4

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), aluminium (Al), gallium (Ga), indium (In) and thallium (Tl) (Figure 4.1).

All elements within group 13 show a wide variety of properties. It is important to note that boron is a metalloid (semi-metal) whereas aluminium is a metal but shows many chemical similarities to boron. Aluminium, gallium, indium and thallium are considered to be metals of the 'poor metals' group.

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

In this chapter, the general chemistry of group 13 elements is discussed as well as some clinical applications for boron and aluminium. Further clinical applications for boron as well as applications for thallium can be found in the chapter on radiochemistry (Chapter 10).

4.1 General chemistry of group 13 elements

Group 13 elements are characterised by having three electrons in their valence shell. Therefore, all elements form the stable cation M^{3+}. Most elements (with the exception of B) form additionally the singly positively charged ion M^{+}, which is indeed the more stable oxidation state for Tl.

Boron and aluminium 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 ionisation energies (Table 4.1).

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

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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 4.1 *The periodic table of elements, group 13 elements are highlighted*

Table 4.1 *Ionisation energy (kJ/mol) for group 13 elements [1]*

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

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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.

4.1.1 Extraction

Boron (B) can be extracted from borax by converting the latter to boric acid (Equation 4.1) and subsequently to the corresponding oxide (Equation 4.2). 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.

$$Na_2[B_4O_5(OH)_4] \cdot 8H_2O + H_2SO_4 \rightarrow 4B(OH)_3 + Na_2SO_4 + 5H_2O \quad (4.1)$$

$$2B(OH)_3 \rightarrow B_2O_3 + 3H_2O \quad (4.2)$$

Al is extracted from ores such as bauxite or cryolite in the so-called Bayer process. Bauxite contains mainly a mixture of aluminium 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 aluminium hydroxide will go into solution. This will result in the separation of Fe_2O_3. The solution is cooled down and seeded with $Al_2O_3 \cdot 3H_2O$ in order to precipitate

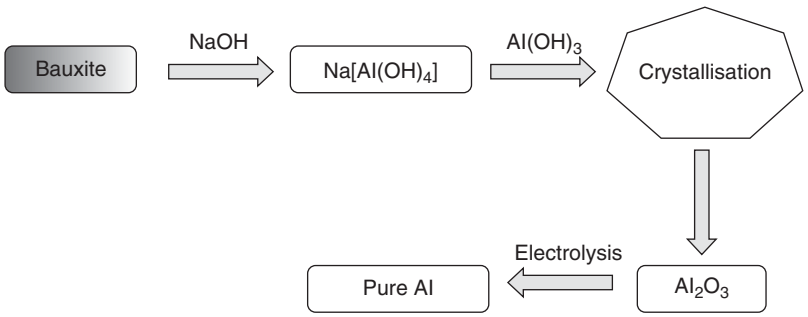

Figure 4.2 *Bayer process*

$Al(OH)_3$. Pure Al can be produced by electrolysis of molten Al_2O_3 (melting point 2345 K), with Al being obtained at the cathode (Figure 4.2).

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.

4.1.2 Chemical properties

4.1.2.1 Reactivity

B is chemically unreactive except at high temperatures. Al is a highly reactive metal, which is readily oxidised 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 (Equation 4.3) and can react with strong alkalis, the product being the tetrahydroxoaluminate ion $[Al(OH)_4{}^-]$ and H_2 (Equation 4.4).

$$Al + 3H_2SO_{4(aq)} \rightarrow Al(SO_4)_3 + 3H_2 \tag{4.3}$$

$$2Al + 2MOH + 6H_2O \rightarrow 2M[Al(OH)_4] + 3H_2 \tag{4.4}$$

Aluminium 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 (Equation 4.5).

$$2Al_{(s)} + Fe_2O_{3(s)} \rightarrow 2Fe_{(l)} + Al_2O_{3(s)} \tag{4.5}$$

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.

4.1.2.2 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) as a result of its extended covalently bonded network structure. Aluminium oxide (Al_2O_3, Equations 4.6 and 4.7) as well as aluminium hydroxide ($Al(OH)_3$, Equations 4.8 and 4.9) are amphoteric compounds.

