

The influence of hydrogen peroxide on the rheological behaviour of Ultrez-21 gels

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ABSTRACT

Objectives. The aim of this study was to analyse the influence of hydrogen peroxide (H₂O₂) and its concentrations on the rheological characteristics of Ultrez-21 1% gel, in order to develop and optimize formulations easy to prepare in the pharmacy, for various pharmaceutical or cosmetic applications.

Material and methods. A series of gels containing 5-29.5% H₂O₂ were analysed and compared to the gel base in terms of rheological properties induced by the action of forces applied either with constant intensity (adhesiveness, consistency, extensibility, viscosity) or with variable intensity (viscous structural flow, thixotropy). Perhydrol has been selected as a source of H₂O₂, as it is a product commonly used in pharmacy, and which, being a concentrated solution (30% m/m H₂O₂), can be very easily diluted by mixing with water to obtain the desired concentration in gels.

Outcomes. Even if the presence of H₂O₂ causes changes in adhesiveness, consistency, extensibility and viscosity of gels, they do not correlate with the H₂O₂ contents, each gel having its own specific behaviour. The gels have a lower flow threshold when are sheared at $D = 0.33 \text{ s}^{-1}$ than the gel base. Differences between shear flows are statistically significant both in terms of the deviation from linearity (Runs test) and the deviation from zero value (F test). The slopes of the regression lines have positive values in all cases, but statistically different ($p < 0.0001$, Anova test). Gels containing >15% H₂O₂ decrease the thixotropic capacity of the Ultrez-21 gel with comparable values (32, 38, 35 and 28%).

Conclusions. All the studied gels have a plastic-thixotropic behaviour which changes both with the presence and the concentration of hydrogen peroxide. The differences in consistency, adhesion and extensibility between the gels cannot be attributed to the viscosity, but rather to the degree of homogeneity and / or strength of the dispersed system formed by hydrogen peroxide in the Ultrez-21 gel. The flow behaviour of the gels correlates with the variation of pH, consistency and adhesiveness, and less with the spreading properties.

Keywords: hydrogen peroxide, Ultrez-21, carbopol gels; structural viscosity, share flow, tixotropy

INTRODUCTION

Hydrogen peroxide is used in applications on skin and mucous membranes as disinfectant (1), antimicrobial (2) and mechanical

cleansing agent as it produces oxygen bubbles (3), based on the oxidation processes (4). Applications in the form of mouthwashes (1.5%) are useful in

gingivitis or periodontitis (5). Application on tooth enamel (3-38%) causes bleaching, its effectiveness depending on concentration, pH, salivary flow and

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other factors (6), e.g. it was verified that the discoloration constant depends on pH increase, contributing favourably to increase the reaction rate (7,8). Gels with low concentrations are indicated for whitening techniques at home (for 7-10 days, with the help of gutters) and those with high concentrations are indicated in the techniques performed in the doctor's office, in such cases the treatment having a shorter duration (2-3 hours, possibly repeatedly), usually using the acceleration of the oxidative fading process by exposure to heat, light or laser (9,10).

Ultrez-21 is a carbopoly (synthetic polymer, also called carbomer) from the group of acrylic acid copolymers, modified with long chain alkyl acrylates (C₁₀-C₃₀) and cross-linked with allylpentaerythrol, known in cosmetics as Acrylates / C₁₀₋₃₀ Alkyl Acrylate Crosspolymer (INCI) (11,12). Ultrez-21 is compatible with electrolytes in high concentrations, surfactants, high pH, and solvents other than water. It is easy to disperse and use. The recommendations are based on the high viscosity of the dispersions over a wide pH range, the ease of dispersion (short wetting time, without stirring when soaked), as well as the aesthetic qualities (clarity, appearance etc.) made in gels, or other products especially in cosmetic field (12,13). Of the other polyacrylic acid derivatives, the most compatible with hydrogen peroxide is Carbopole-943, Ultrez-10 has sufficient compatibility (13,14,15), and Ultrez-20 and Ultrez-21 has not yet been tested.

