Chapter

Electrochemical Anticoagulant Method

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Abstract

Delving into the science of electrochemistry to test living cells under the influence of metabolic disorders, infections, and injuries has been the focus of a group of interdisciplinary science researchers for decades. Considering that blood is an environment with chemical and physical properties, using non-chemical methods to influence this environment is not out of mind. Due to the presence of ions in the bloodstream and their role in blood coagulation, this passage can be used to obtain desired results in various clinical fields like preventing the clotting of blood. The use of chemical anticoagulants for research and therapeutic purposes is widespread; this group of anticoagulants is replaced under certain conditions due to their side effects. However, the chronic use of some anticoagulants has a potential impact on the future treatment decisions of patients.

Keywords: anticoagulants, blood coagulation, calcium, electrochemical techniques, treatment

1. Introduction

Today there are several anticoagulants with different applications according to the nature of their chemical structure and their function. Some utilize research and laboratory goals, while others are employed in medicinal and clinical centers. For instance, Ethylenediaminetetraacetic acid (EDTA), as a calcium-chelator, is suitable for counting the blood cell; citrate is used in testing the coagulation pathways such as Prothrombin time (PT) and partial thromboplastin time (PTT) [1]. Some anticoagulants with unique features are more useful in specific uses; for example, fluoridated anticoagulant compounds prevent blood sugar reduction by inhibiting glycolysis pathway enzymes [2]. In contrast, anticoagulants such as warfarin and heparin, which also originate biologically and act with a mechanism other than calcium chelation, are administered as medicine. Since small changes in calcium concentration can cause irreparable damage, the second category of the mentioned anticoagulants is used for medical-clinical goals because they do not affect this ion concentration [3]. This is more significant when the blood is taken from the patient and returned to it again, such as through hemodialysis, open heart surgery, and blood entering the artificial heart and lung machine [4], Extracorporeal Membrane Oxygenation device [5], and the device that separates platelets from donor blood (Apheresis) [6]. In mentioned processes, heparin is used to prevent blood coagulation; however, under certain conditions, citrate is sometimes used as an anticoagulant in hemodialysis [7].

Long-term use of heparin causes unwanted side effects such as bleeding, immune reaction, heparin-induced thrombocytopenia (HIT), heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), eosinophilia, and osteoporosis [8, 9]. To eliminate these complications, light heparin molecule is used [10]. On the other hand, in some cases, such as patients with hemophilia and sensitivity to heparin, heparin application is bounded, so this group will not be able to benefit from facilities such as hemodialysis or open heart in the future [11].

In addition to common chemical anticoagulant compounds, there are natural plant products with anticoagulant properties such as turmeric curcumin, polysaccharide HAF0, total saponins from *Polygala fallax* Hesml, hyperoside isolated from the leaves of *Rhododendron brachycarpum*, Polysaccharide from *Umbilicaria esculenta*, Withaferin A from *Withania somnifera*, Wogonin and its metabolite wogonoside from *Scutellaria baicalensis* Georgi. In previous research, the anticoagulant properties of the mentioned items have been reported by examining PT and PTT time, but they are not applicable in the clinic [12].

In this chapter, after a brief overview of conventional anticoagulants, we will investigate the effect of electrochemistry on blood coagulation and then describe two electrochemical methods that raised blood clotting time without chemicals.

2. The common chemical anticoagulants and their clinical application

Anticoagulants increase blood clotting time and are also called blood thinners. Anticoagulants act at different levels of the blood coagulation pathway; they are divided into four main groups: coumarins and indane diones; factor Xa inhibitors; heparins; and direct thrombin inhibitors [13].

2.1 Coumarins and indanediones

Warfarin is the only coumarin that is used in humans. Coumarin-like drugs bind to vitamin K epoxide reductase complex 1 in the liver and prevent the conversion of inactive oxidative vitamin K to active reducing vitamin K. Therefore, this compound is an anti-coagulant that limits access to vitamin K; this vitamin affects the blood coagulation pathway via coagulation factors II, VII, IX and X. Pindone and Diphenadione are indane diones with anti-coagulant effects in a similar way to coumarins and are mainly used for pest control, mouse, rat, and rabbit population control [14].

2.2 Factor Xa inhibitors

Factor Xa inhibitors such as apixaban, edoxaban, fondaparinux, and rivaroxaban act on factor Xa, which is responsible for converting prothrombin to thrombin and preventing the formation of blood clots [15].

2.3 Heparins

Heparins are a group of anticoagulants, including unfractionated heparin, low molecular weight heparins (LMWH), and heparinoids. Unfractionated heparin is also called high molecular weight heparin and is an inhibitor of thrombin and factor Xa. This type of heparin is only injected intravenously. The LMWHs, such as Dalteparin,

Nadroparin, Enoxaparin, Tinzaparin, Parnaparin, Certoparin, and Reviparin, act on thrombin and factor Xa. LMWHs last much longer in the body than heparin and can be injected subcutaneously. Heparinoids, such as danaparoid (Orgaran), Dermatan sulfate, Mesoglycan, and Pentosan polysulfate, with the same function as heparin, are extracted from animal and plant tissues or made artificially. Some of them are applied topically and are easily absorbed by the skin, reducing blood clots, inflammation, and associated pain [16].

