656014

AUSTRALIA
PATENTS ACT 1990
NOTICE OF ENTITLEMENT

We, **Laevosan-Gesellschaft mbH,** the applicant/Nominated Person in respect of Application No. 22775/92 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to co-inventor, Ernst Nitsch be entitled to have his interest in the patent assigned to the Nominated Person, and because the Nominated Person derives title to the respective interest of the other co-inventors, Harald Förster and Fatima Asskali, by assignment.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this EIGHTEENTH day of JANUARY 1994

.....
a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1638737)

AU9222775

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(54) Title
METHOD OF PREPARING STARCH ESTERS FOR CLINICAL, IN PARTICULAR PARENTERAL, APPLICATIONS

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(56) Prior Art Documents
US 2363382
US 3639389
GB 1476057

(57) The acylation is carried out in the presence of an alkalising agent by which means acids which are formed at the same time are neutralised.

CLAIM

1. Process for the production of water-soluble, physiologically compatible starch esters, wherein a starch is converted by acid hydrolysis or enzyme hydrolysis into a partial hydrolysate with an average molecular weight Mw in the range 10000 to 500000 Daltons, this partial hydrolysate is acylated in aqueous solution with the anhydride or halogenide of an aliphatic monocarboxylic acid with 2 to 4 carbon atoms or the anhydride or mono-halogenide of an aliphatic dicarboxylic acid with 3 to 6 carbon atoms or mixtures thereof and an alkalisation agent up to a molar substitution in the range 0.1 to 1.0 mol/mol and the salts are removed from the reaction mixture obtained in this way and low molecular weight components are removed before and/or after the acylation.

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P 41 23 000.0 11. Juli 1991 (11.07.91) DE

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(81) Bestimmungsstaaten: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Veröffentlicht
Mit internationalem Recherchenbericht.

656014

(54) Title: METHOD OF PREPARING STARCH ESTERS FOR CLINICAL, IN PARTICULAR PARENTERAL, APPLICATIONS

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON STÄRKEESTERN FÜR KLINISCHE, INSBESONDERE PARENTERALE ANWENDUNG

(57) Abstract

In order to prepare physiologically tolerated water-soluble starch esters, the invention proposes that starch is converted by acid hydrolysis or enzymatic hydrolysis to a partially hydrolysed form with a mean molecular weight in the range from 10,000 to 500,000 Daltons. This partial hydrolysate is then acylated, in aqueous solution, with the anhydride or halide of an aliphatic monocarboxylic acid with 2 to 4 carbon atoms or an aliphatic dicarboxylic acid with 3 to 6 carbon atoms, or mixtures thereof, and an alkalinization agent, to give a product with a substitution ratio in the range from 0.1 to 1.0 mole/mole. Salts are removed from the resulting reaction mixture. The starch esters thus obtained are highly suited for clinical use, in particular parenteral administration and administration in the diet.

(57) Zusammenfassung

Zur Herstellung von wasserlöslichen, physiologisch verträglichen Stärkeestern wird Stärke durch Säurehydrolyse oder Enzymhydrolyse in ein Teilhydrolysat mit einem mittleren Molekulargewicht Mw im Bereich von 10000 bis 500000 Dalton überführt, dieses Teilhydrolsat in wässriger Lösung mit dem Anhydrid oder Halogenid einer aliphatischen Monocarbonsäure mit 2 bis 4 Kohlenstoffatomen oder einer aliphatischen Dicarbonsäure mit 3 bis 6 Kohlenstoffatomen oder Gemischen davon und einem Alkalisierungsmittel bis zu einer molaren Substitution im Bereich von 0,1 bis 1,0 Mol/Mol acyliert. Aus dem so erhaltenen Reaktionsgemisch werden die Salze entfernt. Die so erhältlichen Stärkeester sind sehr gut für klinische, insbesondere parenterale und diätetische Anwendungen geeignet.

Process for the production of starch esters for clinical, in particular parenteral use

D e s c r i p t i o n

The invention concerns a process for the production of water-soluble, physiologically compatible starch esters for clinical and in particular parenteral uses.

There is a great need for water-soluble biocompatible polymers for infusion solutions, as plasma substitutes, for haemodilution or in solutions for peritoneal dialysis as well as for tube feeding. In particular gelatins, gelatin derivatives, dextran and hydroxyethyl starch have previously been used for such purposes (cf. e.g. US-A-3937821; DE-A-3313600; "Römpp's Chemie Lexikon", Vol. 9, page 1509 and 1509).

