hypochlorous acid (the active ingredient in bleach), which is a mechanism by which saline has antiviral properties. By inhaling heated sodium chloride (NaCl) particles into the lungs, Gupta (2020) showed that heated NaCl particles can kill viruses, leading to self-immunization in the lungs via SARS CoV-2 self-



attenuation. Hypochlorous acid and the chloride ion were shown to be responsible for inactivation, while heated NaCl particles were also capable of inactivating SARS-CoV-2. Edible salt, or sodium chloride (NaCl), can be applied as a further deactivating agent. With fewer than 2 milligrams of NaCl, micronized hot, dry NaCl particles can reach the pulmonary region (Luo et al 2017). Johnson et al (2020) developed a model for thermoplastic 3D printing of facemasks coated with NaCl or clay/biocellulose soaked with NaCl to aid in preventing the spread of COVID-19.

Coronaviruses, particularly SARS-CoV-2, destroy the ciliated epithelial lining of the nose and airways. Nasal irrigation or nebulizing aerosol of isotonic or hypertonic saline is a common respiratory or nasal care method. Saline's moisturizing effect improves mucociliary clearance on the respiratory epithelium and its ability to gel mucus. If given as soon as the first signs of a cold appear, it may be a helpful supplement to standard COVID-19 treatment. Children with bronchiolitis who use it as an aerosol are less likely to be hospitalized (Huijghebaert et al 2021). There is evidence that nasal saline rinses can reduce their severity (Singh et al 2020). SARS-CoV-2 viral load in recovered patients may be decreased by hypertonic saline, which may help break the transmission chain. Because of NaCl's broad antiviral properties and cleansing activity associated with gargling and nasal irrigation, these maintenance techniques function as gatekeepers for oral and nasal portals/passages (Panta et al 2021). Increased NaCl concentration outside of nasal and oral cell membranes may benefit SARS-CoV-2. This would also aid in releasing mucous secretions and reducing SARS-CoV-2 symptoms such as vomiting and coughing (Stathis et al 2021).

The SARS-CoV-2 epidemic has driven a surge in demand for medical equipment and medications. There was a critical lack of programmable syringe pumps in intensive care units, which are used to provide various drugs. Tarantini et al (2022) mixed five drugs in 26 ways and kept them at 25 °C for 14 days in glass vials or polypropylene syringes. The drug mixtures were evaluated in their purest form and diluted in NaCl 0.9% or G 5%. Combining more than two drugs can reduce individual doses while also reducing undesired side effects.

5.2. Sodium Chloride in SARS-CoV-2 Vaccine Development

The COVID-19 vaccine provides acquired immunity against the virus that causes coronavirus SARS-CoV-2 disease (Jamkhande et al 2021). Numerous worldwide immunization campaigns were launched after the new pathogen was discovered and sequenced. At this time, a few have been approved due to their excellent safety and efficacy records (Baden et al 2020; Dagan et al 2021; Voysey et al 2021). The SARS-CoV-2 vaccine's immune response elicitation is focused on the receptor-binding domain (RBD), which contains multiple neutralizing epitopes (Liu et al 2020; Robbiani et al 2020; Barnes et al 2020; Watanabe et al 2021). Vaccines assist the immune system in recognizing and fighting pathogens like viruses and bacteria, reducing the risk of infection. As a result of discovering the SARS-CoV-2 virus, scientists have made an extraordinary effort to produce several vaccines (Rutkowski et al 2021; Mehata et al 2021; Jamkhande et al 2021; Fiolet et al 2021; Kim et al 2021). More than ten potential vaccines have been given the green light for deployment in an emergency worldwide. A recent study found that the COVID-19 pandemic vaccines effectively protect individuals and limit their spread. Long-term consequences and unanswered questions about vaccination use, on the other hand, need to be assessed over time (Jamkhande et al 2021). Table 1 included the application of sodium chloride (NaCl) in medical as well as in the treatment of SARS-CoV-2 and the approved vaccines.

0.9% NaCl is commonly utilized as a control material in SARS-CoV-2 vaccination research (Abdul 2021). Walls et al (2020) utilize NaCl in protein and microbial purification process SARS-CoV-2- receptor-binding domains (RBDs) nanoparticle vaccine study. An et al (2021) and van Doremalen et al (2021) experimented with a PIV5-based mucosal vaccine that provides a strategy to induce protective innate and cellular immune responses where NaCl is one of the wash and elution buffer elements in the purification step. Johnson & Johnson's COVID-19 vaccine was developed with the help of its subsidiary, Janssen Pharmaceuticals. The vaccine is injected intramuscularly (IM) (0.5 mL) as a single dose vaccine where Cohorts 1 and 3 administered Ad26COV2.S at low, high, or placebo (0.9% NaCl solution) 56 days apart (Tiboni et al 2021). According to study conducted by Watanabe et al (2021), 293 Freestyle cells from human embryonic kidneys were used to generate SARS-CoV-2 where cells were incubated at 37 °C for 48 h and pelleted in a centrifuge. Pellets were dissolved in 50 mM sodium phosphate, 300 mM sodium chloride, pH 7.