This paper presents experimental studies that aimed to analyse the influence of hydrogen peroxide and

its concentrations on the rheological characteristics of Ultrez-21 1% gel, carbopol selected by previous studies as suitable for such gels (16,17), in order to develop and optimize formulations easy to prepare in the pharmacy, for various pharmaceutical or cosmetic applications.

MATERIALS AND METHODS

Formulation and preparation of gels

Materials

Ultrez-21 (Lubrizol Advanced Materials Inc., Cleveland, Ohio USA); Triethanolamine – TEA (Dow Chemical, Midland, Michigan USA); Distilled water (produced in the laboratory); Perhydrol – Hydrogen Peroxide 30% (Chemical Company SA, Iasi, Romania).

Gel formulations

The gel formulations were designed to contain 1% Ultrez-21 (in water gel-forming agent) and 0.7% triethanolamine – TEA (pH modifier that causes gelation by partially neutralizing carboxyl groups in the structure of the gel-forming agent). Perhydrol (aqueous solution containing 30% hydrogen peroxide – H₂O₂) was used in the amounts presented in table. I, so as to obtain 6 gels (G₁₋₆) containing 5, 10, 15, 20, 25, 29.5% H₂O₂ (as active component in gels). The gel base (G₀) was prepared using only distilled water and was used as control sample.

Preparation method and storage of gel samples

Ultrez-21 was dispersed in distilled water, neutralized by the addition of TEA and stirred for 1 min at 100 rpm. Perhydrol was incorporated at the end. Except for G₆ – when dispersion and neutralization were

TABLE 1. Composition of gel samples

Gel sample (% m/m)	G ₁	G ₂	G ₃	G ₄	G ₅	G ₆	G ₀
Ultrez-21	1.0	1.0	1.0	1.0	1.0	1.0	1.0
TEA	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Distilled water	81.64	64.97	48.30	31.64	14.97	-	98.30
Perhydrol (30% H ₂ O ₂)	16.66	33.33	50.00	66.66	83.33	98.30	-
H₂O₂ content (m/m)	5%	10%	15%	20%	25%	29.5%	0%

carried out directly in perhydrol, and for G₀ – when perhydrol was not used. The gels were stored in the refrigerator (2-8 °C), packed in tightly closed brown glass containers. Prior to use, each sample was kept at room temperature for 30 minutes.

Apparatus and methods

Determination of pH

It was performed by the potentiometric method using a Multi-Parameter Consort C831 (Consort nv, Belgium). 1.00 g of the gel sample was dissolved in 20 ml of distilled water and the pH of the filtered solution was measured at 20 °C ± 5 °C.

Adhesiveness

The vertical tensile force was measured using a laboratory balance adapted to determine the weight that causes the detachment of two smooth plates between which the gel sample was interposed. 1.00 g of the gel sample was deposited on the bottom plate, in a space in the shape of a flat cylinder with diameter (\emptyset) = 2.2 cm, depth (h) = 0.2 cm, exposure surface (S) = 3.80 cm² and volume (v) = 0.76 cm³. The top plate (one of the balance plates) was placed and kept fixed for 1 min in a pressed state on the exposed surface of the sample by depositing a weight of 50.0 g on the plate. On the other plate of the balance, calibrated weights of 2 grams each were added at intervals of 1 minute, up to the weight that determined the

detachment of the two plates between which the gel sample was placed.

The vertical traction force – F (N) is calculated based on the relation: $F = m \times g$, where m = the weight that produces the detachment (kg), g = the gravitational acceleration (9.81 m×s⁻²). The adhesiveness – A (N×cm⁻²) was calculated using the relation: $A = F \times S^{-1}$.

Consistency

A Labor-type penetrometer with a metal cone weighing 21.21 g was used. Weights of up to 10 grams (2 g extra each) are added successively to the penetration cone, each time recording the depth of penetration – P (mm⁻¹). The pressing force – F (N) was calculated using the relation: $F = m \times g$, where m = the weight that produced the penetration (kg), g = the gravitational acceleration (9.81 m×s⁻²).

