Lecture No:3 [Theoretical]
Inorganic pharmaceutical Chemistry
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The Boron Group – Group 13

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The Boron Group – Group 13

- **Group 13** (13th vertical column of the periodic table) is called the *boron group* and it consists of boron (B), aluminum (Al), gallium (Ga), indium (In) and thallium (Tl) (Figure 1).
- All elements within group 13 show a wide variety of properties.
- It is important to note that boron is a metal- loid (semi-metal) whereas aluminum is a metal but shows many chemical similarities to boron. Aluminum, gallium, indium, and thallium are metals of the ‘poor metals’ group.

***Metalloids** are elements that display some properties characteristic for metals and some characteristic for nonmetals.*

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 1 *The periodic table of elements, group 13 elements are highlighted*

General chemistry of group 13 elements

- Group 13 elements are characterized by having three electrons in their valence shell. Therefore, all elements form the stable cation M^{3+}.

- Most elements (except for B) form additionally the singly positively charged ion M^{+}, which is indeed the more stable oxidation state for Tl.

- Boron and aluminum occur only with oxidation number +3 in their compounds, and with a few exceptions their compounds are best described as ionic.

- The electronic configuration shows three electrons outside a noble gas configuration, two in an s shell and one in a p shell.

- The outermost p electron is easy to remove as it is furthest from the nucleus and well shielded from the effective nuclear charge. The next two s electrons are also relatively easy to remove. Removal of any further electrons disturbs a filled quantum shell and is therefore difficult. This is reflected in the ionization energies (Table 1).

- The main sources of B are the two minerals borax ($Na_2[B_4O_5(OH)_4]\cdot 8H_2O$) and kernite ($Na_2[B_4O_5(OH)_4]$), which are generally used as components in many detergents or cosmetics.

- Al occurs widely on earth, and it is the most abundant metal and the third most abundant element in the earth's crust. Aluminosilicates, such as clays, micas, feldspar, together with bauxite, are the main sources of Al.

- Ga, In and Tl occur in traces as their sulfides.

Table 1. *Ionization energy (kJ/mol) for group 13 elements*

	First	Second	Third
B	801	2427	3659
Al	577	1816	2744
Ga	579	1979	2962
In	558	1820	2704
Tl	589	1971	2877

1)Extraction

- Boron (B) can be extracted from borax by converting the latter to boric acid and subsequently to the corresponding oxide.

$$Na2[B4O5(OH)_4] \cdot 8H2O + H2SO4 \rightarrow 4B(OH)_3 + Na2SO4 + 5H2O$$

$$2B(OH)_3 \rightarrow B2O3 + 3H2O$$

- Boron of low quality can then be obtained by the reduction of boron oxide with Mg, followed by several steps of washing with bases and acids. Al is extracted from ores such as bauxite or cryolite in the so-called Bayer process.

- Bauxite contains mainly a mixture of aluminum oxides with Fe_2O_3, SiO_2 and TiO_2 as impurities.

- In the Bayer process, hot aqueous NaOH is added to the crude ore under pressure and aluminum hydroxide will go into solution. This will result in the separation of Fe2O3. The solution is cooled down and seeded with Al2O3·3H2O to precipitate $Al(OH)_3$.

- Pure Al can be produced by electrolysis of molten Al_2O_3 (melting point 2345 K), with Al being obtained at the cathode.

- The main source of Ga is bauxite, but it can also be obtained from the residues from the Zn processing industry. It can be found in the zinc sulfide ore sphalerite. Tl can be obtained as by-product of the processing of Cu and Zn ores.

- The demand for In and Tl is rather low.

