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(57) **Abrégé/Abstract:**

The present invention relates to topical compositions containing choline alfoscerate for use in maintaining and restoring the integrity of the mucous membranes.

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(54) Title: TOPICAL COMPOSITIONS FOR PRESERVING OR RESTORING THE INTEGRITY OF MUCOSAE

(57) Abstract: The present invention relates to topical compositions containing choline alfoscerate for use in maintaining and restoring the integrity of the mucous membranes.



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**TOPICAL COMPOSITIONS FOR PRESERVING OR RESTORING
THE INTEGRITY OF MUCOSAE**

Field of invention

The present invention relates to topical compositions containing choline alfoscerate which are useful to maintain and restore the integrity of the mucous membranes.

5 **State of the art**

Choline alfoscerate is known as a nootropic substance, namely a substance which improves the trophism of the brain cells (by activating the blood supply and cell metabolism), and consequently the intellectual functions.

10 As disclosed in WO93/19730, choline alfoscerate is practically devoid of systemic toxicity, and has marked topical tolerability and a low incidence of skin irritation, eye irritation and skin sensitisation.

It is known in the pharmaceutical field for its use in injectable compositions and oral compositions for the treatment of alterations of the
15 cognitive functions, and as a possible growth hormone secreting factor.

Its use in diet supplements for the same purposes as described for the pharmaceutical industry is also known.

In the dermatological and cosmetic field, for example in WO93/19730, its use on the skin and hair with a moisturising, emollient, elasticising,
20 restorative and volume-enhancing action is disclosed.

The integrity of the mucous membranes can be affected by a variety of exogenous and endogenous causes, such as vitamin deficiencies, incorrect diet, poor hygiene, bacterial, viral or fungal infections, intestinal dysbiosis, alterations of the mucosal microbial flora, endocrine imbalances, debilitating
25 diseases, hereditary factors, mechanical, physical, chemical and traumatic

factors, radiation, etc.

There is still a need for new compositions useful to maintain and restore the integrity of the mucous membranes.

Description of the invention

5 Is it has surprisingly been found that topical use of choline alfoscerate on the mucous membranes aids its cell trophism, thus maintaining and restoring the intactness of the mucosal tissue.

The term “trophism” means the general state of nutrition of an organism or part thereof.

10 The present invention therefore relates to topical compositions containing choline alfoscerate and hyaluronic acid or pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable excipient or carrier for use in the maintenance and restoration of the integrity of the mucous membranes.

The mucous membranes are preferably those commonly called external
15 mucous membranes, such as those of the mouth and oral cavity in general, the nasal mucosa, ocular mucosa, auricular mucosa, the male and female genital mucosa, and the anal and rectal mucosa.

According to a preferred aspect of the invention, topical compositions containing choline alfoscerate are useful, for example, in the prevention and
20 treatment of inflammatory disorders and/or lesions of the oral mucosa, and in the prevention and/or treatment of damaged and/or inflamed gums.

Inflammation and lesions of the oral mucosa means, for example, gingivitis, mucositis (mouth ulcers, including recurrent mouth ulcers), stomatitis, glossitis, etc. These disorders can have different etiologies; for example, they
25 may have mechanical, chemical or pathological causes (infections, dysbiosis of the oral cavity or intestinal dysbiosis).

It has also been found that topical use of choline alfoscerate is useful to maintain the correct pH value of the oral mucosa.

According to a further aspect of the invention, the compositions are

suitable for either human or veterinary use.

Choline alfoscerate is the internal salt of L-alpha-glycerylphosphorylcholine; it is an ampholyte, is highly soluble in water and ethanol, possesses high chemical and microbiological stability, and has special
5 organoleptic properties in that it is practically flavourless, odourless and colourless.

These organoleptic properties facilitate its use in the topical compositions to which this invention relates, which are useful for the treatment of the mucosa of the mouth and oral cavity and the nasal mucosa in
10 particular.

Choline alfoscerate is commercially available in both anhydrous and hydrated form; as the compound is markedly hygroscopic, the preferred form is the hydrated form.