Extensibility

A laboratory extensometer was used (upper plate mass of 82.26 g). 1.00 g of the gel sample was pressed successively at 1 min intervals, adding increasing calibrated weights, each time recording the diameter – d (cm²) of the gel spreading area. The surfaces of the stretching areas – S (cm²) were calculated. The pressing force – F (N) was calculated using the relation: $F = m \times g$, where m = the weight that produced the penetration (kg), g = the

gravitational acceleration ($9.81 \text{ m}\times\text{s}^{-2}$).

Viscosity and shear flow

Rheotest RV (Mechanik Prüfgeräte Medingen, Dresden, Germany) with the pair of H/H cylinders was used. The gel sample was subjected successively to shearing with 12 increasing speeds (destructuring stage – d) and then decreasing speeds (restructuring stage – r). At each applied shear rate – D (s^{-1}), the tangential flow stress – τ ($\text{dyn}\times\text{cm}^{-2}$) and the viscosity – η (Pa.s) were calculated.

Software and statistical methods

GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA) was used, running: area under curve and linear regression followed by the runs test and F-test, as XY analysis; two-way Anova and paired t-test as grouped analysis, with the statistical significant difference set at $p < 0.05$, for a CI of 95% (18,19).

RESULTS AND DISCUSSIONS

A series of six gels (G_1 - G_6) was prepared under the same conditions, with a single variable in the formulation – the hydrogen peroxide (H_2O_2) content which was determined by calculation to represent 5, 10, 15, 20, 25, and respectively 29.5% in the gels proposed in this study. At these concentrations of H_2O_2 , the pH of the gels is very slightly acidic, which results from the pH values determined for the G_1 - G_6 series of gels: 6.5, 6.6, 6.3, 6.1, 6.2 and 6.1, respectively.

Perhydrol has been selected as a source of H_2O_2 , as it is a product commonly used in pharmacy, and which, being a concentrated

solution (30% m/m H_2O_2), can be very easily diluted by mixing with water to obtain the desired concentration in gels.

The base of the gels consists in all cases of the aqueous dispersion of 1% Ultrez-21 gelled by neutralization with 0.7% TEA. The amount of TEA was established so that the gel prepared only with water, so without the addition of H_2O_2 , used as a control (G_0) to have a pH = 7.0 (determined value).

Rheological properties at the action of forces applied with constant intensity (fig. 1)

The adhesiveness of the gels (fig. 1, A) generally increases to some extent by the presence of hydrogen peroxide in the gel structure (adding ≈ 0.005 - $0.030 \text{ N}\times\text{cm}^{-2}$), compared to the gel base – G_0 ($0.180 \text{ N}\times\text{cm}^{-2}$). However, these variations cannot be correlated with the increase of H_2O_2 content in gels. A special behaviour is found in the case of the gel containing 15% H_2O_2 (G_3) which shows an adhesion with $0.015 \text{ N}\times\text{cm}^{-2}$ lower than the gel base ($\approx -8\%$).

The presence of hydrogen peroxide causes differences in the consistency (hardness) of the gels (fig. 1, B). Comparing the consistency of the gels expressed by the depth of penetration at a single pressing force ($F = 0.306 \text{ N}$), it is found that the influence of hydrogen peroxide on the consistency of the gels cannot be correlated with its concentration in gels.

The extensibility of the gels expressed by the spreading capacity determined under the action of a pressing force $F = 7.720 \text{ N}$ (fig. 1, C), shows that each gel manifests specific behaviours, with

