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Research Paper: Formulation and Physicochemical Control of Local Anti-hemorrhage Solution of Aluminum Chloride for Oral and Dental Surgeries

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ABSTRACT

Introduction: During oral surgery, bleeding is one of the expected side effects, specifically in the critical areas such as head and neck. Accordingly, developing optimal homeostatic agents is of concern in this study in order to produce more efficiently optimal homeostasis both in terms of cost and performance.

Materials and Methods: To make a 25% aluminum chloride solution, aluminum chloride (hexa-hydrate) powder, propylene glycol, ethanol or distilled water were used, sodium bicarbonate solution with different concentrations was utilized to adjust the pH of the solution, after that, physicochemical evaluations were performed including appearance (transparency), viscosity and drug content by complexometric titration.

Results: Two final formulations (B_{12} and B_{13}) with acceptable pH, viscosity and drug content i.e., pH: 2.29 and 2.5 with respective viscosities: 7.55 and 5.12 cp as well as drug content of 100 % for both of them were selected.

Conclusion: The outcome revealed that formulations (B_{12} and B_{13}) of 25% aluminum chloride, propylene glycol (6 &8 mL, respectively) and 1 M sodium carbonate was made, which had an acceptable pH and viscosity while maintaining its therapeutic properties.

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1. Introduction

There is conclusive evidence that hemorrhage is an expected complication following dental surgeries. Accordingly, patients' medical conditions should be evaluated before surgery. To be more precise, excessive bleeding can prolong surgery time, increase surgical risk, and even lead to medical complications. Effective control of blood loss can save time and improve patient survival rates (1). However, various conditions leading to critical illness are associated with inflammation-induced coagulation, the most important of which is sepsis. Inflammation-induced coagulation is characterized by decreased clotting factors and platelets, as well as decreased anticoagulant proteins and inhibition of fibrinolysis (2). Furthermore, bleeding during and after surgical procedures poses a significant threat to both patients and physicians and initiates uncontrolled and undesirable consequences. To control bleeding, one must be familiar with the blood coagulation pathway, which is divided into three fundamental stages: To begin with, endothelial cells of injured vessels secrete a polypeptide factor called paracrine, leading to vasoconstriction and temporary reduction of blood flow. In the second stage, mechanical blockade occurs by platelets adhering to collagen, followed by cytokine secretion around the wound site. Platelet factor secretion strengthens vascular contraction and activates more platelets, which adhere and form a platelet plug. Simultaneously, the third stage of coagulation begins in the presence of collagen and tissue factor, initiating cascading coagulation reactions that culminate in fibrin clot formation (3).

Normally, local hemostatic agents are classified into two categories: active and inactive hemostatic factors. Inactive hemostatic factors, also known as mechanical factors, provide a framework for platelets to form a stable clot. These factors are readily available, cost-effective, and do not require special equipment for storage (4). Active hemostatic factors demonstrate hemostatic activity within 10 seconds and control bleeding more effectively than inactive factors. Chemical hemostatic solutions such as aluminum chloride (AlCl3) and solutions containing ferrous sulfate and its compounds are among these them (4). More exactly, aluminum chloride is a chemical compound with the formula AlCl3, possessing acidic properties. It exhibits strong clotting properties and rapidly induces coagulation upon contact with proteinaceous substances. The ions existing in this compound react with blood proteins, causing protein precipitation and closure of small blood vessel's openings (5). Most significantly, optical studies on the coagulant effect of aluminum chloride at different concentrations have demonstrated a significant reduction in blood clotting time (6). Additionally, it has been reported as one of the most effective drugs for controlling bleeding in over 90% of oral surgeries (7).