Commercially available pharmaceutical-grade choline alfoscerate
15 hydrate, with the following chemico-physical characteristics, can preferably be used to prepare the compositions:

Appearance: a clear, highly viscous fluid

Titre: 98.0-102.0% (on an anhydrous base)

Water (K.F.): 13.5%-16.5%

20 **Specific rotation:** between 2.40° and 2.95° (on an anhydrous base)

Solubility (in water 10% w/v): complete

pH: 5.0-7.0.

The concentration of choline alfoscerate in the topical compositions according to the present invention can be selected on the basis of the type of
25 mucous membranes to be treated and the type of composition; for example, it can be between 0.001% w/v and 99% w/v.

The concentration of choline alfoscerate is preferably between 0.010% w/v and 50% w/v.

According to a further aspect, the topical compositions to which the present invention relates can also include further active constituents known for topical treatment of the mucosa, such as those described in Martindale, The Complete Drug Reference, 34th Edition.

5 The further active ingredients are preferably mesalazine, liquorice and derivatives thereof, silver and derivatives thereof, aloe vera, allantoin and derivatives thereof, chlorhexidine and benzalkonium chloride.

Topical compositions in the form of an anorectal or rectal enema containing choline alfoscerate and mesalazine can, for example, be
10 advantageously used for the prevention and treatment of ulcerative colitis and Crohn's disease.

The compositions according to the invention can be formulated in a way suitable for topical administration, and can be prepared according to conventional methods well known to the prior art, such as those described in
15 Remington, The Science and Practice of Pharmacy, 20th Edition.

Known excipients or carriers can also be added to optimise the specific use of the compositions, such as those described in the Handbook of Pharmaceutical Excipients, 6th Edition, Pharmaceutical Press, including film-forming agents, for example.

20 Examples of preferred formulations according to the present invention are gels, emulsions (oil in water (o/w) or water-in-oil (w/o)), creams, ointments, sprays, powders, lotions, mousses and mouthwashes.

The compositions more preferably take the form of an aqueous gel.

The aqueous gel can be prepared with a pharmaceutically acceptable
25 polymer able to absorb a considerable quantity of water, and thus adhere to the mucous membranes (mucoadhesion).

The mucoadhesion of the compositions according to the invention ensures an adequate residence time on the mucous membranes, which are

subject to the leaching action of physical and mechanical factors that can reduce the residence time of the active ingredient, for example in the case of the oral mucosa.

According to a further aspect of the invention, the compositions can also contain hyaluronic acid or pharmaceutically acceptable salts thereof, as a mucoadhesive polymer.

Hyaluronic acid or pharmaceutically acceptable salts thereof, with a molecular weight of between 800.000 and 4,000.000 Da, can preferably be used.

Even more preferably, the pharmaceutically acceptable salt of hyaluronic acid is the sodium salt.

Hyaluronic acid is extensively present in various tissues of the human and animal body; moreover, it is able to retain up to 1000 times its weight in water, and has a high viscoelasticity level.

It has surprisingly been found that choline alfoscerate markedly improves the mucoadhesive property of the aqueous gel of hyaluronic acid, performing the role of enhancer of the mucoadhesion of hyaluronic acid, particularly hyaluronic acid sodium salt, and even more particularly that with a molecular weight of between 800.000 and 4,000.000 Da, and vice versa.

This particular synergic action of the two compounds leads to greater therapeutic efficacy of both choline alfoscerate and hyaluronic acid.

In view of the results obtained with the compositions according to the invention, it can be assumed, by way of example but not of limitation, that the ingredients of the compositions according to the invention act through a reciprocal synergy mechanism; for example, due to its high level of hygroscopicity, choline alfoscerate can stabilise the composition containing hyaluronic acid, for example in gel form, and this allows hyaluronic acid to perform its mucoadhesive property as well as possible, and choline alfoscerate

to be more therapeutically effective.

Moreover, in aqueous systems, an interaction may occur between the anionic function of hyaluronic acid and the cationic function of choline alfoscerate, which may help to further improve the mucoadhesion of hyaluronic acid and promote the residence of choline alfoscerate and hyaluronic acid on the mucous membranes.