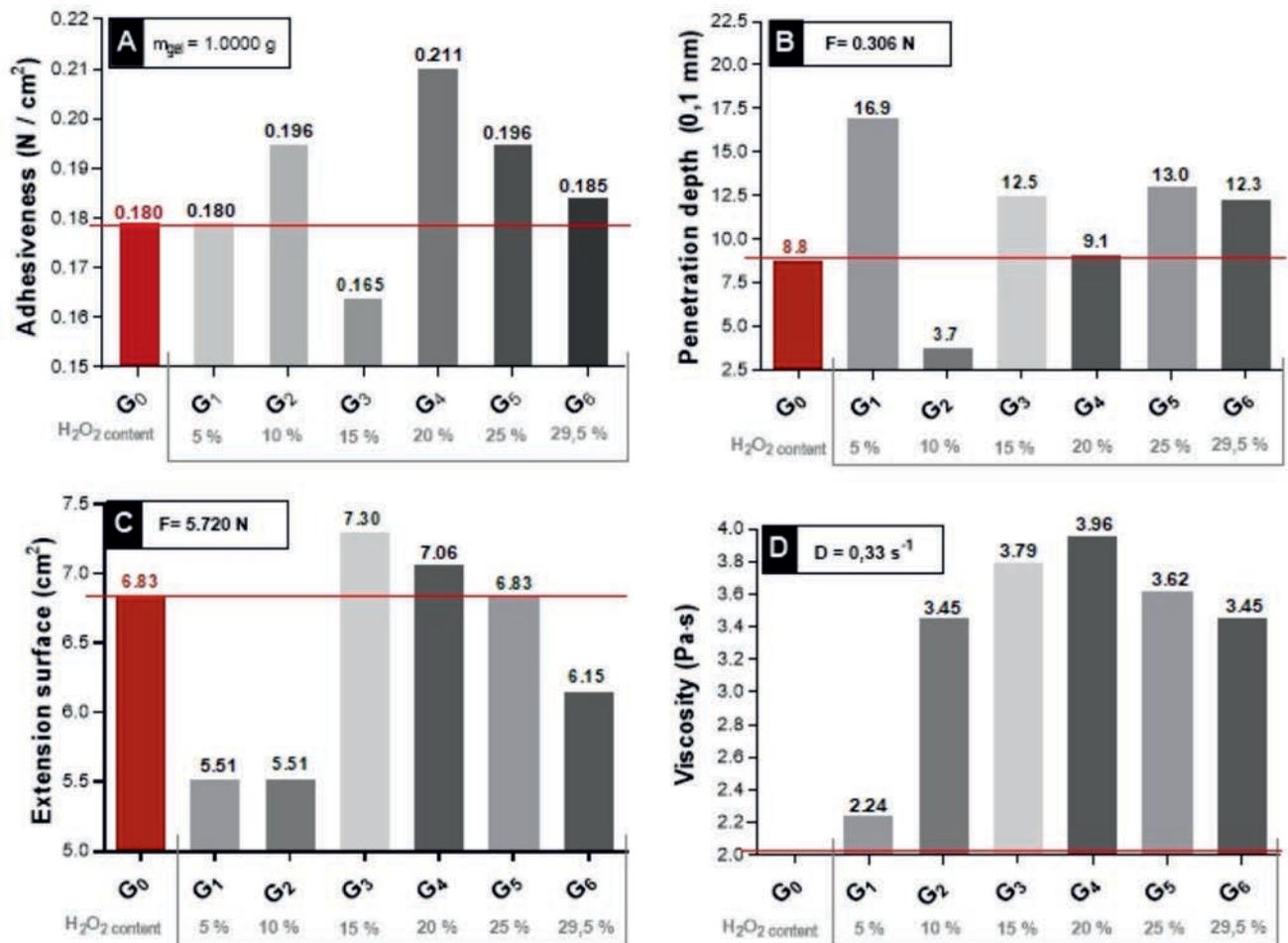


FIGURE 1. Rheological parameters that characterize the studied gels: adhesiveness (A), consistency (B), extensibility (C), viscosity (D)

no correlation with the H₂O₂ content.

Structural viscosity (fig. 1, D) is significantly influenced by the H₂O₂ content, as all gels (G₁-G₆) have a lower flow threshold when are sheared at $D = 0,33 \text{ s}^{-1}$ than the gel base (G₀), which shows an immeasurable viscosity of this shear rate.

Rheological properties to the action of forces applied with variable intensity

Structurally viscous flow curves (fig. 2)

When comparing G₁-G₆ vs. G₀, it is found that the presence of hydrogen peroxide facilitates the destructuring of the system, the

resistance to shear being lower and it can be assumed that the differences shown by the flow curves are due to hydrogen peroxide molecules which, by interposing between the polymer chains, facilitate the sliding of the gel layers during shearing. This would also explain the extremely low correlation between the variation of viscosity and the other parameters previously discussed.