2.4 Direct inhibitors of thrombin

Thrombin can be inhibited directly or indirectly by binding thrombin-inhibiting drugs to one or two of its three domains: the active site and exosites1,2. Exosite 1 is the binding site of thrombin to fibrin, and exosite 2 acts as the binding site of heparin [17].

Direct thrombin inhibitors, such as Bivalirudin, Dabigatran, Desirudin, and Argatroban, bind directly to thrombin and inhibit the function of thrombin without the need for a cofactor such as antithrombin. Desirudin and Argatroban are direct injectable thrombin inhibitors; Desirudin binds to both the active site of the enzyme and Exosite 1; Argatroban binds only to the active site of the enzyme. Dabigatran is a direct oral thrombin inhibitor that reversibly binds to the active site of the enzyme [18].

3. The role of calcium ions in blood coagulation

Calcium ion plays a role in both the internal and external coagulation pathways, and the activation of many coagulation factors depends on the presence of calcium. Probably, the functional effect of this ion is related to its electric charge [19]. The presence of ɣ-carboxy glutamyl (Gla) residues in the structure of some coagulation factors turns them into excellent calcium chelators. Gla is an amino acid formed post-ribosomally in the liver with the help of vitamin K. These residues strongly tend to bind to calcium due to two carboxyl groups (COO-). For example, prothrombin has 10 Gal residues at its amino terminus and forms a strong negative charged terminus. Due to its positive charge, calcium forms a complex with Gla residues, which induces conformational and electronic states in blood coagulation factors and facilitates the binding of them to the cell membrane. In addition, calcium can induce conformational changes by binding to parts other than Gla (such as the second catalytic) that accelerate the catalytic activities of coagulation factors [20]. Gla residues are generally present in the amino part of molecules (**Figure 1**), so the positive calcium ion, by binding to the Gla residue in prothrombin and neutralizing its negative charge, facilitates the binding of this factor to the cell membrane and the formation of the prothrombinase complex. The binding of prothrombin and other coagulation proteins dependent on vitamin K to the cell membrane of platelets (membrane phospholipid) is also done through the positive charge of calcium (**Figure 2**) [21].

In addition, the activation of factor XIII requires more than the physiological level of calcium. Ca^{2+} ions are necessary to control the coagulation cascade and maintain homeostasis. Ca^{2+} chelation leads to changes in coagulation factors V, VIII, and XIII; therefore stops pro-coagulation activity. Several coagulation factors, especially coagulation factor XIII, are activated by calcium ions and converted to factor FXIII, which is responsible for tightly binding the fibrin clot and inhibiting premature fibrinolysis [22].