At present the polysaccharides dextran and hydroxyethyl starch are mainly used for clinical applications, in particular for plasma substitute solutions. The primary disadvantage of dextran is that anaphylactic reactions can occur due to the presence of preformed antibodies, which make the use of this substance dangerous or complicate it by a compulsory pretreatment with a neutralizing low molecular hapten. Although direct side-effects were only seldom observed in a short-term direct administration of hydroxyethyl starch, the prolonged administration of hydroxyethyl starch is, however, very limited by its storage especially in reticuloendothelial tissue. Hydroxyethyl starch can only be slowly and incompletely degraded by endogenous enzymes because the etherification impedes attack by endogenous

glycosidases. Although it is not yet known with certainty whether this storage impairs the function of the reticuloendothelial system, the occurrence of itching for example as a side-effect which is observed when administering hydroxyethyl starch has been linked to this storage. Recently the use of starch esters with lower aliphatic mono or dicarboxylic acids, in particular of acetyl starch, has also been proposed which compared to the aforementioned substances have a major advantage in that they lack antigenicity and can be completely excreted or metabolized.

A polymer which is intended for clinical and in particular parenteral use must, apart from a good water-solubility, also meet the following requirements:

- The polymer solution should have a viscosity at the concentrations used therapeutically which is not higher than that of plasma;

- The substance should have a retention time in the organism which is adapted to the respective application and should be completely degradable after parenteral administration. This requirement can be accomodated in the case of acyl starches by means of the degree of esterification because the degradability by endogenous α-amylase slows down with increasing molar substitution.

- The substance should not be toxic, pyrogenic or antigenic.

The previously known starch esters do not meet some or all of these requirements.

For application in foods, acetyl starch of high viscosity is used with a maximum acetyl content of 2.5 % corresponding to a molar substitution (MS) of 0.064 mol/mol maximum. Such products are not suitable for clinical applications because of the pastiness of aqueous dispersions and because of their rapid degradation due to the low molar substitution. Acetyl starches of low viscosity with a low molecular weight are used to dress textiles and to size paper; such products are also unsuitable for clinical uses because of their low molar substitution, undefined distribution of molecular weight and low purity (for the state of the art cf. e.g. O.B. Wurzburg, Modified Starches, Properties and Uses, CRC Press Inc.; Boca Raton, Florida, 1986, page 55 to 74).

The object of the present invention is therefore to provide suitable water-soluble, physiologically compatible starch esters for clinical and in particular parenteral uses which avoid the aforementioned disadvantages of the products which have previously been used for such applications and which in particular meet all requirements that are required of polymers for clinical and in particular parenteral use. This object is achieved by the present invention.

The invention concerns a process for the production of water-soluble, physiologically compatible starch esters which is characterized in that a starch is converted by acid hydrolysis or enzyme hydrolysis into a partial hydrolysate with an average molecular weight Mw in the range 10000 to 500000 Daltons, this partial hydrolysate is acylated in aqueous solution with the anhydride or halogenide of an aliphatic monocarboxylic acid with 2 to 4 carbon atoms or of an aliphatic dicarboxylic acid with

the anhydride or mono-halogenide

3 to 6 carbon atoms or mixtures thereof and an alkalisation agent up to a molar substitution in the range 0.1 to 1.0 and the salts are removed from the reaction mixture obtained in this way and low molecular weight components are removed before and/or after the acylation.

A starch which is preferably used according to the invention is a starch which is composed of virtually amylose-free amylopectin that contains no more than 1 % by weight amylose. Preferred examples of a starch used according to the invention are wax corn, wax rice or wax sorghum starch.

A process for the production of acetyl starches is known from US-A 2,362,282 with which starch hydrolysates with a low dextrose equivalent value (D.E.) should be produced which are intended as adhesives. In this case a depolymerization and acetylation is carried out at the same time by heating in high-percentage acetic acid. This acid hydrolysis is difficult to control and the final product is not physiologically compatible due inter alia to its molecular weight which is too low.

GB-A-1 476 057 teaches the use of a starch derivative containing mixtures for the production of throat lozenges. In this case an amylopectin esterified with vinyl acetate is set forth as a starch derivative without details about production procedures, degree of substitution and molecular weight. Such a product is unsuitable for parenteral use.

Clear soluble, low substituted starch syrups are known from US-A-3 639 389 which are produced starting with starch hydrolysates with a D.E. value of less than 30.

Such products are unsuitable for parenteral uses due to their low molecular weights alone.

The molecular structure of amylopectin corresponds to a large extent to that of endogenous glycogen so that no antigenicity or toxicity would be expected. After cleavage of the acyl groups that can be readily hydrolysed by endogenous enzymes, the residual molecule is virtually indistinguishable from glycogen and is subjected to the same metabolism.

