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COMMUNICATIONS

THE INFLUENCE OF ANTIOXIDANTS ON THE SPREADABILITY OF α-TOCOPHEROL GELS

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ABSTRACT

This study is based on the elaboration of α-Tocopherol gels containing the antioxidants butylated hydroxitoluene and ascorbic acid for the purpose of subjecting them to a rheological study aimed at evaluating the influence of the components of the various preparations.

INTRODUCTION

In recent years the effects that α-Tocoperol (E) has on the prevention of celular damage are being studied (1 - 5).

Two antioxidants were used: butylated hydroxitoluene (BHT) and ascorbic acid (AA) (6). Because of its lipophilic character, the first is more adequate for avoiding the "in vitro" oxidation of (E) (an oily substance). Ascorbic acid however, appears to strengthen its antioxidizing action "in vivo", since along with the enzime glutation it favors the reduction of tocopherylquinona (inactive form) in E (active form) (3, 7).

Carbomer® 940, widely used in the Industry, was chosen as a gelling substance because it is easy to manage and it provides highly stable gels. Additionally, these gels must have an adequate consistency not

only for their application, but also and fundamentally with respect to the bioavailability or therapeutic activity that these substances may produce (6, 8, 9).

The rheological study was focused on the spreadability shown by semisolid dispersed systems after they are subjected to a compression process.

METHODS AND MATERIALS

Semisolid Preparations

Hydrophylic gels, having the following formulas, were used:

	G	EBHT	EAA
Carbomer® 940	1 g	1 g	1 g
Ascorbic acid	-	-	0.1 %
Butylated hydroxytoluene.	-	0.1 %	-
Ethanol (96 %)	15 ml	15 ml	15 ml
Triethanolamine	X g	X g	X g
α-Tocopherol	-	2.5 g	2.5 g
Purified Water	85 ml	85 ml	85 ml

Once the various preparations were formulated, they were left to stand at room temperature for 24 hours previous to the start of the experiment.

Rheological Test: Spreadability

The aforementioned method, previously described by some authors, was followed (10) and suitably modified (11 - 14) for which a manual microtome (Ranvier type) with the following characteristics was used:

- perfectly flat slide, 5 cm in diameter
- 1.2 cm wide screwhole
- 0.68 mm screwturn length

A sequence of weights of 80 g, 150 g, 300 g and 500 grams respectively, were place on the sample cylinder (77 mm^3) for one minute each, with rest intervals of 30 seconds between weights. This proceedure was carried out under normal temperature conditions.

To evaluate the spreadability of the excipient and the topical application preparations, the technique of Jiménez-Castellanos et al. (11) was followed; at the end of each interval of action of the weights, impressions were made on photographic plates of the surface occupied by the spreading of each sample.

Finally, the surface area in each sample was calculated from the photographic plates using a planimeter (Staedtler Mars 927).

The study of spreadability was conducted as a funtion of storage times, using periods of 24 hours, 1 and 2 months from the time of elaboration of the excipient and topical application preparations.

RESULTS AND DISCUSSION

The rheology of the base gel (gel G) is conditioned by the three-dimentional structure that Carbomer® 940 forms in the solvent (water:ethanol, 85:15). In this situation the polymer molecules become entangled with a large quantity of acid residues (pH ≈ 3) (6). As a consequence of this, the acidity had to be reduced to approximately pH 5.4, ideal for the chemical stability of AA (antioxidant used in one of the formulas) (9 - 11).

The spreading behaviour observed in each gel is different as a consequence of the reactions produced between Carbomer® 940 and AA or BHT. Logically, when applied weight increases, we can expect an increase in spreadability according to the increase in applied weight for exerting pressure (17).

Therefore, in gel EBHT, given that the base excipient was not neutralized, hydrogen bonds were produced between the hydroxil groups of E and of BHT and the free radicals -C=O of the Carbomer® 940 molecule. This led to an unwinding of the polymer resin and a consequent rise in viscosity as a result of its thickening (9). In gel EAA, a repulsion between charges of like signs (negative), originating in AA and along the polymer is produced. As in the preceeding case, a

loss of spiral structure of the resin is produced, forming another spreading with higher viscosity.

Despite the fact that in both cases an unwinding of the Carbomer® 940 molecule is produced, the rheological behaviour is different.

Lastly, the comparative study of the gels was carried out as a function of weight and time of test. Statistical proofs were founded upon the Analysis of Variance (Table 1). The Fisher Test was applied to determine which formulation was reponsible for any differences found.

For TIME 0 (24 hours) (Figure 1) applying a weight of 80 g led to a statistical difference in the spreadability produced in the three gels. In the corresponding Fisher Test, a significant difference is not found between gel G and BHT, but is seen between these gels and gel EAA. Conversely, no significant difference is found between gels G and EAA, but is encountered between these gels and gel EBHT.

