



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>5</sup> :</b>  <b>A61K 9/18, 9/22</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 92/10171</b>  <b>(43) International Publication Date:</b> 25 June 1992 (25.06.92)
<b>(21) International Application Number:</b> PCT/SE91/00814 <b>(22) International Filing Date:</b> 3 December 1991 (03.12.91)  <b>(30) Priority data:</b> 9003903-3                      7 December 1990 (07.12.90)    SE  <b>(71) Applicant:</b> AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE).  <b>(72) Inventors:</b> LINDSTEDT, Bengt ; Torsgatan 29, S-431 38 Mölndal (SE). LUNDBERG, Per, Johan ; Dalhemsgatan 14, S-431 67 Mölndal (SE).  <b>(74) Agents:</b> LINDEROTH, Margareta et al.; AB Astra, Patent Department, S-151 85 Södertälje (SE).	<b>(81) Designated States:</b> AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU <sup>+</sup> , TD (OAPI patent), TG (OAPI patent).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> NEW PHARMACEUTICAL FORMULATIONS CONTAINING A PHARMACOLOGICALLY ACTIVE IONIZABLE SUBSTANCE AS WELL AS PROCESS FOR THE PREPARATION THEREOF		
<b>(57) Abstract</b>  <p>A preparation of a pharmacologically active ionizable substance, wherein active substance is ionically complexed to an ion-exchanger resin, which is embedded in a hydrophilic eroding matrix as well as a process for the manufacture thereof.</p>		

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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New pharmaceutical formulations containing a pharmacologically active ionizable substance as well as process for the preparation thereof

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Field of the invention

The present invention is directed to pharmaceutical formulations and their manufacture. One or more pharmacologically active substances are incorporated into the new formulations in order to be released over a desired period of time and, at the same time the dependence of the release rate on the fraction substance remaining in the formulation, is minimized.

Background of the invention

Pharmaceutical preparations based on eroding, hydrophilic matrices, showing extended release properties, have been described for pharmacologically active substances of low and high water solubility. The release may be described by a simple exponential function,

$$25 \quad M(t)/M(\infty) = k \cdot t^n \quad (1)$$

where n reflects the basic kinetics of the release (Ritger and Peppas, J. Contr. Rel. 5 (1987) 23-26). The most beneficial situation is when the release rate is totally independent of the fraction substance remaining in the formulation that is n=1.

Active substances showing low water solubility have successfully been formulated into hydrophilic, eroding matrices. This has been described in US 4 803 081, which shows favourable release kinetics. The same technique applied on substances of higher water solubility, such as

metoprolol succinate, do not give the same beneficial release kinetics. This has limited the medical usefulness of this pharmaceutical principle.

5 Attempts have been made to improve the release kinetics of the hydrophilic eroding matrix, by using special geometrical arrangements, or introducing a gradient in drug concentration, of the formulations (P.I.Lee, Proc. Int. Symp. Contr. Rel. Bioact. Matr., 15 (1988) 97-98). It has  
10 also been proposed to restrict the access of water to the eroding matrix by applying coatings on selected surfaces, which raised the kinetic exponent  $n$  in Equation 1 (P.Colombo et al Int J Pharm., 63 (1990) 43-48). Probably none of these concepts has reached the open market, as the  
15 complicated manufacturing processes will make the products comparably expensive.

The technique to complex pharmacologically active substances to ionizable, crosslinked polymer particles  
20 (ion-exchange resins) is well known (A.T.Florence and D. Attwood, Physiochemical Principles of Pharmacy, Macmillan Press, London, 1982, 297-300, GB Pat 907,021 (1962)). The release of active substance can be controlled by varying the crosslinking density and particle size of the resin.  
25 The release rate is, however, depending on the fraction substance remaining in the particles. The complex has also been coated to further reduce the release rate (US Patent 4,221,778 (1980)). To reach an improvement in the overall release kinetics pellets with different coatings have to  
30 be mixed.

It has been suggested to use ion-exchange resins to reduce the release rate from hydrophilic matrices (L.C.Feeley and S.S.Davis, Int.J.Pharm. 44 (1988) 131-139). The pure  
35 resins were mixed with a pharmacologically active substance as a salt and a gel-forming polymer, a high viscosity hydroxypropyl methylcellulose (HPMC). No complex

was, however, formed per se and the effect of the ion-exchange resin was only a reduction in the release rate.