The examples given below further illustrate the invention.

The percentages are expressed as parts by weight of the total volume of the composition.

10 **Example 1 - Liquid composition for the oral mucosa**

Choline alfoscerate	10.00%
Preservative	q.s.
Flavouring	q.s.
Purified water	q.s. for 100%

15 **Example 2 - Mucoadhesive liquid composition for the oral mucosa**

Choline alfoscerate	1,000%
Sodium hyaluronan (mean MW 1,500.000 Da)	0.200%
Preservative	q.s.
Flavouring	q.s.
Purified water	q.s. for 100%

20 **Example 3 - Gel composition for the treatment of mouth ulcers**

Choline alfoscerate	5,000%
Sodium alginate	0.700%
Sorbitol	7,000%
Preservative	q.s.
Flavouring	q.s.
Purified water	q.s. for 100%

25

Example 4 - Mucoadhesive gel composition for the treatment of**mouth ulcers**

	Choline alfoscerate	0.500%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.100%
5	Sodium alginate	0.600%
	Sorbitol	5,000%
	Preservative	q.s.
	Flavouring	q.s.
	Purified water	q.s. for 100%

Example 5 - Liquid composition in drop form for use on the nasal**mucosa**

	Choline alfoscerate	0.100%
	<i>Camomile</i> distilled water	10.000%
	Sodium chloride	0.800%
15	Dibasic sodium phosphate dodecahydrate	0.300%
	Monobasic sodium phosphate monohydrate	0.030%
	Preservative	q.s.
	Purified water	q.s. for 100%

Example 6 - Liquid composition in mucoadhesive gel form for use**on the nasal mucosa**

	Choline alfoscerate	0.050%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.200%
	<i>Euphrasia</i> distilled water	10.000%
	Sodium chloride	0.800%
25	Dibasic sodium phosphate dodecahydrate	0.300%
	Monobasic sodium phosphate monohydrate	0.030%
	Preservative	q.s.
	Purified water	q.s. for 100%

Example 7 - Liquid composition for use on the ocular mucosa

	Choline alfoscerate	0.010%
	<i>Witch hazel</i> distilled water	10.000%
	<i>Camomile</i> distilled water	10.000%
5	Sodium chloride	0.800%
	Dibasic sodium phosphate dodecahydrate	0.300%
	Monobasic sodium phosphate monohydrate	0.030%
	EDTA	0.050%
	Purified water	q.s. for 100%

10 **Example 8 - Mucoadhesive liquid composition for use on the ocular**
mucosa

	Choline alfoscerate	0.010%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.050%
	<i>Witch hazel</i> distilled water	10.000%
15	<i>Camomile</i> distilled water	10.000%
	Sodium chloride	0.800%
	Dibasic sodium phosphate dodecahydrate	0.300%
	Monobasic sodium phosphate monohydrate	0.030%
	EDTA	0.050%
20	Purified water	q.s. for 100%

Example 9 - Liquid composition for use on the auricular mucosa

	Choline alfoscerate	0.100%
	Glycerol	50.000%
	Purified water	q.s. for 100%

Example 10 - Mucoadhesive liquid composition for use on the auricular mucosa

	Choline alfoscerate	0.100%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.100%
5	Glycerol	50.000%
	Purified water	q.s. for 100%

Example 11 - Liquid composition for use on the vaginal and vulvar mucosa

	Choline alfoscerate	0.100%
10	Sodium chloride	0.800%
	Preservative	q.s.
	Perfume	q.s.
	Purified water	q.s. for 100%

Example 12 - Mucoadhesive liquid composition for use on the vaginal and vulvar mucosa

	Choline alfoscerate	0.050%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.200%
	Sodium chloride	0.800%
	Preservative	q.s.
20	Perfume	q.s.
	Purified water	q.s. for 100%

Example 13 - Mucoadhesive gel composition for use on the vaginal and vulvar mucosa

	Choline alfoscerate	0.025%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.150%
5	Carboxymethylcellulose sodium salt	4,500%
	Sodium chloride	0.800%
	Preservative	q.s.
	Perfume	q.s.
	Purified water	q.s. for 100%