Linear regression of flow curves (fig. 3)

From the statistical probability values (p), it is found that the differences between the flow behaviours of the analysed gels are statistically significant, both in terms of the deviation from

linearity (Runs test) and the deviation from zero value (F test). It is also observed that the slopes of the regression lines have positive values in all cases, but statistically different ($p < 0.0001$, Anova test).

Thixotropic properties of gels (fig. 4)

In general, the availability of the active substance from the gel is considered to be favoured by the plastic – thixotropic behaviour (20,21).

The difference between the areas under the two portions of the flow curve ($AUC_d - AUC_r$) reflects the amplitude of the hysteresis (fig. 4, A). The results correlate with the significance of the parameters

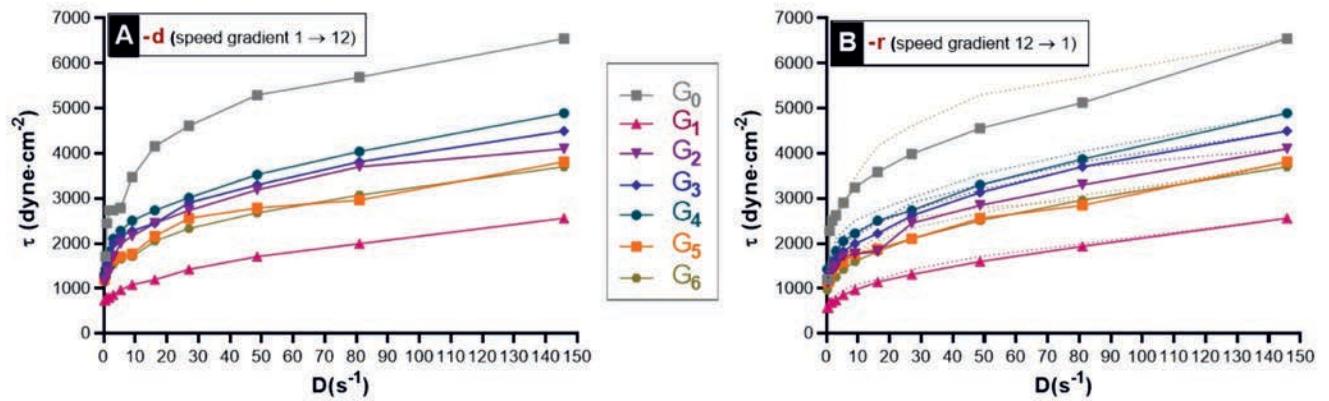


FIGURE 2. Flow curves: destructuring stage - d (A), restructuring stage - r (B)