> ***Amphoteric compounds*** *are substances that can react either as an acid or as a base.*

$$Al_2O_3 + 3H_2O + 2(OH^-) \rightarrow 2[Al(OH)_4]^- \quad (4.6)$$

$$Al_2O_3 + 3H_2O + 6[H_3O]^+ \rightarrow 2[Al(H_2O)_6]^{3+} \quad (4.7)$$

$Al(OH)_3$ can neutralise a base and therefore act as an acid (Equation 4.8); it can also neutralise an acid and act as a base (Equation 4.9).

$$Al(OH)_3 + NaOH \rightarrow NaAl(OH)_4 \quad (4.8)$$

$$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O \quad (4.9)$$

4.1.2.3 Halides

The most important halide of boron is the colourless gas boron trifluoride (BF_3). Aluminium chloride ($AlCl_3$) is a volatile solid which sublimes at 458 K. The vapour 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 aluminium trichloride ($AlCl_3$) act as Lewis 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 in order 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 compounds 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).*

The following sections will describe the clinical application of boron, aluminium and gallium. It is important to note that more information on the clinical use of gallium and thallium can be found in Section 10.4, where radiopharmaceuticals are discussed.

4.2 Boron

4.2.1 Introduction

Boron has the atomic number 5 and the symbol B, and is a so-called metalloid (see Chapter 4). 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.

At the beginning of the nineteenth century, it was recognised 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 [2].

Borax ($Na_2[B_4O_5(OH)_4]\cdot 8H_2O$) can be applied as a fertiliser and, together with kernite ($Na_2[B_4O_5(OH)_4]\cdot 2H_2O$), forms the two most commercially available borates. Borates find a wide range of practical applications

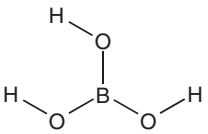

Figure 4.3 *Chemical structure of boric acid*

such as in detergents, cosmetics, antifungal mixtures as well as components in fibreglass 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 tumours. The latter application will be discussed in the chapter on radiopharmaceuticals (Chapter 10).

4.2.2 Pharmaceutical applications 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 *sal sedativum*, which was discovered by Homberg, the Dutch natural philosopher, in 1702 [3]. 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 4.3) [4].

Boric acid can be prepared by reacting borax with a mineral acid:

$$Na_2B_4O_7 \cdot 10H_2O + 2HCl \rightarrow 4B(OH)_3[\text{or } H_3BO_3] + 2NaCl + 5H_2O$$

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.

4.2.3 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 4.4) [5].

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 [5].

4.3 Aluminium

4.3.1 Introduction

The element aluminium has the atomic number 13 and chemical symbol Al. Aluminium forms a diagonal relationship with beryllium. The name 'aluminium' derives from the salt alum (potassium alum,

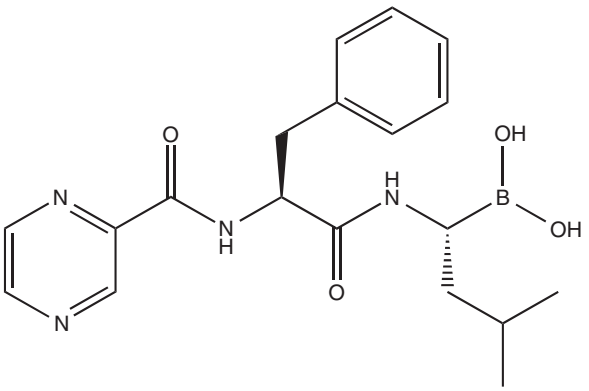

Figure 4.4 *Chemical structure of bortzemib*

$KAl(SO_4)_2 \cdot 12H_2O$), which was used for medicinal purposes in Roman times. Initially, it was very difficult to prepare pure aluminium and therefore it was regarded as a very precious substance. In the mid-1800s, aluminium cutlery was used for elegant dinners, whereas it is nowadays used as lightweight camping cutlery. In 1886, the manufacture of aluminium by electrolysis of bauxite started, and the price for pure aluminium dropped significantly. Aluminium is a soft, durable and lightweight metal, which makes it attractive to many applications. Nowadays, aluminium is mainly used for the construction of cars and aircrafts and can be found in packaging and construction materials.

4.3.2 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 fairly 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 (see Equations 4.8 and 4.9) [6].

