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(54) Title: HYALURONIC ACID ESTERS, THREADS AND BIOMATERIALS CONTAINING THEM, AND THEIR USE IN SURGERY

(57) Abrégé/Abstract:

The application discloses esters of hyaluronic acid, wherein a first part of the carboxy functions is esterified with an araliphatic alcohol and a second part is esterified with long-chain, straight aliphatic alcohols with between 10 and 22 carbons atoms. The possible remaining non-esterified carboxy functions, if present, are salified. The application further discloses biodegradable threads constituted by the aforesaid esters, and their use in the fields of medicine and surgery.

**PCT**

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**(54) Title:** HYALURONIC ACID ESTERS, THREADS AND BIOMATERIALS CONTAINING THEM, AND THEIR USE IN SURGERY

**(57) Abstract**

The application discloses esters of hyaluronic acid, wherein a first part of the carboxy functions is esterified with an araliphatic alcohol and a second part is esterified with long-chain, straight aliphatic alcohols with between 10 and 22 carbons atoms. The possible remaining non-esterified carboxy functions, if present, are salified. The application further discloses biodegradable threads constituted by the aforesaid esters, and their use in the fields of medicine and surgery.

# Hyaluronic acid esters, threads and biomaterials containing them, and their use in surgery

## TECHNICAL FIELD

The present invention concerns the preparation of a new series of ester derivatives of hyaluronic acid, biodegradable threads essentially constituted by such derivatives, and their use in the fields of medicine and surgery.

## BACKGROUND ART

Suture threads are now widely used in modern surgical practice and can be made of a wide range of materials, according to the type of surgery to be performed (Abraham R. Katz et al. "A new synthetic monofilament absorbable suture made from polytrimethylene carbonate" Surgery, Gynecology & Obstetrics, September 1985, vol. 161, pages 213-222; Abraham R. Katz et al. "Evaluation of tensile and absorption properties of polyglycolic acid sutures" Surgery, Gynecology & Obstetrics, October 1970, vol. 131, pages 701-716). It is possible, therefore, to imagine different types of suture thread with different characteristics of gauge, tensile strength, biocompatibility and biodegradability, according to whether they are intended for extensive lacerations (abdominal wall, thorax, lower limbs), or for small cuts and wounds as on the face, mouth and soft tissues. Some conditions require the material to be biocompatible but not biodegradable (as in cardiovascular surgery), while others necessitate both these characteristics (as in surgery to the urinary tract). The suture threads currently on the market vary first and foremost in the type of polymer with which they are made. Indeed, they vary from non-reabsorbable threads based on polyester, polypropylene, nylon and silk, such as Surgilene®, Surgilon®, Novafil® and Dermalon® by DG (Davis + Geck - American Cyanamid Company), to reabsorbable threads based on glycolic acid and collagen, such as Vicryl® and Catgut® by Ethicon (A. Pavan et al. "A Comparative Study of Poly Glycolic acid) and Catgut as Suture Materials. Histomorphology and Mechanical Properties", Journal of Biomedical Materials Research, vol. 13, pages 477-496, 1979). As these materials all have a synthetic polymeric matrix, they are poorly biocompatible and only some of them are biodegradable, so they may cause inflammatory reactions at the lesion site where they are applied (E. A. Bakkum et al. "Quantitative analysis of the inflammatory reaction surrounding sutures commonly used in operative procedures and the relation to postsurgical adhesion formation" Biomaterials 1995, vol. 16, No. 17, pages 1283-1289) and may necessitate a second surgical operation to remove them from the application site. Lastly, the use of ester derivatives of hyaluronic acid is known in the preparation of biomaterials, including suture threads, in the medical-surgical sector (European Patents EP 341745 and EP 216453)

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Testing the tensile properites of hyaluronic acid esters according to the present invention.

"Eicosanyl": hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol, 20% esterified with eicosanyl alcohol (arachidyl alcohol; $CH_3(CH_2)_{18}$-$CH_2$-OH) and the remaining 5% salified with sodium. (obtained in example 4)

"Octadecyl": hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol and the remaining 25%

esterified with octadecyl alcohol (stearyl alcohol; $CH_3-(CH_2)_{16}-CH_2-OH$) (obtained in example 3).

"Hexadecyl": hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol (and the remaining 25% esterified with hexadecyl alcohol (cetyl palmityl alcohol; $CH_3-(CH_2)_{14}-CH_2-OH$) (obtained in example 2).

"Dodecyl": hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol ($C_6H_5-CH_2OH$) and the remaining 25% esterified with dodecyl alcohol (Lauril alcohol; $CH_3-(CH_2)_{10}-CH_2-OH$) (obtained in example 1).

HYAFF11: total ester of hyaluronic acid with benzylic alcohol (reference compound).

Figure 2: testing the tensile properites of hyaluronic acid esters according to the present invention.

Figure 3: Testing the dry tensile resistance of the multifilament made with the ester derivative prepared according to Example 3, compared with that of the multifilament based on the totally esterified benzyl ester (Hyaff 11).

Figure 4: Testing the wet tensile resistance of the threads made with the ester derivatives prepared according to Examples 1 and 3 compared with that of the threads based on totally esterified benzyl and ethyl esters (Hyaff 11 and Hyaff 7, respectively).

Figure 5: comparing the tensile resistance of hyaluronic acid derivatives.

"HYAFF 11": multifilament thread made of the total benzylic ester of hyaluronic acid.

"EICOSANOL": multifilament thread made of the ester of hyaluronic acid obtained in example 4.

"CATGUT" chromic collagen monofilament for surgical suture.

Figure 6: resistance to tension one week after implant.

Figure 7: resistance to tension two weeks after implant.

DISCLOSURE OF THE INVENTION

The present invention describes new ester derivatives of hyaluronic acid, wherein the first part of the carboxy functions is esterified with an araliphatic alcohol, such as benzyl alcohol, and the second part with at least one long-chain, straight (unbranched) aliphatic alcohol with between 10 and 22 carbon atoms, i.e., in the range $C_{10}$-$C_{22}$.

The hyaluronic acid which can be used in the present invention may be derived from any source, for example it may be obtained by extraction from rooster combs (EP 0138572; WO 92/18543), by fermentation (WO 95/04132) or by biotechnological means (WO 95/24497), and its molecular weight can range from 10,000 to 10,000,000 Da, particularly from 150,000 to 1,000,000 Da.

