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 (71) Demandeur/Applicant:
SOOFT ITALIA SPA, IT
 (72) Inventeurs/Inventors:
FOSCHINI, FULVIO, IT;
STAGNI, MARCELLO, IT;
LUCIANI, GIULIO, IT;
ROY, PIERRE, FR
 (74) Agent: BERESKIN & PARR LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : COMPOSITION DE RETICULATION AMELIOREE ADMINISTREE PAR IONOPHORESE, UTILE POUR LE
TRAITEMENT DU KERATOCONE
 (54) Title: IMPROVED CROSS-LINKING COMPOSITION DELIVERED BY IONTOPHORESIS, USEFUL FOR THE
TREATMENT OF KERATOCONUS

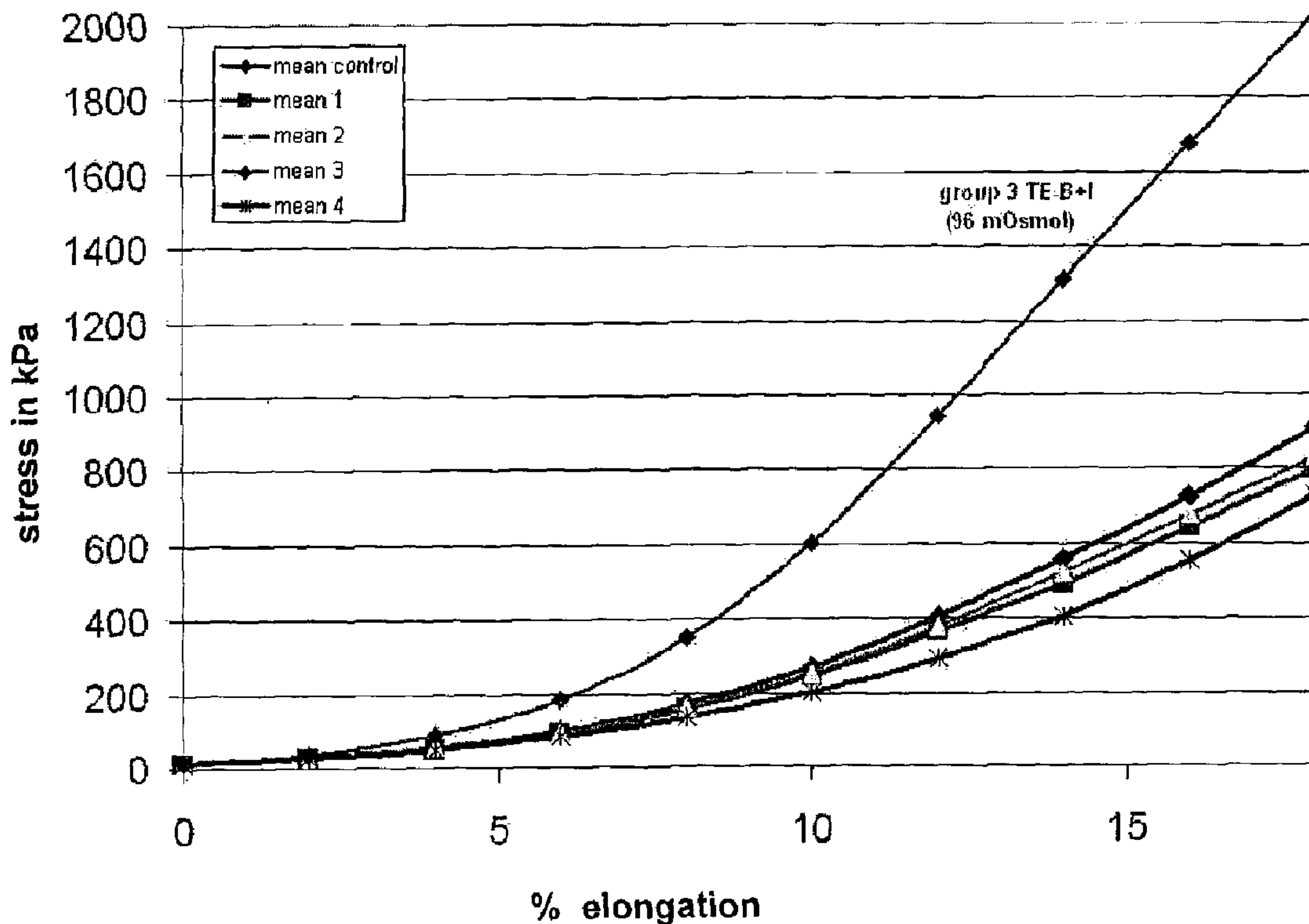


Figure 1

(57) Abrégé/Abstract:

The present invention relates to an improved formulation of an ophthalmic composition containing riboflavin, as cross-linking agent of corneal collagen, administered by corneal iontophoresis, able to guarantee an increased capacity of permeation of riboflavin of the corneal stroma and therefore greater therapeutic efficacy in the treatment of keratoconus.



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(71) Applicant: **SOOFT ITALIA SPA** [IT/IT]; Contrada Molino, 17, I-63833 Montegiorgio (FM) (IT).(72) Inventors: **FOSCHINI, Fulvio**; Via Anassagora, 59, I-00124 Roma (IT). **STAGNI, Marcello**; Via A.S. Fulci, 31/G, I-95127 Catania (IT). **LUCIANI, Giulio**; Via Roma, 231, I-50012 Bagno a Ripoli (FI) (IT).(74) Agent: **SARPI, Maurizio**; Studio Ferrario, Via Collina, 36, I-00187 Rome (IT).