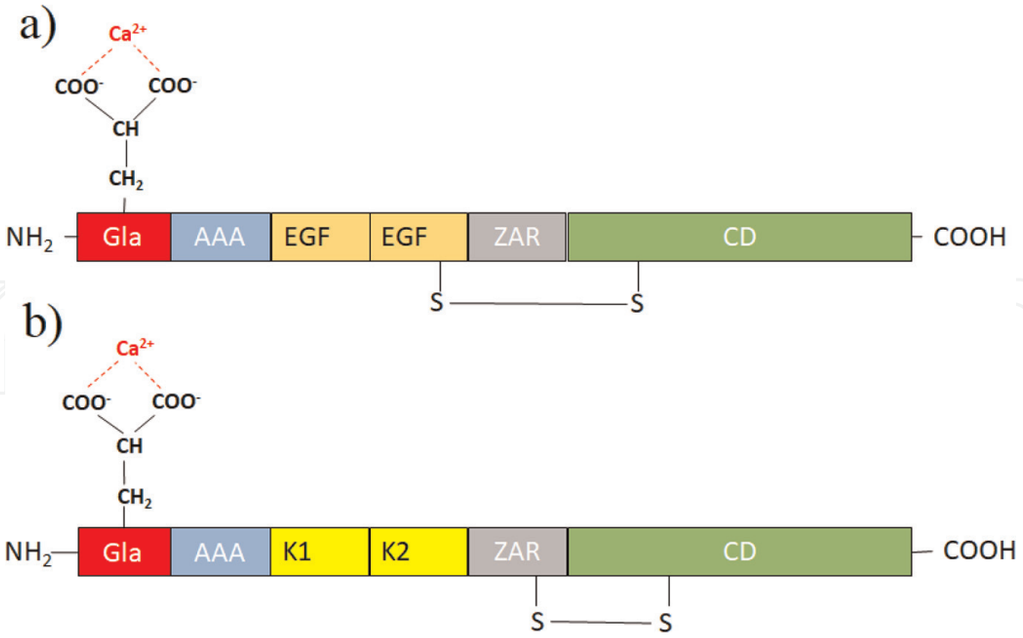

Figure 1.
(a) The γ-carboxy glutamyl (Gla) residues in the structure of coagulation factors VII, IX, and X. the second Gla, which contains the γ-carboxy glutamyl, is the binding site of calcium ion to the coagulation factor, and (b) prothrombin sequence. AAA: The second aromatic amino acid stack domain. EGF: Epidermal growth factor; ZAR: The zymogen activation region; CD: Catalytic domain; K1: Kringle Domain1; K2: Kringle Domain2.

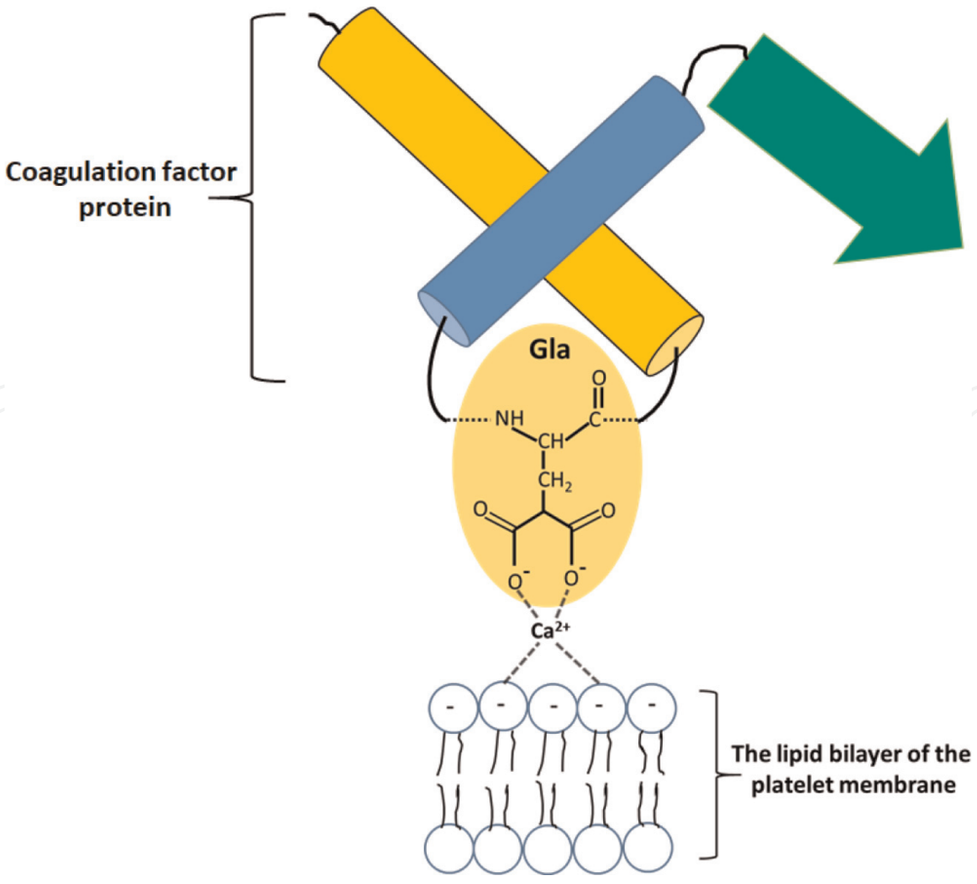

Figure 2.
Prothrombin and other coagulation proteins dependent on vitamin K bind to the cell membrane of platelets due to the positive charge of calcium. Because of the phosphate group, the phospholipid of the membrane has a negative charge.

4. Application of electrochemistry in biology

Referring to the research of Professor Philip N. Sawyer (1926–2014), who focused on the reactions between different parameters of blood and electrolysis for two decades, he can be called the pioneer of electrochemistry in biology.

In 1964, Philip N. Sawyer and colleagues investigated the behavior of blood cells and blood thrombus with two electrodes. In their study, after using platinum and gold electrodes, under a potential difference of 0.33 V, blood cell deposition was observed around the positive electrode. The results of their studies led to the presentation of a mechanism based on the presence of electric charge in blood cells, which prevents the deposition of blood cells on the vessel wall [23].

Durliat et al. showed that different voltages in the blood affect the blood clotting process, so a potential difference of 1.15–1.35 volts in the presence of a platinum electrode causes the conversion of prothrombin to thrombin and thrombin causes the conversion of fibrinogen to fibrin and It forms a clot. However, the potential difference of more than 1.45 V with the same platinum electrode has a destructive effect on prothrombin and prevents the formation of blood clots [24].