A normal adult diet contains typically between 2.5 mg/day and up to 13 mg/day Al^{3+}, but patients on aluminium-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 aluminium citrate (Figure 4.5) [6b].

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. Nevertheless, 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 haemodialysis for 15 months or more. The symptoms include speech disorders, problems with the bone mineralisation and general signs of dementia. Investigations showed that brain scans were normal and that there was no connection to the Alzheimer's disease, as neither neurofibrillary tangles nor senile plaques were found. Increased serum and bone concentrations of Al^{3+} were

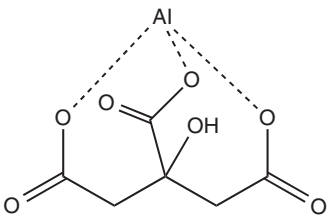

Figure 4.5 *Chemical structure of aluminium citrate*

found in patients who were on haemodialysis, 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' [6a].

4.3.3 Al^{3+} and its use in water purification

Al^{3+} is used in the purification of water. Lime (CaO) and aluminium sulfate $Al_2(SO_4)_3$ are added to waste water in order to accelerate the settling or sedimentation of suspended matter [7]. The addition of lime increases the pH of the water slightly (Equation 4.10). The water becomes more basic, which promotes the precipitation of Al^{3+} as $Al(OH)_3$ (Equation 4.11).

$$CaO_{(s)} + H_2O_{(l)} \rightarrow Ca^{2+}{}_{(aq)} + 2OH^-{}_{(aq)} \tag{4.10}$$

$$Al^{3+}{}_{(aq)} + 3OH^-{}_{(aq)} \rightarrow Al(OH)_{3(s)} \tag{4.11}$$

$Al(OH)_3$ precipitates as a gelatinous precipitate which slowly settles. During this process, it incorporates suspended soil, colloidal material and most bacteria. The water is filtered before leaving the treatment plant in order to remove the flocculate and the vast majority of the Al^{3+}. WHO guidelines allow a maximum concentration for Al^{3+} of 0.2 mg/l [8].

4.3.4 Aluminium-based adjuvants

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 in order to increase the antibody responses to the vaccination and/or to stabilise 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 aluminium-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.

Aluminium-based adjuvants have a long-standing tradition and have been used for more than 50 years. 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, haemophilus influenzae type B, hepatitis A, hepatitis B, Lyme disease, pertussis and tetanus vaccines. In many countries, vaccines for children contain aluminium-based adjuvants [9].

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 [9].

Subsequent research showed that aluminium hydroxide ($Al(OH)_3$) hydrogels can be pre-formed in a standardised 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 co-precipitate aluminium phosphate ($AlPO_4$) and the diphtheria toxoid in order to form active vaccines. These vaccines are called *aluminium-absorbed vaccines* and, in contrast to alum-precipitated vaccines, the antigens are distributed homogeneously. Nowadays, aluminium-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 [9].

In summary, immunisation 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 aluminium 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. Aluminium phosphate gels are typically produced by reacting Al^{3+} salts in the presence of phosphate ions under alkaline conditions [9].

The mode of action is highly complex and still not fully understood. Initial theories included the physical absorption of the antigen, which is still considered as an important feature, and the gradual release of antigen from the injection side with the adjuvant working as an agglomeration. The latter theory was disproved quickly. Research has shown that antigens need to be adsorbed to the adjuvant before the immunisation reaction. It is believed that the adjuvant will then present the antigen to the immunocomponent of the targeted cell [9].

4.3.5 Antacids

The function of antacids is to neutralise excess stomach acid. They also exhibit cytoprotective effects towards attacks against the gastric mucosa. They are additionally known to heal gastric and duodenal ulcerations; nevertheless, the mechanism is still uncertain.

Antacids have been in use for the past 2000 years, and the initial formulations were based on $CaCO_3$ (coral and limestone). Nowadays, the antacid/anti-gas market is a significant income stream for the pharmaceutical industry and the demand for antacids is expected to grow. The number of people suffering from heartburn increases with an ageing population, more stressful lifestyles and changing eating habits such as eating out more often.

Aluminium hydroxide ($Al(OH)_3$) has several medical applications. It is used as an antacid for treating heartburn as well as acid indigestion (reflux oesophagitis). It is also known to have healing properties of peptic ulcers. In patients suffering from kidney failure, who show elevated serum phosphate levels (hyperphosphataemia), $Al(OH)_3$ is used as a phosphate binder (see Section 4.3.7).