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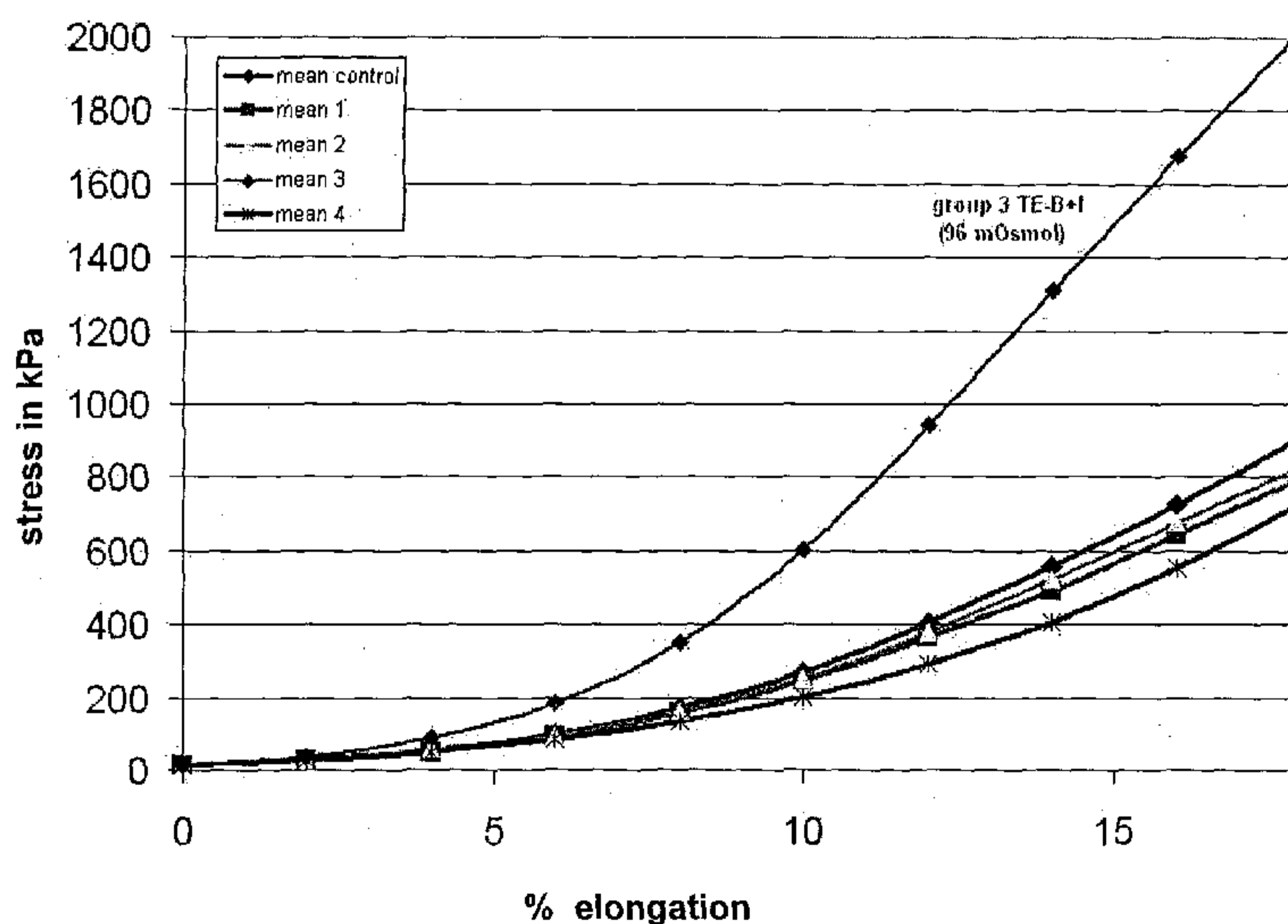


Figure 1

(57) Abstract: The present invention relates to an improved formulation of an ophthalmic composition containing riboflavin, as cross-linking agent of corneal collagen, administered by corneal iontophoresis, able to guarantee an increased capacity of permeation of riboflavin of the corneal stroma and therefore greater therapeutic efficacy in the treatment of keratoconus.

WO 2013/061350 A1

IMPROVED CROSS-LINKING COMPOSITION DELIVERED BY
IONTOPHORESIS, USEFUL FOR THE TREATMENT OF KERATOCONUS

The present invention relates to the medical pharmaceutical field and, more specifically, the field of preparations for topical ophthalmic use to be administered by means of iontophoresis to perform the cross-linking (CXL) of corneal collagen useful in the treatment of keratoconus, in particular an improved formulation of an ophthalmic composition containing riboflavin.

The collagen cross-linking induced by riboflavin and UV-A, is a practice widely used in ophthalmology, it consists in the photopolymerization of stromal collagen fibrils with the purpose of increasing its rigidity and resistance to progressive keratoectasia of keratoconus through the combined action of a photosensitizer and light-absorbing substance, the riboflavin precisely, by irradiation with ultraviolet light from UV-A type illuminator.

The purpose of the present invention is to provide an ophthalmic solution of riboflavin, as improved cross-linking agent, to be administered by means of iontophoresis in the practice of the treatment of keratoconus, or of other ectatic corneal diseases, having improved permeation and penetration characteristics in the corneal stroma, considerably reducing the time required for the treatment and improving performance and therapeutic outcomes.

