

INFLUENCE OF SOME ANIONIC POLYMERS ON PH OF TRIETHANOLAMINE AQUEOUS SOLUTIONS

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Summary

One of the suggested approaches in the management and prophylaxis of acne involves binding of free fatty acids in the form of soap with alcoholamines. Due to a possible irritating effect of alcoholamines associated with a relatively high pH of their aqueous solutions, complexation of alcoholamines with acid polymers is advocated. Triethanolamine is one of the best recognized alcoholamines. It was conventionally neutralized with Carbopols, Eudragits, alginic acid and pectin. During neutralization of polymer dispersions with triethanolamine, variations in the course of the neutralization curve have been observed among individual macromolecular compounds.

The pH of 0.1 mol/l triethanolamine solution reaches 10.51, while following a complete neutralization with anionic polymers, such as Carbopols, Eudragits, alginic acid and pectin, pH ranges from 3.88 for systems neutralized with alginic acid to 8.50 for the system neutralized with Eudragit S-100. Complexation of triethanolamine with anionic polymers decreases its pH, and it is possible to find such pH range in which pH of the preparation containing the polymer and triethanolamine will correspond to the physiological pH of the skin.

Key words: acne, pH, anionic polymers, triethanolamine, sebum

INTRODUCTION

One of the suggested approaches to the management and prophylaxis of acne involves binding of free fatty acids in the form of soap with alcoholamines [1-5]. Alcoholamines diffuse to the ducts of the sebaceous glands and, forming amine soaps, change the lipophilic properties of sebum into hydrophilic ones. As a result of binding of water by the formed soaps, the amount of sebum increases. Thus it is evacuated from the sebaceous ducts, which become cleansed of sebum, what is accompanied by a simultaneous removal of bacteria. Binding of free fatty acids should ameliorate their irritating effect on the sebaceous duct epithelium, preventing at the same time its keratosis. Since alcoholamines may exert an irritating effect associated with a relatively high pH of their aqueous solutions, their complexation with acid polymers is advocated.

Triethanolamine is one of the best recognized alcoholamines. In Britain and USA, triethanolamine salicylate in the amount of 10% is often added to creams and ointments for

topical application [6]. A carbopol gel preparation with ethacrydine lactate and triethanoloamine as an adjuvant substance to be applied on wounds and mucous membrane has recently appeared on the Polish market [7]. Triethanoloamine is also used in gel for acne containing clindamycin to be applied on the affected skin [8]. Triethanoloamine is also used in the form of borolactate as antifungal agent in veterinary treatment [9], and the antifungal properties of triethanoloamine as well as of other alcoholamines were confirmed in the studies of Baran and Witek [10]. Ionic polymers are widely applied as substances prolonging the effect of active substances as well as substances used in the preparation of drug forms with a prolonged release of the active substance. Among the polymers which were investigated and used in pharmaceutical formulations to bind the active substance, we can also find acrylic acid polymers – Carbopols, polymers and co-polymers of the metacrylic acid – Eudragits, as well as natural polymers, such as alginic acid or pectin.

MATERIAL AND METHODS

Material

Tris-(2-hydroxyethyl)-amine (triethanoloamine, TEA) (Sigma – Aldrich), acrylic acid polymers cross linked transversely with pentaerythritol: Carbopol 934P®, Carbopol 971P® and Carbopol 980® (BF Goodrich, Germany), acrylic and metacrylic acid co-polymers: Eudragit L-100®, Eudragit L-100-55® and Eudragit S-100® (Roehm, Germany), alginic acid with *Macrocystis pyrifera* (Sigma – Aldrich), citrus pectin (Sigma – Aldrich), demineralized and bi-distilled water.

Methods

Determination of molar equivalents of the investigated anionic polymers

Molar equivalent of an acid polymer, i.e. weight of the polymer in grams capable of binding 1 mol of a strong base can be calculated on the basis of titration of the polymer in an aqueous system by means of a titrated solution of a strong base, e.g. sodium hydroxide. The methods of determination of acid group content in polyacids such as Carbopols and Eudragits as well as in alginic acid and pectin are provided as a norm in European and American Pharmacopoeias. The determination of equivalents allows to predict the end point of titration with other basic substances as well as the amount of the basic substance necessary to neutralize the acidic groups of polymers.