$Al(OH)_3$ is an amphoteric compound (see Section 4.1.2.2), which means it can react as a base or as an acid. In its application as an anti-acid, $Al(OH)_3$ reacts with any excess stomach acid (mainly HCl) with the formation of $AlCl_3$ and water (Equation 4.12).

$$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O \tag{4.12}$$

$Al(OH)_3$ is known to cause constipation, so formulations of anti-acids often include a combination with Mg^{2+} antacids. Usually, oral antifoaming agents, such as simethicone, are added in order to reduce bloating

Table 4.2 *Typical formulation of an antacid/antigas mixture (maximum strength Maalox®, Max®, Norvatis)*

Active ingredient	Quantity (mg)	Purpose
$Al(OH)_3$	400	Antacid
$Mg(OH)_2$	400	Antacid
Simethicone	40	Anti-gas

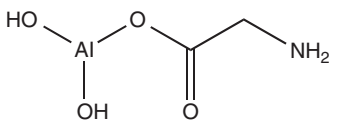

Figure 4.6 *Chemical structure of dihydroxy aluminium glycinate*

and discomfort/pain. Simethicone is a mixture of poly(dimethyl siloxane) and silica gel, which decreases the surface tension of gas bubbles (Table 4.2).

Ancient anti-acid formulations contained sodium bicarbonate (baking soda, $NaHCO_3$), which resulted in a rapid reaction with the gastric acid. The result was an increase in the gastric pH and the production of CO_2 gas as a by-product (Equation 4.13). Large doses of $NaHCO_3$ can cause alkaline urine and this can result in kidney problems. Acid neutralisation using $Al(OH)_3$ does not produce CO_2 and therefore these side effects can be avoided.

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2 \tag{4.13}$$

Aluminium glycinate [$Al(NH_2CH_2COO)(OH)_2$] (Figure 4.6) is also used in anti-acid formulations. For example, Gastralgine® contains, amongst other ingredients, dihydroxy aluminium glycinate [$Al(NH_2CH_2COO)(OH)_2$], $Al(OH)_3$, magnesium trisilicate and simethicone. It is known to have additionally protective effects from ulcers.

4.3.6 Aluminium-based therapeutics – alginate raft formulations

Heartburn is the primary symptom of the so-called gastro-oesophageal reflux disease (GERD), which is caused by the oesophageal influx of gastric HCl from the stomach. There are also close links to oesophageal cancer, which has a very low survival rate. Relief can be achieved with the use of alginate raft formulations, which typically contain alginic acid, $NaHCO_3$, magnesium trisilicate and $Al(OH)_3$. Alginates are natural polysaccharide polymers which are isolated from brown seaweeds.

In the acidic stomach, alginate salts and alginic acids precipitate to form a low-density viscous gel. When the mixture comes into contact with gastric HCl, the gel matrix formation occurs. HCO_3^-, which is trapped in the gel, leads to the formation of CO_2 gas (Equation 4.13). The gas bubbles trapped in the gel convert it to foam and provide buoyancy, allowing the gel to float on the surface of stomach contents (like a raft on water). $Al(OH)_3$ provides an additional capacity to neutralise any excess stomach acid (Equation 4.12). The raft physically acts as a barrier to gastric reflux and moves into the oesophagus during reflux. It acts as mobile neutralising sealant in the oesophageal space when the gastric pressure is high. Once the pressure reduces, the raft drops back into the stomach and can be digested (Figure 4.7).

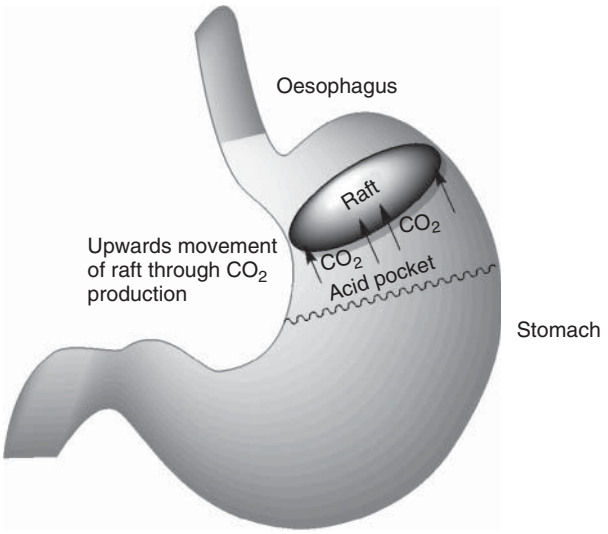

Figure 4.7 *Illustration of the stomach, showing the acid pocket and the alginate raft floating on top of it protecting the oesophagus*