5 GB 2 218 333 describes a preparation containing one active ingredient, namely ranitidine together with a synthetic cation exchange resin. Hydroxylpropyl methylcellulose may be added and is in that case used as granulating additive and does not control the release rate.

10 EP 241 178 describes a pharmaceutical composition comprising one or more therapeutically active ingredients dispersed in a carrier. In this case no complex is formed.

15 EP 338 444 describes a composition containing azelastin which may be bound to a cation exchange resin. It has however not been proposed that a hydrophilic eroding matrix should be added.

20 EP 195 643 describes release by diffusion through a gel-forming layer in a transdermal preparation. Also a salt must be added to the composition in order to make the composition suitable for use.

#### Brief description of the invention

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Active substances, available as dissociated ions, are complexed to insoluble, oppositely charged polymers, such as an ion-exchange resin. The particles formed, the complex, are embedded into a hydrophilic eroding matrix. 30 Surprisingly, the release kinetics obtained were more beneficial, showing a higher value of the exponent  $n$  (Equation 1) than for the ordinary salt, base or acid.

#### Description of the invention

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The new preparations defined above give an even release of the active substance with high solubility in water. The

different ingredients in the preparation are defined more in detail in the following:

5 Active substances are defined as compounds, which give a pharmacological effect when administered to humans or animals. To be useful in the present invention the substance must be available as dissociated ions. Therefore substances like glucose cannot be used. Instead bases, acids or amphoteric substances can be used.

10

It is preferable to use an active substance, which has a solubility greater than 10 mg/ml in water.

15 The ion-exchange resin has to be matched to the active substance and its physicochemical properties. Weak bases are best complexed with strong acid exchangers like sulphonic acids. These are often based on polystyrene crosslinked with divinylbenzene, and marketed under trademarks Resonium, Amberlite and Dowex.

20

The active substances may be used in the process as a salt or free base. The resin may be used in the acid form or as a salt of a suitable cation, such as sodium.

25 Stronger bases can be complexed to ion-exchange resins of lower acidity, such as crosslinked poly (acrylic acid) or styrene-divinylbenzene modified to contain carboxylic groups. It is also possible to use the mentioned sulphonic acid ion-exchangers.

30

Acids may be complexed with crosslinked polystyrene with quarternary amines, or other basic anion-exchangers. The acids may be used as free acids or suitable salts. The anion-exchanger may be used as base, with a hydroxylic  
35 ion on every amine, or a salt of a suitable anion, such as chloride.

The hydrophilic eroding matrix may consist of a polysaccharide. Especially useful are derivatised celluloses such as methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), both marketed under the tradenames Metolose and Methocel, and ethylhydroxy ethylcellulose (EHEC). We have found a grade HPMC, Metolose 60SH50 (viscosity 2% solution in water at 20°C of approx. 50 mPas, 27.0-30.0 %w/w methoxy groups and 7.0-12.0 %w/w hydroxypropoxy groups) especially useful. Also a mixture of low and high molecular weight HPMC can be used. The use of different mixtures of HPMC gives according to known technique different release rates of the active ingredient. Cf J. Contr. Rel. 5 (1987) p. 159-172. The eroding matrix may also consist of synthetic hydrophilic polymers, such as polyvinylalcohol or polyvinylpyrrolidone.

Other useful materials are bioeroding polymers such as polyorthoesters and polyanhydrides, such as those described by Nguyen et al (J. Contr. Rel. 4 (1986) 9-16) and polyanhydrides (R. Langer et al, Proc. Int. Symp. Control. Rel. Bioact. Mater., 16 (1989) 119-120, 161-162, 338-339).

#### Process

25

The tablets are preferably prepared by embedding the complex into a hydrophilic eroding matrix by compression in an ordinary tablet press. Processes including solvent evaporation (casting), precipitation or polymerisation may also be used.

30

35

EXAMPLESExample 1.