Obviously, it is apparent that all chemical substances used as hemostatic agents have low acidity in the pH range of 1 to 3. This acidity, present in all forms of these substances as solutions and gels, can affect the structure of gingival and dental tissues (8). Consequently, due to the widespread use of aluminum chloride and its products in dentistry and its high effectiveness, efforts have been made in this study to modify formulations to minimize their side effects. That is to say, based on the above studies, this research was conducted with the aim of localizing the aluminum chloride solution, determining the formulation, and, if possible, reducing the acidity of the drug while maintaining its coagulant properties. For this purpose, a 25% aluminum chloride solution in three different solvents, including water, ethanol, and/or propylene glycol, was prepared in the presence of a pH regulator (sodium bicarbonate). Various concentrations of sodium bicarbonate were used to create different pH levels of the solution. After measuring the pH and viscosity of the prepared solutions, quantitative viscosity tests and drug content tests were evaluated using the titration complexometric method.

2. Materials and Methods

To prepare a 25% $AlCL_3$ solution with suitable viscosity and acceptable pH, multiple samples were created as shown in Table 1. Initially, 5 g of $AlCl_3.6H_2O$ powder was added to 20 mL of base solution containing varying amounts of water, ethanol, and propylene glycol (as viscosity modifying and preservative agent), along with 0.7 M sodium bicarbonate (to adjust the pH of the solution).

Table 1. Formulation of chloride company solutions using 0.7 M sodium bicarbonate

An	distilled water (ml)	Ethanol (ml)	Propylene glycol (ml)	Sodium bicarbonate 0.7 M (ml)
A1	0	0	12	8
A2	0	0	10	10
A3	0	0	8	12
A4	0	0	6	14
A5	0	0	4	16
A6	0	0	2	18
A7	0	0	1	19
A8	0	10	0	10
A9	0	12	0	8

Similarly, to prepare a 25% $AlCL_3$ solution with suitable viscosity and acceptable pH, multiple samples were created, as shown in Table 2. Initially, 5 g of $AlCl_3.6H_2O$ powder was added to 20 milliliters of base solution containing varying amounts of water, ethanol, and propylene glycol, along with 1 M sodium bicarbonate (to adjust the pH of the solution).

Table 2. Formulation of chloride company solutions using 1 M sodium bicarbonate

Bn	distilled water (ml)	Ethanol (ml)	Propylene glycol (ml)	Sodium bicarbonate 1M (ml)
B1	0	2	0	18
B2	0	4	0	16
B3	0	6	0	14
B4	0	8	0	12
B5	0	10	0	10
B6	0	12	0	8
B7	0	14	0	6
B8	0	16	0	4
B9	0	18	0	2
B10	0	0	2	18
B11	0	0	4	16
B12	0	0	6	14
B13	0	0	8	12

Organoleptic properties include the appearance characteristics of the solution such as consistency, color, odor, and other sensory attributes perceived during use. The solution should be transparent with medium viscosity and uniformity.

Due to the importance of pH in product stability and mucosal stimulation assessment, pH was measured using ProLine pH meter B210 (Oosterhout, Netherland) at room temperature (25ºC).

Solution viscosity was measured qualitatively and quantitatively. Qualitative evaluation was done visually, while quantitative evaluation was conducted using a Cone viscometer (DVIII-Brookfield, USA) at 25° C.

Based on United States Pharmacopeia (USP), the standard solution consists of 20 mg per mL of aluminum chloride in water (9). Hence, the research sample contains 25% aluminum chloride, needs a dilution factor of 50 to achieve the desired concentration for assay of the sample solution.

To prepare the blank sample, distilled water replaces aluminum chloride in the standard solution.

A reverse titration protocol was used, with the titrant of a 0.5 molar solution of zinc sulfate. Endpoint determination was done visually. 10 mL of the standard solution were transferred to a 250 mL Erlenmeyer flask, followed by the addition of 25 mL of 0.05 M ethylene diamine tetra acetic acid (EDTA) and 20 mL of acetic acid-ammonium acetate buffer TS. The mixture was gently heated for 5 minutes and then allowed to cool to 25°C. Subsequently, 50 mL of alcohol (ethanol) and 2 mL of Dithizone TS were added, and zinc sulfate solution (titrant) was initiated until the color

changed from gray-green to light pink.