4.3.7 Phosphate binders

Hyperphosphataemia, that is, increased levels of serum phosphate, is a disorder commonly seen in patients with end-stage renal (kidney) disease where the kidneys are not able to excrete excess phosphate as a result of a low renal clearance rate. This disorder is often seen in patients who are on dialysis treatment. Persistent hyperphosphataemia results in renal osteodystrophy, that is, the weakening of bones due to disturbances in the calcium and phosphate metabolism.

Generally Al^{3+}-containing drugs are given in order to promote the binding of phosphate in the gut. Antacids containing $Al(OH)_3$ can be used as phosphate binders. When $Al(OH)_3$ enters the acidic stomach (pH $\sim$ 1), Al^{3+} ions are formed. Some Al^{3+} ions will be absorbed in the stomach, but the majority is passed to the distal intestines, where the pH is significantly increased (pH 6–8.5). In this high pH range, Al^{3+} freshly precipitates as a colloidal, amorphous $Al(OH)_3$. Its large surface area adsorbs phosphate ions (usually in form of HPO_4^{2-}) and passes them through the remaining intestine without decomposition, as the pH is too high. The Al^{3+}-phosphate complex ($AlPO_4$) is then excreted via the faeces.

Aluminosilicates can also be used as a phosphate binder and is, for example, the active ingredient in Malinal®. In contrast to $Al(OH)_3$, which acts as an efficient PO_4^{3-} binder directly, aluminosilicates need prior exposure to a acid in order to produce free Al^{3+}. Once the free Al^{3+} is formed, it follows the same mode of action.

Initially, aluminium-based phosphate binders were also used in dialysis exchange fluids, especially in patients being treated with haemodialysis. Nevertheless, as a result of the exposure to high concentrations of Al^{3+} salts, relatively high concentrations were found in patients. A significant number of patients developed dementia symptoms after 15 or more months of treatment, which was linked to the high Al^{3+} concentrations in the body including the brain (see Section 4.3.2) [6a, 10].

4.3.8 Antiperspirant

Aluminium trichloride ($AlCl_3$) was the first compound that was used as an antiperspirant. The mechanism of action is still under investigation, but it appears to act by forming a plug of $Al(OH)_3$ within the sweat

duct. $AlCl_3$ is a very strong antiperspirant and only advised by doctors if normal antiperspirants do not work. Leading brands of antiperspirants contain usually a ~20% aluminium hexahydrate solution in an alcoholic base. It is thought to work by blocking the openings of the sweat ducts. It tends to work best in the armpits. However, it may also work for sweating of the palms and soles. It can also be applied to the face, taking care to avoid the eyes.

4.3.9 Potential aluminium toxicity

The excessive use of aluminium preparations negatively influences human health. Excessive intake of Al^{3+} has been found to accumulate in sensitive loci and can lead to pathological aberrations and result in dialysis dementia or similar symptoms. It is important to note that Al^{3+} is a major component in over-the-counter drugs such as antacids. Special attention has to be given by the dispensing pharmacist, and the patient has to be made aware of the consequences of overdoses of Al^{3+}-containing products. Al^{3+} is known to have embryonic and foetal toxic effects in humans and animals, causing osteomalacia, which is the softening of the bones due to defective bone mineralisation [5].

Albumin and transferrin bind around 95% of serum aluminium, which is then cleared mainly via the kidneys (a small amount can be found in the faeces). In healthy humans, only 0.3% of orally administered aluminium is absorbed, whereas it has the potential to accumulate when the GI tract is bypassed, for example, in intravenous infusions [10].