5 1 kg Dowex 50W-X4, 200-400 mesh, was washed with 2L 1 M NaOH, 8L deionized water, 2L 0.1 M NaOH, 8L deionized water, 0.8L methanol, 4L water, 1.6L 10% HCl and 12L deionized water. The resin was dried overnight at 80°C, yielding 352 g resin with 8.5% moisture and 4.86 mekv/g dry resin. 30.15 g resin was slurried in deionized water and a solution containing 44.06 g metoprolol succinate was added. After 10 minutes stirring, the resin was filtered on a sintered glass funnel. Another 8.01 g metoprolol succinate in water was added to the resin, and filtered off. The resin was rinsed with 2L deionized water and dried overnight at 80°C, giving 64.44 g complex with a metoprolol content, determined spectrophotometrically at 274 nm, of 1.98 mmol/g. 1 g of the complex was carefully mixed with 3 g Metolose 60SH50 (viscosity 49 mPas in 2% water solution, 28.2% methoxy groups and 8.2% hydroxypropoxy groups) with a mortar and pestle. 400 mg of the mixture was filled by hand into 20 mm flat punches and compressed into tablets. The release of metoprolol was measured in a USP apparatus no 2 (paddle) at 50 rpm, with the tablets mounted in a stationary basket, in 1L phosphate buffer at pH 7.5 and 37°C. The amount drug released was measured spectrophotometrically, for metoprolol at 274 nm.

30 Reference Example 1. 1 g metoprolol succinate was mixed with 3 g Metolose 60SH50 (same lot as above) with a mortar and pestle. 400 mg of the mixture was filled by hand into 20 mm flat punches and compressed into tablets.

35 The fraction drug released is plotted versus time in Figure 1. The exponent describing the release kinetics, defined in Equation 1, is evaluated using non-linear least



square fitting available in the software package RS/1 (RTM). The exponent was found to be 0.92 for the tablet containing the complexed drug and 0.61 for the low molecular weight salt, the succinate.

5

Example 2.

0.9 kg Dowex 50W-X8 200-400 mesh was treated similarly as in Example 1. The resin contained 5.10 mekv/g dry resin and 7.3% moisture. 30.02 g resin was treated with 44.06 g  
10 and 8.00 g metoprolol succinate in a similarly way as in Example 1. 57.76 g complex with 1.80 mmol/g was obtained. The tablets were manufactured and analyzed similarly as in Example 1 and the same reference may be used. The release  
15 of the tablets is shown in Figure 2. The release-describing exponent of Equation 1 was 0.97 for the tablets made according to this invention, compared to 0.61 for the reference tablet.

Example 3.

20 1 g of the complex of Example 1 was mixed with 3 g Metolose 65SH50 (viscosity 47 mPas of 2% water solution, 27.3% methoxy groups and 4.2% hydroxypropoxy groups), compressed into tablets and analyzed similarly.

25 Reference Example 3: 1 g metoprolol succinate was mixed with 3 g Metolose 65SH50 (same lot as above), compressed into tablets and analyzed with the method described in Example 1.

30 The kinetic exponent, defined in Equation 1, increased from 0.44 for the succinate salt to 0.68 for the complex.

Example 4.

1 g of the complex of Example 1 was mixed with 3 g  
35 Methocel E4MCR (viscosity 4077 of 2% water solution, 30.0% methoxy groups and 8.6% hydroxypropoxy groups), compressed into tablets and analyzed similarly.

Reference Example 4: 1 g metoprolol succinate was mixed with 3 g Methocel E4MCR (same lot as above), compressed into tablets and analyzed with the method described in  
5 Example 1.

The exponent describing the kinetics of release increased from 0.46 (low molecular weight salt) to 0.66 (ion exchange resin complex).

10

Example 5.

14.67 g Dowex 50W-X4 (from Example 1) was slurried in water. A water solution of 20.25 g lidocaine HCl·H<sub>2</sub>O was added. After 10 minutes stirring the complex was filtered  
15 and washed with 4L deionized water. After drying, the complex (24.84 g) contained 1.86 mmol/g, determined spectrophotometrically at 262 nm. Tablets were made according to Example 1 with the same lot of polymer and analyzed.

20

Reference Example 5: Tablets were also made from lidocaine-HCl·H<sub>2</sub>O and Metolose 60SH50.

The kinetic exponent of Equation 1 was 0.95 for the tablet  
25 containing the complex, and only 0.58 for the low molecular weight salt.

Example 6.

14.67 g Dowex 50W-X4 (from Example 1) was slurried in  
30 water. A water solution of 19.20 g terbutaline sulphate was added. After 10 minutes stirring the complex was filtered and washed with 4L deionized water. After drying, the complex (25.57 g) contained 1.91 mmol/g, determined spectrophotometrically at 278 nm. Tablets were made  
35 according to Example 1 and analyzed.