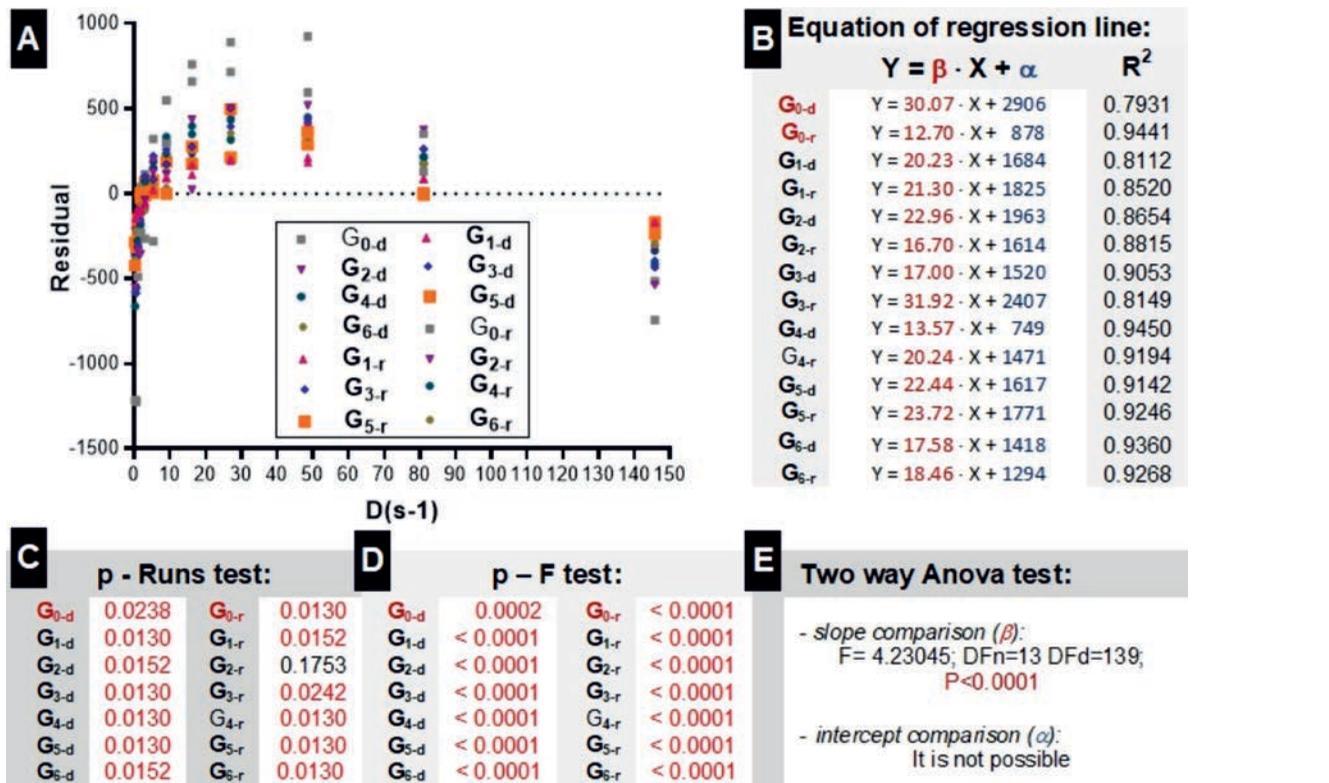


FIGURE 3. Analysis of flow curves by linear regression: residuals (A), equation of regression lines (B), deviation from linearity (C), deviation from zero (D), results of the variance test (E)

calculated by the linear regression of the flow curves. G₀ exhibits a different behaviour from G₁-G₆, in the sense that the gel base has a slower flow (AUC_d and AUC_r have higher values) than the other gels. It turns out that H₂O₂, by its presence in the structure of the gel, causes a faster fluidization of the structure, but without influencing the viscosity (friction between

layers). The H₂O₂ contents cannot be correlated with the changes in the magnitude of the flow of sheared systems, each gel having its own specific behaviour.

All gels show thixotropy, but with low values (AUC_r). To find out the statistical significance of these values, the t-paired test was applied (fig. 4, B), comparing for

each gel the AUC variations during destructuring vs. restructuring (AUC_r vs. AUC_d). p values calculated for a 95% confidence interval show that the differences observed between the two portions of curve are statistically significantly different in all gels. It also can be seen that the gel base (G₀) shows a more pronounced thixotropy than G₁-G₆, and in the latter case the size