The long-chain aliphatic alcohols are those with a straight chain of 10 to 22 carbon atoms. The increase in the number of carbon atoms in the alkyl chain and the number of carboxy functions involved in the esterification with the abovesaid alcohols, yields ester derivatives of hyaluronic acid with an increasingly high degree of lipophilia generally leading to hydrophobic interactions when they come into contact with solutions or biological fluids, with the result that the tensile strength varies from one product to another as does the biodegradability time, according to the length of the lipid alcohol introduced.

Moreover the combination of the aliphatic and araliphatic esters on the hyaluronic acid molecule allows to obtain compounds showing good biodegradability and at the same time a significant medium-term tensile strength.

The extent of esterification with aliphatic alcohols may vary from 1 to 50%, and in particular from 10 to 25%. The extent of esterification with araliphatic alcohol may vary from 50 to 75%. A preferred araliphatic alcohol is benzylic alcohol.

The esterification with aliphatic and araliphatic alcohols may involve the totality or part of the available carboxy functions of hyaluronic acid. In the latter case, the remaining non-esterified carboxy functions are salified with alkaline, alkaline earth metals and quaternary ammonium salts. Sodium in particular is used.

The long alkyl chains introduced, with 10 to 22 carbon atoms, give the ester derivatives of hyaluronic acid tensile properties never observed before and not foreseeable in other hyaluronic acid-based thread forms. Indeed, besides having a biocompatible and biodegradable polysaccharide matrix, thus belonging to that class of compounds which, like hyaluronic acid, have bioplastic and pharmaceutical properties, they can be given varying degrees of lipophilia according to the use they are intended for. Their lipophilia can be adjusted by modulating the insertion of a lipid chain starting from the ester matrix itself (benzyl ester of hyaluronic acid, 50 to 75% esterified). Indeed, the increase in the lipid chain of the polymer (from C10 to C22) gives the material a structure with greater hydrophobic characteristics and modulates its degradation over time.

The present invention also comprises biodegradable threads essentially constituted by the esters described above.

The preparation of these threads first involves the synthesis of such esters. This can be done by esterification of a first part of the carboxy functions of hyaluronic acid with araliphatic alcohol, esterification of a second part of the carboxy functions of hyaluronic acid with C10-C22 straight akyl chain alcohols, and salification of the possible remaining carboxy functions not involved in the esterification steps.

The remaining steps to form the esters into threads are those commonly available in the field of thread preparation, e.g. via extrusion techniques. An application of these techniques is shown in the experimental part, example 6.

The threads can be used as suture, or for the preparation of gauzes, non-woven fabrics, meshes, tubes, and products composed of associations of such forms, which present different degrees of biodegradability and residence times, as needed. Given the excellent biodegradability of threads made of these esters, it is possible to avoid operating a second time to remove them, as is normally the case with the suture threads on the market.

Especially when present in the form of surgical suture threads, the threads are preferably characterized by a multifilament conformation, a diameter which varies in the range of 75 to 800 microns and a tensile strength which varies, according to the ester derivative used, in the range of 300 to 1800 g/cm$^2$.

The main characteristic of these materials is their tensile strength which can be obtained on the basis of the following parameters:

- the molecular weight of the starting hyaluronic acid;

- the type of long-chain aliphatic alcohol used in the second esterification step;
- the percentage of carboxy groups involved in the esterification reaction with the long-chain lipid alcohol.

Figure 1 shows the different tensile properties of an ester derivative with benzyl alcohol of hyaluronic acid (Hyaff 11) from those of the derivatives of the present invention (examples 1-4) in a wet environment (saline solution), particularly as the substituted alkyl chain increases (dodecyl alcohol; hexadecyl alcohol; octadecyl alcohol; eicosanyl alcohol).

The threads thus constituted can be used to advantage in surgery, such as in maxillofacial surgery, in suture to tissues requiring a long degradation time, as in the case of materials which come into constant contact with biological fluids, or tissues requiring rapid degradation, as in the case of contact with soft tissues such as occurs in plastic surgery, as fillers in aesthetic surgery, and in dentistry.

Moreover, due to their content in hyaluronic acid derivatives, the threads according to the invention are able to act as bacteriostats and to limit the proliferation of inflammatory cells.

## EXPERIMENTAL PART

The tensile properties of the ester derivatives of hyaluronic acid have been assessed using a computerized tensiometer T-10 from MONSANTO, an instrument which can control the tensile stress applied to a given material. Generally speaking, the tensile properties of a material are measured according to its resistance to stress. When calculating tensile resistance, three main correlated values must be considered: load at break, elongation at break and shear modulus.

load at break gives the amount of stress necessary to cause the thread to break.

- elongation at break is the extent to which the thread is stretched when it breaks.
- the shear modulus represents the amount of stress which must be applied before the thread begins to stretch.

The shear modulus is, therefore, correlated with the elongation of the thread. Indeed, the greater the elastic properties of the thread, the higher the percentage of elongation at breaking point.

In particular, according to the variations in the lipid chain which was introduced, the ester derivatives of hyaluronic acid reported hereafter showed more marked elongation as the number of carbon atoms in the alcohol increased. Indeed, processing of the data reported in Figure 2 showed that the various hyaluronic acid ester threads presented various degrees of elongation. In the case of the benzyl ester derivative, elongation was virtually nil, while the dodecyl and hexadecyl derivatives showed an increase in elongation of the material which was proportional to the lipid chain introduced (hexadecyl>dodecyl).

**Example 1**

Preparation of a hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol ($C_6H_5$-$CH_2OH$) and the remaining 25% esterified with dodecyl alcohol (lauryl alcohol; $CH_3$-$(CH_2)_{10}$-$CH_2$-OH).

6.21 gr of tetrabutyl ammonium salt of hyaluronic acid with a molecular weight of 180,000 Da (10 meq) is solubilized in 248 ml of dimethylsulfoxide (DMSO) at room temperature. This solution is supplemented with 0.89 ml of benzyl bromide (7.5 meq) and then warmed to 30°C for 12 hours. It is then allowed to return to room temperature and supplemented with 0.62 gr of dodecyl bromide (2.5 meq). It is rewarmed to 30°C for 24 hours. A solution of 2.5% (w/w) of NaCl in water is then added and the resulting mixture is poured into 750 ml of acetone under agitation. A precipitate is formed which is filtered and washed three times in 100 ml of acetone/water 5:1, three times with 100 ml of acetone and then vacuum-dried for 24 hours at 30°C. 4.8 gr of the desired product is thus obtained. Quantitative determination of the benzyl alcohol and dodecyl alcohol content is performed by gas chromatography after alkaline hydrolysis. The total ester group content is quantified by the saponification method described on pages 169-172 of "Quantitative organic analysis via functional groups" 4th edition (J. Wiley & Sons Publication).