4.4 Gallium

4.4.1 Introduction

Gallium has atomic number 31 in the periodic table of elements. It has a silvery-white colour with a melting point of only 29 °C, which means that it melts when held in the hand. It has no known physiological role in the human body, but it can interact with cellular processes and proteins that are normally involved in iron metabolism.

Gallium tartrate has a long research history. Researchers showed in the 1930s that it could be used to treat syphilis in rabbits with no significant toxicity [6a]. In subsequent studies, it has been shown that gallium ions predominantly accumulate in the bone and therefore would be a good candidate for radiotherapy of bone cancer. Unfortunately, the radioactive isotope ^{72}Ga has only a half-life of around 14 h, which is not long enough for effective radiotherapy. Nevertheless, current clinical developments involve the use of radioactive gallium isotopes as tumour imaging reagents (see Chapter 10), gallium nitrate in metabolic bone disease, hypercalcaemia and as anticancer drug, as well as up-to-date research in the area of chemotherapeutic applications.

4.4.2 Chemistry

Gallium exists as the trivalent cation Ga^{3+}, and in aqueous solution it presents as a hydrated complex. Depending on the pH, a variety of hydroxyl species are formed, some of which are insoluble, such as $Ga(OH)_3$. At physiological pH, nearly no free Ga^{3+} is present and the hydroxyl species $Ga(OH_4)^-$ (gallate, the dominant species) and $Ga(OH)_3$ are formed. Gallium hydroxide species are amphoteric, analogous to aluminium hydroxide compounds.

It is important to note that the stability of solutions containing gallium chloride or gallium nitrate for oral administration is affected by the pH. They might not be stable over extended periods and gallium hydroxide precipitates.

4.4.3 Pharmacology of gallium-based drugs

Ga^{3+} has an ionic radius and binding properties similar to those of Fe^{3+} (ferric iron). Unlike Fe^{3+}, it cannot be reduced to its divalent state, which means that it follows a completely different redox chemistry compared to iron. The oxidation and reduction of iron is important in many biological processes, which therefore cannot be mimicked by gallium. One example includes the uptake of Fe^{2+} by the haeme group (see Chapter 8). As Ga^{3+} is not readily reduced to it +II state, it cannot bind to the haeme group.

Transferrin is an important transport protein that controls the level of free Fe^{2+} in the blood plasma. Free iron ions are toxic to most forms of life, and therefore transferrin binds Fe^{2+} and removes it from the blood. There is an excess of transferrin present in the blood, and it has been shown that Ga^{3+} can also bind to this glycoprotein but with a lower affinity than Fe^{3+}. Once the binding capacity of gallium ions to transferrin is exceeded, it is believed to circulate as gallate [$Ga(OH)^{4-}$] [6a].

The therapeutic action of Ga^{3+} is very much based on the pharmacological activity of Fe^{3+} which it mainly mimics. Ga^{3+} is transported via transferrin to areas of the body that require increased Fe^{3+} levels, including proliferating cancer cells [11]. Ga^{3+} can interrupt the cell cycle and DNA synthesis by competing with iron for the active sites in essential enzymes [12]. Ga^{3+} accumulates in the endosomes mediated by transferrin uptake and transported into the cytosol, where it can bind to the enzyme ribonucleotide reductase. Ribonucleotide reductase has been proposed as the main target for Ga^{3+}. Binding to this enzyme will impair DNA replication and ultimately lead to apoptosis [13]. *In vitro* studies have shown that Ga^{3+} can bind directly to DNA [14].

4.4.4 Gallium nitrate – multivalent use

In clinical trials, gallium nitrate has proved to be highly active as an antitumour agent especially against non-Hodgkin's lymphoma and bladder cancer. The cytotoxic activity of gallium nitrate has been demonstrated as single agent and as part of combination therapy, for example, together with fluorouracil. Gallium nitrate shows a relatively low toxicity and does not produce myelosuppression, which is a significant advantage over other traditional anticancer agents. Furthermore, it does not appear to show any cross-resistance with conventional chemotherapeutic agents (Figure 4.8) [15].

These studies have also shown that gallium nitrate is able to decrease serum calcium levels in patients with tumour-induced hypercalcaemia. Subsequently, several studies have been carried out comparing traditional bisphosphonate drugs with gallium nitrate in their ability to decrease the calcium levels that are elevated as a result of cancer. Based on the clinical efficacy, gallium nitrate injections (Ganite™) was granted approval by the FDA for the treatment of cancer-associated hypercalcaemia. Gallium nitrate is also believed to inhibit the bone turnover and therefore to decrease osteolysis, the active reabsorption of bone material, in patients with bone metastasis secondary to other cancers.