Example 14 - Mucoadhesive gel composition for use on the mucosa of the male genitals

	Choline alfoscerate	0.500%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.250%
	Carboxymethylcellulose sodium salt	4,500%
15	Sodium chloride	0.800%
	Preservative	q.s.
	Purified water	q.s. for 100%

Example 15 - Mucoadhesive gel composition for anorectal use

	Choline alfoscerate	0.500%
20	Sodium hyaluronan (mean MW 1,500.000 Da)	0.250%
	Carboxymethylcellulose sodium salt	4,500%
	<i>White thyme</i> distilled water	10.000%
	<i>Lavender</i> distilled water	10.000%
	<i>Cornflower</i> distilled water	10.000%
25	Sodium chloride	0.800%
	Preservative	q.s.
	Purified water	q.s. for 100%

Example 16 - Mucoadhesive gel composition for the treatment of inflamed gums

	Choline alfoscerate	1,000%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.200%
5	Xylitol	3,500%
	Carboxymethylcellulose sodium salt	3,500%
	Polyvinyl alcohol	0.300%
	Polycarbophil	0.300%
	Preservative	q.s.
10	Flavouring	q.s.
	Colouring	q.s.
	Purified water	q.s. for 100%

Example 17 - Mucoadhesive gel composition for the treatment of damaged gums

15	Choline alfoscerate	0.500%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.240%
	Xylitol	3,500%
	Carboxymethylcellulose sodium salt	3,700%
	PEG 40 hydrogenated castor oil	0.500%
20	Polyvinyl alcohol	0.100%
	Polycarbophil	0.100%
	Propylene glycol	7,000%
	Sodium benzoate	1,000%
	Preservative	q.s.
25	Flavouring	q.s.
	Colouring	q.s.
	Purified water	q.s. for 100

Example 18 - Mucoadhesive composition in the form of a vaginal**pessary**

	Choline alfoscerate	0.100%
	Sodium hyaluronan (mean MW 1,500.000 Da)	0.200%
5	Gelatin	20.000%
	Glycerol	70.000%
	Purified water	q.s. for 100%

Example 19 - Mucoadhesive anorectal enema composition

	Choline alfoscerate	0.300%
10	Sodium hyaluronan (mean MW 1,500.000 Da)	0.300%
	Colloidal silicon dioxide	1,700%
	Polyvinylpyrrolidone	0.840%
	Methylcellulose	0.840%
	Sodium benzoate	0.400%
15	Potassium metabisulphite	0.250%
	Phosphoric acid	0.100%
	Purified water	q.s. for 100%

Example 20 - Rectal enema composition (ulcerative colitis/Crohn's**disease)**

20	Choline alfoscerate	0.050%
	Mesalazine	4,000%
	Monobasic sodium phosphate monohydrate	0.045%
	Dibasic sodium phosphate dodecahydrate	0.620%
	Sodium chloride	0.900%
25	Gum tragacanth	0.400%
	Preservative	q.s.
	Purified water	q.s. for 100%.

Example 21 - Viscometric rheological measurements of aqueous solutions of hyaluronic acid

List of samples analysed:

1. **Solution B1: 1.0% hyaluronic acid (HA), 0.3% choline
alfoscerate (Co): G7933**

2. **Solution B2: 1.0% hyaluronic acid (HA): G7934**

Instrumentation

Instrument: Paar Physica, mod. RHEOLAB MC 1

Geometry: Z1DIN double gap, sample volume ~20ml

Shear rate: 1-150s⁻¹ (log scale)

Number of points: 20 (duration of each point 30s)

Temperature: 25°C

The experiment was conducted by increasing the shear rate (up curve) and reducing that parameter (down curve) in such a way as to verify the stability of the solution under stress.

Preparation of sample

The test solutions were placed directly in the measuring rotor, and left for the time required to thermostat the sample.