One million doses of the Pfizer/BioNTech vaccine resulted in 11.1 adverse reactions (including anaphylaxis), with 71% occurring within 15 minutes after the initial injection. As a result, if hypotension and rapid volume loss occur within 10–20 minutes after vaccination, an intravenous line for volume replacement will be placed, and 2–3 L of intravenous 0.9 % NaCl will be given in 10–20 minutes to treat anaphylaxis (Kounis et al 2021). After one dosage of BNT162b2 (Pfizer/BioNTech), 26 out of 8680 individuals had an allergic response or anaphylaxis, whereas 27 out of 11141 people had one after two doses of BNT162b2 or mRNA-1273 (Moderna) or one after one dose of JNJ-78436735 (Johnson & Johnson) (Beatty et al 2021). Anaphylaxis has not been identified in clinical investigations because of the low incidence of hypersensitivity reactions and the exclusion of people who have a history of them. Some of the COVID-19 vaccines (such as the mRNA vaccines) have a novel mechanism of action (Turner et al 2021). To treat severe allergic reactions following the SARS-CoV-2 vaccine, intravenous access is obtained, volume replacement with intravenous 0.9 percent NaCl is initiated, and checking vital signs and clearing the airways with an oxygen facial mask. An intravenous NaCl solution containing 0.9% sodium chloride (NaCl) given over 10–20 minutes may be required if the patient has severe volume loss or hypotension (Sokolowska et al 2021).

Table 1 Summary of Sodium Chloride application in medical and SARS-Cov-2 pandemic.

Author	Field of study	Purpose/Objective of the study	NaCl Application/Method in the study	Findings/Results/Conclusion
Meng et al (2018)	Hypertonic saline solution	Understanding the impact of peripheral intravenous (PIV) catheters application for long-term infusions of 3% sodium chloride at rates up to 100 mL/hr.	An academic medical center conducted a 13-month quality assurance project to examine the frequency of catheter phlebitis and patient phlebitis among adult inpatients who received both 3% sodium chloride infusion and routine-care solutions (RCS) infusions through separate PIV catheters during the same hospital stay.	Patient and catheter phlebitis rates were not substantially different between 3% sodium chloride injection infusions and routine care solution (RCS).
Dillon et al (2018)	Hypertonic saline solution	To determine whether sodium chloride 3% administered via peripheral venous system was safe.	Intensive Care Unit (ICU) patients who received sodium chloride 3% were studied in a retrospective manner.	The sodium chloride 3% via PVCs infusion rate of Infusion-related adverse events (IRAEs) looks similar and could be used for patients requiring time-sensitive therapy.
Smart et al (2019)	Hypertonic saline solution	This pilot randomized controlled trial examined the effects of hypertonic saline and isotonic saline on indices of endothelial glycocalyx (EG) shedding and inflammation in emergency care patients with suspected sepsis.	For those in the hypertonic group, the dose was 5 mL/kg of 3% saline, whereas those in the isotonic group received a dose of 10 mL/kg of 0.9 % saline.	Though hypertonic saline did increase the serum osmolality, it did not affect the indicators of inflammation or endothelial glycocalyx (EG) degradation compared to those who received an isotonic solution.
Mullaguri et al (2020)	Hypertonic saline solution	The sodium and volume abnormalities in aneurysmal subarachnoid haemorrhage (aSAH) patients with cerebral salt wasting (CSW) can be even more difficult to manage if antidiuretic hormone (ADH) is dysregulated.	Intravenous 1-deamino-8-D-arginine vasopressin (DDAVP) and hypertonic saline treated CSW-refractory polyuria and probable ADH dysregulation in the hospital course of treatment. This combination ensured that the serum salt level and euolemia were maintained.	Hyponatremia and refractory polyuria can be efficiently treated with DDAVP and hypertonic saline in the presence of ADH insufficiency and CSW.
Quan et al (2017)	Respiratory filter	To demonstrate the effectiveness of a salt recrystallization virus deactivation system, an intermediate layer of a three-ply surgical mask was fitted with a microfiber filter coated with salted polypropylene (PP).	The addition of surfactant to the coating formulations increased the wetting of saline solution on hydrophobic polypropylene fiber (PP). When drying a pre-wetted filter, the amount of NaCl salt coated per unit area was controlled by the volume of the coating solution.	Salt-coated filters have been shown to be particularly effective at deactivating influenza viruses regardless of subtype and after storage in harsh environmental conditions.
Rubino et al (2021)	Respiratory filter	To develop antimicrobial filters and salt-based formulations for coating membrane fibers.	The salt recrystallization after aerosol exposure was evaluated over time on sodium chloride (NaCl), potassium sulfate (K ₂ SO ₄), and potassium chloride (KCl) powders and coatings, which demonstrated that NaCl and KCl begin to recrystallize after 5 minutes and K ₂ SO ₄ within 15 minutes.	The H1N1 influenza virus and Klebsiella pneumonia have been reported to be destabilized by salt recrystallization. Regardless of the method of transmission, the pathogen viability was reduced in both DI water and artificial saliva solutions by the salt-coated filters (aerosols or droplets).
Park et al (2021)	Respiratory filter	To design anticoronavirus principles of air filters, face masks, and other protective equipment.	Functionalize nonwoven sheets using sodium chloride. As a result of collision atomization and diffusion drying, these NDS particles were subsequently deposited on electret melt-blown nonwovens in a single-pass airflow.	Airborne human coronaviruses (surrogates of SARS-CoV-2) were significantly deactivated by modified nonwovens, which retained their filtration capacity.