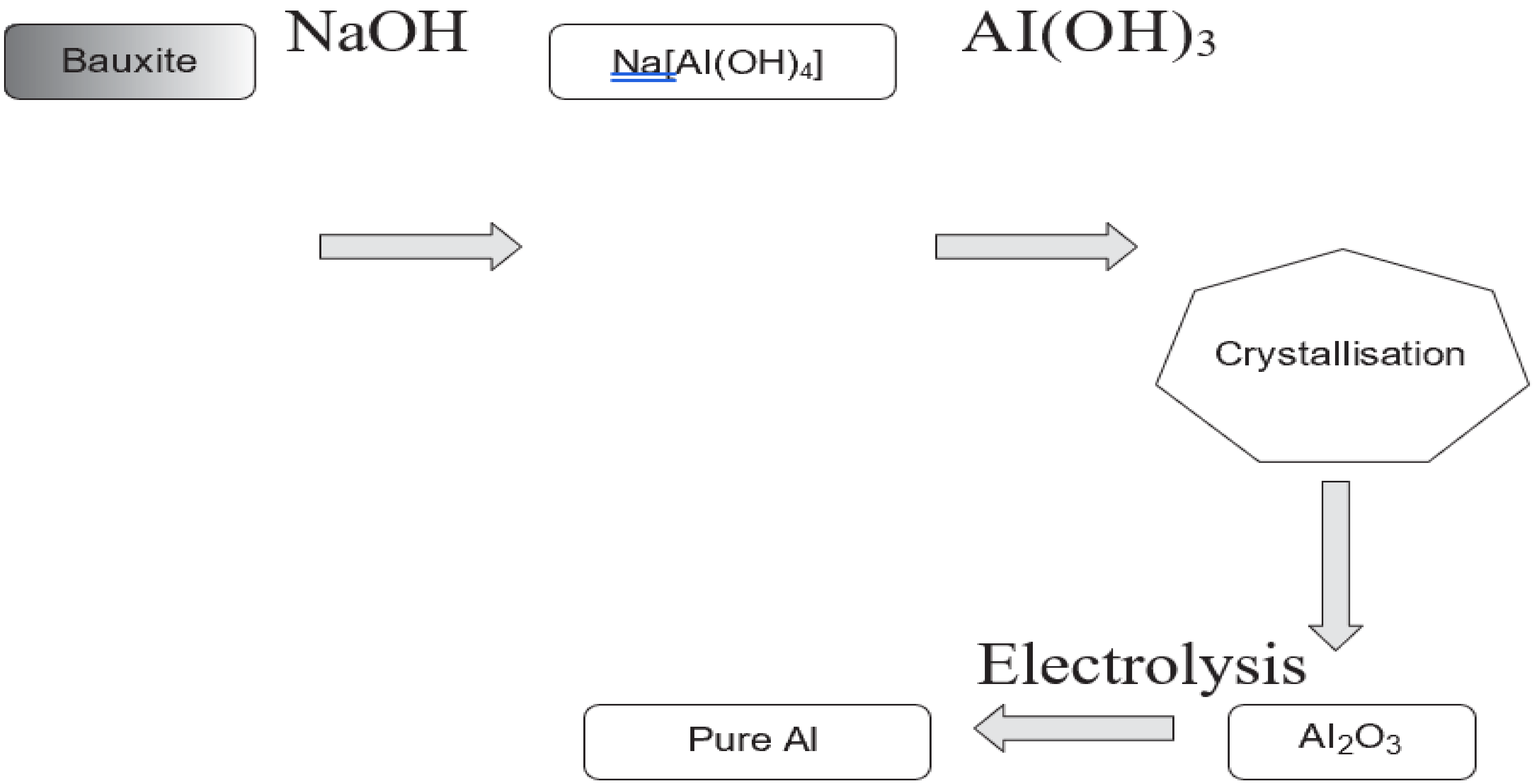

Figure 2 *Bayer process*

2) Chemical properties

a) Reactivity

- B is chemically unreactive except at high temperatures.
- Al is a highly reactive metal, which is readily oxidized in air to Al_2O_3. This oxide coating is resistant to acids but is moderately soluble in alkalis.
- Al itself dissolves in diluted mineral acids and can react with strong alkalis, the product being the tetrahydroxoaluminate ion [Al(OH)4−] and H_2.