The partial degradation of the starch which occurs by the process according to the invention enables the viscosity of the solutions which are to be used therapeutically to be brought into the required range. The starch is preferably hydrolysed until the average molecular weight Mw is in the range 40000 to 250000 Daltons.

The hydrolysis can be carried out in a well-known manner by means of an acid hydrolysis or an enzyme hydrolysis. Strong mineral acids such as hydrochloric acid or sulphuric acid are preferably used for the acid hydrolysis. α-amylase is preferred as the enzyme for the enzyme hydrolysis. It is also possible to combine an acid hydrolysis with an enzyme hydrolysis and namely in any desired order.

The degree of hydrolysis can be easily monitored by measuring the viscosity of a sample diluted with water in order to thereby determine the desired degradation and end of the hydrolysis reaction.

In the step in the procedure according to the invention which follows the hydrolytic degradation, the partially hydrolysed starch is acylated in aqueous solution with the anhydride or halogenide of an aliphatic monocarboxylic acid with 2 to 4 carbon atoms or of an aliphatic dicarboxylic acid with 3 to 6 carbon atoms up to a molar substitution in the range 0.1 to 1.0 mol/mol, a range of 0.3 to 0.7 mol/mol being preferred. The anhydride or halogenide which is used for this is derived from an aliphatic monocarboxylic acid with 2 to 4 carbon acids or from an aliphatic dicarboxylic acid with 3 to 6 carbon atoms. Aliphatic monocarboxylic acids are for example butyric acid, isobutyric acid, propionic acid, and in particular acetic acid. The aliphatic dicarboxylic acids with 3 to 6 carbon atoms used according to the invention can be saturated or unsaturated; they are preferably derived from α-dicarboxylic acids and are for example glutaric acid, adipic acid and in particular succininic acid and maleic acid. The chlorides are preferred as halogenides, but bromides and iodides are also well suited. According to the invention it is particularly preferable to use acetyl chloride and in particular acetic anhydride.

It is also possible to use a mixture of two or several of the mono or dicarboxylic acids according to the invention.

The acylation is carried out in the presence of an alkalising agent by which means acids which are formed at the same time are neutralised. Alkaline and alkaline earth hydroxides, carbonates or oxides are preferably used as alkalising agents and in particular sodium hydroxide, sodium carbonate, calcium hydroxide and/or

magnesium oxide.

The reaction conditions for the acylation with the acid anhydride or the acid halogenide correspond to the usual conditions for such acylations; the reaction is preferably carried out at room temperature while stirring vigorously.

The salts are preferably removed from the reaction mixture obtained after the acylation by means of dialysis, ultrafiltration (diafiltration) or ion exchange. It is also possible to use two or several consecutive desalting procedures which may be identical or different.

Depending on the intended use of the starch esters according to the invention, it may also be expedient to also remove, at least to a substantial extent other low molecular weight components apart from the salts, such as low molecular weight degradation products of the initial starch. This can be carried out before and/or after the acylation step by e.g. dialysis and in particular by ultrafiltration (diafiltration) in which membranes with an appropriate exclusion limit can be selected depending on the intended use. It is expedient to remove the low molecular weight components together with the salts after the acylation. Depending on the desired degree of removal, it is possible to carry out two or several consecutive purification steps.

The reaction mixture obtained after the hydrolysis (partial hydrolysate) and/or in particular the reaction mixture obtained after removing the salts and, if desired, other low molecular weight components is preferably

subjected to sterilization by filtration before further processing or use.

The starch ester solution obtained after removing the salts and, if desired other low molecular weight components, can be used directly as such; the starch ester solution is preferably converted into a dried product for better handling and shelf-life. This is carried out in particular by gentle concentration of the solution in a vacuum and subsequent drying in a vacuum. It is, however, also possible to convert the starch ester solution into a freeze-dried product by lyophilization.

Due to their properties, in particular their good water-solubility and physiological compatibility, the starch esters obtainable by the process according to the invention are very well suited for clinical and in particular parenteral uses.

Starch esters according to the invention are in particular used for the production of pharmaceutical compositions for peritoneal dialysis as well as for the production of blood plasma substitutes (cf. the German patent application P 41 22 999.1 "Metabolizable plasma substitute" and the German patent application P 41 23 001.9 "Pharmaceutical composition for peritoneal dialysis" by the same applicant and with the same application date).

The following examples are intended to elucidate the invention in more detail. If not stated otherwise the percentages stated above and below refer to % by weight and parts refer to parts by weight. Details of temperatures refer to the celsius scale.