Reference Example 6: Tablets were also made from terbutaline sulphate.

The release profiles of Figure 4 demonstrate that the kinetic exponent was improved to 1.00 from 0.60 for the corresponding sulphate salt.

Example 7.

13.70 g Dowex 50W-X4 (from Example 1) was slurried in water and filtered on a sintered glass funnel. The resin was washed with 1 L water containing 5% NaCl. The resin was further washed with 2L deionized water. The resin was slurried in 100mL water containing 20.05 g alprenolol HCl. After 10 minutes stirring the complex was filtered and washed with 4L deionized water. After drying, the complex (27.15 g) contained 1.97 mmol/g, determined spectrophotometrically at 270 nm. Tablets were made according to Example 1 and analyzed.

Reference Example 7: Tablets were also made from alprenolol HCl.

The hydrochloric salt had an exponent of 0.63, significantly lower than the complex, 1.16.

25

Example 8.

100 g Dowex 1X-2 was washed with 0.5 L 0.1 M HCl, 1 L water, 200 mL methanol, 0.5 L water, 0.5 L 0.5 M NaOH, 200 mL methanol, 0.5 L water, 1 L 5% NaCl followed by 2 L deionized water. The resin was dried at 80°C overnight yielding approx. 60 g resin containing 11.5% water and 4.49 mekv/g dry resin. 6.68 g resin was treated with 100 mL 1M NaOH, filtered and washed with 2 L water and 2 lots of 200 mL ethanol 95% and slurried in 200 mL ethanol. 3.46 g salicylic acid was added and the slurry was agitated for 9 hours. The complex was filtered and washed with two lots of 200 mL ethanol and 2 L water. 6.25 g

complex containing 19.5% salicylic acid, measured spectrophotometrically at 296nm, was obtained after drying overnight. 1 g complex was mixed with 3 g Metolose 60SH50 and tablets were prepared according to Ex.1.

5

Reference Example 8: 1 g salicylic acid was mixed with 3 g Metolose 60SH50 and compressed to tablets by the method described in Ex. 1.

10 The release curves were fitted to Equation 1, giving an exponent of 0.56 for the acid and 0.96 for the complex.

15

CLAIMS

1. A preparation of a pharmacologically active ionizable substance for extended release of active substance,  
5 whereby the active substance is ionically complexed with an ion-exchange resin and the complex formed is embedded in a hydrophilic eroding matrix.
2. A preparation according to claim 1 intended for oral  
10 use.
3. A preparation according to claim 2, wherein the ion-exchange resin is a crosslinked polymer oppositely charged to the active substance.  
15
4. A preparation according to claim 2, wherein the hydrophilic matrix to more than 10 % consists of a polysaccharide or a derivative thereof.
- 20 5. A preparation according to claim 4 wherein the hydrophilic matrix is hydroxypropyl methylcellulose.
6. A preparation according to claim 5 wherein the hydroxypropyl methylcellulose contains both low and high  
25 molecular weight hydroxypropyl methylcellulose.
7. A preparation according to claim 3 wherein the active substance is a base and the resin is a cation-exchanger.
- 30 8. A preparation according to claim 3 wherein the active substance is an acid and the resin is an anion-exchanger.
9. A preparation according to claim 7 wherein the active substance is metoprolol and the resin is polystyrene  
35 sulfonate.

10. A preparation according to claim 7 wherein the active substance is terbutaline and the resin is polystyrene sulfonate.
- 5 11. A preparation according to claim 2 wherein the active ionizable substance has a solubility greater than 10 mg/ml.
12. A process for the manufacture of a preparation  
10 according to claim 1 wherein
- a) the active substance is ionically complexed to an oppositely charged ion-exchanger whereby a complex is formed,  
15
- b) said complex is embedded into a hydrophilic eroding matrix and
- 20 c) the resulting mixture is formed to tablets according to any suitable known method.

Figure 1. Release of metoprolol at pH 7.5 from tablets of Example 1.