$$Al + 3H_2SO4(aq) \rightarrow Al(SO4)_3 + 3H_2$$

$$2Al + 2MOH + 6H_2O \rightarrow 2M[Al(OH)_4] + 3H_2$$

- Aluminum can be used to reduce metal oxides, the most famous example being the *thermit process.* Al reacts violently with iron(Ill) oxide to produce iron in this highly exothermic process, where Fe is obtained in its liquid form.

$$2Al(s) + Fe_2O_3(s) \rightarrow 2Fe(l) + Al_2O_3(s)$$

- Ga, In and Tl dissolve in most acids, and as a result the salts of Ga(III), In(III) and Tl(I) are obtained, whereas only Ga reacts with aqueous alkali with the production of H_2.

b) Oxides/hydroxides: amphoteric compounds

- Boron oxide (B_2O_3) is an acidic oxide and an insoluble white solid with a very high boiling point (over 2000 K) because of its extended covalently bonded network structure.
- Aluminum oxide (Al2O3) as well as aluminum hydroxide (Al(OH)3, are amphoteric compounds.

$$Al_2O_3 + 3H_2O + 2(OH–) \rightarrow 2[Al(OH)_4]^-$$

$$Al_2O_3 + 3H_2O + 6[H_3O]+ \rightarrow 2[Al(H_2O)6]_3^+$$

- $Al(OH)_3$ can neutralize a base and therefore act as an acid; it can also neutralize an acid and act as a base.

$$Al(OH)_3 + NaOH \rightarrow NaAl(OH)_4$$

$$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$$

c) Halides

- The most important halide of boron is the colorless gas boron trifluoride (BF_3). Aluminum chloride ($AlCl_3$) is a volatile solid which sublimes at 458 K. The vapor formed on sublimation consists of an equilibrium mixture of monomers ($AlCl_3$) and dimers (Al_2Cl_6). It is used to prepare the powerful and versatile reducing agent lithium tetrahydridoaluminate ($LiAlH_4$).

- Both boron trichloride (BCl_3) and aluminum trichloride ($AlCl_3$) act as Lewis's acids to a wide range of electron-pair donors, and this has led to their widespread use as catalysts. In the important *Friedel – Crafts acylation*, $AlCl_3$ is used as a strong Lewis acid catalyst to achieve the acylation of an aromatic ring.

- *A **Lewis acid** is defined as a compound that can accept electrons pairs with the formation of a coordinate covalent bond. Any type of electrophile can be a Lewis acid. In contrast, **Brønsted – Lowry acids** are com- pounds that transfer a hydrogen ion (H^+) and they are the more commonly known type of acids. Analogous definitions apply for a Lewis base (electron donator) and a Brønsted – Lowry base (H^+ acceptor).*

Boron

1) Introduction:

- Boron has the atomic number 5 and the symbol B, and is a so-called metalloid. Boron compounds have been known for many centuries and especially used in the production of glass.

- Boric acid[$B(OH)_3$] is used in the large-scale production of glass. Borosilicate glasses (Pyrex® glass), which are produced by a fusion of B_2O_3 and silicate, are extremely heat resistant and often used in laboratories.

- It was recognized that boron is an essential micronutrient for plants. A deficiency of boron can lead to deformation in the vegetable growth such as hollow stems and hearts. Furthermore, the plant growth is reduced and fertility can be affected.

- In general, boron deficiency leads to qualitative and quantitative reduction in the production of the crop.

- Boron is typically available to plants as boric acid [$B(OH)_3$] or borate [$B(OH)_4$]$^-$. The exact role of boron in plants is not understood, but there is evidence that it is involved in pectin cross-linking in primary cell walls, which is essential for normal growth and development of higher plants.
- Borax (Na2[B4O5(OH)4]·8H2O) can be applied as a fertilizer and, together with kernite (Na2[B4O5(OH)4]· 2H_2O), forms the two most commercially available borates.
- Borates find a wide range of practical applications such as in detergents, cosmetics, antifungal mixtures as well as components in fiberglass and others. The toxicity of borates in mammals is relatively low, but it exhibits a significantly higher risk to arthropods and can be used as an insecticide.
- Boron-based compounds are used in a wide range of clinical applications including their use as antifungal and antimicrobial agent, as proteasome inhibitors and as a noninvasive treatment option for malignant tumors.