Similarly to the brain, eye is protected by biological barriers (the blood-eye barrier, the blood-

vitreous barrier) that make difficult the administration of medicaments at sufficient concentration, especially in the posterior segments of the eye. Through the systemic via (by oral or intravenosa dministration) only a small fraction of the initial amount of drug may be delivered to interior eye tissues, so it is insufficient.

As topical application of eye drops fails to treat the posterior segment of the eye, the penetration is very limited (normally less than 5%), techniques for local administration of medicaments to the eye have been developed and are subjected to continuous and intense study to improve its efficiency. The direct injection around the eyeball (peribulbar, retrobulbar), or within the eyeball (intraocular), is very traumatic. The photodynamic therapy, consisting in the injection of the medicament and in its systemic activation *in situ* using a laser at specific wavelengths, takes advantage of the transparency of the cornea but it has the disadvantage that the patient must remain in the dark, the medicament must be modified by the addition of a photosensitizing agent preventing the active principle from acting before it is activated by light, also requires the use of special and expensive instrumentation in order to be carried out. Numerous devices designed to convey medicaments in a continuous or programmed manner by the use of medicament tanks placed on the surface of the eye have been also developed, said devices are therefore non-invasive, or in the form of lenses or rings in the conjunctival sac. However, the passage of substance to the posterior

segment of the eye is limited, therefore the use of these devices is limited to the treatment of pathologies of the anterior ocular segment, for example, for the treatment of conjunctivitis.

5 Intraocular implants for the programmed release of medicaments surgically positioned in the vitreous humor have the serious risk to damage the retina by contact, since incisions of relatively large size (5 mm) are required to place the implant. Another significant

10 drawback concerns the possible need to replace the implant, or to intervene to interrupt or modify the treatment as a function of how the disease responds to treatment.

In order to improve the corneal absorption of the

15 riboflavin, commonly used as a photosensitizing and curing agent in the process of corneal cross-linking, without having to resort to removal of corneal epithelium, and to obtain in such a way a non-invasive corneal cross-linking, eliminating or reducing

20 anesthesia and resulting in a more rapid healing, patent application WO 2010/023705 has suggested the use of absorption enhancers, including EDTA associated with tromethamine and/or salts of EDTA associated with tromethamine, to form an ophthalmic composition

25 administered in the form of eye drops to be instilled on the corneal surface.

Another possible solution is to use ocular iontophoresis.

This is another technique for administrating

30 active ingredients with therapeutic action which allows to reduce most of the disadvantages of other techniques

for ocular administration. In fact it makes possible, in a non-invasive manner, to reach concentrations and residence times in the eye, and hence transfer efficiencies, equal to or greater than those obtained
5 with other techniques of the state of the art.

The principle underlying the iontophoresis involves the application of an electric field to an electrolyte composition containing at least one medicament in order to transport the medicament or
10 medicaments in the body through biological membranes. The technique has long been clinically used in dermatology, in the treatment of osteoarticular disorders, but more recently has proved being particularly suitable for transferring active
15 ingredients and drugs into the eye.

However, because the eye is extremely different from most of the organs of the other body districts, ocular iontophoresis must submit technical specificities different from those of other types of
20 iontophoresis (intensity and current density, duration and control of the applied electric field, physical aspects of the chemical substances to be administered, electrochemical phenomena that occur in the solution during administration).

25 In particular, international patent application WO 2011/130356 claims a method to activate the cross-linking in at least one component of the eye comprising the transport of the electrically charged cross-linking agent to the ocular component pushing it in depth using
30 the iontophoretic process and the activation of the cross-linking agent conveying an initiation element to

the eyepiece element, wherein the eyepiece element is the cornea, the limbus, the sclera and the retina. According to the teachings of said patent application the cross-linking agent, such as riboflavin, can be
5 combined in various concentrations with other agents such as EDTA, benzalkonium chloride, or an alcohol to promote the further transfer across the corneal surface. However, the description does not define amounts or concentrations of the various components of
10 the cross-linking agent.

There is an ongoing debate in the ophthalmic field about the best way to transfer to the cornea riboflavin to perform cross-linking of corneal collagen, the results of clinical studies indicate that the
15 iontophoretic application of riboflavin should decrease processing time and eliminate the recourse to corneal epithelium removal before treatment. The internet publication of the document of George Waring: "Old
20 technique, new delivery", Ophthalmology Times Conference Brief, October 22, 2011,
URL: <http://ophthalmologytimes.modernmedicine.com/ophthalmologytimes/ModernMedicine+Now/Old-technique-new-delivery/ArticleStandard/Article/detail/745363>,
discloses that the iontophoretic treatment accelerating
25 the riboflavin transfer eliminates the need of corneal epithelium removal.

The applicants of the present patent application have already described in patent application WO 2012/095877, filed on 12.01.2011, the use of
30 iontophoresis to deliver ophthalmic compositions, preferably containing riboflavin or other agents

promoting cross-linking, designed to permeate the corneal stroma in the practice of corneal cross-linking of collagen in the treatment of keratoconus and other ectatic conditions of the eye. Due to the increased transfer efficiency promoted by the electric current, the administration time is significantly reduced, and the procedure is much more comfortable for the patient.

The ophthalmic compositions described in the aforementioned patent application are specifically designed to increase their transfer ability within and through the eye, by means of iontophoresis. In particular, the compositions described are based on riboflavin, between 0.1 and 1%, or other cross-linking agents that at the same time are also characterized by buffering properties, such as sodium phosphate. In such a way the described compositions improve permeation and penetration in the corneal stroma without having to proceed to the removal of the corneal epithelium in the treatment of keratoconus, or of other corneal ectatic diseases, by means of cross-linking corneal. According to said patent application, the ophthalmic solutions to be transferred by means of iontophoresis must have a initial value of pH in the range between 5 and 8 in order to act as a buffering agent and reach a final value not greater than 9. Furthermore, the presence of dextran guarantees a good adhesiveness to the ocular surface, ensures a better contact and thus a better permeation of the corneal stroma by the riboflavin solution.

