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(12) (19) (CA) **Demande-Application**

(21) (A1) **2,305,764**
(86) 1997/10/09
(87) 1999/04/22

(72) BARTOLI, ENZO, IT
(72) PALMIERI, BENIAMINO, IT
(72) MEDICI, ALESSANDRO, IT
(71) ICE S.R.L., IT
(71) PALMIERI, BENIAMINO, IT
(71) MEDICI, ALESSANDRO, IT

(51) Int.Cl.[6] C07J 9/00, A61K 31/575, C07J 51/00, C07J 41/00

(54) **SELS D'ACIDES BILIAIRES DE METAUX COMPORTANT UNE ACTION PHYSIOLOGIQUE, ET UTILISATION DE CEUX-CI EN THERAPIE**

(54) **BILE ACID SALTS OF METALS WITH PHYSIOLOGICAL ACTION AND THE USE THEREOF IN THERAPY**

(57) L'invention a trait à des sels d'acides biliaires de métaux qui présentent un intérêt thérapeutique, ainsi qu'à des compositions pharmaceutiques et vétérinaires contenant lesdits sels.

(57) The present invention relates to bile acid metal salts of therapeutical interest, as well as to pharmaceutical and veterinary compositions containing said salts.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07J 9/00, A61K 31/575, C07J 41/00, 51/00

A1

(11) International Publication Number: **WO 99/19342**

(43) International Publication Date: 22 April 1999 (22.04.99)

(21) International Application Number: PCT/EP97/05555

(22) International Filing Date: 9 October 1997 (09.10.97)

(71) Applicant *(for all designated States except US)*: ICE S.R.L. [IT/IT]; Via Sicilia, 8/10, I–42100 Reggio Emilia (IT).

(71)(72) Applicants and Inventors: PALMIERI, Beniamino [IT/IT]; Via Bisi, 125, I–41100 Modena (IT). MEDICI, Alessandro [IT/IT]; Via Libia, 10, I–40138 Bologna (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BARTOLI, Enzo [IT/IT]; Via Sicilia, 8/10, I–42100 Reggio Emilia (IT).

(74) Agent: MINOJA, Fabrizio; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I–20122 Milano (IT).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BILE ACID SALTS OF METALS WITH PHYSIOLOGICAL ACTION AND THE USE THEREOF IN THERAPY

(57) Abstract

The present invention relates to bile acid metal salts of therapeutical interest, as well as to pharmaceutical and veterinary compositions containing said salts.

WO 99/19342 PCT/EP97/05555

BILE ACID SALTS OF METALS WITH PHYSIOLOGICAL ACTION AND THE USE THEREOF IN THERAPY

The present invention relates to therapeutically interesting bile acid metal salts.

The invention also relates to pharmaceutical and veterinary compositions containing said salts.

A number of metal cations exist playing a physiological role: in addition to iron, which is a component of hemoglobin, varying amounts of zinc, copper, selenium, molybdenum, cobalt, manganese etc., known as oligoelements, are necessary for a correct function of the enzyme and physiological systems. These elements are usually absorbed through the diet, but pathological or alimentary deficiency conditions exist in which a pharmacological supply or the dietary supplement through the administration of suitable salts or complexes is desired.

The problem is particularly felt in the case of iron, the administration of which is often required for the treatment of iron-deficiency anemias. For this purpose, salts such as ferrous gluconate or sulfate or complexes of iron with succinylated proteins are used at present.

Now it has been found that the above cited bile acid metal salts provide a high, gradual absorption of the metal cation which can selectively be carried into the entero-hepatic circle.

The use of the bile acids as carriers for iron or for oligoelements turned out to be particularly advantageous and allowed to overcome some of the drawbacks affecting the compounds of the prior art.

Bile acids, in fact, acting as intestinal barrier permeation factors, provide a higher bioavailability also thanks to their recycle effect through the entero-hepatic circle, thereby assuring a gradual absorption kinetics. Moreover, particularly in the case of the iron salts, the typical side-effects of the oral administration of these compounds, such as constipation, gastroenteral intolerance, meteorism, epigastralgias, are avoided.

The salts of the invention can be prepared according to conventional methods, reacting natural bile acids or the derivatives thereof with metal hydroxides, or by interchange reactions between suitable metal salts and bile acid alkali or alkaline-earth salts.