SIMONA [25], designed electrodes to measure various substances in direct contact with blood. According to this study, interactions between fibrinogen and factor XIII of the blood coagulation cascade at the level of the electrodes lead to decreasing the level of blood coagulation at the cathode.

N. Ramasamy et al. showed that fibrinogen protein is deposited on the platinum cathode electrode even in low concentrations during electrolysis(voltage $\sim$ 600 to 800 mV). According to this study, the inherent potential of the electrode metal is critical in the compatibility of the electrolyte (normal saline or blood) with the electrode [26].

L. Duic et al. investigated the effect of an electrochemical reaction by applying a voltage of 500–1200 millivolts with a platinum electrode on blood coagulation. They found that the conditions described in their study lead to a decrease in prothrombin, a slight conversion of prothrombin to thrombin, and ceasing the conversion of prothrombin to thrombin in the middle of the process and thus reducing blood clotting [27].

Tara and Sarkar showed that the electric current passing through the blood is related to the blood sugar level. They used electrolysis to predict the level of blood sugar and found that the more the blood sugar increases, the more the electric current in the blood decreases. However, at a level of hypoglycemia, the electrical current is extremely reduced and reaches zero [28].

Abdalla et al. investigated electrical conductivity in healthy and diabetic blood in the 10-KHz-1-MHz frequency range. They proved that diabetic blood is not more conductive than normal blood [29].

5. Principles of electrolysis

Electrochemistry is one of the sub-branches of thermodynamics in chemistry that examines the relationship between electrical work and chemical changes that are generally carried out by oxidation and reduction reactions (electron transfer). In electrolysis, through an electrode, an electric current is established in the solution to excite the ions needed to carry out a reaction. If electrical energy is used in a system to perform a chemical reaction in an electrolyte solution, an electrolytic cell is formed. An electrolytic cell includes a source of electrical energy, an electrolyte solution,

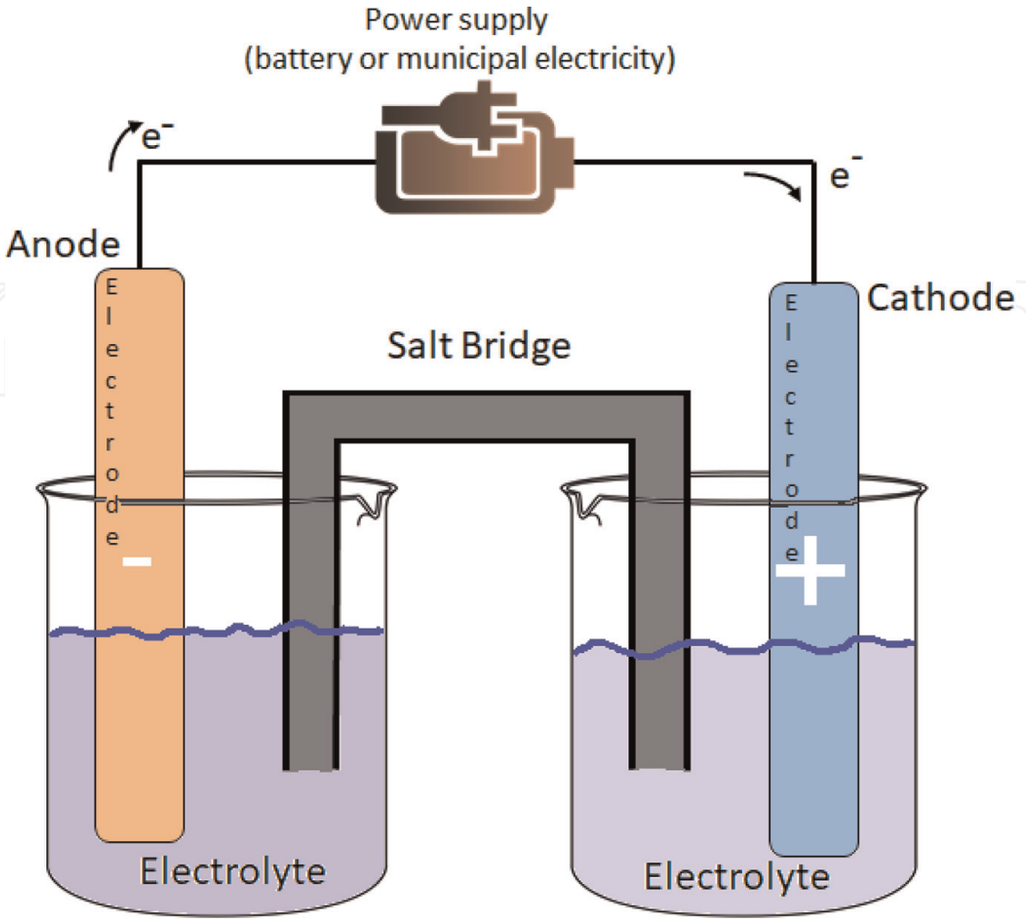

Figure 3.
Electrolytic cell and its components. An electrolytic cell includes; the source of electrical energy, the electrolyte solution, electrodes, a connector, and a salt bridge. In an electrolytic cell, the electrode that is connected to the power source has a negative charge (it carries the electrons entering the system); by giving electrons to the cations, it reduces them, and that is why it is called the cathode, and the opposite electrode which is connected to the positive pole of the power supply is called the anode. Anode is a path for the electrolytic cell's electrons to return to the power source.

electrodes, and their interfaces, and if needed, a salt bridge (**Figure 3**). The voltage required to perform electrolysis is called "Decomposition Potential" [30, 31].