The viscosity of Newtonian fluids is constant, whereas the viscosity of non-Newtonian fluids is a function of the velocity gradient. In macromolecular systems such as hyaluronic acid, pseudoplastic behaviour is often observed whereby the viscosity declines as the velocity gradient increases; this means that these fluids are highly viscous at low deformation speeds, and become mobile at high speeds.

Results

Figure 1 shows the experiment conducted on solution G7933, containing 1% HA and 0.3% choline alfoscerate, wherein the deformation rate was varied and the stress and viscosity were measured.

As expected for a pseudoplastic fluid, the viscosity of the solution declines as the deformation rate increases, falling from a value of approx. 2.7 Pa.s to 0.3 Pa.s.

The same experiment was conducted on solution **G7934**, containing 1% HA: the results are set out in figure 2.

Unlike the preceding solution, the viscosity of the sample increases at low deformation rates, and then remains almost constant, or declines very slowly as $\dot{\gamma}$ increases. Moreover, the viscosity values are considerably lower than G7934, not exceeding the value of 0.1 Pa.s, regardless of the velocity gradient applied.

The addition of choline alfoscerate therefore modifies the rheological properties of the hyaluronic acid solution, considerably increasing the viscosity of the fluid.

In view of these findings, rheological tests were conducted, again with a rotational viscometer, to determine the variation in viscosity (expressed in Pa.s) of a mixture containing the two solutions **G7934 and G7933** and **mucin**, compared with the sum of the single contributions due to the solutions and mucin. This variation, called rheological synergy, is calculated in accordance with the following formula:

$$\Delta\eta(\text{mixture}) - [\eta(\text{solution}) + \eta(\text{mucin})]$$

As the viscosity values of the solutions present different orders of magnitude, normalised rheological synergy is used to make the data comparable:

where $\Delta\eta/\eta$ = normalised rheological synergy.

In the presence of interactions between the solution and mucin, the parameter acquires positive values, and is an indicator of bioadhesion (S. Rossi, F. Ferrari, M.C. Bonferoni and C. Caramella - "Characterization of chitosan hydrochloride-mucin interaction by means of viscosimetric and

turbidimetric measurements". - *Eur J Pharm Sci.* 2000;10(4):251-7).

The viscosity of the systems formed by a mixture of equal volumes of the two test solutions and mucin solutions with three different percentages (1%, 2% and 3% w/v) was measured (figure 3).

- 5 As will be seen from the above graph, the concentration of HA bipolymer being equal, the addition of choline alfoscerate leads to a proportional increase in rheological synergy, and therefore increases the bioadhesiveness of the mixture.

CLAIMS

1. A topical composition containing choline alfoscerate and hyaluronic acid or pharmaceutically acceptable salts thereof and at least one
5 pharmaceutically acceptable excipient or carrier, for use to maintain and restore the integrity of the mucous membranes.
2. The topical composition as claimed in claim 1, wherein the concentration of choline alfoscerate is between 0.001% w/v and 99% w/v.
3. The topical composition as claimed in claim 2, wherein the
10 concentration of choline alfoscerate is between 0.010% w/v and 50% w/v.
4. The topical composition as claimed in claim 1, wherein hyaluronic acid is in the form of sodium salt.
5. The topical composition as claimed in claim 1 or 4, wherein hyaluronic acid or a pharmaceutically acceptable salt thereof has a molecular weight of
15 between 800,000 and 4,000,000 Da.
6. The topical composition as claimed in any one of claims 1-5, containing at least one further active ingredient selected from the group consisting of mesalazine, liquorice, silver, aloe vera, allantoin, chlorhexidine and benzalkonium chloride.
- 20 7. The topical composition as claimed in claim 6, wherein the active constituent is mesalazine.
8. The topical composition as claimed in any one of claims 1-7, in the form of an aqueous gel.
9. The topical composition as claimed in any one of claims 1-8, for human
25 or veterinary use.
10. The topical composition as claimed in any one of claims 1-9, for use in the prevention and treatment of inflammatory disorders and/or lesions of the oral mucosa.

11. The topical composition as claimed in any one of claims 1-9, for use in the prevention and treatment of damaged and/or inflamed gums.
12. The topical composition as claimed in claim 9, for use in the prevention and treatment of ulcerative colitis and Crohn's disease.