2) Pharmaceutical Application of Boric acid

- Boric acid is a long-standing traditional remedy with mainly antifungal and antimicrobial effects.
- For medicinal uses, it has become known as *salsedativum*, which was discovered by Homberg, the Dutch natural philosopher.
- Diluted solutions were and sometimes still are used as antiseptics for the treatment of athletes' foot and bacterial thrush, and in much diluted solutions as eyewash (Figure 3).
- Boric acid can be prepared by reacting borax with a mineral acid:

$$Na_2B4O_7 \cdot 10H_2O + 2HCl \rightarrow 4B(OH)_3[\text{or } H_3BO_3] + 2NaCl + 5H_2O$$

- In general, there are many other health claims around the clinical use of boric acid and boron-containing compounds, but many of those have no supporting clinical evidence.

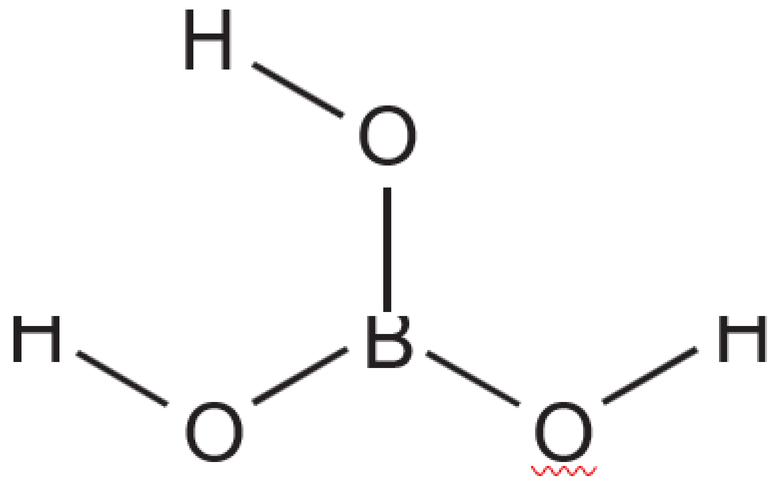

Figure 3. *Chemical structure of boric acid*

3) Bortezomib

- Bortezomib belong to the class of drugs called *proteasome inhibitors* and is licensed in the United States and the United Kingdom for the treatment of multiple myeloma.

- The drug has been licensed for patients in whom the myeloma has progressed despite prior treatment or where a bone marrow transplant is not possible or was not successful.

- It is marketed under the name Velcade® or Cytomib®.

- Velcade is administered via injection and is sold as powder for reconstitution (Figure 4).