However, despite the considerable improvement provided by the ocular iontophoretic administration,

always remains particularly felt the need to improve the effectiveness of the ocular transfer by means of iontophoresis in order to further reduce the risks of causing burns, irritations and general toxicity phenomena in the tissues that in the long may limit the application of ocular iontophoresis. It would be desirable to further reduce the time to achieve iontophoresis to reduce the potential risks during the execution of the process and improve the comfort of the patient.

The parameters on which the expert is able to intervene in order to improve the effectiveness and the success of the ocular iontophoretic procedure are many and of different nature, in fact, they relate to: the area of application of the electric field, sclera rather than cornea, this latter particularly delicate; minimizing the density of the electric field, the application area and the electrode area; controlling the intensity of the electric field applied so as to achieve a good reproducibility; limiting the application; and finally, the characteristics of the solution to be transferred.

DESCRIPTION OF THE INVENTION

The object of the present invention is therefore to provide new formulations, useful for the treatment of keratoconus, based on riboflavin, suitable to be administered by iontophoresis, characterized by a better transepithelial penetration in the corneal stroma compared to the formulations of the state of the art.

The improved capacity of permeation and

penetration into the corneal stroma, without having to proceed to the removal of the corneal epithelium in the practice of the treatment of keratoconus, or of other corneal ectatic diseases, by means of corneal cross-linking, was evaluated as a function of increase in corneal rigidity of the eye treated with the formulations object of the present invention compared to those of the prior art.

Thus, an object of the invention is to provide a formulation of a specific product based on riboflavin, suitable for the permeation of the cornea, in view of CXL treatment, which have to be transferred to the cornea by means of iontophoresis and subsequently irradiated by UV light. More particularly, it is an object of the present invention to provide solutions particularly suitable to be administered by iontophoresis, having values of pH and osmolarity able to ensure an optimal osmotic flow and in the appropriate direction with respect to the transfer of the riboflavin solution, which must operate the cross-linking of the collagen fibers of the corneal stroma in response to irradiation with UV.

Because iontophoresis substantially is the promotion of a movement of a charged substance through a biological membrane by the application of an electric field, osmolarity and pH are very important and determinant physical parameters of transfer effectiveness by means of iontophoresis of a solution. When the electric field is applied across a membrane and yields the movement of solvent bearing neutral or ionic species an electrosmotic flow is established

which is proportional to the concentration of ionic and neutral species of the active ingredient to be transferred. The direction of the electrosmotic flow takes place in the direction of the counterions of the charge of the membrane. At physiological pH value (pH = 5 7.4), the skin, as most of the biological membranes, including cornea and sclera, is negatively charged. Therefore, the electrosmotic current strengthens the anode transfer (+) of the drug positively charged, 10 while the cathode transfer (-) of the drug negatively charged is delayed. At low pH values, the charge of the biological surface shifts to the positive and the osmotic flow is reversed. This explains the importance of the pH value of the solution to be administered by 15 iontophoresis, which in addition to protect from damage to the conjunctiva and the cornea (the eye can tolerate a pH range rather wide and the pH of the ophthalmic solutions can vary from 4.5 to 11.5, however the range of pH values useful for preventing corneal damage is 20 from 6.5 to 8.5), also maintains the relative contribution of the osmotic flow at an appropriate level and direction. In addition, if the duration of the applied current is kept short, the number of ionic species in the solution is stable.

25 In a preferred embodiment of the invention formulations based on riboflavin phosphate have been identified showing optimal parameters relatively to the measurements of pH and osmolarity. In particular, the formulations according to the present invention have a 30 pH value between 6.5 and 8, preferably the pH value of the formulations is between 6.9 and 7.2, even more

preferably the pH value is 7,0, while the value of osmolarity of the formulations is between 90 mOsm/l and 300 mOsm/l, preferably 96 mos/l.

According to a particular embodiment of the invention the formulations are dextran free. In fact, surprisingly, recent studies carried out by the applicants of the present patent application have shown that permeation and penetration characteristics in the corneal stroma of riboflavin, without having to proceed to the removal of the corneal epithelium in the practice of the treatment of keratoconus or of other ectatic corneal diseases, evaluated *a posteriori* as a function of the corneal rigidity following CXL treatment, are significantly improved by using solutions that, in contrast to what had been assumed previously, contain neither dextran nor sodium chloride.

Further advantages and features of the invention will be evident from the detailed description of the invention with reference also to the enclosed figure purely by way of example, and not limitation.

Figure 1 shows the obtained experimental results in a stress vs. tension curve of the eye treated with the formulations according to the present invention, the resistance of the cornea of the treated eye, and hence, the effectiveness of transferring the therapeutic solution for the keratoconus condition, and it is further and substantially increased in case the formulation does not contain NaCl, further demonstrating the importance of the osmolarity of the therapeutic solution to be transferred by the

iontophoretic process.

Surprisingly, the lack of dextran and NaCl in the formulations of the compositions according to the present invention is characterizing and innovative, and provides unexpected advantages as compared to the efficacy of the compositions described in the state of the art in the field of ophthalmic solutions administered by iontophoresis and used in treatment of keratoconus.