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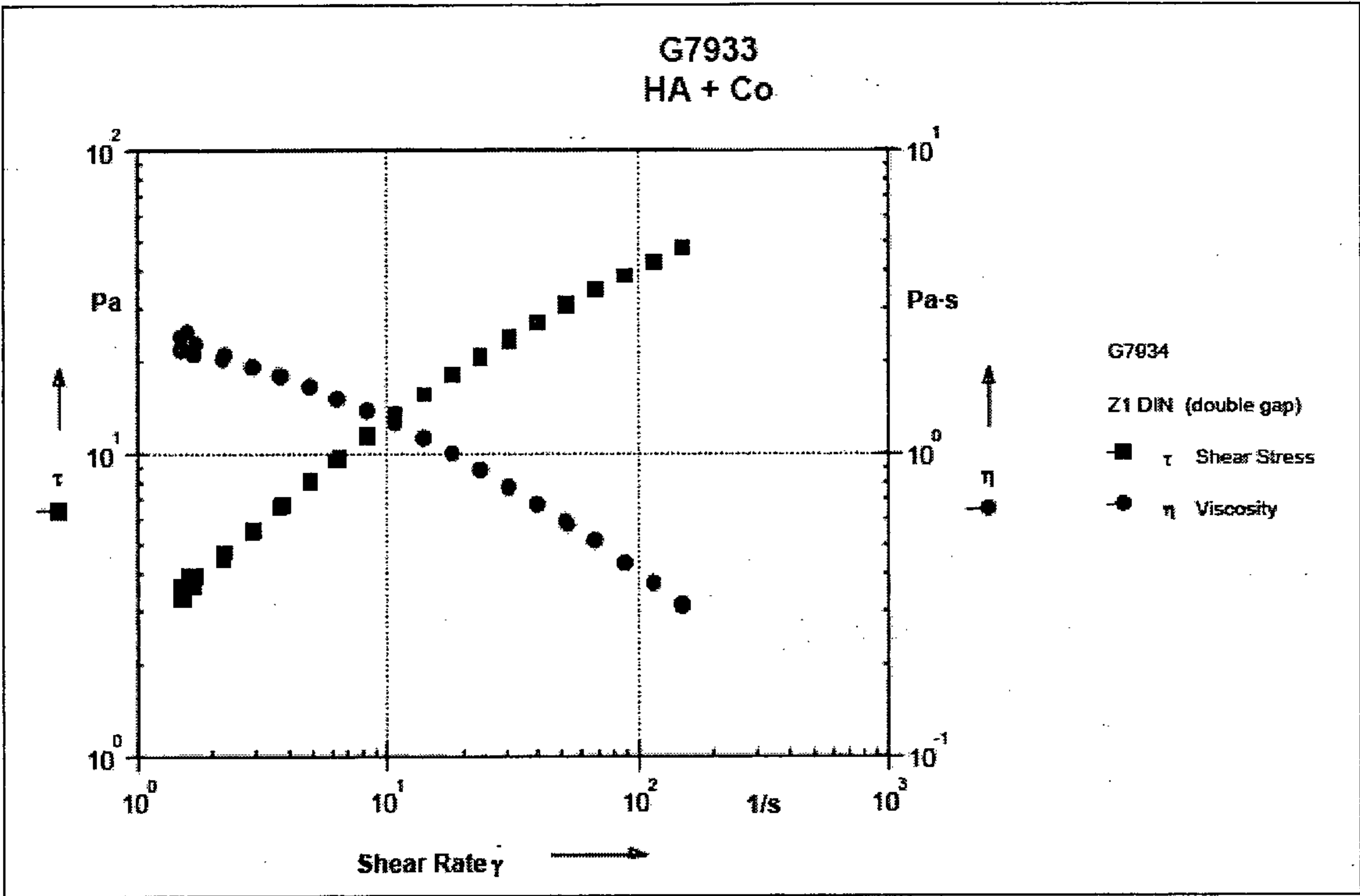