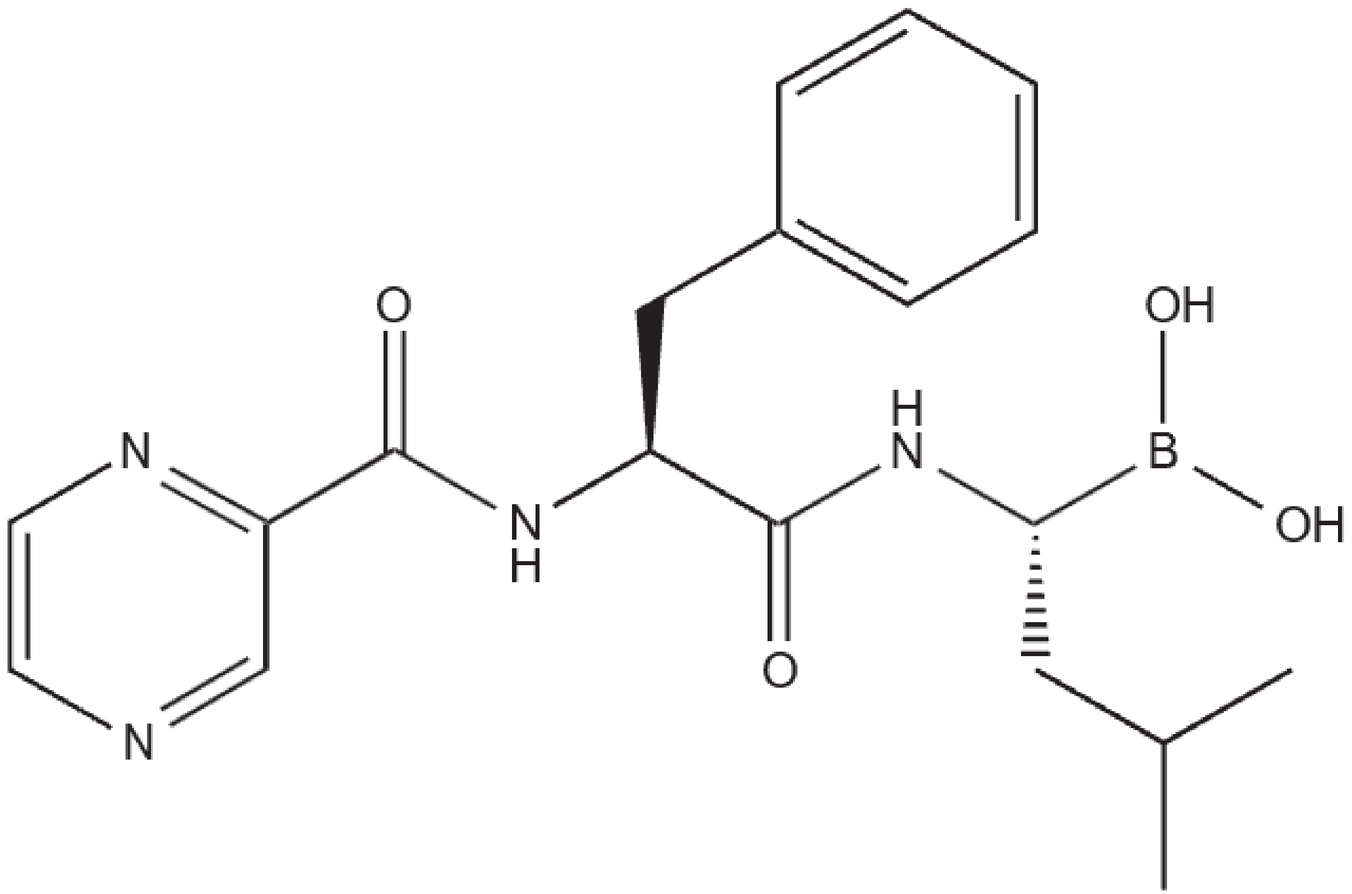

Figure 4 Chemical structure of bortezomib

- Bortezomib was the first drug approved in the new drug class of proteasome inhibitors and boron seems to be its active element.
- For the mode of action, it is believed that the boron atom binds with high affinity and specificity to the catalytic site of 26S proteasome and inhibits its action.

- Therapy with Bortezomib can lead to a variety of adverse reactions, including peripheral neuropathy, myelosuppression, renal impairment and gastrointestinal (GI) disturbances together with changes in taste. Nevertheless, the side effects are in most cases less severe than with alternative treatment options such as bone marrow transplantation.