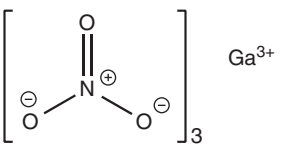

Figure 4.8 *Gallium nitrate*

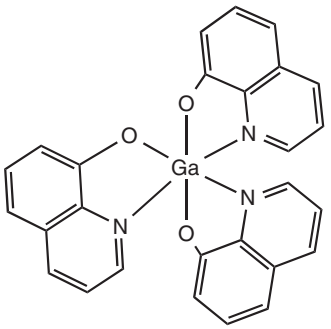

Figure 4.9 *Chemical structure of gallium 8-quinolate*

4.4.5 Gallium 8-quinolinolate

Gallium 8-quinolinolate is a hexacoordinated Ga^{3+} complex in which the central gallium atom is coordinated by three quinolinolate groups. It was developed as an orally available anticancer agent. It was successfully tested *in vitro* against lung cancer and in transplanted rats against Walker carcinosarcoma [16]. Main side effects were detected in experiments on mice at doses of 125 mg/kg/day. These included leukopaenia and some fatalities. The highest concentrations Ga^{3+} were found in the bone, liver and spleen (Figure 4.9) [6a].

Preclinical studies have established the IC_{50} values for a single-agent activity in the lower micromolar range for a variety of cancer cell lines. These cell lines include human lung adenocarcinoma, where gallium 8-quinolinolate was shown to be 10 times more potent than gallium nitrate. Other cell lines include melanoma and ovarian, colon and breast cancer. The inhibitory effect appears to be dose dependent and not time dependent.

Gallium 8-quinolinolate entered phase I clinical trials under the drug name KP46 in 2004 in order to establish its safety and toxicity profile. KP46 was orally administered as a tablet, containing 10–30%w/w. Dose up to 480 mg/m^2 were given to patients with advanced solid malignant tumours. The drug was well tolerated and preliminary success was seen in patients with renal cell cancer.

4.4.6 Gallium maltolate

Gallium maltolate [tris(3-hydroxy-2-methyl-4*H*-pyran-4-onato)gallium(III)] is a coordination complex containing a central Ga^{3+} ion and three maltolate (deprotonated maltol) groups. Clinical studies have shown that oral administration of gallium maltolate leads to significantly increased bioavailability compared to gallium chloride. The oral bioavailability is estimated to 25–57% in comparison to 2% for gallium chloride (Figure 4.10) [17].

Phase I clinical trials on healthy humans showed that doses were well tolerated up to 500 mg. Furthermore, the results suggested the possibility of a once-per-day treatment option as a result of the half-life of the drug in the blood plasma (17–21 h). Orally administered gallium maltolate is excreted significantly more slowly via the kidneys than gallium nitrate injected intravenously. It has been proposed that rapid intravenous administration leads to the formation of gallate, which is quickly cleared as a small molecule via the kidneys. In contrast, oral administration leads to a slow loading of the blood plasma, and Ga^{3+} is bound to

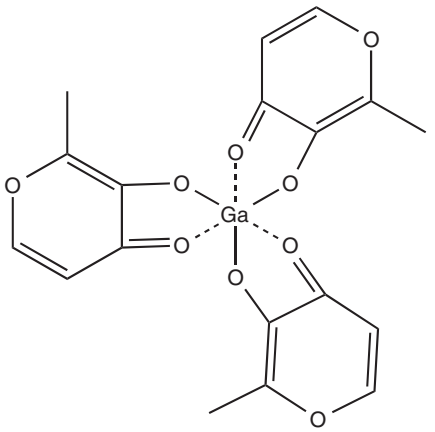

Figure 4.10 *Chemical structure of gallium maltolate*

transferrin. This may lead to a different mechanism of excretion, leading to a reduction in renal toxicity. Also, the transferrin-bound Ga^{3+} has the potential to be directly transported to the cancer cell without causing significant side effects. Therefore, an oral administration seems to be superior to parenteral administration [17].