E x a m p l e s

Example 1

Production of a partial hydrolysate from wax corn starch (Mw ca. 200000)

4000 g wax corn starch with a water content of 10.0 %, corresponding to 3600 g anhydrous starch, was suspended in 12.5 kg desalted water, then 3.85 g calcium chloride dihydrate and 1 g α-amylase (Termamyl 60 L; NOVO Co. Copenhagen) was added and quickly heated to 95°C while stirring. The starch dissolved without forming a highly viscous phase. It was kept at 95°C until a sample diluted to 20 % with water had a relative viscosity of 1.5 at 20°C compared to water. The degradation was stopped by addition of hydrochloric acid until the pH value was 3.0; the reaction mixture was then kept at 95°C for a further 10 minutes, subsequently cooled to room temperature, adjusted to pH = 5.5 with sodium hydroxide solution and filtered over sterile layers. The light-yellow coloured degraded starch solution, 15.6 kg, with a dry solids content of 22.4 % was subjected to diafiltration over an ultrafiltration membrane with an exclusion limit of 30000 Daltons in order to remove low molecular weight components in which 10.2 kg of a 19.6 % solution containing 2.0 kg degraded amylopectin was obtained. Aliquots of this solution were used in the following examples 2 and 3.

Example 2

Production of an acetyl starch (Mw ca. 200000, MS ca. 0.35)

40.8 g (0.40 mol) acetic anhydride was added constantly over a period of one hour to 826.5 g of the degraded starch solution obtained according to example 1 which contained 162 g dry weight (1 mol $CH_6H_{10}O_5$) while stirring vigorously with a magnetic stirrer and at the same time 2 N sodium hydroxide solution was added by means of pH-stat circuit to maintain a pH value between 8.0 to 8.5. 225 ml (0.45 mol) was consumed for this.

The solution obtained in this way was diafiltered over an ultrafiltration membrane (exclusion limit 30000 Daltons) until the conductivity was < 1 micro S/cm. After addition of 1.6 g active charcoal, the solution was filtered over sterile layers, concentrated in a vacuum to form a thick syrup and afterwards oven-dried in a vacuum to yield a brittle, white blistered mass. The yield was 165.0 g after grinding. The molar substitution was determined as being 0.355 mol/mol. The substance proved to be pyrogen-free when tested on rabbits according to Ph.Eur. and was tolerated by the animals without reaction.

Example 3

Production of an acetyl starch (Mw ca. 200000, MS ca. 0.50)

64.85 g (0.635 mol) acetic anhydride was added

constantly over a period of two hours to 826.5 g of a degraded starch solution obtained according to example 1 containing 162 g dry weight (1 mol $CH_6H_{10}O_5$) while stirring vigorously with a magnetic stirrer and at the same time 2 N sodium hydroxide solution was added by means of a pH-stat circuit to maintain a pH value between 8.0 to 8.5. 500 ml (1.0 mol) was consumed for this.

The solution obtained in this way was diafiltered over an ultrafiltration membrane (exclusion limit 30000 Daltons) until the conductivity was < 1 micro S/cm. After addition of 1.6 g active charcoal, the solution was filtered over sterile layers, concentrated in a vacuum to form a thick syrup and afterwards oven-dried in a vacuum to yield a brittle, white blistered mass. The yield was 166.4 g after grinding. The molar substitution was determined as being 0.502 mol/mol. The substance proved to be pyrogen-free when tested on rabbits according to Ph.Eur. and was tolerated by the animals without reaction.

Application example

Production of plasma substitute solutions

An acetyl starch according to the invention with an average molecular weight (Mw) of ca. 200000 Daltons and a degree of substitution of 0.3 or 0.5 was used as the starch ester.

The following plasma substitute solutions were prepared from this:

1. Acetyl starch solution at a concentration of 3, 6 and 10 % by weight in physiological saline solution (0.9 % by weight).

2. Acetyl starch solution at a concentration of 6 % by weight in 2.5 % by weight glycerol solution (electrolyte-free plasma substitute solution)

Investigations on biodegradability

The acetyl starch solutions prepared as described above with a concentration of 3, 6 and 10 % by weight acetyl starch (degree of substitution 0.3 or 0.5) in physiological saline solution were administered intraveneously into rats (18 ml in 3 hours).

The infusions were very well tolerated and no direct side-effects were detected. Immediately after completion of the infusions dose-dependent blood levels of acetyl starch were present (6 to 25 mg/ml). These blood levels were comparable to those which were obtained using hydroxyethyl starch solutions (HES 200/0.5; Mw ca. 200000 Daltons, molar substitution 0.5 mol). Even 3 hours after completion of the infusion acetyl starch was still detectable in the blood of the animals (1.0 to 10 mg/ml); these amounts also corresponded to the amounts which were obtained under comparable conditions with the hydroxyethyl starch solution (HES 200/0.5). However, 24 hours after completion of the infusion no acetyl starch could be detected in the blood of the treated animals.