5.1 The principal elements of the electrolysis process

5.1.1 Electrolyte

The liquid nature of the electrolyte is necessary because it provides an environment for the free movement of ions and electric charge to form an electric circuit, and therefore electrolysis occurs. The liquid state can be a solution containing ions or the molten form of salts. Generally, electrolyte solutions are polymers that cause the passage of electric current in the electrolyte with the help of free ions [32].

5.1.2 Direct power supply

In addition to the electric current outside the electrolyte, which is conducted through an external circuit, the DC electric current, as a power supply for electrolysis, supplies the energy needed to produce or charge ions [33] (**Figure 3**).

5.1.3 Electrodes

They are conductive (such as metals or conductive polymers) or semi-conductive (such as graphite) electrodes in the form of a blade in an electrolyte solution, which in an electric circuit by connecting to the metallic and non-metallic part of the circuit causes communication between these two parts. The electrodes cause the electron transfer of the electrochemical cell to the external circuit or vice versa. Each electrochemical cell has two electrodes, in one of which the oxidation reaction (anode electrode) and in the other the reduction reaction (cathode electrode) takes place. If there is a different concentration or diverse types of electrolyte in two containers, the anodic and cathodic electrodes will naturally encounter dissimilar electrolytes in terms of sort and concentration. In this situation, containers containing electrolytes are connected with the help of a salt bridge. In the presence of a salt bridge, not only the electric current is completed, but also the mixing of electrolytes is prevented. If the electrodes are made of non-reactive materials (i.e. reaction with electrolyte) such as gold, platinum, and some polymers, their function is only to move electrons, and these electrodes are called non-reactive electrodes. If the electrodes are made of reactive materials such as copper or zinc, they react with electrolytes; so, these sorts are called reactive electrodes [33, 34].

6. Electrolysis process

The prominent process in electrolysis is the exchange of atoms and ions by removing or adding electrons through an external circuit. The physical state of the final product in this process is usually different from the electrolyte, and it can be separated from the electrolyte using physical steps. For example, the electrolysis of brine is done to produce hydrogen and chlorine, both of which are in the gas phase [33]. Through electrodes placed in the electrolyte, an electric voltage is applied. Each electrode attracts ions of opposite charge, positively charged ions move toward the cathode, and negatively charged ions move toward the anode. Neutral atoms are charged by gaining or releasing electrons and moving through the electrolyte. The formation of neutral atoms from ions is called "discharging"; when an ion gains or loses enough electrons to form neutral, a new atom is created and separated from the electrolyte. According to the intensity of the electric current, positive metal ions such as Ca^{2+} or Cu^{2+} may be deposited on the cathode; this process is called "Electroplating" or "Electrorefining". The oxidation of ions or neutral molecules takes place at the anode; for example, the oxidation of "Ferrous" and its conversion to "Ferric" occurs in the anode [31]. The reduction of molecules or ions occurs in the cathode; neutral molecules can react in both electrodes.

7. "Energy changes" during electrolysis

The electrical energy that must be given to the system is the Gibbs free energy changes in the reaction plus the energy loss in the system:

$$\text{Energy loss} + \text{Gibbs free energy changes} = \text{electrical energy required}.$$

Theoretically, the wasted energy can be considered zero; therefore, the highest thermodynamic efficiency is obtained by dividing the enthalpy changes or ΔH (the

heat that is exchanged in the conversion of reactant(s) to product(s) in a chemical reaction) by the energy change. In most cases, the electrical energy entered into the system is greater than ΔH, which causes energy to be released in the form of heat. In some cases, for instance, in the electrolysis of steam to hydrogen and oxygen, which happens at high temperatures, heat is absorbed [31].

8. Laws of electrolysis based on Faraday's law

The current through a battery in the external circuit is directly proportional to the number of electrons it transfers from the negative electrode (cathode) to the metal ions or cations. In the case of divalent cations, such as calcium, for each cation, two electrons are transferred from the cathode to the cation. If each electric charge is equal to 1.602×10^{-19} coulomb (we call it e^-), to transfer each calcium atom to the cathode, we need $2e^-$ from the cathode to the cation. Now, for the formation of n calcium atoms on the cathode, the amount of transferred charge will be equal to $2ne^-$ [35].