Shah et al (2022)	Hyponatraemia	To survey pharmacies in children's hospital's policies or guidelines for the administration of % NaCl and if these pharmacies have restrictions on the administration of % NaCl in terms of rate, route, volume and setting.	3% NaCl administration through a peripheral IV in a non-intensive care unit in a children's hospital pharmacy.	In most children's hospital pharmacies, the usage of 3% NaCl is restricted. Due to these constraints, it may be challenging to deliver 3% NaCl in children with hyponatremia symptoms.
Badugu et al (2020)	Ophthalmology	To develop a contact lens that can assess ion concentrations in tears, particularly those of sodium and chloride ions, the main electrolytes in blood plasma and tears, respectively.	This study described the development of a silicone hydrogel lens that responds to sodium and chloride ion-activated fluorescent tears.	A sodium and chloride-sensitive contact lens (NaCl-lens) could be utilized to detect whole-body hydration quickly and non-invasively and illnesses or other infections related to dehydration.
Khan et al (2020)	Dermatology	To evaluate saline injections efficacy in post-acne atrophic scars on the face.	The study included all patients over 15 with mild, moderate, or severe post-acne atrophic scars, regardless of co-morbid disorders. Isotonic saline solution was injected into the scars under a local anaesthetic every week for twelve weeks.	The saline injection was effective in all post-acne atrophic scars but more effective in mild and moderate scars without major adverse effects.
Pravangsuk et al (2021)	Dermatology	To evaluate if needle subcision and saline injection with a pneumatic injector is more effective at treating atrophic acne scars than saline injection alone.	A pneumatic injector was used to inject normal saline on one side of the face three times at four-week intervals.	Pneumatic saline injection and needle subcision improved scar volume and scar diameter with statistically significant differences observed from baseline.
Art et al (2017)	Vaccine study	A study on changing the adsorption conditions such as pH and ionic strength and check if there is any effect on the vaccine's efficacy.	Commercial AH adjuvant particle suspensions with sodium chloride (NaCl) have been studied for physical and chemical properties.	NaCl's effect on the structure of AH adjuvants can modify vaccine formulations and causes misinterpretation of data on antigen adsorption on adjuvant particles.
Zhang et al (2018)	Vaccine study	To check the impact of high concentrations of salt (NaCl) as a significant environmental element that affects immunological response.	Human and mouse macrophages were prepared for improved detection of viruses or viral nucleic acid mimics when exposed to high salt concentrations.	Type I IFN production and signalling were significantly regulated by high salt, which sheds new insight into the regulation of innate immune responses.
Santos et al (2018)	Vaccine study	New vaccines, including DNA vaccines, have been developed as an alternative to traditional techniques of fighting the epidemic.	To test pHEMA cryogel's dynamic binding capacity, NaCl was employed to isolate the supercoiled variant of the NTC7482-41H-VA2 HA plasmid.	Effective and efficient purification method of influenza DNA vaccine.
Yang et al (2020)	Vaccine study	To determine Valproic Acid concentrations in protein samples using a simplified (high-performance liquid chromatography) HPLC technique.	Saturated NaCl salting-out effect to increase extraction efficiency.	Saturated sodium chloride solution increased the extraction of Dole.
Johnson et al (2020)	Covid-19 treatment	To design protective masks that provide significant protection and prophylactic measures to limit the rapid spread of sickness and the transmission of the virus.	This study suggests a thermoplastic 3D printing model for respirator masks coated with NaCl or clay/biocellulose impregnated with NaCl, which may further aid in restricting the spread of COVID-19.	The current COVID-19 pandemic can be contained by applying salt over masks.