Fig. 1 shows the serum content (in mg/ml) after a 3 hour infusion which was determined immediately after the infusion was completed (A to E) and 3 hours after

completion of the infusion (F, G, H).

Fig. 2 shows the content of hydrocolloid in the kidney (in mg/g) which was determined immediately after the infusion was completed (B, C, D, E and NaCl), 3 hours after completion of the infusion (F, G) and 18 to 24 hours after completion of the infusion (I, J, K, L).

Fig. 3 shows the results corresponding to Fig. 2 for the lung.

The data A to L in Fig. 1 to 3 refer to the following plasma substitute solutions:

A - 3 % acetyl starch; B - 6 % acetyl starch; C - 10 % acetyl starch; D - 6 % HES 200/0.5; E - 10 % HES 200/0.5; F - 6 % acetyl starch; G - 10 % acetyl starch; H - 3 % acetyl starch; I - 6 % acetyl starch; J - 10 % acetyl starch; K - 6 % HES 200/0.5; L - 10 % HES 200/0.5. NaCl = sodium chloride.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Process for the production of water-soluble, physiologically compatible starch esters, wherein a starch is converted by acid hydrolysis or enzyme hydrolysis into a partial hydrolysate with an average molecular weight Mw in the range 10000 to 500000 Daltons, this partial hydrolysate is acylated in aqueous solution with the anhydride or halogenide of an aliphatic monocarboxylic acid with 2 to 4 carbon atoms or the anhydride or mono-halogenide of an aliphatic dicarboxylic acid with 3 to 6 carbon atoms or mixtures thereof and an alkalisation agent up to a molar substitution in the range 0.1 to 1.0 mol/mol and the salts are removed from the reaction mixture obtained in this way and low molecular weight components are removed before and/or after the acylation.

2. Process as claimed in claim 1, wherein the starch used is composed of virtually amylose-free amylopectin.

3. Process as claimed in claim 1 or 2, wherein the starch is wax corn, wax rice or wax sorghum starch.

4. Process as claimed in any one of the claims 1 to 3, wherein the starch is hydrolysed until the average molecular weight Mw is in the range 40000 to 250000 Daltons.

5. Process as claimed in any one of the claims 1 to 4, wherein α-amylase is used for enzyme hydrolysis.

6. Process as claimed in any one of the claims 1 to 5, wherein it is acylated until the molar substitution is 0.3 to 0.7 mol/mol.

7. Process as claimed in any one of the claims 1 to 6, wherein an anhydride or halogenide of acetic acid is used as the anhydride or halogenide of a monocarboxylic acid.

8. Process as claimed in any one of the claims 1 to 6, wherein an anhydride or halogenide of succinic acid or maleic acid is used as the anhydride or halogenide of a dicarboxylic acid.

9. Process as claimed in any one of the claims 1 to 8, wherein sodium hydroxide, sodium carbonate, calcium hydroxide or magnesium hydroxide is used as the alkalisation agent.

10. Process as claimed in any one of the claims 1 to 9, wherein salts and/or low molecular weight components are removed by dialysis, ultrafiltration and/or ion exchange.

11. Starch esters obtained by a process as claimed in any one of the claims 1 to 10.

12. Use of a starch ester as claimed in claim 11 for the production of pharmaceutical compositions for clinical and in particular parenteral use or of dietary formulations.

13. Processes for the production of water-soluble, physiologically compatible starch esters, starch esters obtained by said processes or uses of said starch esters, substantially as hereinbefore described with reference to the Examples.

DATED this 4th day of November, 1994
Laevosan-Gesellschaft mbH
By Its Patent Attorneys
DAVIES COLLISON CAVE

A b s t r a c t

For the production of water-soluble, physiologically compatible starch esters, starch is converted by acid hydrolysis or enzyme hydrolysis into a partial hydrolysate with an average molecular weight Mw in the range 10000 to 500000 Daltons, this partial hydrolysate is acylated in aqueous solution with the anhydride or halogenide of an aliphatic monocarboxylic acid with 2 to 4 carbon atoms or an aliphatic dicarboxylic acid with 3 to 6 carbon atoms or mixtures thereof and an alkalisation agent up to a molar substitution in the range 0.1 to 1.0 mol/mol. The salts are removed from the reaction mixture obtained in this way. The starch esters that can be obtained in this way are very well suited for clinical and especially for parenteral and dietary applications.