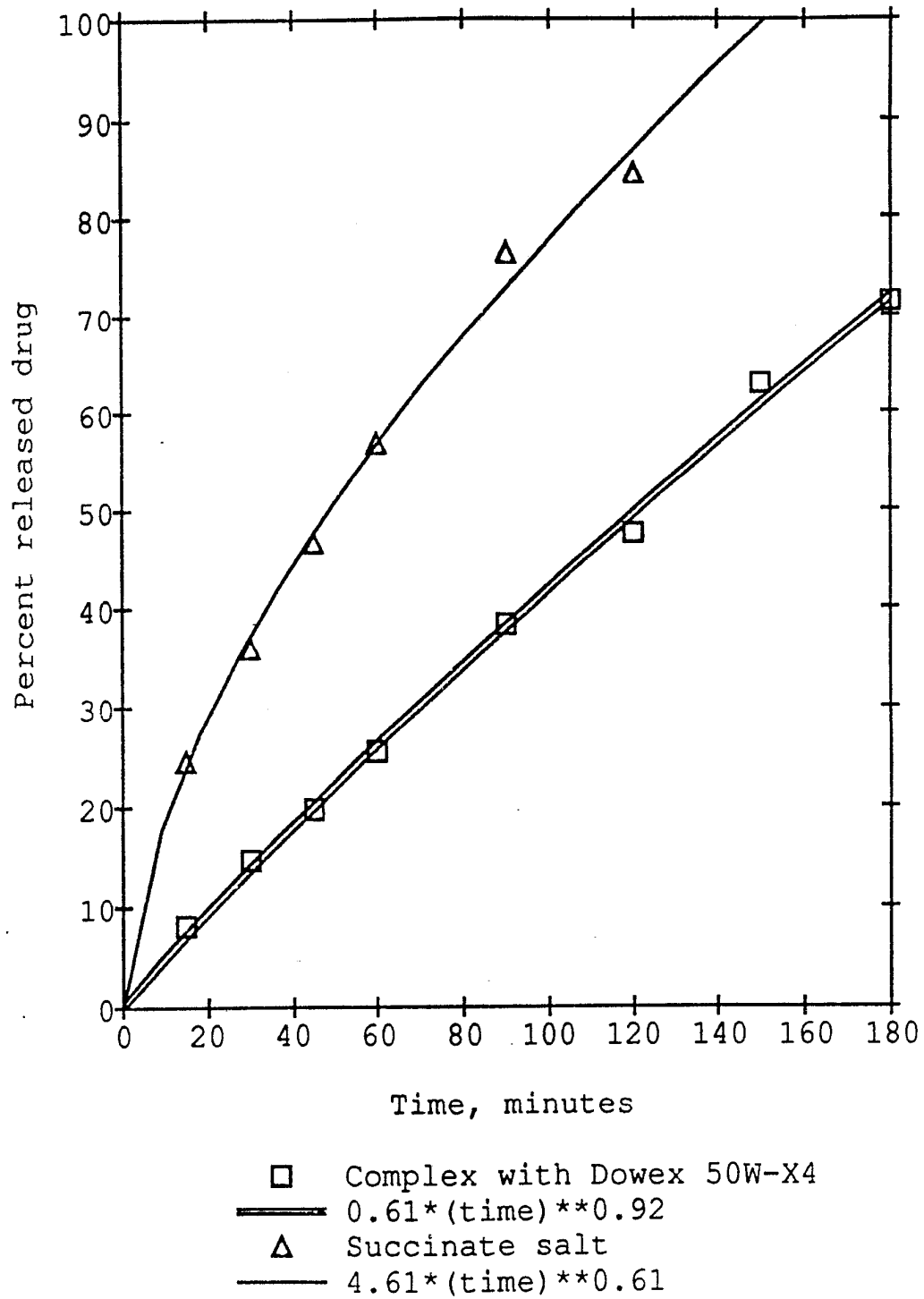


Figure 2. Release of metoprolol at pH 7.5 from tablets of Example 2.