**Example 2**

Preparation of a hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol (and the remaining 25% esterified with hexadecyl alcohol (cetyl palmityl alcohol; $CH_3$-$(CH_2)_{14}$-$CH_2$-OH).

6.21 gr of tetrabutyl ammonium salt of hyaluronic acid with a molecular weight of 180,000 Da (10 meq) is solubilized in 248 ml of dimethylsulfoxide (DMSO) at room temperature. This solution is supplemented with 0.89 ml of benzyl bromide (7.5 meq) and then warmed to 30°C for 12 hours. It is then allowed to return to room temperature and supplemented with 0.76 gr of hexadecyl bromide (2.5 meq). It is rewarmed to 30°C for 24 hours. A solution of 2.5% (w/w) of NaCl in water is then added and the resulting mixture is poured into 750 ml of acetone under agitation. A precipitate is formed which is filtered and washed three times in 100 ml of acetone/water 5:1, three times with 100 ml of acetone and then vacuum-dried for 24 hours at 30°C. 5 gr of the desired product is thus obtained. Quantitative determination of the benzyl alcohol and hexadecyl alcohol content is performed by gas chromatography after alkaline hydrolysis. The total ester group content is quantified by the saponification method described on pages 169-172 of "Quantitative organic analysis via functional groups" 4th edition (J. Wiley & Sons Publication).

**Example 3:**

Preparation of a hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol and the remaining 25% esterified with octadecyl alcohol (stearyl alcohol; $CH_3-(CH_2)_{16}-CH_2-OH$).

6.21 gr of tetrabutyl ammonium salt of hyaluronic acid with a molecular weight of 180,000 Da (10 meq) is solubilized in 248 ml of dimethylsulfoxide (DMSO) at room temperature. This solution is supplemented with 0.89 ml of benzyl bromide (7.5 meq) and then warmed to 30°C for 12 hours. It is then allowed to return to room temperature and supplemented with 0.83 gr of octadecyl bromide (2.5 meq). It is rewarmed to 30°C for 24 hours. A solution of 2.5% (w/w) of NaCl in water is then added and the resulting mixture is poured into 750 ml of acetone under agitation. A precipitate is formed which is filtered and washed three times in 100 ml of acetone/water 5:1, three times with 100 ml of acetone and then vacuum-dried for 24 hours at 30°C. 5.1 gr of the desired product is thus obtained. Quantitative determination of the benzyl alcohol and octadecyl alcohol content is performed by gas chromatography after alkaline hydrolysis. The total ester group content is quantified by the saponification method described on pages 169-172 of "Quantitative organic analysis via functional groups" 4th edition (J. Wiley & Sons Publication).

**Example 4**

Preparation of a hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol, 20% esterified with eicosanyl alcohol (arachidyl alcohol; $CH_3(CH_2)_{18}$-$CH_2$-OH) and the remaining 5% salified with sodium.

6.21 gr of tetrabutyl ammonium salt of hyaluronic acid with a molecular weight of 180,000 Da (10 meq) is solubilized in 248 ml of dimethylsulfoxide (DMSO) at room temperature. This solution is supplemented with 0.89 ml of benzyl bromide (7.5 meq) and then warmed to 30°C for 12 hours. It is then allowed to return to room temperature and supplemented with 0.72 gr of eicosanyl bromide (2 meq). It is rewarmed to 30°C for 24 hours. A solution of 2.5% (w/w) of NaCl in water is then added and the resulting mixture is poured into 750 ml of acetone under agitation. A precipitate is formed which is filtered and washed three times in 100 ml of acetone/water 5:1, three times with 100 ml of acetone and then vacuum dried for 24 hours at 30°C. 5 gr of the desired product is thus obtained. Quantitative determination of the benzyl alcohol and eicosanyl alcohol content is performed by gas chromatography after alkaline hydrolysis. The total ester group content is quantified by the saponification method described on pages 169-172 of "Quantitative organic analysis via functional groups" 4th edition (J. Wiley & Sons Publication).

**Example 5:**

Preparation of a hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol, 15% esterified with docosanyl alcohol ($CH_3$-$(CH_2)_{20}$-$CH_2$-OH) and the remaining 10% salified with sodium.

6.21 gr of tetrabutyl ammonium salt of hyaluronic acid with a molecular weight of 180,000 Da (10 meq) are solubilized in 248 ml of dimethylsulfoxide (DMSO) at room temperature. This solution is supplemented with 0.89 ml of benzyl bromide (7.5 meq) and then warmed to 30°C for 12 hours. It is then allowed to return to room temperature and supplemented with 0.58 gr of docosanyl bromide (1.5 meq). It is rewarmed to 30°C for 24 hours. A solution of 2.5% (w/w) of NaCl in water is then added and the resulting mixture is poured into 750 ml of acetone under agitation. A precipitate is formed which is filtered and washed three times in 100 ml of acetone/water 5:1, three times with 100 ml of acetone and then vacuum-dried for 24 hours at 30°C. 4.9 gr of the desired product is thus obtained. Quantitative determination of the benzyl alcohol and docosanyl alcohol content is performed by gas chromatography after alkaline hydrolysis. The total ester group content is quantified by the saponification method described on pages 169-172 of "Quantitative organic analysis via functional groups" 4th edition (J. Wiley & Sons Publication).

**Example 6:**

Preparation of a multifilament from the hyaluronic acid derivative prepared according to Example 3.

The ester derivative prepared according to Example 3 is solubilized in DMSO to a concentration of 150 mg/ml at a temperature of 30°C. The solubilized derivative is filtered through a 20 micron mesh and placed in an extrusion reactor connected to a spinneret with 100 80-micron holes. The product is extruded in a coagulation bath containing a solvent which allows the DMSO to be extracted from the product (for example, ethanol), and the material coming out of the spinneret is wound onto a series of drafting bobbins and blown dry.

**Example 7**

Testing the dry tensile resistance of the multifilament made with the ester derivative prepared according to Example 3, compared with that of the multifilament based on the totally esterified benzyl ester (Hyaff 11)

The ester derivative prepared according to example 3 is processed according to the procedure described in Example 6 and the multifilament thus obtained is placed under stress to measure its tensile resistance. A T10 Tensiometer from Monsanto is used for this purpose. The results obtained are shown in Figure 3. As can be seen, the "lipid" derivative presented better resistance to stress than the multifilament based on the totally esterified benzyl ester did.