Fig.1

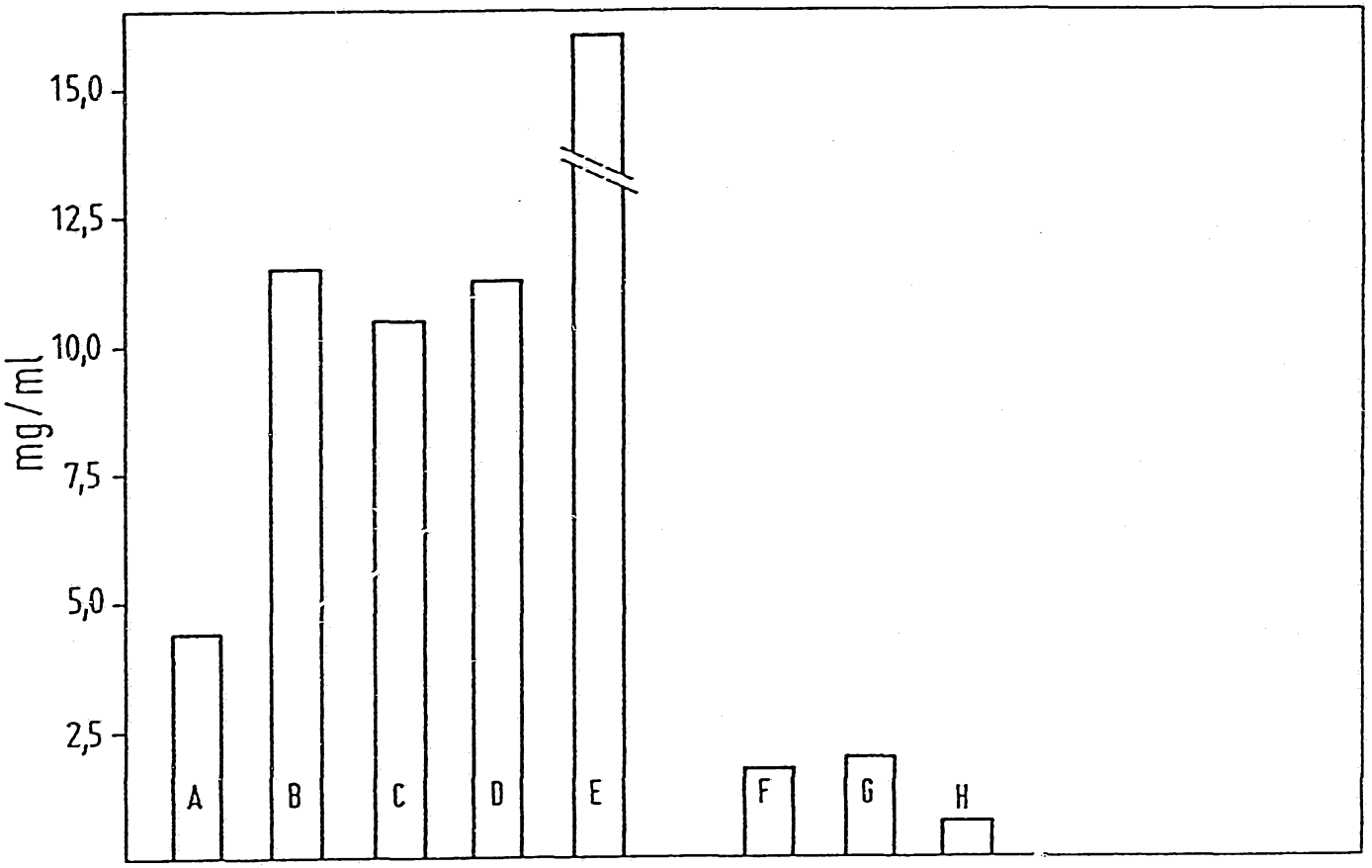


Fig. 2