In particular, the very low osmolarity value, due to the lack of sodium chloride, characterizes the composition showing the best performance in terms of increased resistance of the eye treated with corneal cross-linking following iontophoretic transfer of a solution based on riboflavin.

The solutions according to the present invention may further comprise a buffering system to maintain the pH value in the optimal range between 6.9 and 7.2. A variety of buffering systems are known to the skilled in the art and may be employed in some embodiments according to the present invention. However, in some preferred embodiments of the present invention the sodium phosphate monobasic/dibasic system provides an adequate buffering capacity, such as to maintain the pH in the desired range.

The ophthalmic compositions of the present invention also contain salts of EDTA in the ophthalmologically acceptable form that can be associated, or not associated, to Tris-(hydroxymethyl) aminomethane, also known as tromethamine.

The ophthalmic compositions of the present

invention can be prepared in the technical form of collirium and eye drops, gels, and in any case in all pharmaceutical forms that make possible a corneal application followed by iontophoresis according to known techniques; below are examples provided for illustrative purposes, without implying any limitation to the present invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the technical field of the invention.

Pharmaceutical compositions

The pharmaceutical compositions of the formulations according to the invention are given below, wherein the dosage of the individual components is expressed in percentage by weight.

EXAMPLE 1 - PREP A

Ingredient	% by weight
Riboflavin sodium phosphate	0.147
Sodium-EDTA	0.1
Tris-(hydroxymethyl)aminomethane	0.05
NaH ₂ PO ₄ ·2H ₂ O	0.385
Na ₂ HPO ₄ ·2H ₂ O	0.217
NaCl	0.5
H ₂ O	amount up to 100 ml
pH	7
Osmolarity	270 mOsm/kg

EXAMPLE 2 - PREP B

Ingredient	% by weight
Riboflavin sodium phosphate	0.147

	Sodium-EDTA	0.1
	Tris-(hydroxymethyl)aminomethane	0.05
	NaH ₂ PO ₄ ·2H ₂ O	0.385
	Na ₂ HPO ₄ ·2H ₂ O	0.217
5	H ₂ O	amount up to 100 ml
	pH 7	
	Osmolarity	96 mOsm/kg

EXPERIMENTAL DATA

10 In order to evaluate the improved ability of transepithelial penetration in rabbit eye of new formulations based on riboflavin delivered by means of iontophoresis compared to those known in the state of the art, the following pilot study was conducted taking
15 in account the effect of the transfer on corneal rigidity.

For the experimental study, which was conducted in compliance with the declarations for the use of animals in ophthalmic and vision research by the European
20 Commission and the Association for Research in Vision and Ophthalmology (ARVO), 12 rabbits, strain GD79b (pigmented), aged 2 and 3 months and weighing between 2.0 and 2.5 kg were used. All animals were identified by an ear tag on arrival and examined prior the test
25 providing particular attention to the condition of the eyes. Before undergoing the experimental procedure all animals were observed for at least three days and used only in the absence of signs of disease.

The twelve pigmented rabbits GD79b strain were
30 randomly divided into four groups of three animals each corresponding to the four types of treatment considered

in the study.

Table 1 below summarizes the assignment of the animals in the four treatment groups.

Table 1

5

Group	Treatment	Animal identification number
1	Application by iontophoresis for 5 minutes and 1mA of the solution described in patent application RM2008A00472	11 9 4
2	Application by iontophoresis for 5 minutes and 1mA of the PREP A solution	6 7 3
3	Application by iontophoresis for 5 minutes and 1mA of the PREP B solution	2 12 5
4	Traditional passive application for 30 minutes (0mA) of the solution described in patent application RM2008A00472	10 1 8

- Group 1 has received corneal administration in the right eye of 0.1% solution described in patent application RM2008A00472 by means of iontophoresis for 5 minutes at the 1mA current intensity.

- Group 2 has received corneal administration in the right eye of 0.1% PREP A solution by iontophoresis for 5 minutes at the 1mA current intensity.

- Group 3 has received corneal administration in the right eye of 0.1% PREP B solution by iontophoresis for 5 minutes at the 1mA current intensity

- Group 4 has received corneal administration in the right eye of 0.1% solution described in patent application RM2008A00472 by passive diffusion for 30 minutes.

Iontophoresis procedure

Animals were subjected to iontophoresis at right

eye, while the left eye was used as an untreated control, using an iontophoretic device consisting of two disposable components: an ocular applicator and a return electrode, connected to a reusable generator.

5 The ocular applicator, composed of a polycarbonate reservoir of 10 mm diameter and 4.5 mm height, was filled with the medical foam PUR (Advanced Medical Solutions BV - ref MCF03) and a stainless steel electrode (AISI 304) connected to a generator (cathode)

10 through a cable. The return electrode is an intradermal needle 25G, inserted into the neck of the animal and connected to the generator (anode) through a clip and a cable. The generator delivers a constant current with adjustment range from 0.25 mA to 2.5 mA (10 increments

15 of 0.25 mA for current) and 0.5 min - 5 min (10 increments of 0.5 min). During the procedure, the applied voltage is measured with a multimeter.

UV irradiation

The irradiation by UV-A for the cross-linking of

20 corneal collagen with riboflavin was performed using the medical device VEGA CBM X-Linker constructed by CSO Ophthalmic. The device is equipped with an array of LEDs for emitting light at a wavelength of 370 nm, a diaphragm capable of varying the area to be treated, a

25 system of focus with two intermittent red light LEDs, a micro-camera with the LCD monitor to capture real time images of the procedure, a coaxial fixation light incorporated on the camera that allows the patient to maintain the proper alignment. The power is controlled

30 with a power meter and maintained at 3.0 mW/cm².