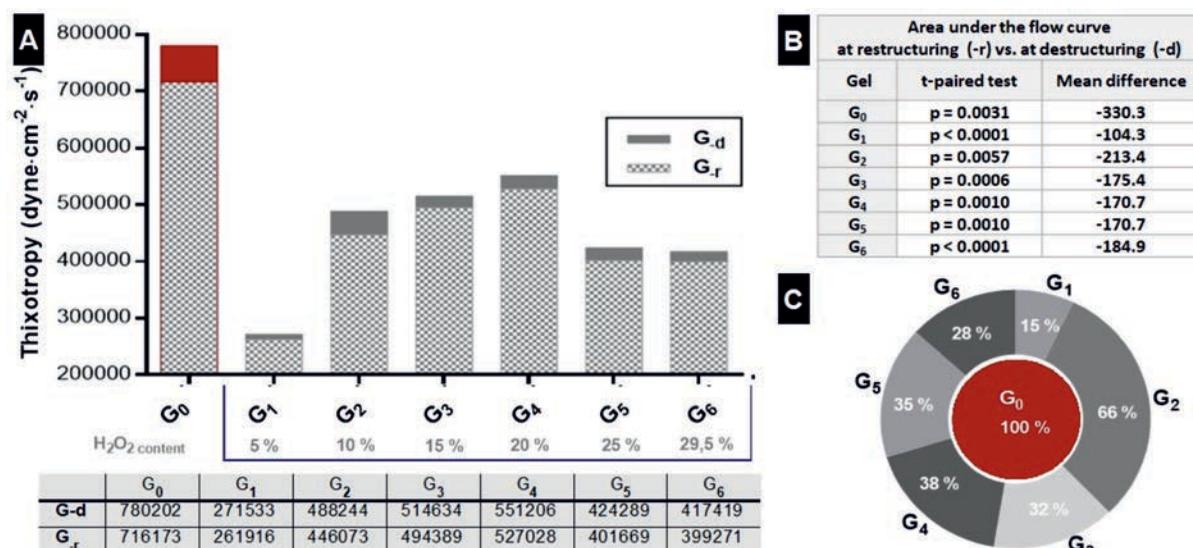


FIGURE 4. Thixotropic behavior of gels: thixotropy expressed as $AUC_r = AUC_r - AUC_d$ (A), statistical probability p – values (B), the size by which the thixotropy of gels decreases due to the presence of H_2O_2 (G) expressed as a percentage of the thixotropy of the Ultrez-21 1% gel (G₀)

of thixotropy cannot be correlated with the H_2O_2 contents.

In order to be able to quantify the thixotropic differences, for each gel the difference $(AUC_r \text{ of } G_0) - (AUC_r \text{ of } G)$ was calculated, and the values obtained were expressed as a percentage of the gel base thixotropy (AUC_r of G_0). The results show that there are differences in behaviour in the restructuring stage (fig. 4, C). Thixotropy of gels containing $>15\%$ H_2O_2 (G_3 , G_4 , G_5 and G_6) is lower than the others and decrease the thixotropic capacity of the Ultrez-21 gel (G_0) with comparable values (32, 38, 35 and 28%).

CONCLUSIONS

All the studied gels have a plastic-thixotropic behaviour, with

statistically significant differences between flow rheograms.

Both the presence and the concentration of hydrogen peroxide in the 1% Ultrez-21 gel neutralized with 0.7% triethanolamine cause changes in rheological behaviours induced by the action of forces applied either with constant intensity (adhesiveness, consistency, extensibility, viscosity) or with variable intensity (viscous structural flow, thixotropy), but without these changes to correlate with the hydrogen peroxide content, each gel having its own specific behaviour.

The differences in consistency, adhesion and extensibility between the gels cannot be attributed to the viscosity, but rather to the degree of homogeneity and / or strength of

the dispersed system formed by hydrogen peroxide in the Ultrez-21 gel. It can be assumed that hydrogen peroxide does not interact with polymer molecules, but rather causes relaxation of the gel structure, by releasing water and consequently facilitating flow, and molecular oxygen that disrupts the reorganization of polymer chains in the sheared dispersion. The hydrogen peroxide effects seem to appear especially at concentrations of hydrogen peroxide lower than 15%, above this concentration their consequences become more uniform and in some cases even comparable. The flow behaviour of the gels correlates with the variation of pH, consistency and adhesiveness, and less with the spreading properties.