Determination of molar equivalents of Carbopols

Investigation of Carbopols was carried out according to the method presented by Barreiro et al. [11] and French et al. [12]. The determination of carboxyl groups content as well as Carbopols molar equivalents was performed according to the method presented in European Pharmacopoeia IV. 0.120 g aliquots of polymer were weighed and dispersed in 400 ml of water, stirring intensively for 15 minutes with a magnetic stirrer. Next it was titrated with 0.2 mol/l solution of sodium hydroxide and end point of titration was determined potentiometrically by means of a combined electrode. Approaching the predicted titration endpoint values, accuracy of the measurement was increased by using smaller volumes of the basic solution. The content of the beaker was stirred for 1 minute after each increment of 0.2

mol/l sodium hydroxide solution. One milliliter of 0.2 mol/l sodium hydroxide solution corresponded to 9.0 mg of the carboxyl group (COOH) [13].

Determination of molar equivalents of Eudragits

The determination of methacrylic acid radicals in Eudragits as well as calculation on this basis of the polymer molar equivalents was carried out according to European Pharmacopoeia IV. 1.000 g of methacrylic acid polymer was dissolved in a mixture containing 40 ml of water and 60 ml of 2-propanol. The mixture was titrated by means of 0.5 mol/l sodium hydroxide solution. The end point of titration was determined on the basis of a change in the colour of the indicator – phenolphthalein. One milliliter of 0.5 mol/l solution of sodium hydroxide corresponded to 43.05 mg of methacrylic acid radical ($C_4H_5O_2$) [14].

Determination of molar equivalent of alginic acid

The determination of the content of carboxyl groups in alginic acid was carried out according to European Pharmacopoeia IV. Accurately weighed aliquots of 0.2500 g of alginic acid were dispersed in 25 ml of water and next 25 ml of 0.1 mol/l solution of sodium hydroxide were added. The excess of sodium hydroxide was titrated with 0.1 mol/l hydrochloric acid in the presence of phenolphthalein as an indicator. One milliliter of 0.1 mol/l solution of sodium hydroxide corresponded to 4.502 mg of carboxyl group (COOH) [15].

Determination of molar equivalent of pectin

European Pharmacopoeia IV does not give a method for the determination of galacturonic acid, methoxyl or carboxyl groups in pectin. According to US Pharmacopoeia XXIII, the determination can be carried out by titration of dissolved pectin with 0.5 mol/l sodium hydroxide. The process consists of initial titration, in which free carboxyl groups are neutralized, followed by hydrolysis of ester-bound methoxyl groups with 20.0 ml of 0.5 mol/l sodium hydroxide carried out for 15 minutes. The second stage of titration (saponification titer) with 0.5 mol/l sodium hydroxide indicates the content of methoxyl groups in the investigated sample. In order to determine the equivalent weight basing on free carboxyl groups content in pectin, the initial titer was assessed and it was used to calculate the molar equivalent of pectin. One milliliter of 0.5 mol/l sodium hydroxide solution corresponded to 97.07 mg of galacturonic acid radical ($C_6H_{10}O_7$) [16].

Assessment of the effect of anionic polymers on the pH of triethanolamine solution

Interactions between protons and macromolecules have a sophisticated character. Methacrylic polyacid with a molecular weight of 139.000 and structure approaching this of the investigated acid polymers, has about 1600 proton binding sites [17]. Thus the anionic polymers neutralization reactions can be considered, according to Rossotti “compensating the complexity of the system by a simplified approach” [18]. As indicated in the Introduction, solutions of the investigated anionic polymers form complicated systems. However we can treat them as solutions of polyelectrolytes and try to determine their acid dissociation constant as a simple function of pH and dissociation rate depending on the extension of the polymer particle in aqueous system [19].

The method of potentiometric titration was used by a number of authors to investigate the phenomena occurring between the macromolecule and the active substance bound to it [20]. The method may be applied in the evaluation of aqueous gel preparations containing

complexes of polyelectrolytes with various active substances of counter-ionic character. Its additional advantage is associated with the fact that the presence of water in the system does not interfere with the measurements. Crea et al., using the method of pH-metric titration, demonstrated binding of anionic polymers such as polyacrylic and polysulphonic acid with diamines [21].

Changes in triethanoloamine pH were determined on the basis of data from 5 times repeated potentiometric titration of pure, degassed water with 0.1 mol/l solution of triethanoloamine. Changes in pH of polymer solutions were assessed on the basis of findings of 5 times repeated pH-metric titration of polymers dispersions with 0.1 mol/l solution of triethanoloamine. The determination of pH was carried out using a 302 pH potentiometer (Hanna Instruments, USA) with a combined electrode ESAgP-301 W (Eurosens, Poland), exact to 0.01 pH unit.