Each mL of EDTA is equivalent to 14.24 mg of AlCl3.6H_2O. The acceptable range of drug content within the prepared solution, as per pharmacopoeia, is 95% to 101% for $AlCl_3$.6H_2O.

3. Results

Physicochemical Properties of 25% Aluminum Chloride Solution with 0.7 M and 1 M Sodium Bicarbonate were evaluated among organoleptic properties such as transparency or turbidity, odor, viscosity, and pH were measured and presented in Table 3 & 4. Samples A5, B12, and B13 were selected with suitable pH along with desirable viscosity for further evaluation (quantitative viscosity tests and drug content assay using complexometric titration).

Based on the results cited in Table 5, formulations B_{12} and B_{13} containing 100% API were selected as the final drug formulations of the topical aluminum chloride solution.

Table 3. Results related to 25% aluminum chloride solution with 0.7 M sodium bicarbonate

An	pH	viscosity	Visual features
A1	2.24	medium	Clear with an acidic smell
A2	2.25	medium	Clear with an acidic smell
A3	2.28	medium	Clear with an acidic smell
A4	2.42	medium	Clear with an acidic smell
A5	2.54	3.8	Clear with an acidic smell
A6	2.75	Very low	Clear with an acidic smell
A7	2.86	Very low	Clear with an acidic smell
A8	2.99	Low	Clear with an acidic smell
A9	2.61	Low	Clear with an acidic smell

Table 4. Results related to 25% aluminum chloride solution with 1 M sodium bicarbonate

Bn	pH	viscosity	Visual features
B_1	3.48	Very low	Clear with an acidic smell
B_2	3.24	Very low	Clear with an acidic smell
B_3	2	Very low	Clear with an acidic smell
B_4	2.86	Very low	Clear with an acidic smell
B_5	2.72	Low	Clear with an acidic smell
B_6	unsolved	not determined	Cloudy with an acidic smell
B_7	unsolved	not determined	Cloudy with an acidic smell
B_8	unsolved	not determined	Cloudy with an acidic smell
B_9	unsolved	not determined	Cloudy with an acidic smell
B_{10}	3.35	Very low	Clear with an acidic smell
B_{11}	3.13	Medium	Clear with an acidic smell
B_{12}	2.92	7.55	Clear with an acidic smell
B_{13}	2.5	5.12	Clear with an acidic smell

Table 5. Results of assay of API using complexometric titration

Sample	Zinc Sulfate for sample (mL)	Zinc Sulfate for blank (mL)	Calculated assay of API (%)
A_5	4.8	13.3	102.595
B_{12}	5	13.3	100
B_{13}	5	13.3	100

4. Discussion

It has been pointed out that hemostatic agents are substances used to prevent bleeding from capillaries and arterioles. More importantly, aluminum chloride is one of the most common hemostatic drugs used in dentistry and dental surgeries to prevent bleeding. A wide range of products based on this substance in different concentrations are manufactured by various factories (10). Studies have shown that aluminum chloride has the least

systemic side effects in concentrations ranging from 5 to 25% (7). Subsequently, temporary changes induced by the use of hemostatic agents on gingival epithelium cells can affect junctional epithelium and underlying connective tissues (11). Although the effects of hemostatic agents may be desirable under clinical conditions, *in vitro* and *in vivo* observations have demonstrated undesirable side effects on gingival and dental tissues (12).

Having considered that aluminum chloride, aluminum sulfate, and ferric sulfate are the most common hemostatic agents used in clinical procedures, Frasin et.al. compared the effect of 25% aluminum chloride, 25% aluminum sulfate, and 20% ferric sulfate on human gingival fibroblasts using the MTT technique. The results showed that the toxicity of aluminum chloride was significantly higher than other hemostatic agents. Similar results were obtained in studies on rat keratinocytes, demonstrating that 25% aluminum chloride induced undesirable changes in cultured cells (13-14).