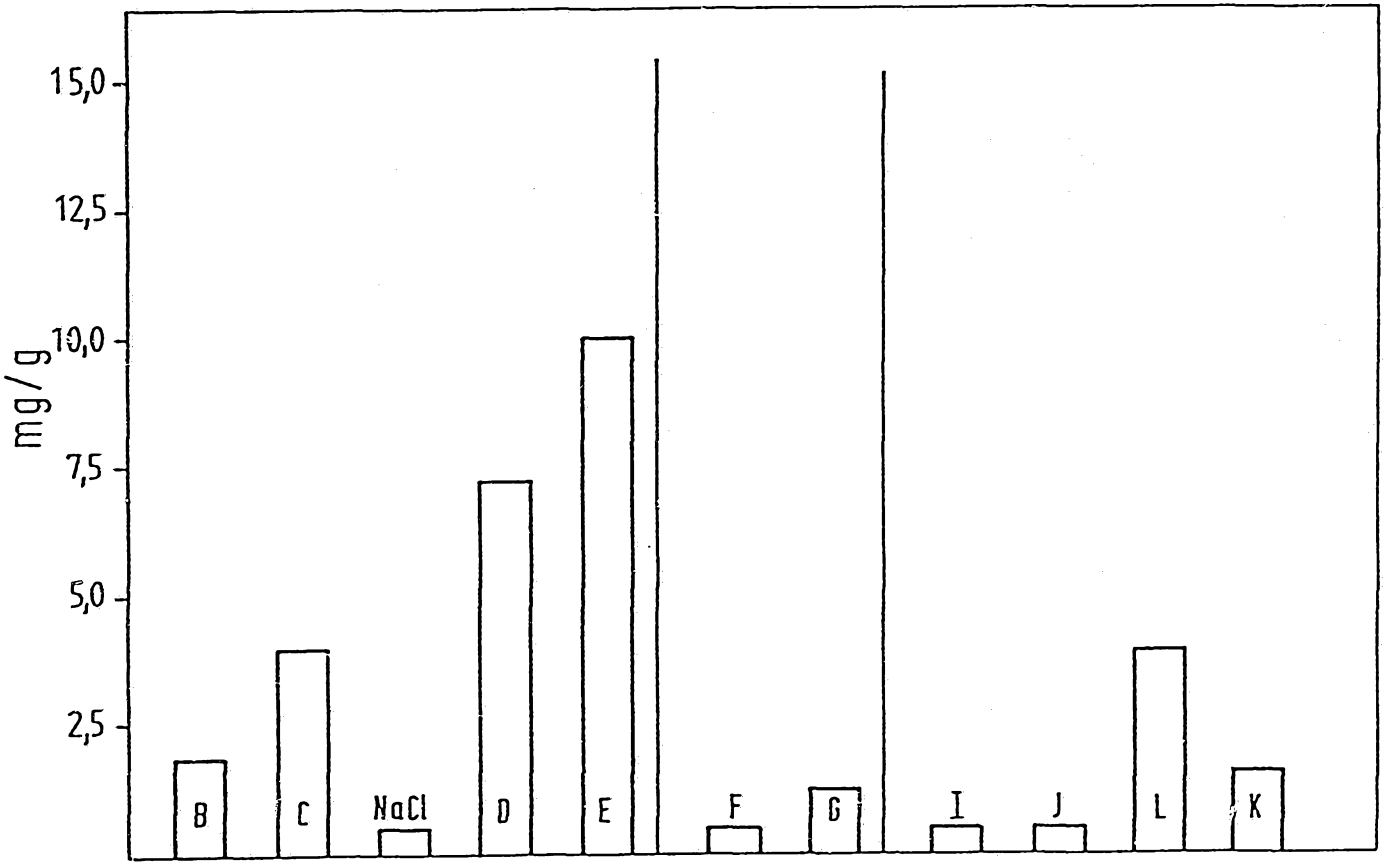
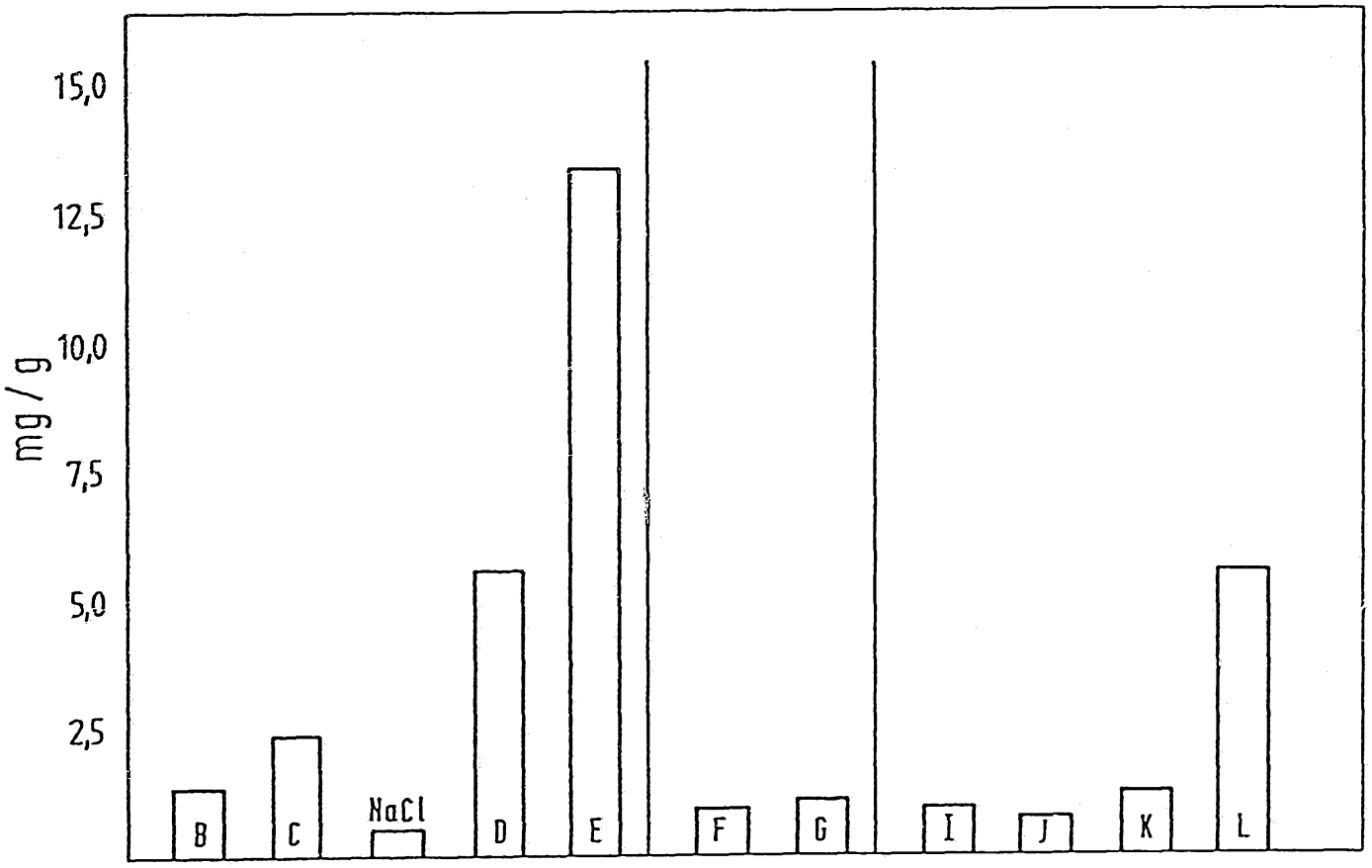