**Example 8**

Testing the wet tensile resistance of the threads made with the ester derivatives prepared according to Examples 1 and 3 compared with that of the threads based on totally esterified benzyl and ethyl esters (Hyaff 11 and Hyaff 7, respectively).

The ester derivatives prepared according to Examples 1 and 3 are processed according to the procedure described in Example 6. The threads thus obtained are immersed for 15 hours in an aqueous solution of 0.9% NaCl w/v and then placed under stress to measure their tensile resistance. A T10 Tensiometer from Monsanto is used for this purpose. The results obtained are shown in Figure 4. As can be seen, the "lipid" derivative presented different resistance to stress, as the chain introduced was varied (dodecyl<octadecyl), from that shown by the threads obtained with the Hyaff 11 and Hyaff 7 derivatives.

**Example 9:**

Testing the tensile resistance of the threads constituted by a hyaluronic acid derivative with 75% of its carboxy functions esterified with benzyl alcohol, 20% esterified with eicosanyl alcohol (arachidyl alcohol $CH_3-(CH_2)_{18}-CH_2OH$) and the remaining 5% salified with sodium following in vivo implantation in an animal model

Materials:

- multifilament thread of total benzyl ester of hyaluronic acid (HYAFF 11);
- multifilament thread of the hyaluronic acid derivative according to Example 4 (HYAFF11/p75+eicosanyl alcohol);
- chromic monofilament for surgical suture, CATGUT_ (collagen);
- biocompatible and biodegradable lubricant SQUALANO, Aldrich;
- T-10 Tensiometer by Monsanto.

Description:

Subcutaneous implant was performed on 14 S. D. Harlan rats using the following types of suture on each rat: HYAFF 11, HYAFF 11 lubricated with Squalane, HYAFF 11/p75+eicosanyl alcohol, HYAFF 11/p75 + eicosanyl alcohol lubricated with Squalane and CATGUT_ commercial sutures.

The threads were lubricated with a lipophilic substance such as Squalane, a saturated aliphatic hydrocarbide of natural origin with 30 carbon atoms, to assess whether this type of treatment affords better protection from biological liquids.

The rats were subdivided into two groups and sacrificed after 7 and 14 days respectively to assess the tensile characteristics of the threads.

Figure 5 compares the tensile resistance of derivatives HYAFF 11 and HYAFF11/p75 + eicosanyl alcohol, both lubricated and not lubricated, with that of CATGUT_ commercial suture before implant.

The tensile characteristics of the materials are similar.

Figure 6 shows the decreased resistance to tension one week after implant. The commercial suture and that of HYAFF11/p75 + eicosanyl alcohol presented similar behaviour and the lubricated threads were the most resistant.

Figure 7 shows the results two weeks after implant. As can be seen, it was impossible to remove the CATGUT_ suture from the site in order to test it for tensile resistance because it was completely degraded. The threads of HYAFF11/p75 + eicosanyl alcohol, on the other hand, presented tensile resistance which was 60% greater than that of the HYAFF 11 threads.

CLAIMS:

1. Ester derivatives of hyaluronic acid, wherein a first part of the carboxylic functions is esterified with an araliphatic alcohol, a second part is esterified with at least one unbranched long chain aliphatic alcohol having 10 to 22 carbon atoms, and wherein non-esterified carboxylic functions, if present, are salified provided that:
when the araliphatic alcohol is benzyl alcohol, and the at least one aliphatic alcohol is an unbranched long-chain aliphatic alcohol having between $C_{10}$-$C_{20}$ carbon atoms, the carboxylic functions of hyaluronic acid esterified with benzyl alcohol are lower than 75%.

2. Ester derivatives of hyaluronic acid according to claim 1, wherein the araliphatic alcohol is benzyl alcohol.

3. Ester derivatives of hyaluronic acid according to claim 1 or 2, wherein the unbranched long chain alcohol is selected from the group consisting of decyl, dodecyl, hexadecyl, octadecyl, eicosanyl and docosanyl alcohol.

4. Ester derivatives of hyaluronic acid according to any one of claims 1-3, wherein the percentage of the carboxylic functions of hyaluronic acid esterified with araliphatic alcohols varies from 50 to 75%.

5. Ester derivatives of hyaluronic acid according to any one of claims 1-4, wherein the percentage of carboxylic functions esterified with long-chain aliphatic alcohols is from 10 to 25%.

6. Ester derivatives of hyaluronic acid according to any one of claims 1-6, wherein the remaining carboxylic functions are salified with alkaline, alkaline earth metals, or quaternary ammonium salts.

7. Ester derivatives of hyaluronic acid according to claim 6, wherein the remaining carboxylic functions are salified with sodium.

8. Ester derivatives of hyaluronic acid according to any one of claims

1-7, wherein the starting hyaluronic acid has a molecular weight of 10,000 to 10,000,000 Da.

9. Ester derivatives of hyaluronic acid according to claim 8, wherein hyaluronic acid has a molecular weight of 150,000 to 1,000,000 Da.

10. Biodegradable threads having a multifilament conformation and a tensile strength of 300 to 1800 g/cm$^2$ consisting essentially of ester derivatives of hyaluronic acid, wherein a first part of the carboxylic function is esterified with an araliphatic alcohol, a second part is esterified with at least one unbranched long chain aliphatic alcohol having 10 to 22 carbon atoms, and wherein non-esterified carboxylic functions, if present, are salified.

11. Biodegradable threads according to claim 10, wherein the araliphatic alcohol is benzyl alcohol.

12. Biodegradable threads according to any one of claims 10-11, wherein the unbranched long chain aliphatic alcohol is chosen from the group consisting of decyl, dodecyl, hexadecyl, octadecyl, eicosanyl and docosanyl alcohol.

13. Biodegradable threads according to any one of claims 10-12, wherein the percentage of the carboxylic functions of hyaluronic acid esterified with araliphatic alcohols varies from 50 to 75%.

14. Biodegradable threads according to any one of claims 10-13, wherein the percentage of carboxylic functions esterified with long-chain aliphatic alcohols is from 10 to 25%.

15. Biodegradable threads according to any one of claims 10-14, wherein the remaining carboxy functions are salified with alkaline, alkaline earth metals, and quaternary ammonium salts.