This indicates that at small weights (80 g) a sufficient deformation is not produced in gel EAA for it to achieve the spreadability values of the base excipient (G) (18). On the other hand, at weights of 150 g, 300 g and 500 grams, this deformation is produced in all samples, with greater spreading in the gels EBHT because of the greater ease with which hydrogen bonds are broken. In the case of gel EAA, the repulsions between like charges are maintained independent of weight, causing spreadings similar to those of gel G.

Time is a factor that can modify the rheology of dispersed systems. In our case, at one month of elaboration (TIME 1) (Figure 2) we observe that a decrease in the spreadability of gel EBHT is produced for all indicated weights until reaching values close to those of gel G, with no significant statistical difference among these.

This is due to the fact that BHT is oxidized by free radicals (3, 19) giving rise to Carbomer® 940 peroxides that then produce a repulsion

TABLE 1
Analysis of Variance of the obtained surface areas (cm^2) as a function of the indicated weights and times.

	TIMES		
WEIGHTS	24 hours	1 month	2 months
80 g	$F_{(2,15)} = 6.38$ $p < 0.05$ (S.)	$F_{(2,15)} = 13.73$ $p < 0.05$ (S.)	$F_{(2,15)} = 29.12$ $p < 0.05$ (S.)
150 g	$F_{(2,15)} = 6.23$ $p < 0.05$ (S.)	$F_{(2,15)} = 13.48$ $p < 0.05$ (S.)	$F_{(2,15)} = 23.10$ $p < 0.05$ (S.)
300 g	$F_{(2,15)} = 9.58$ $p < 0.05$ (S.)	$F_{(2,15)} = 15.88$ $p < 0.05$ (S.)	$F_{(2,15)} = 15.10$ $p < 0.05$ (S.)
500 g	$F_{(2,15)} = 56.15$ $p < 0.05$ (S.)	$F_{(2,15)} = 9.68$ $p < 0.05$ (S.)	$F_{(2,15)} = 12.06$ $p < 0.05$ (S.)

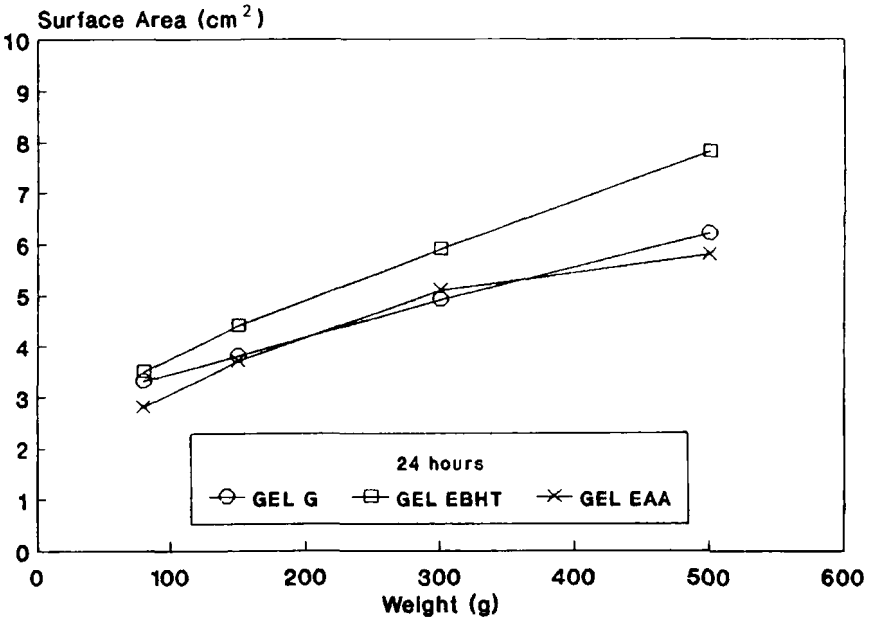

Figure 1.-Spreadablility of the gels at 24 hours.

