BIOTECHNOLOGIES FOR OBTAINING NEW PHARMACEUTICAL FORMULATIONS BASED ON MIXTURES OF TYPE I NON-DENATURED FIBRILLAR COLLAGEN GELS AND EXTRACTS FROM MARINE ALGAE WITH APPLICATIONS IN NANOMEDICINE

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Diseases of the oro-dental tissues are of great interest in dental medicine. On these lines, the interest shown for the parodontal diseases has increased since it has been scientifically proved that there is a connection between cutaneous-mucous diseases and the paradontopathies, with different degrees of severity, within systemic morbidity: arteriosclerosis, myocardial infarction and cerebral haemorrhages, [1]. Anti-inflammatory ingredients can be used in regenerative therapy for tissues affected by the parodonthal disease; these ingredients are obtained from natural resources such as marine algae, which have proved to have an anti-inflammatory action on some negative gram and positive gram germs. The extracts from marine algae are incorporated in type I non-denatured fibrillar collagen matrixes.

Structural modifications of the marine biomass performed by extraction biotechnological processes, the production of type I fibrillar collagen hydrolysate (de-reticulation) by **lyophilization** techniques **in order to obtain hydrogels and porous matrixes or by free drying in order to obtain membranes and atomization in the production of powders, [2,3]** as well as the actions of the active ingredients at the bio-cellular level are **considered to be nanomaterials** acting at trans-dermal and trans-mucous levels.

Based on certain previous rheological measurements performed with type I non-denatured fibrillar collagen gels [4,5], containing ethyl alcohol with a pH of 3 or not, the concentrations selected for preparing gels with hydro-alcoholic extracts of marine algae were 0.6% for collagen and 5 and 10% for extracts from algae, in mass percentages. We have not used higher concentrations for extracts from algae nor for ethyl alcohol when extracting the components thereof, since ethyl alcohol can cause a decrease in the viscosity of the collagen-based gel, large quantities of it being likely to actually lead to its destruction (dissociation into two phases, one rich in water, the other rich in collagen).

Hydroalcoholic extracts from marine algae have been used as they have been obtained, without being previously diluted or concentrated in order to be brought to the same concentration, which means that the gels which contain prepared algae extracts do not have the same concentration of dry ingredients.

The gels with collagen concentrations of 0.6 and hydroalcoholic extract concentrations of 5%, 10% respectively in mass percentages have been prepared at room temperature for the initial gel with a collagen concentration of 1.64% (g collagen per 100 g of gel) by adding the relevant quantities of distilled water and hydroalcoholic extracts from marine algae while shaking.

In order to state, subsequent to rheological measurements, whether there are interactions between the components of the three hydroalcoholic extracts from algae and Type I

fibrillar collagen, we have prepared gels with the same collagen concentration and which also contain a concentration of 5, 10% respectively, of 70% ethyl alcohol solution, which represents the dispersing medium for the collagen gels which contain extracts (the quantities of ingredients introduced together with the extracts are very small in the final gels and can therefore be neglected), and which have been used in order to perform the relevant comparison.
The collagen gels into which a concentration of 5% of 70% ethyl alcohol solution has been introduced contain a concentration of ethyl alcohol of 3.5% in mass percentages and of 4.03% in volume percentages, and the ones with ethyl alcohol concentration of 10% contain double quantities of ingredients, ethyl alcohol concentration of 7% respectively in mass percentages and 8.06% in volume percentages. Ethyl alcohol is also present in the same mass or volume percentages in the collagen gels which contain the relevant quantities of extracts from algae. Both acid (3) and neutral pH gels have been prepared.
The concentrations of 70% ethyl alcohol solution, of extracts from algae with the same concentration of ethyl alcohol solution respectively, of 0.6% collagen gels with a pH of 3 and their appearance are presented in table 1.

Table 1. Collagen gels without/with prepared extracts from algae,

Alga extract	The extract's concentration, %	The gel's aspect
Without alga extract	0 5% of 70% alcohol solution 10% of 70% alcohol solution	Colourless, clear Colourless, clear Colourless, barely opalescent
CYSTOSEIRA BARBATA	5 10	Opalescent, yellowish green More opalescent, brownish yellow
ULVAE LACTUCA	5 10	Clear, barely green Barely opaque, barely green
CERAMIUM RUBRUM	5 10	Barely opalescent, yellowish green A degree more opalescent, brownish yellow

All gels have been introduced in the refrigerator, at a 4^{o}C temperature, for maturation. They have been shaken from time to time during the first four hours, after which they have been left to rest for 12 hours minimum and then subjected to shearing.

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