Fig. 1: G7933 viscosity test, up curve and down curve

Sheet 2/3

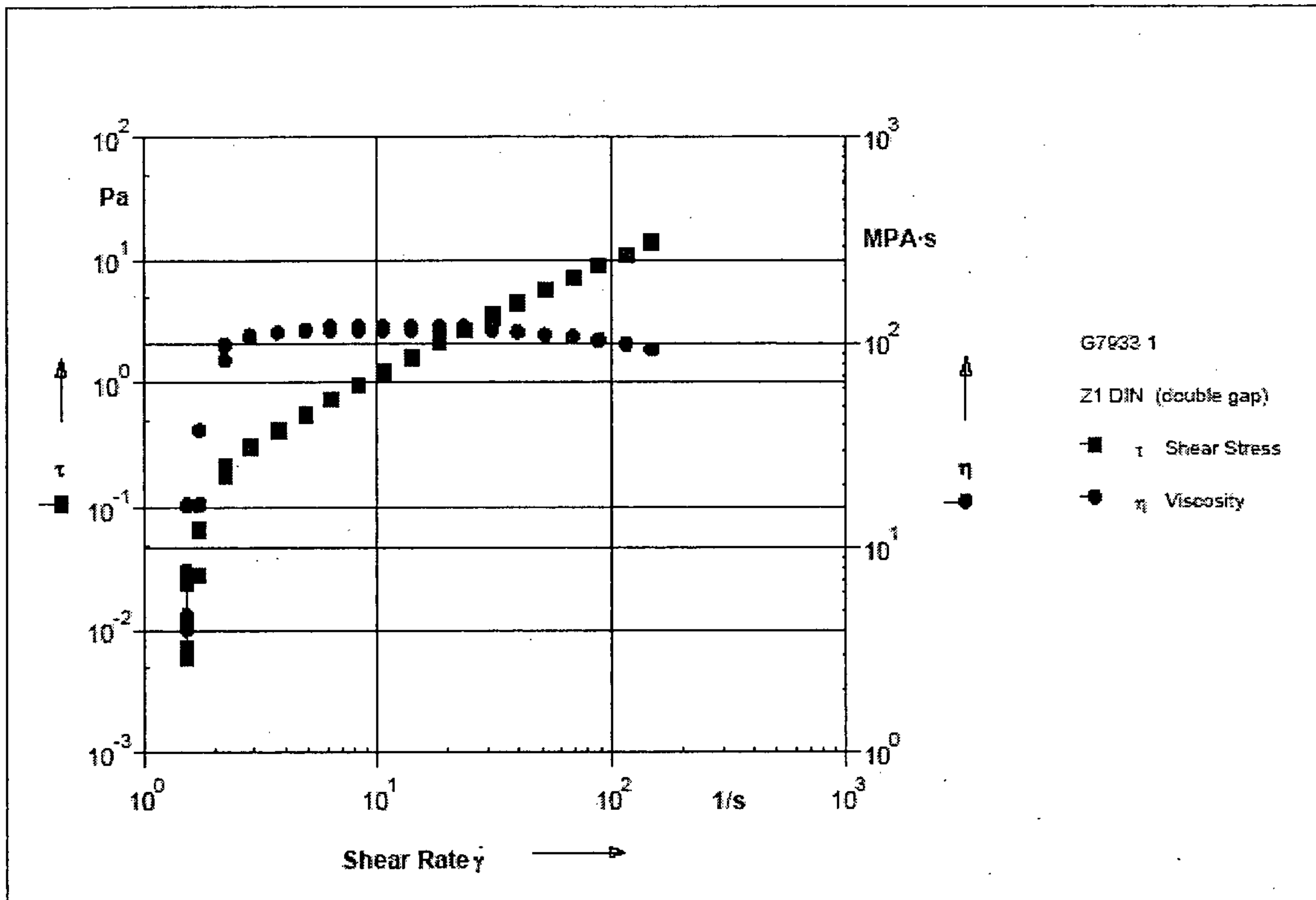


Fig. 2: G7934 viscosity test, up curve and down curve

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Figure 3