Machado et al (2020)	Covid-19 treatment	Hypertonic saline solution was tested in vitro to see if viral replication could be inhibited.	SARS-CoV-2, an RNA-encapsulated virus, was tested in monkey kidney epithelial cells to see how different concentrations of NaCl affected the virus's reproduction (Vero CCL-81).	In Vero cells, a concentration of 260 mM NaCl (1.5%) completely suppresses the replication of SARS-CoV-2.
Gupta (2020)	Covid-19 treatment	Immunization against the SARS CoV-2 virus is required at a cost that exceeds the available resources. It's possible that vaccinations could help us reach our goal The immunization process necessitates the use of attenuated SARS CoV-2.	Viruses in the lungs can be destroyed by heated Sodium Chloride particles (NaCl).	Self-immunization against SARS CoV-2 could be achieved by inhaling heated NaCl particles.
Huijghebaert et al (2021)	Covid-19 treatment	To study the impact of isotonic and hypertonic saline on SARS-CoV-2 infection and respiratory treatment from pharmacological and pharmacodynamic standpoints.	In the nasal cavity, administer respiratory or nasal treatment by nebulizing saline aerosol, either in an isotonic or hypertonic solution.	Nasal and respiratory hygiene can benefit from the interactions of saline at various levels (nasal irrigation, gargling or aerosol). It may be an effective supplement to first-line COVID-19 treatments if given at the first sign of a common cold.
Stathis et al (2021)	Covid-19 treatment	In vitro study on antiseptics that can reduce the viral load of SARS-CoV-2.	NaCl values of 0.9% are considered isotonic and hypertonic, respectively, for commercial saline irrigation solutions and nasal sprays that are tolerable (up to 3.0%)	The use of nasal and oral antiseptics in the fight against SARS-CoV-2 is possible.
Rutkowski et al (2021)	Covid-19 Vaccine	To evaluate COVID-19 vaccines for allergenic components that enable the immunization of most patients with severe allergy problems.	NaCl included as other substances in Pfizer Covid-19 vaccine	UK MHRA approved COVID 19 vaccines as of 27/03/2021
Mehata et al (2021)	Covid-19 Vaccine	Review of the approved vaccines for COVID-19's formulation.	NaCl is included as an excipient in Pfizer (BNT162b2), Sputnik V, Janssen Ad26.COVS Covid-19 vaccine	Salts serve as a buffer to keep the pH level close to the physiological system's pH.
Jamkhane et al (2021)	Covid-19 Vaccine	Analyzes the most recent data on 12 vaccinations that have been approved for use and gives information on their dosage, composition, mode of action, and adverse effects.	NaCl included as composition in ChAdOx1 (AstraZeneca), Ad26.COVS (Johnson & Johnson), and BNT162b2 (Comirnaty®) (Pfizer-BioNTech), Sputnik V (rAd26 and rAd5) and Corona Vac Covid-19 vaccine	The use of the vaccine has shown promising results in to fight against Covid 19
Fiolet et al (2021)	Covid-19 Vaccine	To compare the features, adverse events, efficacy, effectiveness, and impact of 19 COVID-19 vaccine variations of concern.	NaCl is included as part of the composition in Pfizer, AstraZeneca and Coronovac of Covid-19 vaccine, and adverse effect is being studied.	To avoid severe COVID-19, hospitalization, or mortality against all variations of concern, all vaccines appear safe and efficient, however, the level of evidence differs significantly depending on the immunizations considered.
Kim et al (2021)	Covid-19 Vaccine	To review anaphylaxis and allergy to COVID-19 Vaccination	NaCl is included as an excipient in ChAdOx1 (AstraZeneca), Ad26.COVS (Johnson & Johnson), and BNT162b2 (Comirnaty®) (Pfizer-BioNTech) Covid-19 vaccine	Vaccines are responsible for most AEFIs; however, rare but life-threatening allergic reactions, such as anaphylaxis, can occur as well.

6. Final considerations

It has been discovered that sodium chloride has several medical applications and is one of the most significant factors in supporting the SARS-CoV-2 pandemic crisis, as has been previously reported by other researchers. It is important to note

that sodium chloride (NaCl) applications in saline solution content, respiratory filtration, hyponatremia, ophthalmology, dermatology, and vaccine development studies should not be overlooked. Its significant contribution to the SARS-CoV-2 pandemic situation, including treatment and immunization, Covid 19 vaccine development studies, and the reduction of post-Covid 19 vaccine administration adverse effects, was recognized throughout the pandemic situation. Due to its numerous advantages, further uses of sodium chloride should be investigated in the medical field to completely leverage its capabilities for greater utilization in the medical. This will allow it to be fully utilized in the medical field.

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Ethical Considerations

Not Applicable.

Conflict of Interest

The authors declare no conflict of interest on the article.

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