8.1 Faraday's first law

In 1832, Michael Faraday announced that the number of elements separated by passing an electric current through molten salt is proportional to the quantity of electric charge passing through the circuit. This was the basis of the first law of electrolysis. The mass of material with a weight (m) that is deposited in the electrode is directly proportional to the quantity of passing electric charge (Q):

$$m = k.Q$$

In the above relation, K is an electromechanical constant. This relationship can be shown as follows:

$$m = Z.Q$$

Z is the electrochemical equivalent of the metal deposited or the gas released in the electrode. This quantity is equal to the mass that is displaced by 1 coulomb of electric charge.

If Q is equal to 1 then:

$$m = Z$$

It states that the equivalent of any substance is equal to the deposited amount of the same substance in the passage of 1 coulomb of electric charge [35].

8.2 Faraday's second law

The mass of the deposited element in electrolysis is proportional to the quantity of electric charge passing through the electrolyte. The number of atoms deposited on the electrode depends on their valence. The higher the atom's valency, the lower the atoms formed on the electrodes and vice versa. In a certain quantity of electric current passing through different electrolytes, the sediment mass is directly proportional to the atomic number and inversely proportional to the valency of those atoms. Faraday's

second law of electrolysis states that when a certain quantity of electric current passes through several electrolytes, the deposited mass is proportional to their equivalent weight [36].

9. Competition of half-reactions in the electrolysis of solutions

In cells with platinum electrodes, the electrolysis of the aqueous solution of some salts leads to the reduction of cations and the oxidation of anions. The voltage required for the electrolysis of a salt solution is obtained through the standard electrode potential (Standard Electron Potential) for the reaction in the cathode and anode. The standard electrode potential is directly proportional to the Gibbs free energy for each reaction at each electrode. The electrical energy consumed in the electrolysis cell is proportional to the potential difference between the two electrodes, called Cell voltage, cell potential (E), and electromotive force (emf). When the emf is positive, the cell is involved in a spontaneous reaction, when it is negative, the cell is involved in a non-spontaneous reaction [35]. The quantity of emf is related to the type of element that makes up the electrode and expresses the tendency of that element to be oxidized. The emf in standard conditions (E°) (−298°K, 1 atmosphere of pressure, concentration for solutions 1 molar, and pure solid for the electrode) for each element is distinct that is experimentally measured and recorded. For example, the calcium ion half-reaction (the following equation) requires −2.87 volts of electrical energy [31].

$$Ca^{2+}_{(aq)} + 2e^{-} \leftrightarrow Ca_{(s)}$$

10. Factors affecting the electrolysis reaction

Factors affecting the electrolysis reaction are classified as follows:

- **High voltage:** Applying more voltage than expected is used when there is a need to overcome the reactions that take place in the electrode itself. This case is mostly used in gases.
- **Electrode type:** A neutral electrode is where the reaction occurs and does not participate in the reaction, but an active electrode will be part of a half-reaction.
- **Simultaneous reactions at the electrode:** If different half-reactions occur simultaneously, some of them must be eliminated to determine the correct pair of half-reactions for electrolysis.
- **The condition of the reactants:** If the reactants are not in the standard state, the voltage in the half cell is different compared to the standard. In this case, the pH of the solution in the anode is higher or lower than the standard [31, 32, 35].

11. Description of electrochemical anticoagulant method

Jahanbani et al. designed a simple electrolysis device that successfully prevented blood clotting within 20 minutes under controlled in vitro conditions [37]. That

chamber consisted of a cylindrical polypropylene container (diameter 3 cm and height 6 cm), two platinum electrodes (negative pole or cathode), and an aluminum electrode (positive pole or anode). The electrolysis cell was connected to a power source (−3.5 V; 1 mA/cm^2) through a platinum electrode. Also, there was an aluminum electrode in a container containing 0.9% sodium chloride (as a salt bridge) which also was connected to the power supply. To check blood clotting, the desired sample was poured into the main container (which contains aluminum and platinum electrodes), and an electric current was immediately established (3.5-V voltage; 1 mA/cm^2 current), which resulted in driving the electrons toward the cathode or negative pole (**Figure 4**). The calcium ions in the blood are polarized by the negative (platinum) electrode and accumulate around it; so calcium is separated from the blood, and the chance of blood clotting was impossible without the calcium (**Figure 5**). When the electric current was established, all the electrons were not headed toward the platinum electrode, some of them entered the blood as stray electrons. The aluminum electrode was responsible to remove and head the stray electrons to the saline chamber. In the chamber containing 0.9% sodium chloride, the conducted electrons polarized the sodium ions to release; these ions accumulated around the aluminum electrode which was connected to the power source on one side. The mentioned electrode returned the dissolved ions to the power source; as a result, a closed circuit was formed in the electrolysis cell. In the design of the described electrolysis cell, attention to the use of special electrodes and the design of the chamber in two separate containers are among the reasons for its anticoagulant effect. According to Sawyer's report, if two positive and negative electrodes are immersed in a vessel containing