All animals were irradiated totally for 30

minutes, using 6 stages of irradiation each lasting 5 minutes. If necessary, whenever irradiated the cornea becomes dry, one drop of saline was administered. At the end of each irradiation step the cornea was washed with saline solution and one drop of the solution to be administered was added before the beginning of each irradiation step.

After irradiation the animals were sacrificed with an overdose intravenous injection of pentobarbital, both eyes were quickly sampled and used for the biomechanical assay.

The results of the biomechanical assessment of the eyes subjected to the four types of treatment provide an indication of the resistance of the eye following a procedure of cross-linking of the corneal collagen fibers and highlights the differences in the effect produced by the four types of treatment and the three solutions with different composition used.

The data obtained are given in Table 2 below.

20

Table 2

GROUP	RICROLIN TE with dextran + Iontophoresis				RICROLIN TE PREP A + Iontophoresis				RICROLIN TE PREP B + Iontophoresis				RICROLIN TE with dextran				
	1	1	1		2	2	2		3	3	3		4	4	4		
	CCT in µm	700	650	720	mean	890	700	720	mean	728	700	690	mean	730	650	770	mean
	strain in %	r4	r9	r11	mean	r5	r6	r7	mean	r12	r2	r5	mean	r8	r10	r11	mean
control eye	0	12	12	12	12,0	12	12	12	12,0	12	12	12	12,0	12	12	12	12,0
	2	30	34	24	29,3	29	31	30	28,0	28	24	31	27,0	40	34	28	33,3
	4	53	74	40	55,7	43	69	60	57,3	51	44	63	52,7	78	63	60	63,7
	6	80	143	70	101,0	73	135	106	104,7	90	81	113	94,7	137	108	93	112,7
	8	144	265	115	171,3	120	238	105	181,0	150	137	187	160,0	223	176	163	187,3
	10	222	408	183	270,3	192	368	303	287,7	248	228	308	260,7	348	262	271	292,7
	12	328	611	277	404,7	300	613	489	427,3	374	359	470	401,0	514	373	422	436,0
	14	443	841	393	559,0	443	602	858	597,0	524	535	675	578,0	724	493	597	604,7
	16	554	1108	615	725,7	634	898	842	788,0	681	750	894	775,0	880	612	789	792,7
18	683	1390	652	908,3	843	1076	1009	976,0	829	1010	1130	989,7	1280	718	1013	996,3	
	CCT in µm	650	730	700	693,3	660	720	760	710,0	680	760	680	703,3	740	650	650	680,0
	strain in %	r4	r9	r11	mean	r3	r6	r7	mean	r12	r2	r5	mean	r6	r10	r11	mean
treated eye	0	12	12	12	12,0	12	12	12	12,0	12	12	12	12,0	12	12	12	12,0
	2	24	33	25	27,3	27	20	29	28,0	41	43	28	37,3	32	21	31	28,0
	4	45	65	44	51,3	49	58	62	59,3	112	93	60	88,3	61	34	60	51,7
	6	87	126	68	93,7	82	103	105	98,7	284	178	113	184,3	104	58	101	87,0
	8	147	222	104	167,7	133	185	174	164,0	537	318	200	351,7	161	84	157	134,0
	10	237	355	168	249,0	212	285	288	264,3	954	518	338	603,3	249	132	232	201,3
	12	349	515	226	363,3	311	436	384	376,7	1494	761	585	940,0	337	201	337	291,7
	14	471	685	321	492,3	418	625	528	522,3	1988	1031	888	1309,0	469	289	471	409,7
	16	616	889	441	642,0	528	805	892	674,3	2326	1400	1288	1674,0	697	410	658	554,3
18	775	1054	585	788,0	647	970	869	828,7	2516	1823	1739	2026,7	724	562	897	727,7	
	Diff r1	16	-51	-29	-21,3	20	-83	-37	-33,3	708	280	32	342,7	-105	-130	-39	-91,3

CCT = central corneal thickness

RICROLIN TE = trade name of the solution corresponding to composition described in patent application RM2008A00472.

The data have been represented in a graph shown in Figure 1, wherein the stress is represented as a function of elongation or tension.

Stress is indicative of the mechanical property of the sample calculated as the ratio between the force applied to a given section of the sample divided by the surface of the section, while the elongation represents the variation of the length undergone by the body divided by its original length.

As shown by the raw data, which are graphically represented in the curve stress vs. tension in Figure 1, the eyes that have undergone the treatment with the solution of riboflavin corresponding to the PREP B formulation (experimental group 3), containing riboflavin sodium phosphate, EDTA sodium and phosphate

buffer and water, iontophoretically delivered, have a central corneal thickness about 3 times greater than the control eyes, and the eyes that have undergone corneal cross-linking receiving, before UV-A irradiation, the solution of riboflavin PREP A (experimental group 2), also containing dextran, or solution comprising both NaCl and dextran, delivered by means of iontophoresis (experimental group 1) or by simple absorption (experimental group 4), as previously described respectively in the patent applications RM2008A00472, PCT/IT2009/000392, PCT/IT2011/000010. The greater central corneal thickness identified in the eyes of the experimental group 3 is the result of a greater effectiveness of the solution PREP B in promoting the cross-linking of corneal collagen fibers able to give greater rigidity to the cornea. In this way the use of the solution PREP B is therapeutically more advantageous in the treatment of keratoconus and other related corneal diseases.