16. Biodegradable threads according to claim 15, wherein the remaining carboxylic functions are salified with sodium.

17. Biodegradable threads according to any one of claims 10-16, wherein the hyaluronic acid has a molecular weight of 10,000 to 10,000,000 Da.

18. Biodegradable threads according to any one of claims 10-16, wherein hyaluronic acid has a molecular weight of 150,000 to 1,000,000 Da.

19. Biodegradable threads according to any one of claims 10-18, having diameters which vary from 75 to 800 microns.

20. Biodegradable threads according to claim 19, in the form of surgical suture threads.

21. Biomaterials, health-care products, and surgical articles in the form of gauzes, meshes, non-woven fabrics, tubes and association thereof containing the threads according to any one of claims 10-19.

22. A process for preparing the biodegradable threads according to any one of claims 10-19, comprising the following steps:

a) esterifying a first part of the carboxylic functions of hyaluronic acid with an araliphatic alcohol,

b) esterifying the remaining carboxylic functions with at least one unbranched aliphatic long chain alcohol having 10 to 22 carbon atoms;

c) salifying any remaining carboxylic functions of hyaluronic acid not involved in the preceding esterification steps,

d) subjecting the hyaluronic mixed esters obtained in step c) to a conventional thread-forming process.

23. Use of threads consisting essentially of ester derivatives of hyaluronic acid, wherein a first part of the carboxylic functions is esterified with an araliphatic alcohol, a second part is esterified with at least one unbranched long chain aliphatic alcohol having 10 to 22 carbon

atoms, and wherein non-esterified carboxylic functions, if present, are salified, said use being in general surgery, maxillofacial surgery, plastic surgery, and dentistry.

24. Use of threads consisting essentially of ester derivatives of hyaluronic acid, wherein a first part of the carboxylic functions is esterified with an araliphatic alcohol, a second part is esterified with at least one unbranched long chain aliphatic alcohol having 10 to 22 carbon atoms, and wherein any non-esterified carboxylic functions are salified, said use being as fillers in aesthetic surgery.

RIDOUT & MAYBEE LLP
Toronto, Canada
Patent Agents

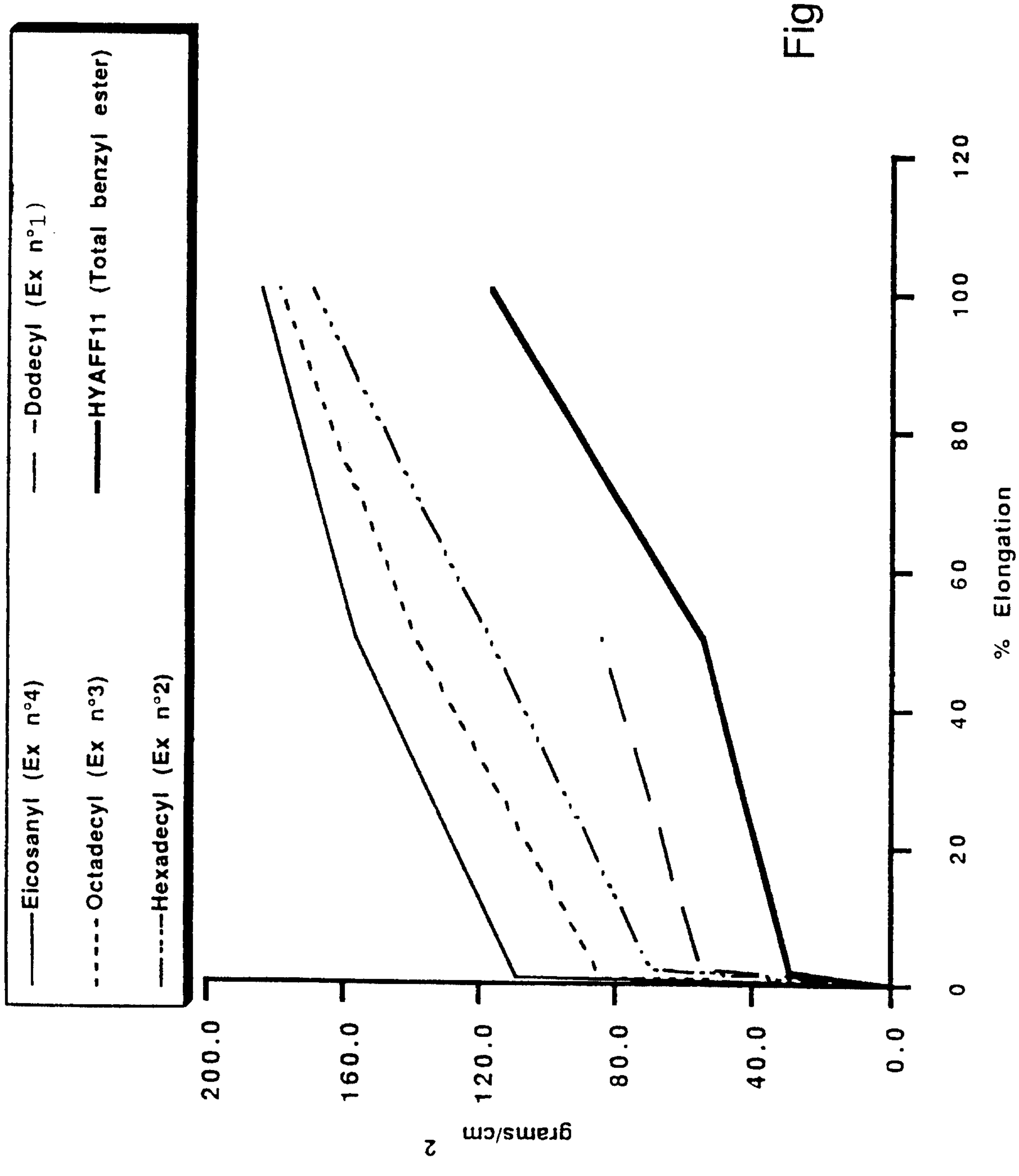

Eicosanyl (Ex n°4)
Octadecyl (Ex n°3)
Hexadecyl (Ex n°2)
Dodecyl (Ex n°1)
HYAFF11 (Total benzyl ester)
grams/cm 2
200.0
160.0
120.0
80.0
40.0
0.0
0
20
40
60
80
100
120
% Elongation