In case of Carbopols, the determinations obtained on titration by means of a method described in Pharmacopoeia were used. In Eudragits, the method was modified by replacing the recommended by Pharmacopoeia mixture of water and an organic solvent – 2-propanol with pure water. This enabled the determination of an unambiguous pH similar to that to be used on the skin. The presence of 2-propanol in the titrated mixture enables instantaneous dissolution of Eudragit. In the presence of water alone, Eudragit dissolves after addition of several successive aliquots of the titrant. The same is observed in case of alginic acid.

The obtained findings were submitted to variation analysis (ANOVA) with the use of straight classification [22].

RESULTS AND DISCUSSION

The pH of polymers dispersions

Table 1 presents the pH as well as conductivity of the investigated polymers in water as well as pH of 0.1 mol/l aqueous solution of triethanoloamine. Carbopols dissolved easily in water, swelling slightly. The pH of their solutions was definitely acid and was from 3.65 to 3.93. Both Eudragits as well as alginic acid did not dissolve in water, while pH of the solution above the sediment was from 4.98 for Eudragit L-100 to 5.08 for Eudragit S-100. pH of the solution above alginic acid sediment was 3.34.

The effect of triethanoloamine on pH of solutions of the investigated acid polymers

Figure presents the effect of triethanoloamine addition on pH of water and polymer dispersions. The changes in pH of triethanoloamine aqueous solution and increase of its concentration have been indicated on the plot with rhombuses. After addition of 2 ml of 0.1 mol/l triethanoloamine solution to 250 ml of water, pH increases dramatically reaching the level of 9.50, and next it increases slightly with subsequent portions of triethanoloamine solution.

During neutralization of polymers dispersions with triethanoloamine solution, differences can be observed in the neutralization curve among individual macromolecular compounds.

The most prominent endpoint of titration is observed in polymers of natural origin. pH of solutions of these polymers changes from about 3.5 to about 8.5. Initially the course of pH changes is almost parallel to the axis of abscissae. Only when pH reaches 4.75, a more pronounced pH increase is observed with subsequent portions of the titrant, i.e.

triethanoloamine solution. After reaching the value of 7.50, pH increase becomes less marked. Titration endpoint for alginic acid and pectin is detected at pH range from 4.75 to 7.50. The intense increase of pH in 3.5 – 4.0 range can be associated with dissolution in water of undissociated fraction of alginic acid and formation of its triethanoloaminic salt.

In Eudragits the changes of pH occur initially dramatically. The addition of as little as 0.5 ml of 0.1 mol/l triethanoloamine solution to Eudragits L-100, L-100-55 and S-100 dispersions results in an increase of pH by about 2. This increase is due to the effect of free carboxyl groups of initially undissolved polymer with triethanoloamine. Further course of Eudragits neutralization is characterized by a markedly milder course of the neutralization curve. End point of titration can be detected at pH range from 7.0 to 8.0 for Eudragits L-100 and L-100-55 and at pH range from 7.5 to 8.5 for Eudragit S-100, which is characterized by a lower content of carboxyl groups.

Carbopols neutralization curve runs in a mild arch with end point of titration occurring at pH of about 7.5. pH increases from about 3.5 to about 8.5.

As shown in Table 1, pH of 0.1 mol/l triethanoloamine solution differs significantly from physiological pH of the skin, and even from a neutral pH and reaches the level of about 10.51.

Binding of triethanoloamine with anionic polymers in the form of complexes leads to decrease of its pH, as shown in Figure. As seen in the plot, a range of pH can be identified in which the formulation containing polymer and triethanoloamine assumes pH corresponding to physiological pH of the skin.

In order to confirm the possibility of reduction of triethanoloamine pH with anionic polymers, a series of formulations was prepared in which equimolar amounts of anionic polymers and triethanoloamine were used. Direct determination of pH of the obtained formulations confirmed the possibility of obtaining systems with pH approaching neutral range as well as physiological pH of the skin. pH of individual formulations is presented in Table 2.

The pH of 0.1 mol/l triethanoloamine solution reaches 10.51, whereas following a complete neutralization with anionic polymers such as Carbopols, Eudragits, alginic acid and pectin, it ranges from 3.88 for the system neutralized with alginic acid to 7.80 for the system neutralized with Eudragit S-100.

CONCLUSIONS

Acidic polymers, such as acrylic acid polymers transversely cross linked with pentaerythritole, i.e. Carbopols 934, 971 and 980, acrylic acid copolymers, i.e. Eudragits L-100, L-100-55 and S-100, as well as pectin and alginic acid can be used as buffers of triethanoloamine for dermatological application.