The experimental data relating to the increased resistance of the eye treated by corneal cross-linking, and thus to the increased capacity of penetration and permeation into the cornea of the composition object of the present invention sodium chloride free, the solution PREP B, appears in contrast with what expected on the basis of the concepts of the iontophoretic mechanism: in fact, it is supposed that the presence of sodium chloride in the solution to be transferred by iontophoresis involves an increased conductivity, and a good conductivity of the solution typically results in a good rate of transfer of electric charged masses.

Contrary to what expected, probably the presence of sodium chloride in dissociated form in the composition to be transferred by iontophoresis exerts a competitive effect against the active ingredient
5 (riboflavin phosphate) in saturating the membranes subjected to iontophoresis; alternatively, the presence of dissociated charges of sodium chloride neutralize the charge of riboflavin phosphate, or of other chemical species that act as enhancers in the
10 composition (for example, salts of EDTA in ophthalmologically acceptable form), negatively charged at pH values of experimentation, resulting in a less effective transfer of the active principle promoted by iontophoresis.

15 Currently applicants of the present patent application are conducting further studies aimed to understand the physic-chemical mechanism at the base of what has been observed.

CLAIMS

1. An ophthalmic composition useful for the treatment of keratoconus to be administered by corneal iontophoresis, wherein the cross-linking agent is riboflavin, characterized in that the pH is between 6.9 and 7.2, and the value of osmolarity is between 90 and 100 mOsm/l, and the following formulation:

	Riboflavin sodium phosphate	0.147 g
	Sodium-EDTA	0.1 g
10	Tris-(hydroxymethyl)aminomethane	0.05 g
	NaH ₂ PO ₄ ·2H ₂ O	0.385 g
	Na ₂ HPO ₄ ·2H ₂ O	0.217 g
	Distilled water	up to 100 g

2. An ophthalmic composition according to claim 1 characterized in that the pH is 7.0, and the osmolarity is 96 mOsm/l.

3. An ophthalmic composition according to claim 1, characterized in that it further comprises salts, preferably NaCl, in an amount such that the value of the final osmolarity of the solution is between 90 mOsm/l and 300 mOsm/l, preferably between 95 mOsm/l and 275 mOsm/l.

4. An ophthalmic composition according to claim 3, characterized in that the pH is between 6.9 and 7.2, and the value of osmolarity is between 250 and 300 mOsm/l, and the following formulation:

	Riboflavin sodium phosphate	0.147 g
	Sodium-EDTA	0.1 g
	Tris-(hydroxymethyl)aminomethane	0.05 g
30	NaH ₂ PO ₄ ·2H ₂ O	0.385 g
	Na ₂ HPO ₄ ·2H ₂ O	0.217 g

NaCl	0.5 g
Distilled water	up to 100 g

5 5. Ophthalmic compositions according to claim 4 characterized in that the pH is 7.0, and the value of osmolarity is 270 mOsm/l.

6. An ophthalmic composition according to claims 1 to 5, wherein the pH value equal to 7.0 is obtained through a buffering system comprising sodium phosphate monobasic dihydrate and/or sodium phosphate dibasic dihydrate, in appropriate amounts.

7. Ophthalmic compositions according to any one of the preceding claims characterized in that they are prepared in the technical form of collirium, eye drops, gels, and in all pharmaceutical forms that enable a corneal application followed by corneal iontophoresis.