Figure 1

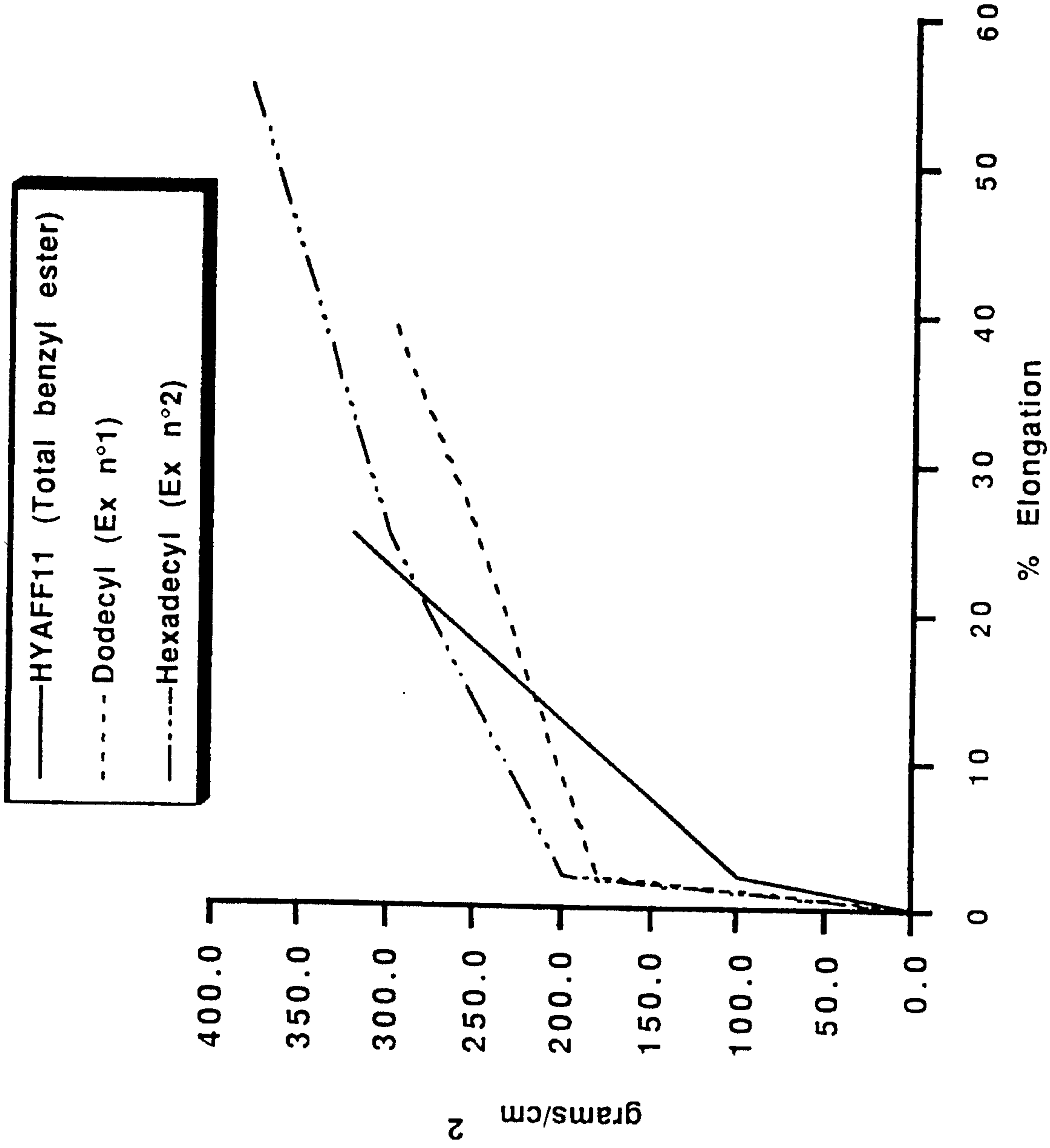

HYAFF11 (Total benzyl ester)
Dodecyl (Ex n°1)
Hexadecyl (Ex n°2)
grams/cm 2
400.0
350.0
300.0
250.0
200.0
150.0
100.0
50.0
0.0
0
10
20
30
40
50
60
% Elongation