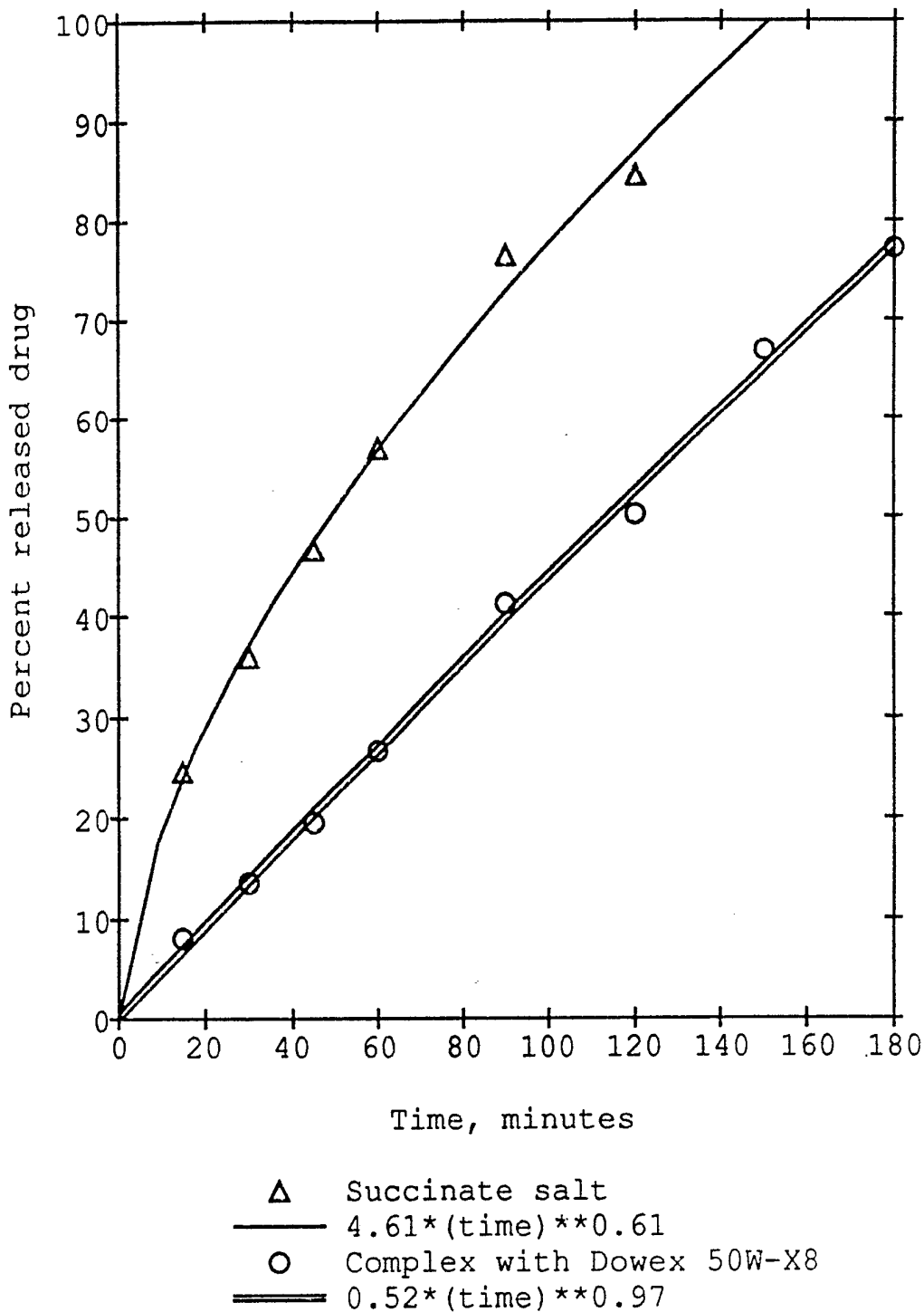




Figure 3. Release of metoprolol at pH 7.5 from tablets of Example 4.