Aluminum

1) Introduction

- The element aluminum has the atomic number 13 and chemical symbol Al. Aluminum forms a diagonal relationship with beryllium.
- The name ‘aluminum’ derives from the salt alum (potassium alum, $KAl(SO_4)_2 \cdot 12H_2O$), which was used for medicinal purposes in Roman times.
- Initially, it was very difficult to prepare pure aluminum and therefore it was regarded as a very precious substance.
- In the mid-1800s, aluminum cutlery was used for elegant dinners, whereas it is nowadays used as lightweight camping cutlery.
- In 1886, the manufacture of aluminum by electrolysis of bauxite started, and the price for pure aluminum dropped significantly.
- Aluminum is a soft, durable, and lightweight metal, which makes it attractive to many applications. Nowadays, aluminum is mainly used for the construction of cars and aircrafts and can be found in packaging and construction material.

2) Biological importance

- The human body contains around 35 mg of Al^{3+}, of which ~50% is found in the lungs and ~50% in the skeleton.

- There is no known biological role for Al^{3+} and, indeed, the human body has developed very effective barriers to exclude it.

- Only a minimal fraction of Al^{3+} is taken up from the diet in the gut, and the kidneys quickly excrete most of it.

- The bones can act as a sink for Al^{3+} if the blood concentration is high and release it slowly over a long period. The brain is vulnerable to Al^{3+} and usually the blood – brain barrier prevents Al^{3+} entering the brain.
- Al^{3+} can sometimes act as a competitive inhibitor of essential elements such as Mg^{2+}, Ca^{2+} and $Fe^{2+/3+}$ because of their similar ionic radii and charges.

- It is important to note that at physiological pH, Al^{3+} forms a barely soluble precipitate $Al(OH)_3$, which can be dissolved by changing the pH.

- A normal adult diet contains typically between 2.5 mg/day and up to 13 mg/day Al^{3+}, but patients on aluminum-containing medication can be exposed to more than 1000 mg/day. Typically, ~0.001% is absorbed in the digestive tract, but it can be around 0.1 – 1.0% when it is in the form of aluminum citrate (Figure 4).

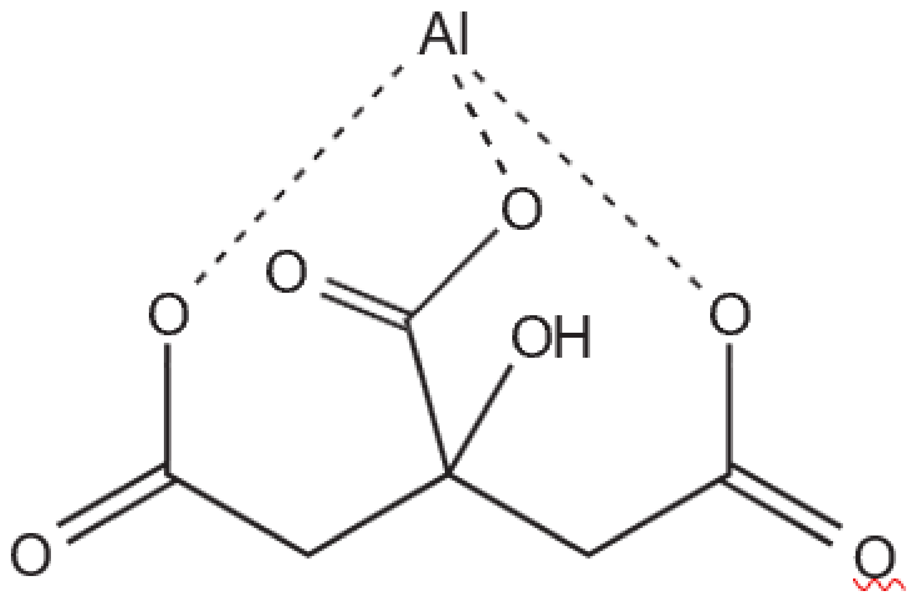

Figure 5 *Chemical structure of aluminum citrate*

- Al^{3+} can accumulate in the human body if natural limits are crossed, for example, intravenous administration or patients on dialysis, or when the kidneys are impaired and therefore not able to excrete Al^{3+} sufficiently.
- Under normal circumstances, Al^{3+} would not accumulate in the human body.
- In 1972, Alfrey *et al.* described the new syndrome of progressive dialysis encephalopathy, the so-called dialysis dementia, which was seen in patients being treated with hemodialysis for 15 months or more. The symptoms include speech disorders, problems with the bone mineralization and general signs of dementia.
- Increased serum and bone concentrations of Al^{3+} were found in patients who were on hemodialysis, and the connection was made to the toxicity of the Al^{3+} present in the dialysate solution.
- Nowadays, the use of modern Al^{3+}-free dialysate solutions or new techniques (e.g. reverse osmosis) prevents ‘dialysis dementia’.