Figure 2

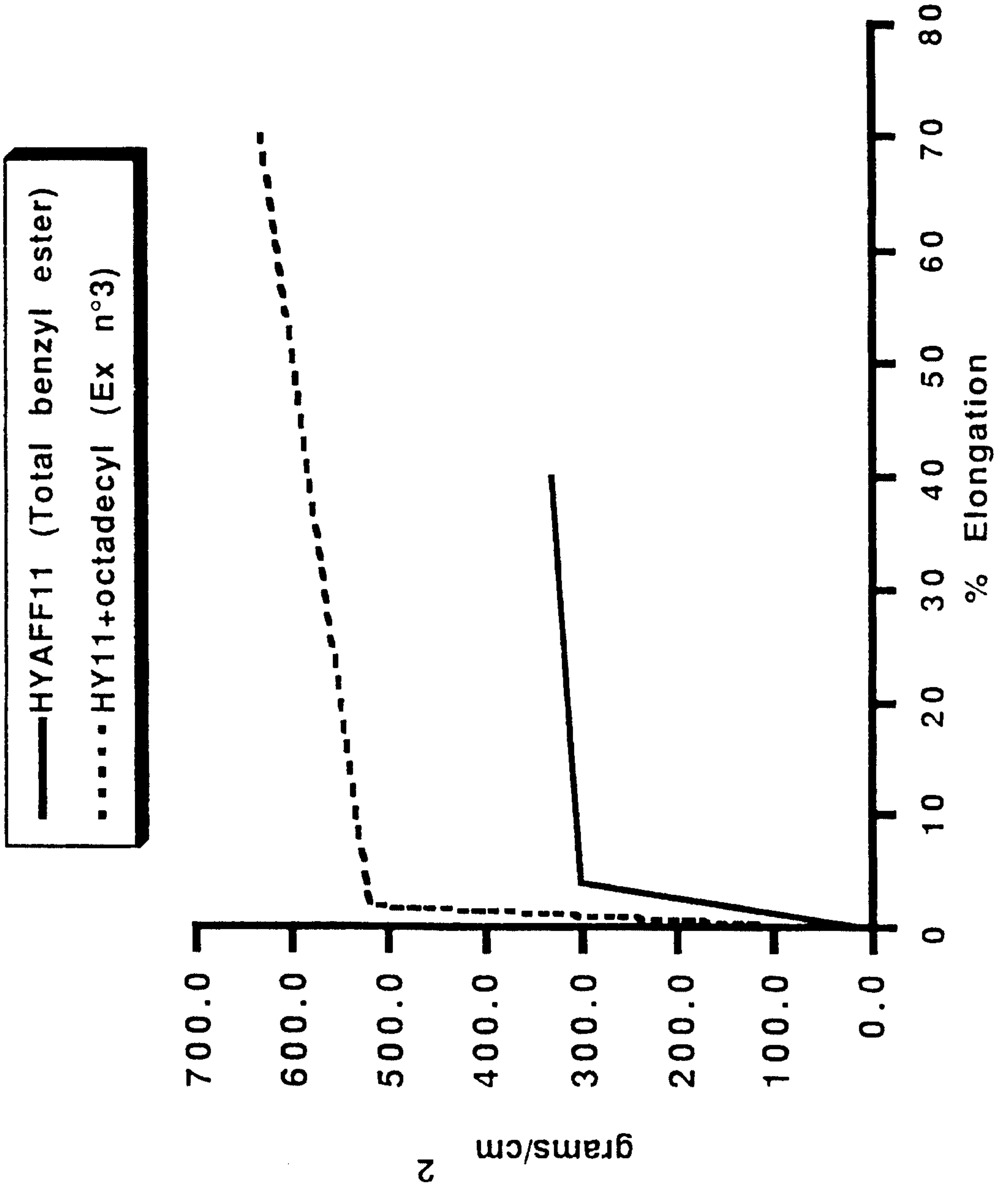

HYAFF11 (Total benzyl ester)
HY11+octadecyl (Ex n°3)
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
grams/cm 2
0
10
20
30
40
50
60
70
80
% Elongation

Figure 3

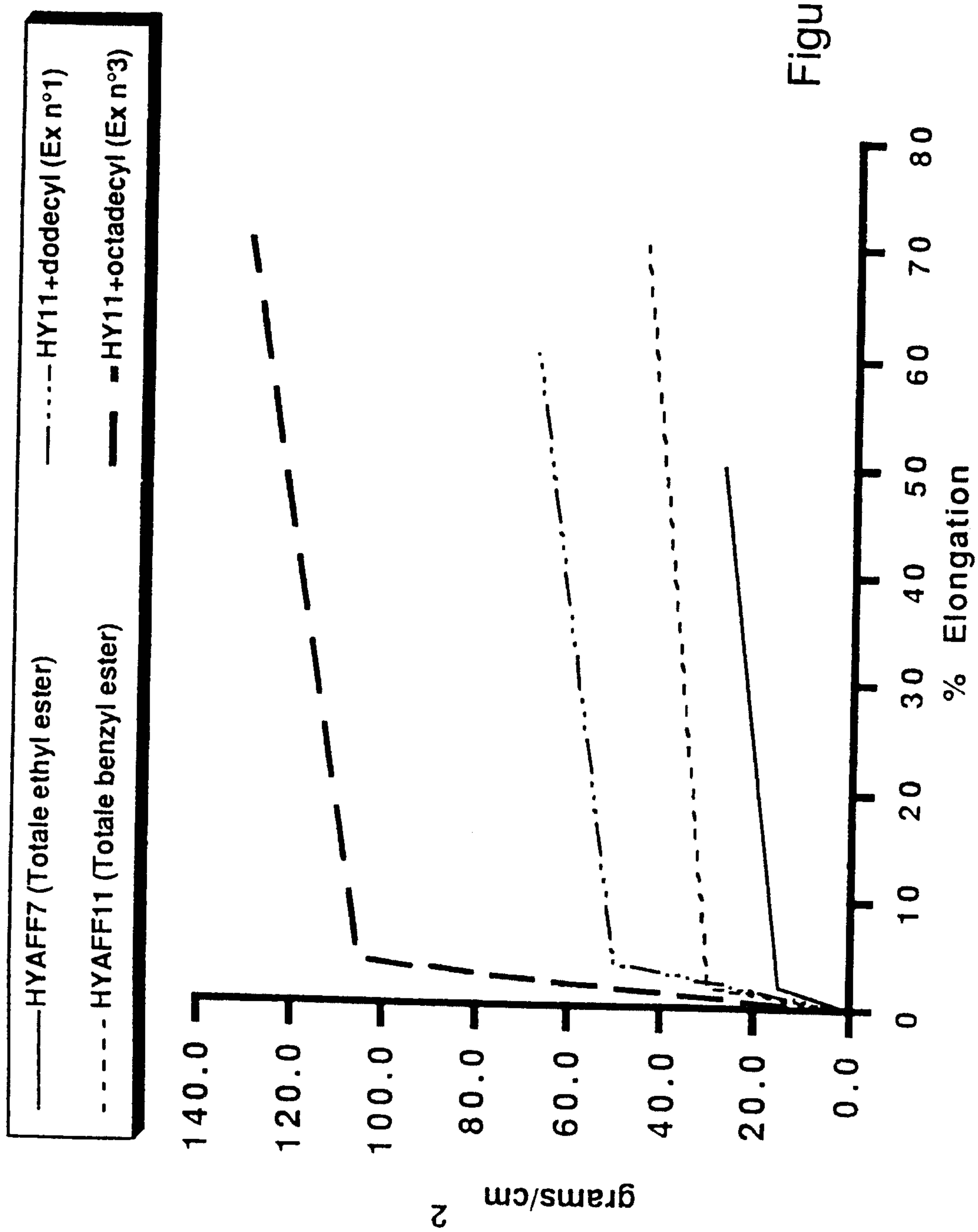
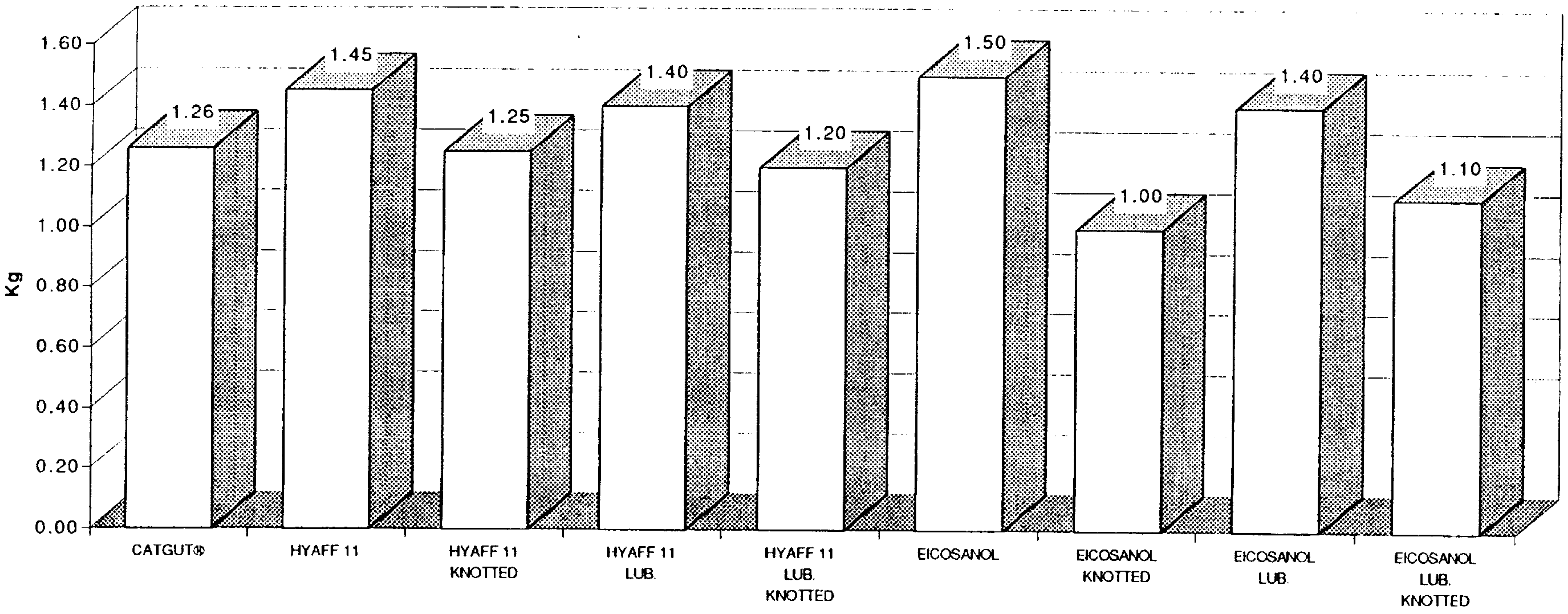