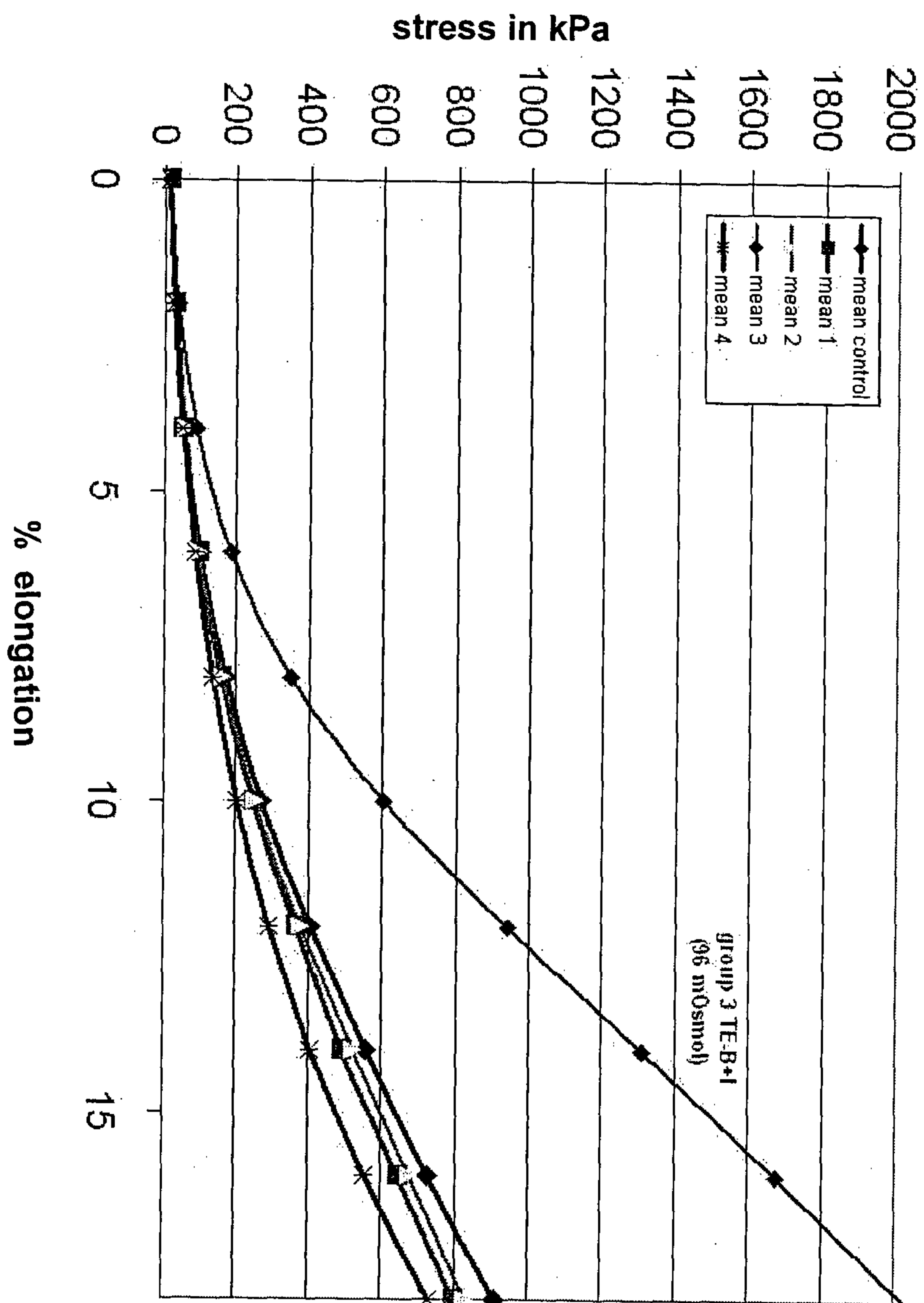


Figure 1

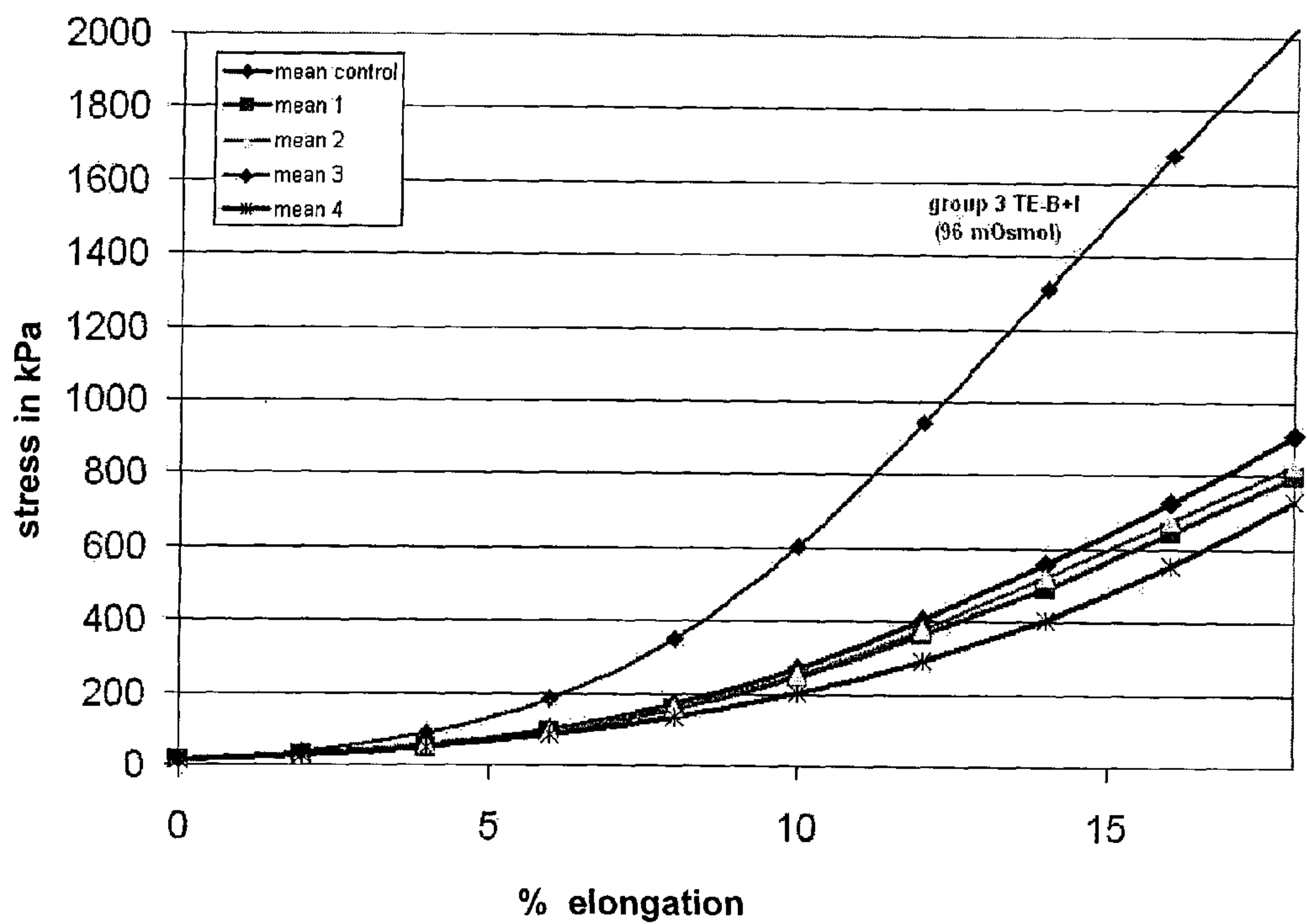


Figure 1