Besides, for the reason that acidic pH is essential for the hemostatic effect of the substance, no studies have reported increasing the pH of these drugs. Notwithstanding, various strategies have been proposed to reduce the negative effects and side effects of hemostatic agents. Thorough rinsing and removal of residual coagulation solution from the oral cavity have been observed to eliminate side effects (15). Additionally, using lower drug concentrations in gel form has been suggested to reduce side effects such as inflammation and tissue necrosis (16).

The formulation proposed by Hiroji Yamamoto for hemostatic compounds for oral and dental use has shown that a topical solution for preventing bleeding in dentistry contains one or more substances from the chelating agent group, one or more surfactants, and a preservative or selective solvent consisting of water or a mixture of water and one or more water-miscible organic solvents. It was also reported that a mixture containing 20% ethanol and 50% propylene glycol can be used with a solution containing 25 grams of aluminum chloride (in the presence of a suitable surfactant) (17). Therefore, in this study, water, ethanol, and propylene glycol were chosen for dissolving the chelating agent.

The formulation proposed by Prevender et.al. for bleeding control in medical and dental uses included several metal salts, aluminum chloride, ferric sulfate, regenerated oxidized cellulose, ammonium aluminum sulfate, absorbable gelatin, and a solvent. These compounds are inherently acidic and usually have a pH between 1 and 4(18). In this study, a combination of several metal salts was used to prepare a formulation with an appropriate pH, but in the current research, only aluminum chloride was used, and the pH of the solution was controlled by sodium bicarbonate.

As stated by the related literature, aluminum chloride at a concentration of 25%, water content of 70-75%, and sodium bicarbonate at 0.5-3% were used, and the results were reported. In a formulation reported in 2015 regarding oral hemostatic agents, the aluminum chloride content was 5-15%, choline 2-15%, structurant 10-20%, water 50-70%, and homogenate 0-20% (total water and water content 55-75% of the total composition). This combination has very good hemostatic effects and is only used in dentistry without any analgesic properties (19). In this formulation, water was used as the solvent for aluminum chloride, but our study results did not show satisfactory results in terms of viscosity and pH after testing formulations containing aluminum chloride and water alone without propylene glycol.

In the light of the attained results, propylene glycol has been used at various concentrations to increase viscosity while maintaining desirable physical properties. In the formulation proposed by Fischer et. al. for periodontal therapeutic compounds, propylene glycol was used to dissolve aluminum chloride. The use of an inorganic filler or a high molecular weight polyol in this formulation aims to reduce the acidity and other chemical activities of the hemostatic agent, such as reducing the caustic effect of unshielded hydronium ions in hemostatic compounds. The effective amount of the polyol in the composition should be such that it does not interfere with the hemostatic properties of the substance. In Fischer's formulation, the appropriate percentage of polyol used in the composition ranged from 10% to 50% (preferably 5% to 40%) by weight (20). Similar to this formulation, which used propylene glycol as a solvent for aluminum chloride, our study results also showed that formulations containing aluminum

chloride and propylene glycol, after quantitative and qualitative tests, had favorable results in terms of viscosity and pH (21).

5. Conclusion

From an overall perspective, formulations B12 and B13, using propylene glycol and sodium bicarbonate (1 M), have succeeded in providing a 25% aluminum chloride topical solution that maintains acceptable pH and viscosity while preserving its therapeutic properties.

Ethical Considerations

This study was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1397.380).

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None.

Authors' Contributions

Mohamad Roholamin: Writing - Review & Editing, Methodology **Fateme Alzain**: Investigation, Resources **Ehsan Jafari**: Writing - Original Draft, Data Curation **Zahra Hesari**: Supervision, conceptualization, Methodology, project administration.

Conflict of Interests

The authors declare no conflict of interest.

Availability of data and material

All data materials have been included in paper manuscript.

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