4.4.7 Toxicity and administration

Gallium nitrate is usually administered as a continuous intravenous infusion (200 mg/m^2 for 5 days) for the treatment of cancer-induced hypercalcaemia. This dose is well tolerated even by elderly patients. Higher doses are usually used in the treatment of cancer. Renal toxicities being the dose-limiting factor are normally seen when gallium nitrate is administered as a brief intravenous infusion. With the long-term regime as described above, diarrhoea is the most common side effect. Renal toxicity can normally be minimised by adequate hydration of the patient [15].

The advantage of gallium nitrate therapies is that platelet count and white blood cell counts are not suppressed, which means that no myelosuppression takes place, which represents a major advantage over conventional chemotherapeutic agents [15].

4.5 Exercises

4.5.1 Draw the Lewis structure or chemical formula of the following aluminium-based drugs

(a) Aluminium acetate
(b) Aluminium chloride
(c) Aluminium oxide

4.5.2 Research different antacids mixtures, state their content and calculate the weight/volume percentage (%w/v) for each active pharmaceutical ingredient (API).

Drug name	Aluminium hydroxide	%w/v	Magnesium hydroxide	%w/v
Maalox®	220 mg/5 ml	???	195 mg/5 ml	???

4.5.3 A typical antacid capsule contains 475 mg aluminium hydroxide as the active ingredient. How many milligrams of stomach acid (HCl) can be neutralised by one tablet?

4.5.4 An aluminium hydroxide suspension (30 ml) containing 500 mg/5 ml aluminium hydroxide is prescribed to the patient. The prescription states the patient has to take 30 ml four times a day.

(a) What is the chemical formula of aluminium hydroxide?
(b) How many grams of Al^{3+} is given to the patient per single dose?
(c) What is the weight/volume percentage (%w/v) of aluminium hydroxide in the suspension?

4.5.5 Write the chemical equations explaining the amphoteric behaviour of gallium hydroxide.

4.6 Case studies

4.6.1 Boric acid – API analysis

Boric acid is known to have antifungal and antimicrobial properties and therefore has a clinical use. Typical pharmaceutical analysis of boric acid as an API includes its reaction with a known amount of mannitol and subsequent titration of unreacted mannitol.

(a) Research the chemical structure of mannitol including its stereochemistry.
(b) Describe the reaction of boric acid and mannitol, including relevant chemical equations.
(c) For the analysis of boric acid as an API, 1.0 g of the acid is typically dissolved in 100 ml of water, and 15.0 g of mannitol is added. The solution is then titrated with 1 M sodium hydroxide (NaOH) solution using phenolphthalein as indicator.
Calculate the volume of NaOH needed in this titration if the API has a purity of 99%.
(d) Research the typically accepted error margins for the purity of boric acid as an API.

4.6.2 Aluminium hydroxide tablets

Your pharmaceutical analysis company has been contacted by an important client and asked to analyse a batch of aluminium hydroxide tablets. The description of your brief states that you are supposed to analyse the API in these tablets following standard quality assurance guidelines.

Typical analysis methods used for quality purposes are often based on titration reactions, but also a variety of other quantitative analysis methods such as gravimetric analysis can be used. Typically, a certain amount of the tablet powder is dissolved in water, and hydrochloride acid (HCl) is added. An excess of the precipitation reagent is added, and the solution is stirred until precipitation is completed. The precipitate is then filtered, dried to constant weight and weighed.

(a) Draw the chemical formula of aluminium hydroxide.
(b) Research the type of analysis used. Within your studies, you should look at a variety of precipitation reagents and understand how different factors can influence this method.
(c) Formulate the relevant chemical equations.
(d) The package states that each tablet contains 475 mg aluminium hydroxide. For the experiment, 20 tablets are weighed (total weight 12.5 g) and powdered. An amount of powder containing 0.4 g aluminium hydroxide is dissolved in water and HCl, and reacted with excess 8-hydroxy quinolone. After stirring this solution for 2 h near the boiling point, the precipitate is filtered and dried overnight in the oven at 100 °C.

The precipitate weighs 2.0 g.

Calculate the amount of aluminium hydroxide present in your sample. Express your answer in grams and moles.
(e) Critically discuss your result in context with the stated value for the API.
(f) Research the typically accepted error margins.

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