[Logo: VIVACY LABORATORIES]	**Opposition to the patent EP2 349 203 B1 (Anteis):** ***TESTS CONDUCTED WITHIN THE FRAMEWORK OF ANOTHER PROJECT***	*RA1336402* *Version A* *Page 1 of 6*

1) Objective - Aim

These tests were conducted by Vivacy within the framework of of a project. They are reused as part of the argument provided in the notice of opposition filed against the issuing of patent EP 2 349 203.

2) Protocol - Method

a. Manufacture of gels

- Cross-linked hyaluronic acid gels

Gels containing cross-linked hyaluronic acid are obtained according to the operating method described in the patent application WO 2009/071697 in the name of the requester from sodium hyaluronate fibers (NaHa) and butanediol diglycidyl ether (BDDE). The final gels have a hyaluronic acid concentration of around 20 mg/g.

The conditions for cross-linking are as follows: 50.5°C - 2h 45min. The cross-linking ratio is defined as the relationship between the number of moles of cross-linking agent introduced into the reaction medium and the number of moles of disaccharide motifs introduced into the reaction medium.

Several cross-linking ratios were deployed: X=0.06, X=0.07 and X=0.12.

Several molecular weights of hyaluronicacid were deployed: 1 MDa and 3 MDa.

- Non-cross-linked hyaluronic acid gels

High-quality injectable sodium hyaluronate (NaHa) fibers are weighed in a receptacle. An aqueous phosphate buffer solution is added, the whole is homogenized for around 1 hour with a spatula, at ambient temperature and under atmospheric pressure of 900 mmHg. The final gels have a hyaluronic acid concentration of around 20 mg/g.

Just one molecular weight of hyaluronic acid was deployed: 3 MDa.

- Lidocaine

Lidocaine is prepared in a phosphate buffer solution at pH levels close to 7.

Additional compounds (magnesium ascorbyl phosphate, sucrose octasulfate)

The additional compounds are solubilized in a phosphate buffer solution before being incorporated in hyaluronic acid gels.

- Sterilization

The formulations thus obtained are packaged in syringes which are sterilized by autoclaving in steam (T=121°C, 10 min).

b. Measurement of rheological properties

The elastic G' components of formulations containing cross-linked hyaluronic acid before and after sterilization by steam autoclaving were measured on a TA Instruments AR 2000ex rheometer, oscillating at 25°C, the values for the elastic G' component being noted at a frequency of 1 Hz.

The viscous components were also measured.

The viscosity η of formulations containing non-cross-linked hyaluronic acid is measured on a TA Instruments AR 2000ex rheometer, under imposed stress at 25°C. The viscosity value is noted at a stress of 0.02 s^{-1}.

3) Results

The results below illustrate the influence of lidocaine in the presence of mannitol on the degradation during heat sterilization of the rheological properties of a hyaluronic acid gel with a weight-average molecular weight of 3 MDa with a cross-linking ratio X=0.12 at a concentration of 20 mg/g.

At 0.1 % lidocaine there is no detrimental effect, mannitol succeeds in compensating for the effects of lidocaine. Conversely from 0.3% upwards the beneficial effects of mannitol are destroyed by lidocaine.

Sterilization	Rheological characteristics measured at 25°C						
121°C-10 min	Before sterilization			After sterilization			Variation
	G' (1Hz)	G" (1Hz)	Tan δ	G' (1Hz)	G" (1Hz)	Tan δ	G' (1Hz)
3.5% Mannitol 1% Lidocaine	252	31.8	0.1265	141	22.4	0.1593	-44%
3.5% Mannitol 0.6% Lidocaine	258	32.3	0.1252	151	23.2	0.1535	-41%
3.5% Mannitol 0.3% Lidocaine	252	31.4	0.1246	175	25.4	0.1450	-31%
3.5% Mannitol 0.1% Lidocaine	256	32.0	0.1256	205	27.25	0.1329	-20%
3.5% Mannitol	254	32.0	0.1256	197	27.4	0.1391	-22%
8.5 g/l NaCl	221	27.3	0.1233	140	21.1	0.1511	-37%

Table 1

The results below illustrate the influence of lidocaine in the presence of mannitol on the degradation during heat sterilization of the rheological properties of a hyaluronic acid gel with a weight-average molecular **weight** of 1 MDa at a concentration of 20 mg/g, with a cross-linking ratio X= 0.07.

Whatever the concentrations of lidocaine tested, the beneficial effects of mannitol are destroyed by lidocaine.

Sterilization	Rheological characteristics measured at 25°C						
121°C-10min	Before sterilization			After sterilization			Variation
	G' (1Hz)	G" (1Hz)	Tan δ	G' (1Hz)	G" (1Hz)	Tan δ	G'(1Hz)
3.5% Mannitol 0.6% Lidocaine	437	55.8	0.1276	288	35.4	0.1248	-34%
3.5% Mannitol 0.3% Lidocaine	437	: 56.2	0.1276	315	41.4	0.1307	-28%
3.5% Mannitol	459	| 55.2	0.1202	373	47.3	0.1268	-19%
8.5 g/l NaCl	422	51.8	0.1227	286	33.3	0.1166	-32%

Table II

The results below illustrate the influence of lidocaine in the presence of mannitol on the degradation during heat sterilization of the rheological properties of a hyaluronic acid gel with a weight-average molecular weight of 3 MDa at a concentration of 20 mg/g with a cross-linking ratio X=0.06.