Examples of natural bile acids comprise cholic, deoxycholic, chenodeoxycholic, chenocholic, ursocholic, ursodeoxycholic, hyodeoxycholic acids and the corresponding tauro- and glyco- conjugates.

The natural bile acids can optionally be derivatized introducing further salifiable acid groups, for example by reaction with anhydrides of di- or poly-carboxylic acids, such as succinic, glutaric, cyclohexanedicarboxylic acids.

Some of said derivatives are known and can anyway be prepared according to conventional methods, such as those described in Italian Patent n. 1.163.090.

A different approach is the ketalization of the keto groups present in the bile acid molecule with tartaric acid, and of hyocholic acid with ketomalonic acid.

The presence of more salifiable groups per bile

acid molecule provides an increase in the metal cation/bile acid molar ratio, when this is desirable for therapeutical and application purposes.

Natural or semisynthetic bile acids can be salified according to the invention with metals selected from the group consisting of iron (II), iron (III), copper (I), copper (II), zinc, cobalt, molybdenum, platinum, gold, manganese, vanadium, selenium, tin, nickel.

Particularly preferred are ferrous or ferric salts, particularly the ferric ones, which can be used for the treatment of iron deficiencies in man and animals.

For the envisaged therapeutical uses or for further uses, the salts of the invention can be formulated in pharmaceutical compositions, according to conventional techniques and excipients such as those described in Remington's Pharmaceutical Sciences Handbook, Mack. Pub., N.Y., U.S.A.

Examples of said compositions comprise capsules, tablets, syrups or drinkable solutions, gastric and/or controlled release forms and the like. The daily dosage will depend of course on the type of cation: in the case of iron, the salts of the invention can be administered in doses varying from 100 mg to 3 g, one to four times daily.

The salts of the invention can moreover be present in the composition of dietetic or alimentary formulations for the human or veterinary use, optionally in combination with other components with a complementary or anyway useful activity.

The following examples further illustrate the invention.

EXAMPLE 1

Preparation of bile acid iron (II) salts

PREPARATION

10 g of acid are dissolved in 7.5 volumes of water with the minimum amount of sodium hydroxide (= 10%, 20% for the emisuccinate), at pH 8.

When dissolution is complete, the mixture is added at 35°C, under stirring, with a $FeCl_3$ 6 H_2O aqueous solution previously prepared dissolving 2.42 g (stoichiometric + 10% excess to cholic or dehydrocholic acid), 2.53 g (stoichiometric + 10% excess to deoxy cheno and ursodeoxy acids), or 5.02 g (stoichiometric + 10% excess to emisuccinate) of ferric salt slowly dissolved in 25 ml of water.

The mixture is stirred to complete precipitation, then the precipitate is washed until chlorides disappear. Yield: above 95%.

In the following, the characteristics of the obtained salts are reported.

Salt	M.p.	Iron content
Ferric cholate ferric (3α, 7α, 12α trihydroxide 5β-cholanate)	237-239° C	4.07-4.67
Ferric deoxycholate ferric (3α, 12α dihydroxy-5β-cholanate)	218-219°C	4.24-4.84
Ferric dehydrocholate iron (3, 7, 12, 5β triketocholanate)	216-218°C	4.13-4.73

Ferric chenodeoxycholate ferric (3α, 7α-dihydroxy-5β-cholanate)	214-218°C	4.24-4.84
Ferric ursodeoxycholic ferric (3α, 7α-dihydroxy-5-β-cholanate)	200°C	4.24-4.84
Ferric hyodeoxycholate ferric (3α, 6α-dihydroxy-5-β	193°C	4.24-4.84
Disuccinyl ursodeoxy-cholate (ferric bio-emisuccinate 3α, 7α-dihydroxy-5β- cholanate)	268-270°C	8.05-9.25

EXAMPLE 2

Fig. 1 and 2 show the results of serum Fe obtained after administration of 19.2 mg Fe/day in the form of ferric ursodeoxycholate to two Fe-deficient patients.

CLAIMS

1 Bile acid salts with metal selected from the group consisting of iron (III), copper (I), copper (II), zinc, cobalt, molybdenum, platinum, gold, manganese, vanadium, selenium, tin, nickel.

2. Salts according to claim 1, wherein the metal is iron (III).

3. Salts according to the claims 1-2, wherein the bile acid is selected from the group consisting of cholic, deoxycholic, chenodeoxycholic, chenocholic, ursocholic, ursodeoxycholic, hyodeoxycholic acids and the corresponding tauro- and glyco-conjugates.