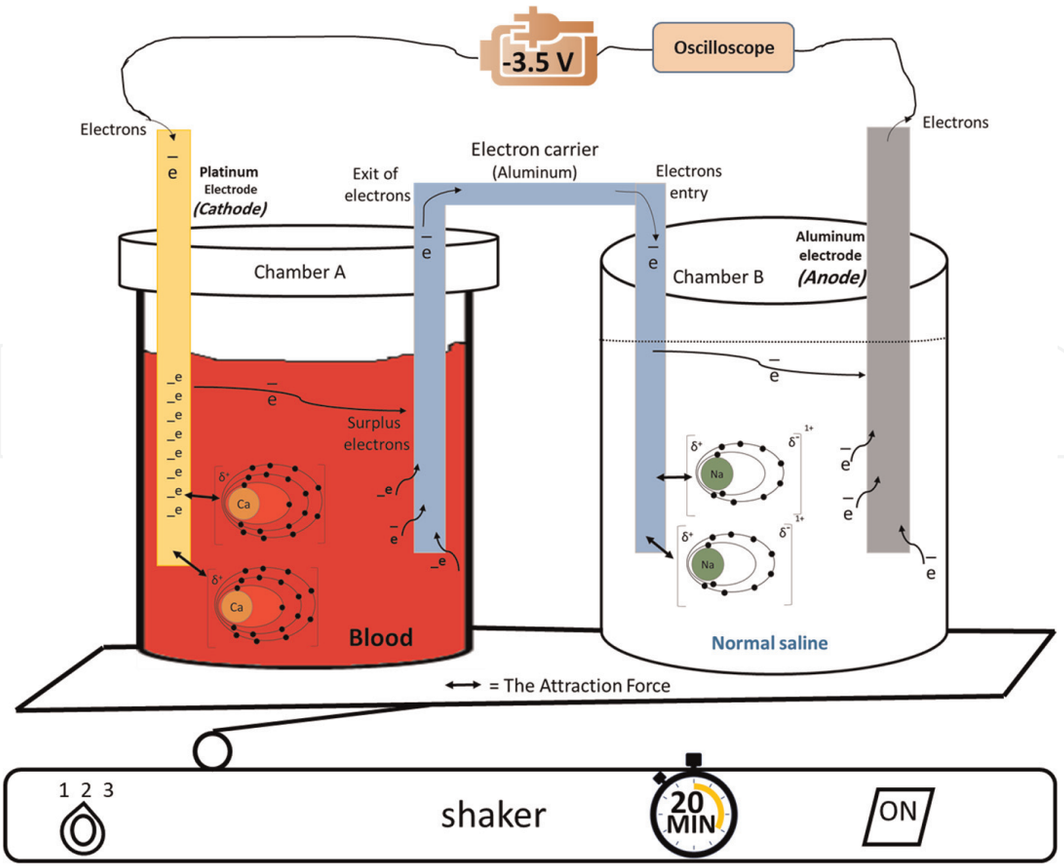

Figure 4.
The electrolysis device consists of a cylindrical container made of polypropylene.