Whatever the concentrations of lidocaine tested, the presence of lidocaine destroys the effects of mannitol.

Sterilization	Rheological characteristics measured at 25°C						
121°C-10 min	Before sterilization			After sterilization			Variation
	G' (1Hz)	G" (1Hz)	Tan δ	G' (1Hz)	G" (1Hz)	Tan δ	G' (1Hz)
3.5% Mannitol 0.3% Lidocaine	149	26.6	0.1785	99	22.6	0.2278	-34%
3.5% Mannitol	147	26.3	0.1794	129	25.1	0.1955	-12%
8.5 g/l NaCl	157	25.5	0.1628	114	22.4	0.1968	-27%

Table III

The results below illustrate the influence of lidocaine in the presence of mannitol and of SOS on the degradation during heat sterilization of the rheological properties of hyaluronic acid gels with a weight-average molecular weight of 3 MDa with a cross-linking ratio X=0.12 at a concentration of 20mg/g.

In the presence of SOS the effects of mannitol are destroyed by lidocaine at a concentration of 0.3%,

Sterilization	Rheological characteristics measured at 25°C						
121°C-10 min	Before sterilization			After sterilization			Variation
	G'(1Hz)	G" (1Hz)	Tan δ	G' (1Hz)	G" (1Hz)	Tan δ	G'(1Hz)
0.1% Sucrose octasulfate 3.5% Mannitol 0.3% Lidocaine	256	31.55	0.1233	187	25.88	0.1389	-27%
0.1% Sucrose octasulfate 3.5% Mannitol	254	31.31	0.1234	197	26.6	0.1350	-22%
8.5 g/l NaCl	221	27.3	0.1233	140	21.1	0.1511	-37%

Table IV

The results below illustrate the influence of lidocaine in the presence of mannitol and of MAP at a concentration of 0.3 mg/g, on the degradation during heat sterilization of the rheological properties of hyaluronic acid gels with a weight-average molecular weight of 3 MDa with a cross-linking ratio X=0.12 at a concentration of 20 mg/g.

In the presence of MAP, the effects of mannitol are destroyed by lidocaine at a concentration of 0.3%.

Sterilization 121°C-10 min	Rheological characteristics measured at 25°C						Variation
	Before sterilization			After sterilization			
	G' (1Hz)	G" (1Hz)	Tan δ	G' (1Hz)	G" (1Hz)	Tan δ	G' (1Hz)
0.03% Magnesium ascorbyl phosphate 3.5% Mannitol 0.3% Lidocaine	264	38.39	0.1454	187	31.93	0.1708	-30%
0.03% Magnesium ascorbyl phosphate 3.5% Mannitol	270	38.6	0.1431	209	33.63	0.1607	-23%
8.5 g/l NaCl	221	27.3	0.1233	140	21.1	0.1511	-37%

Table V

The results below illustrate the influence of lidocaine in the presence of mannitol and of MAP at a concentration of 0.7 mg/g, on the degradation during heat sterilization of the rheological properties ofhyaluronic acid gels with a weight-average molecular weight of 3 MDa with a cross-linking ratio X=0.12 at a concentration of 20mg/g.

In the presence of MAP, the effects of mannitol are destroyed by lidocaine at a concentration of 0.3%.

Sterilization 121°C - 10 min	Rheological characteristics measured at 25°C						
	Before sterilization			After sterilization			Variation G' (1Hz)
	G' (1Hz)	G" (1Hz)	Tan δ	G' (1Hz)	G" (1Hz)	Tan δ	
0.07% Magnesiumascorbyl phosphate 3.5% Mannitol 0.03%Lidocaine	264	41.00	0.1464	190	32.35	0.1705	-28%
0.07% Magnesiumascorbyl phosphate 3.5% Mannitol	266	38.03	0.1430	208	33.90	0.1628	-22%
8.5 g/l NaCl	221	27.3	0.1233	140	21.1	0.1511	-37%

Table VI

The results below illustrate the influence of lidocaine in the presence of mannitol on the degradation during heat sterilization of the rheological properties of a hyaluronic acid gel with a weight-average molecular weight of 3 MDa at a concentration of 20 mg/g, non cross-linked.

Whatever the concentrations of lidocaine tested, the detrimental effects of this substance on the viscosity of the formulations lead to the systematic procurement of formulations with properties that are more degraded than formulations without lidocaine.

Sterilization	Rheological characteristics measured at 25°C		
121°C -10 min	Before sterilization	After sterilization	Variation
	η (Pa.s)	η (Pa.s)	η
3.5% Mannitol 1.0% Lidocaine	1708	20	-99%
3.5% Mannitol 0.6% Lidocaine	1670	27	-98%
3.5% Mannitol 0.3% Lidocaine	1696	59	-96%
3.5% Mannitol 0.1% Lidocaine	1660	215	-87%
3.5% Mannitol	1673	700	-58%
8.5 g/l NaCl	1407	479	-66%

Table VII

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