4. Salts according to claims 1-3, derivatized with further salifiable groups.

5. Salts according to claim 4, wherein said salifiable groups are selected from di- or poly-carboxylic acids, preferably succinic, glutaric, cyclohexanedicarboxylic acids.

6. Salts according to claims 1-3, wherein any keto groups are ketalized with tartaric acid.

7. The use of the salts of claims 1-6 or of bile acid ferrous salts, for the preparation of a medicament supplying oligoelements to the entero-hepatic circle.

8. The use of a salt of iron of claims 1-6 for the preparation of a medicament for the iron therapy.

9. Pharmaceutical compositions containing an effective amount of at least one salt of claims 1-6 as active ingredient, in admixture with conventional carriers and excipients.

AMENDED SHEET

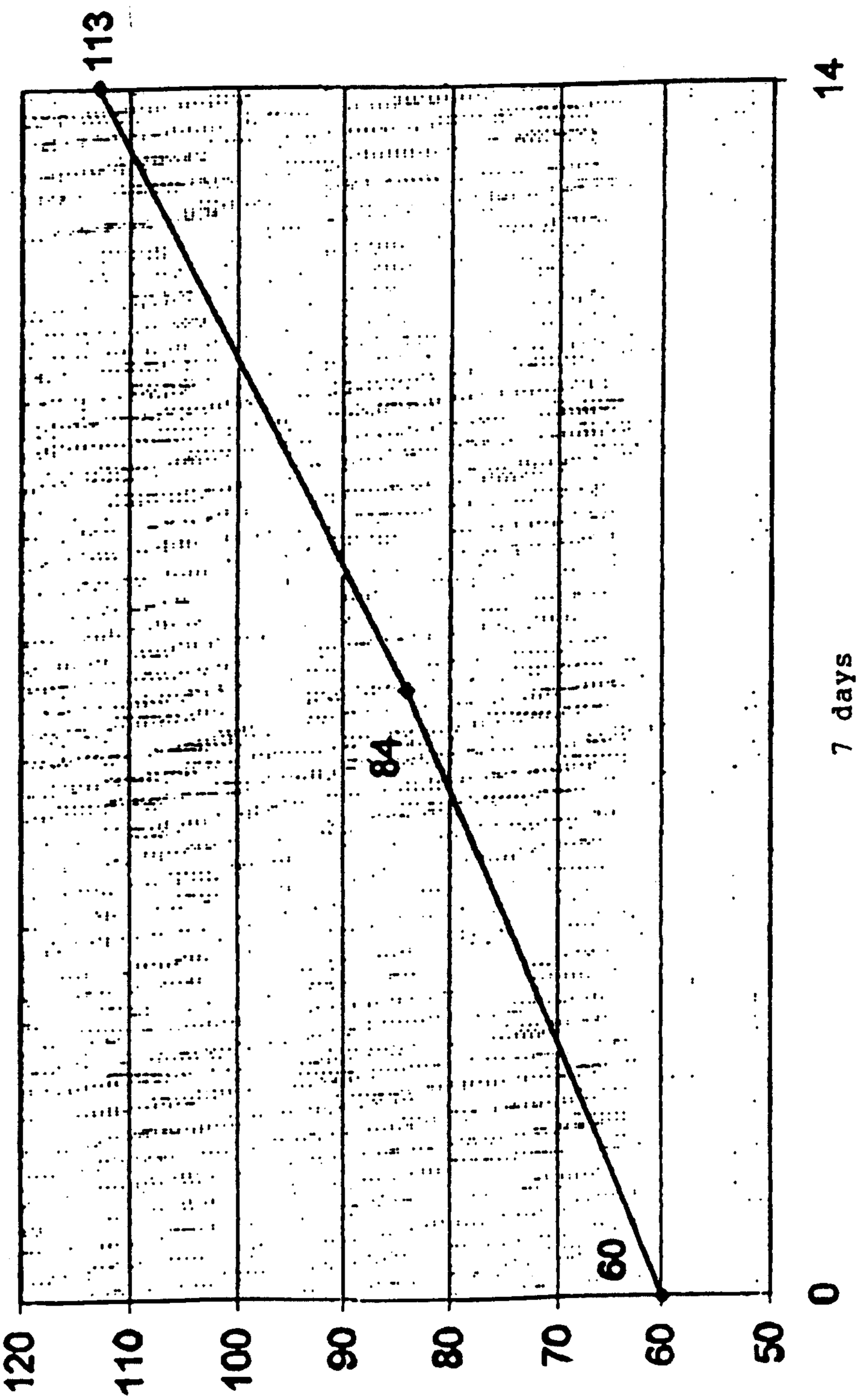

FIG. 1

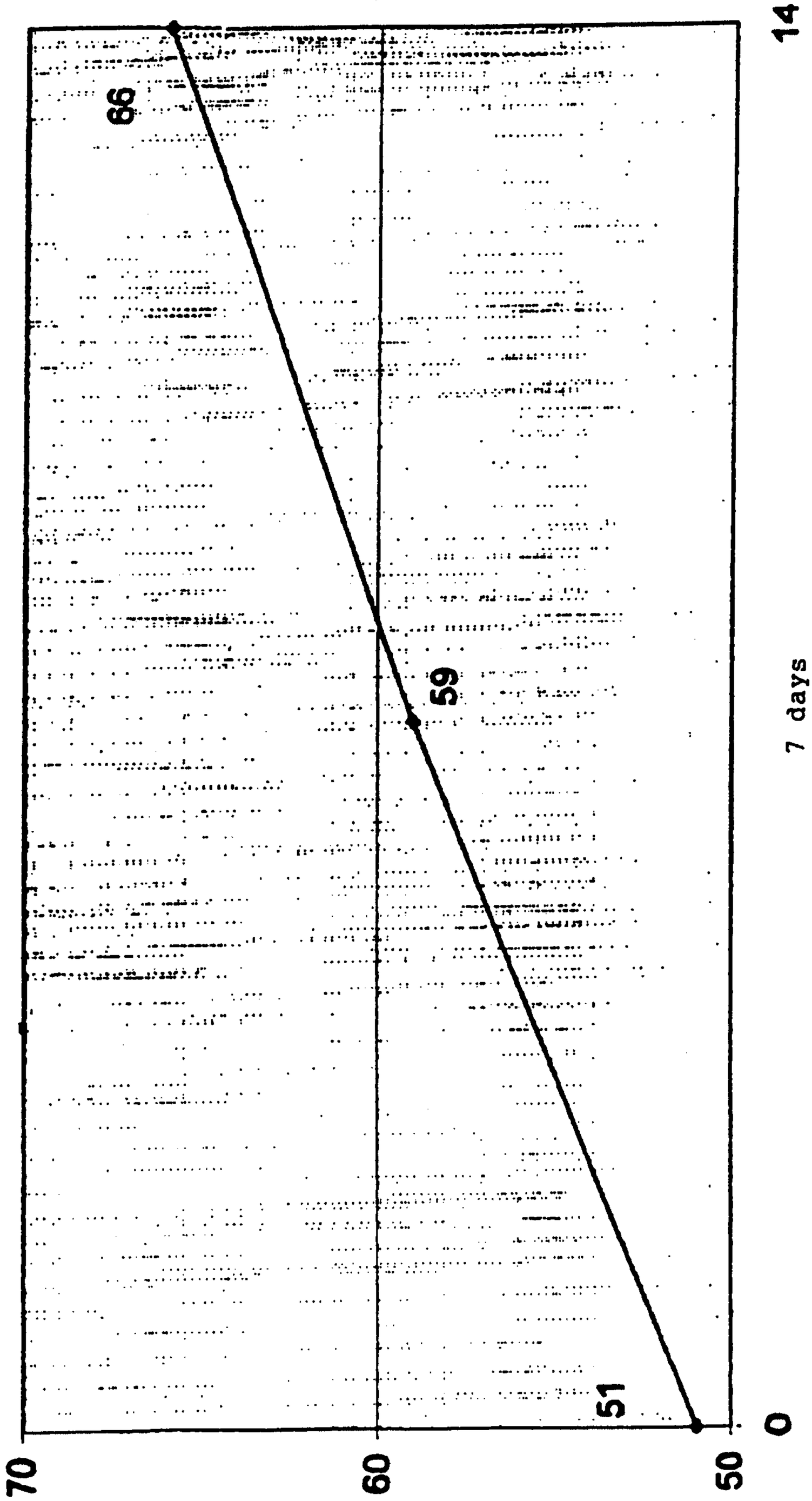

FIG. 2