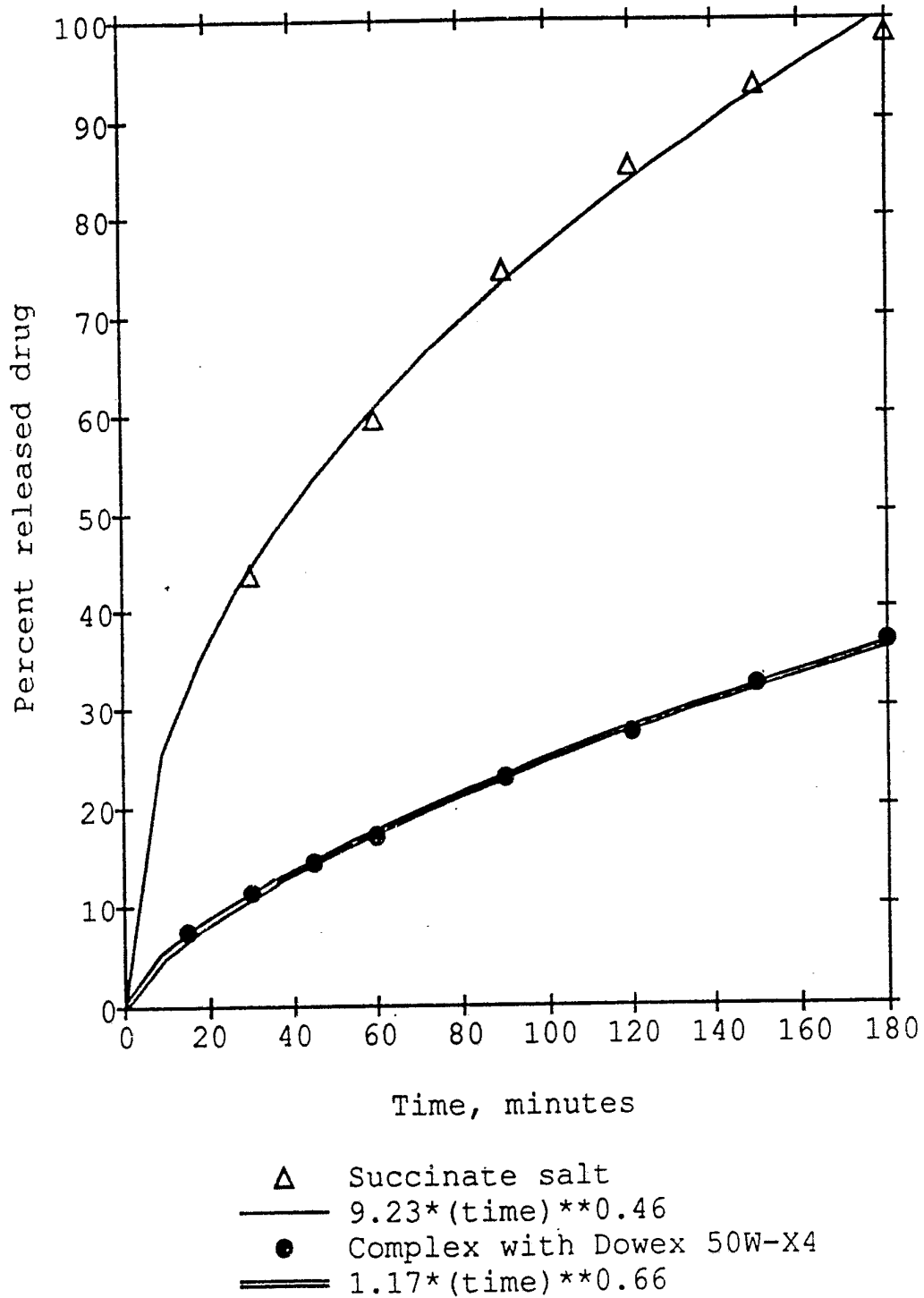
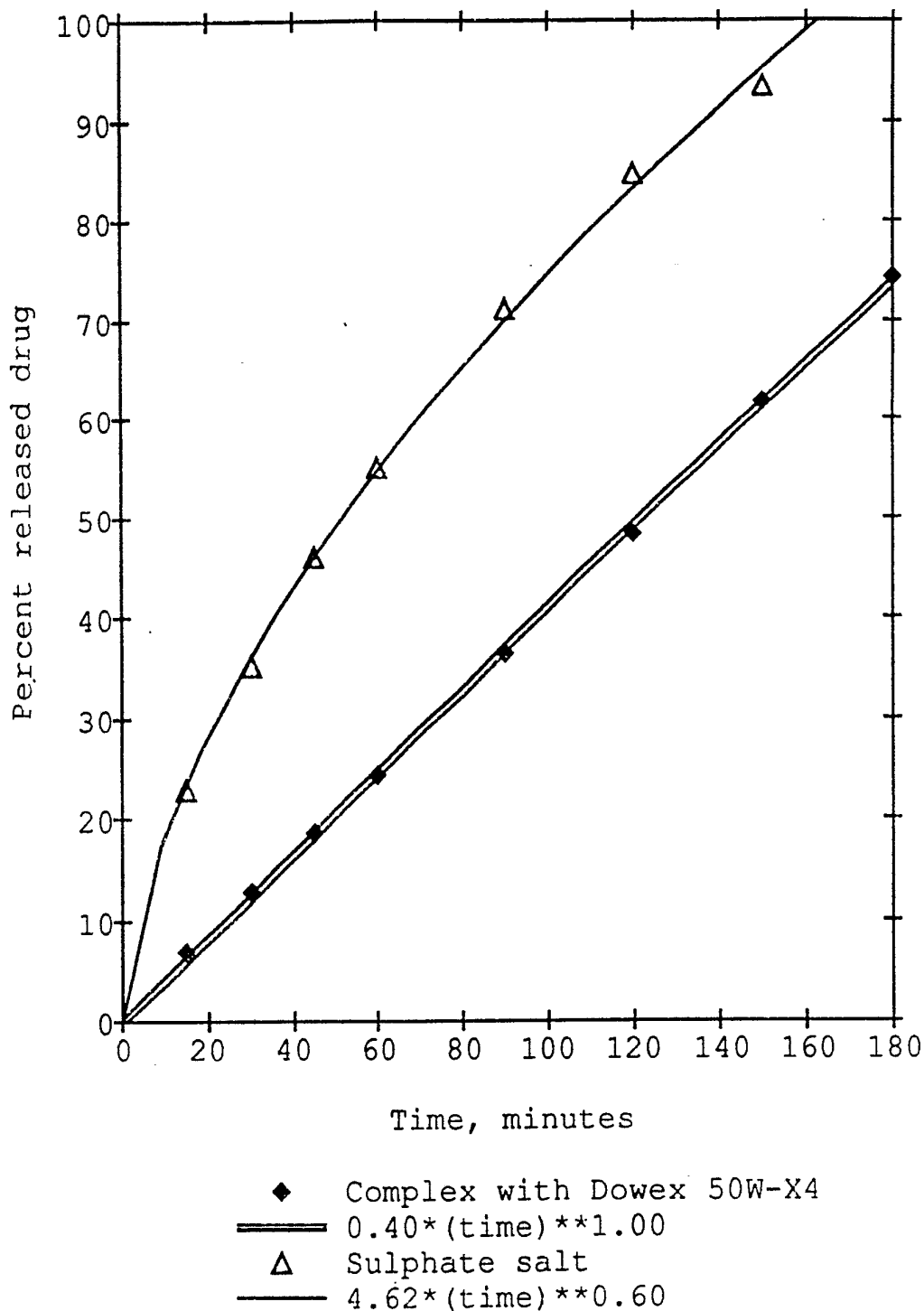
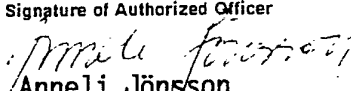