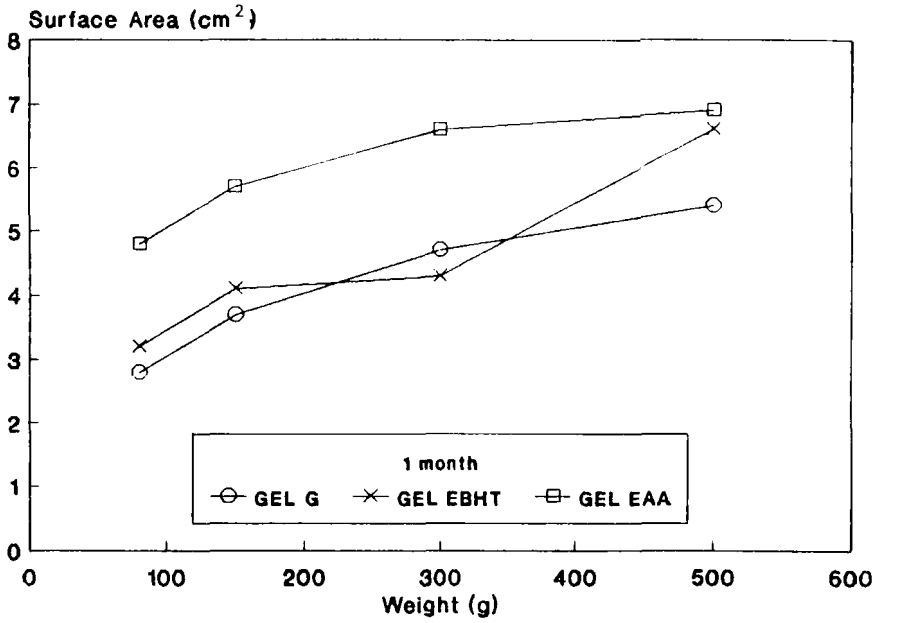

Figure 2.- Spreadability of the gels at 1 month.

of like charges between the free radicals -ROO· and the resin. The variation observed at 500 g could be due to the plasticity that the gels show. In other words, for weights of 300 g or smaller, deformation of the fluid is not produced because of the existence of a yield value of plasticity.

Gel EAA possesses greater spreadability (statistically significant) than the base. In this case, AA oxidizes an intermediate free radical, monodehydroascorbic acid, that rapidly reacts with either itself, producing ascorbic acid or dehydroascorbic acid, or with other free radicals to achieve the reactions of radicals (20, 21). This entire process causes a modification of the interaction between AA and Carbomer® 940 resin and permits the repulsion of like charges to form hydrogen bonds between the hydroxil groups of dehydroascorbic acid and the carboxils of the polymer. As a consequence, an increase in spreadability is observed because of the greater ease with which this

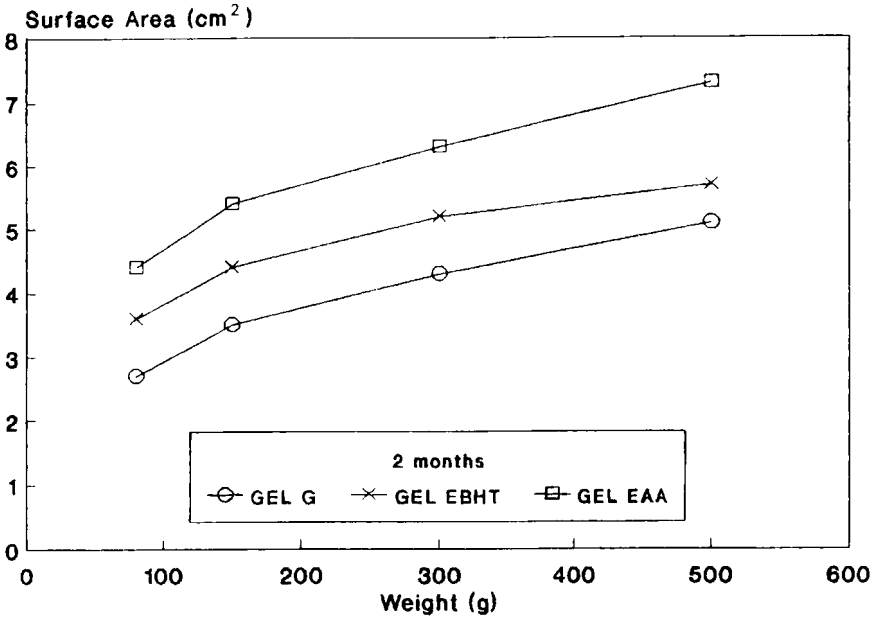

Figure 3.- Spreadability of the gels at 2 months.

union is broken because of the nature of the bonds of the new situation.

Finally, at TIME 2 (2 months) (Figure 3), small modifications are observed in gels EBHT and EAA, probably as a consequence of the reactions of both the antioxidants and of the newly formed bonds.

CONCLUSIONS

In light of the results obtained, the addition of butilhydroxitoluene or ascorbic acid can condition the rheology of gelled dispersed systems. Therefore, choosing between these substances is of great importance since the first results in a decrease in spreadability of the gel as storage time increases, while the second produces an increase in spreadability in the first month of storage and no modification thereafter.

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