HYAFF7 (Totale ethyl ester)
HYAFF11 (Totale benzyl ester)
HY11+dodecyl (Ex n°1)
HY11+octadecyl (Ex n°3)
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
grams/cm 2
0
10
20
30
40
50
60
70
80
% Elongation

Figure 4

Figure 5



TRACTION TESTS IN DRY CONDITIONS ON STERILE SAMPLES

Figure 6

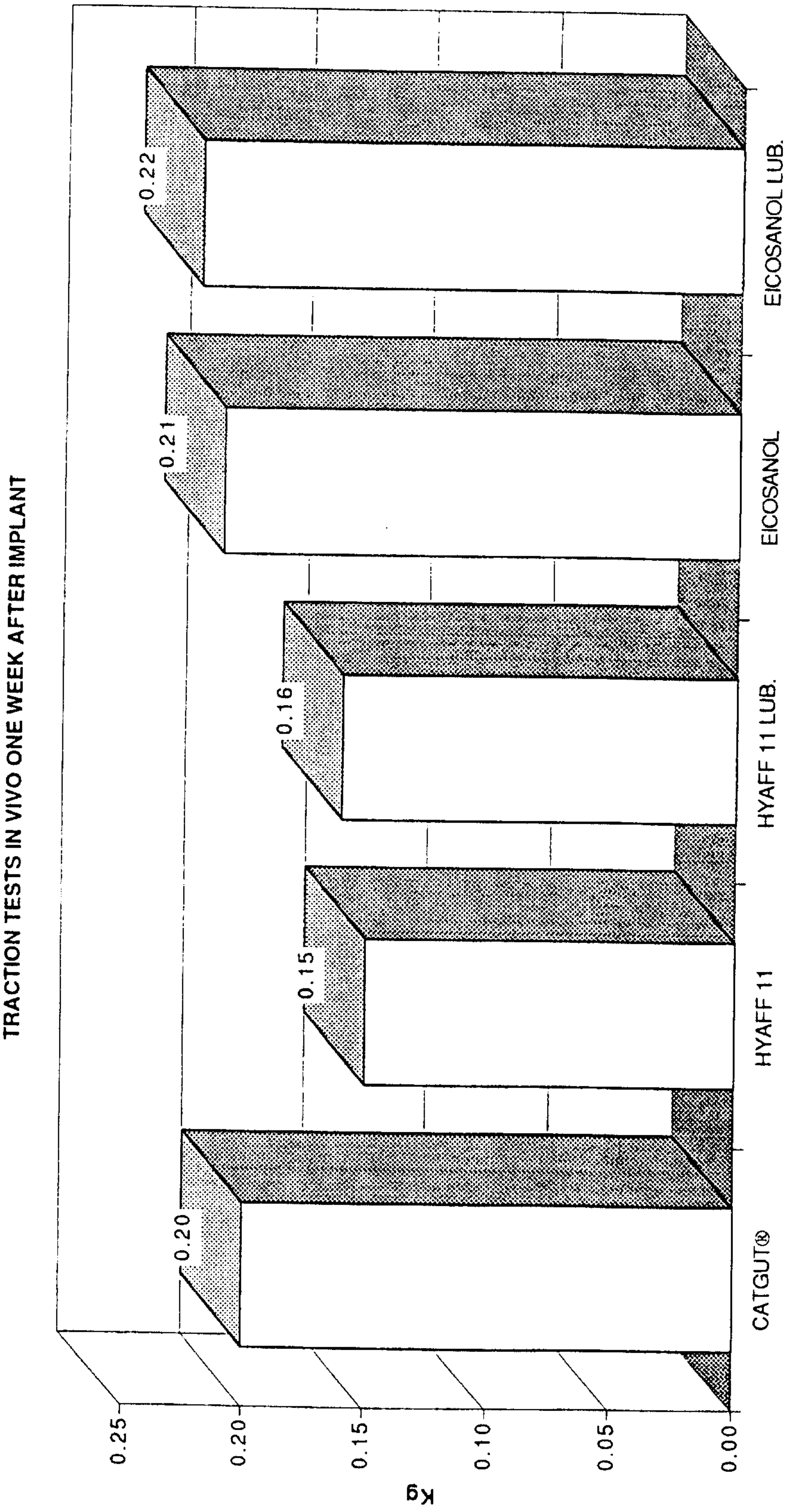

TRACTION TESTS IN VIVO ONE WEEK AFTER IMPLANT

Figure 7

TRACTION TESTS IN VIVO TWO WEEKS AFTER IMPLANT