Figure 4. Release of terbutaline at pH 7.5 from tablets of Example 6.



# INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00814

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC5: A 61 K 9/18, 9/22		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched <sup>8</sup>		
SE,DK,FI,NO classes as above		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP, A1, 0338444 (ASTA PHARMA AG) 25 October 1989, see page 3, line 34 - line 56; page 5, line 53 - page 6, line 26 --	1-5,9
X	EP, A1, 0241178 (ROHTO PHARMACEUTICAL CO., LTD) 14 October 1987, see column 4, line 1 - column 5, line 15 --	1-6,9
X	EP, A2, 0195643 (MENLEY & JAMES LABORATORIES, LIMITED) 24 September 1986, see page 4, line 5 - line 20; page 5, line 12 - line 30; claims 1-9 --	1-5,9
X	GB, A, 2218333 (GLAXO GROUP LIMITED) 15 November 1989, see page 4, line 34 - page 5, line 6; example 1 --	1-5,9
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<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
16th March 1992	1992-03-17	
International Searching Authority	Signature of Authorized Officer	
SWEDISH PATENT OFFICE	 Anneli Jönsson	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Chemical Abstracts, volume 109, no. 10, 5 September 1988, (Columbus, Ohio, US), Feely Liam C. et al.: "The influence of polymeric excipients on drug release from hydroxypropyl methyl cellulose matrixes ", see page 402, abstract 79581r, & Int. J. Pharm. 1988, 44(10), 131- 139 --	1-9
A	US, A, 4774083 (TAN ET AL) 27 September 1988, see column 1, line 59 - column 2, line 48 --	1-9
A	EP, A2, 0254811 (PENNWALT CORPORATION) 3 February 1988, see the whole document -- -----	1-9

ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 91/00814

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NL-A- 8901188	89-12-01
		SE-A- 8901671	89-11-12
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