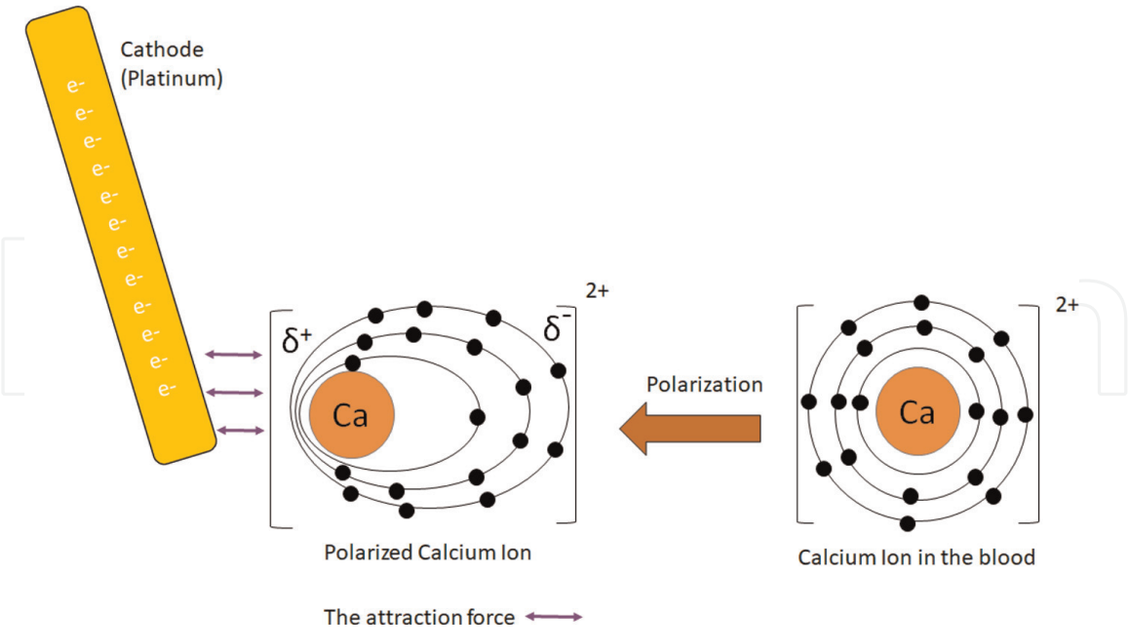

Figure 5.
Polarization of calcium ion in blood under the influence of electricity by the cathode electrode.

blood at the same time, a clot forms around the positive electrode [23]. In the described cell, the chambers were designed in two parts, which separated the cathode and anode electrodes. An electron transporter, similar to a salt bridge made of aluminum, was used to establish a circuit between two chambers because blood clots do not form around this metal. The negative electrode, or cathode, was in direct contact with the blood and was made of platinum; this non-reactive electrode was only responsible for electron transfer.

In summary, the characteristics of a suitable anticoagulant include the following: Anticoagulation should not change the size of blood cells, not cause hemolysis, prevent platelet aggregation or minimize their aggregation, not change the morphology of blood cells, and easily dissolve and spread in the blood [38, 39]. Except for the last, which is related to chemical anticoagulants, according to the results of blood tests under the influence of electricity, it can be claimed that the described electrolysis cell of Jahanbani et al., includes the general characteristics of a safe anticoagulant [37]. Although the described electrolysis cell is intelligible and effective, it has not been investigated for implementation in clinical systems such as continuous blood flow; it is not yet clear whether this design can be used in systems with high blood flow rates (100-350 mL/min) and high blood volume that is maintained for a longer period to have the desired effect. In this system, the embedded platinum electrode has a saturable property and therefore responds to a specific volume of blood, and this does not affect the maintenance of calcium ion concentration.

In the design of an electrolytic cell, Delangis and Yen used a capillary glass chamber with two platinum positive and negative electrodes in direct contact with the blood. The electric current was 1 mA/cm^2, and the potential difference was 50 mV. Between the negative electrode and the power supply, a resistance of 20 kOhm was installed to control the current. They used an oscilloscope to record all possible fluctuations in voltage and electrical current. They prevented blood coagulation until the 12th minute. Electron microscope images showed changes in the morphology of red blood cells such as macrocytic and rouleaux formation. To experiment with the blood

that was affected by electrolysis, they injected that into the experimental animal (sheep), but the animal died 2 days later due to lung impairments [40].

Delangis and Yen's electrolytic cell design to prevent blood coagulation was a pioneer in this field; therefore, there were errors in this design that were addressed in subsequent research. Their capillary chamber was made of glass, and this material drives the blood coagulation process [41]. Also, the stirrer, which was inserted into the blood to detect the clot strands, was made of glass. They designed the chamber as a capillary; so, the maximum contact between the electrodes and the blood was achieved. However, that chamber was static, so there was no uniform contact between the electrodes and the blood. On the other hand, the one-part chamber and the simultaneous placement of the electrodes in the same chamber caused the process of clot formation to accelerate around the positive electrode [23]. According to the mentioned reasons, it is possible to explain why their electrolysis cell could not prevent blood coagulation for more than 12 minutes, and the resulting blood was not safe for injection into the animal.

12. Conclusion

Common anticoagulant drugs of synthetic or biological origin are used for specific purposes in vivo and in vitro conditions. By reviewing the list of oral and parenteral anticoagulants, we get that the list of drugs approved by the FDA is limited. This feedback was not a testament to their efficacy and safety but because of a failure to develop more effective and improved anticoagulant agents. Sometimes, the available agent's behavior is a cumbersome agent to use regarding the delayed onset of action, unpredictable efficacy that is affected by genetics, co-administered drugs or diet, patient weight and age, periodic monitoring to achieve the therapeutic levels, etc. In addition to the therapeutic aspects of anticoagulants, anticoagulants are also used in cases such as hemodialysis to prevent blood clotting in the extracorporeal system. In these patients, the medicinal use of anticoagulants is limited to a particular group; for example, vitamin K antagonists are prohibited in this category of patients due to the high risk of bleeding. However, turning to drugs such as heparin and its derivatives chronically will have pathological consequences. The presence of ions in the blood and its electrochemical properties provide a basis for non-chemical intervention to prevent blood clotting. In this regard, research has been conducted on the effect of electrical currents in the blood, in some of which blood coagulation has been emphasized, and initial experiments have brought promising results. It is expected that with the continuation of research in this field, in the foreseeable future, we will catch the use of this method along with chemical drugs to prevent blood coagulation.

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