Fig. 3



2275192

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 92/01553

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.^{5} C 08 B 35/02; C 08 B 31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl.^{5} C 08 B; A 61 K; C 08 L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 2362282 (WESLEY N. LINDSAY), 7 November 1944 see column 1, line 45 - line 54, see column 2, line 22 - line 27 --	1-12
X	GB, A, 1476057 (UNICLIFFE LIMITED) 10 June 1977 see page 1, line 13 - line 26 --	1-12
X	US, A, 3639389 (GLENN ARDEN HULL) 1st February 1972 see column 4, line 50 - line 67, see example I ----------	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 1992 (02.10.92)	12 October 1992 (12.10.92)
Name and mailing address of the ISA/ European Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9201553
SA 61928

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-2362282		None	
GB-A-1476057	10-06-77	None	
US-A-3639389	01-02-72	None	

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen PCT/EP 92/01553

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)[6]

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

Int.Kl. 5 C08B35/02; C08B31/04

II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff [7]

Klassifikationssytem	Klassifikationssymbole
Int.Kl. 5	C08B ; A61K ; C08L

Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen [8]

III. EINSCHLAGIGE VERÖFFENTLICHUNGEN [9]

Art.°	Kennzeichnung der Veröffentlichung [11], soweit erforderlich unter Angabe der maßgeblichen Teile [12]	Betr. Anspruch Nr.[13]
X	US,A,2 362 282 (WESLEY N. LINDSAY) 7. November 1944 siehe Spalte 1, Zeile 45 - Zeile 54 siehe Spalte 2, Zeile 22 - Zeile 27 ---	1-12
X	GB,A,1 476 057 (UNICLIFFE LIMITED) 10. Juni 1977 siehe Seite 1, Zeile 13 - Zeile 26 ---	1-12
X	US,A,3 639 389 (GLENN ARDEN HULL) 1. Februar 1972 siehe Spalte 4, Zeile 50 - Zeile 67 siehe Beispiel I -----	1-12

° Besondere Kategorien von angegebenen Veröffentlichungen [10] :

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

IV. BESCHEINIGUNG

Datum des Abschlusses der Internationalen Recherche	Absendedatum des Internationalen Recherchenberichts
02.OKTOBER 1992	12. 10. 92
Internationale Recherchenbehörde	**Unterschrift des bevollmächtigten Bediensteten**
EUROPAISCHES PATENTAMT	LENSEN H.W.M.

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

EP 9201553
SA 61928

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 02/10/92
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
US-A-2362282		Keine	
GB-A-1476057	10-06-77	Keine	
US-A-3639389	01-02-72	Keine	

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82