3) Aluminum Based Adjuvant

- An adjuvant is an agent or a mixture of agents that possesses the ability to bind to a specific antigen.
- Adjuvants are added to vaccines to increase the antibody responses to the vaccination and/or to stabilize the preparation.
- Adjuvants can absorb many antigenic molecules over a wide surface area, thus enhancing the interaction of immune cells with the presenting antigens and leading to an increase of the immune response stimulation.
- Some adjuvants (including aluminum-based ones) can function as a slow-release delivery system. They trap the antigen in a depot created by the adjuvant at the injection site. From there, the antigen is slowly released, which causes a steady stimulation of the immune system.

- Aluminum-based adjuvants have a long-standing tradition They are the most widely used adjuvants in human and veterinary vaccines and regarded as safe if applied correctly.
- Al^{3+} salts are the only kind of adjuvant licensed by the FDA.
- They are also the only kind of adjuvants used in anthrax vaccines for humans in the United States.
- Anthrax vaccine contains $Al(OH)_3$, as do the FDA-licensed diphtheria, haemophiles influenzae type B, hepatitis A, hepatitis B, Lyme disease, pertussis, and tetanus vaccines.
- The adjuvant effect of potassium alum ($KAl(SO_4)_2 \cdot 12H_2O$) was first discovered in 1926.
- Researchers examined diphtheria toxoids precipitated with alum and were able to show that an injection of this alum precipitate led to a significant increase in immune response. Leading on from this research, alum has found widespread use as an adjuvant.

- Vaccines containing alum as adjuvant are referred to as *alum-precipitated vaccines*.
- Unfortunately, it has been shown that alum precipitations can be highly heterogeneous. The homogeneity of the preparation depends on the anions and the conditions present at the point of precipitation.

- Subsequent research showed that aluminum hydroxide ($Al(OH)_3$) hydrogels can be performed in a standardized manner and be used to absorb protein antigens to form a homologous preparation.
- Following on from this research, researchers have shown that it is possible to coprecipitate aluminum phosphate ($AlPO_4$) and the diphtheria toxoid to form active vaccines.
- These vaccines are called *aluminum-absorbed vaccines* and, in contrast to alum-precipitated vaccines, the antigens are distributed homogeneously.

- Nowadays, aluminum-absorbed vaccines have taken over from alum-precipitated ones. Nevertheless, there is a lot of ambiguity found in the literature, where both terms are interchangeably used.

- In summary, immunization vaccines containing adjuvants are more effective than those without them.

- Typical adjuvants are alum [$KAl(SO_4)_2 \cdot 12H_2O$], $Al(OH)_3$, $AlPO_4$, Al_2O_3, but oxides of other metals, such as ZrO_2, SiO_2 and Fe_2O_3, are also under investigation.

- The formation of the aluminum hydrogels is generally achieved by reacting Al^{3+} ions (from compound such as $AlCl_3$) under alkaline aqueous conditions. Conditions are strongly regulated, as even smallest changes to parameters such as temperature, concentration and others can influence the quality of the hydrogel.

- Aluminum phosphate gels are typically produced by reacting Al^{3+} salts in the presence of phosphate ions under alkaline conditions.

- The mode of action is highly complex and still not fully understood.

- Research has shown that antigens need to be adsorbed to the adjuvant before the immunization reaction. It is believed that the adjuvant will then present the antigen to the immunocompetent of the targeted cell.