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REFERENCES

1. Medina-Cordoba L, Valencia-Mosquera L, Tarazona-díaz G, Arias J. Evaluation of the efficacy of a hydrogen peroxide disinfectant. *Int J Pharm Pharm Sci.* 2018;10(10):104.
2. Akujl MA, Chambers DJ. Hydrogen peroxide: more harm than good?. *Br J Anaesth.* 2017;118(6):958-959.
3. Urban MV, Rath T, Radtke C. Hydrogen peroxide (H₂O₂): a review of its use in surgery. *Wien Med Wochenschr.* 2019; 169:222-225.
4. Guan R, Yuan X, Wu Z, Jiang L, Li Y, Zeng G. Principle and application of hydrogen peroxide based advanced oxidation processes in activated sludge treatment: A review. *Chem Eng J.* 2018;339:519-530.
5. Rashed HT. Evaluation of the effect of hydrogen peroxide as a mouthwash in comparison with chlorhexidine in chronic periodontitis patients: A clinical study. *J Int Soc Prev Community Dent.* 2016; 6(3):206-212.
6. Bizhang M, Domin J, Danesh G, Zimmer S. Effectiveness of a new non-hydrogen peroxide bleaching agent after single use – a double-blind placebo-controlled short-term study. *J Appl Oral Sci.* 2017; 25(5):575-584.
7. Xu B, Li Q, Wang Y. Effects of pH Values of Hydrogen Peroxide Bleaching Agents on Enamel Surface Properties. *Operative Dentistry.* 2011;36:554-562.
8. Washington N, Washington C, Wilson CG. Dental systems, in *Physiological Pharmaceutics – Barrier to drug absorption*, 2nd ed. Taylor @ Francisc Library. 2003: 53.
9. Junior MT, Rodrigues CA, Bernardes VL, Araujo TSB, Nicoli GA, et al. Dental Bleaching and New Possibilities – Literature Review. *Health Sci J.* 2018;12(6):600.
10. Féliz-Matos L, Hernández LM, Abreu N. Dental Bleaching Techniques; Hydrogen-carbamide Peroxides and Light Sources for Activation, an Update. Mini Review Article. *Open Dent J.* 2015;8:264-268.
11. Rowe RC, Sherskey PJ, Quinn ME. Carbomer, in *Handbook of Pharmaceutical Excipients*, 6th ed. Pharmaceutical Press and the American Pharmaceutical Association, London, 2009:110-114.
12. <https://www.lubrizol.com/Health/Pharmaceuticals/Excipients/Carbopol-Polymer-Products>.
13. Carbopol® Ultrez 21 Polymer Technical Data Sheet. Lubrizol Advanced Materials, Inc. 2007. (www.lubrizol.com).
14. Stability of Pharmaceutical Carbopol® Polymer Gels Containing Hydrogen Peroxide. Lubrizol Advanced Materials, Inc. 2007. (www.lubrizol.com).
15. Schmucker-Castner J, Desai D. Rheology Modification of Hydrogen Peroxide-based Applications Using Cross-linked Polyacrylic Acid Polymers. *Int J Cosmet Sci.* 1999; 21(5):313-25.
16. Todoran N, Pușcaș CR, Ciurba A, Jung A, Imre S. Preformularea unor geluri dentare cu peroxid de hidrogen, Simpozionul „Actualități și perspective în cercetarea farmaceutică”, Craiova, România; 26-28 sept 2012; vol rez:37-38.
17. Todoran N, Drașoveanu A, Imre S, Ciurba A, Iștoan RO. Two methods for testing the whitening teeth capacity of hydrogen peroxide used in dental gels, *Acta Medica Marisensis*, 2012;58(Supl 3):70.
18. Motulsky HJ, Christopoulos A. Fitting models to biological data using linear and nonlinear regression. A practical guide to curve fitting. *GraphPad Software Inc, San Diego CA*, 2003: 134-160. (www.graphpad.com).
19. Motulsky HJ. Analyzing data with GraphPad Prism, GraphPad Software Inc., San Diego CA, 1999: 29-32 (www.graphpad.com).
20. Chi HL, Venkat M, Yuguoung L. Thixotropic property in pharmaceutical formulations (Review). *J Control Release.* 2009; 136(2):588–598.
21. Sklupalová Z, Zatloukal Z. Area under rheogram as multi-point viscosity characteristic of the sterilized hypromellose hydrogels. *Acta Pol Pharm.* 2011; 68(4):565-569.