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(54) Title: THERAPEUTIC COMPOSITIONS FOR VETERINARY USE			
(57) Abstract			
A therapeutic composition for veterinary use comprises a therapeutic agent, such as an anthelmintic drug, associated by sorption and/or adsorption with a substrate selected from zeolites and/or pillared clays. Preferably, the drug is present in an amount in the range from 5 to 300 mg per gram of substrate.			

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1 THERAPEUTIC COMPOSITIONS FOR VETERINARY USE

 This invention relates to compositions having therapeutic properties, which are particularly useful in veterinary practice.

5 It is common practice to administer drugs and other therapeutic agents to animals, either to treat infections and other undesirable conditions or to produce and/or maintain good health and other desirable conditions. It has now been discovered that a wide range
10 of compositions for such purposes can be made, by a number of methods which also form aspects of this invention. The compositions of the invention contain the desired therapeutic agent or agents in association with carrier or substrate substances as explained below. It has also been dis-
15 covered that known beneficial effects of the carrier substances can be produced in conjunction with the desired effects of the therapeutic agents. Furthermore, the preferred carrier substances have been found to act as slow-release agents and so give improved performance by
20 the therapeutic agent involved.

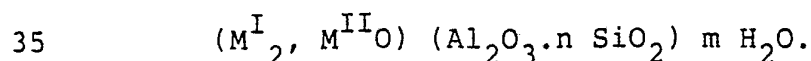
 In accordance with an aspect of this invention, a therapeutic composition comprising at least one veterinary therapeutic agent is characterised in that the

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1 composition includes at least one substrate selected from
zeolites and pillared clays, with which the therapeutic
agent is associated by internal sorption and/or external
adsorption. For simplicity, the term "drug" is used below
5 to describe any therapeutic agent suitable for use in
accordance with this invention. A preferred feature of
the invention is the use, as the therapeutic agent, of at
least one anthelmintic agent.

In accordance with another aspect of this
10 invention, a method of manufacture of a therapeutic
composition comprising at least one veterinary therapeutic
agent is characterised in that the therapeutic agent in
solution or vapour form is brought into contact with a
substrate selected from zeolites and pillared clays
15 comprising at least one zeolite compound and/or pillared
clay, for a time sufficient to allow a significant amount
of the agent to become associated by internal sorption
and/or external adsorption with the substrate and, if
required, the resultant composition is caused or allowed
20 to dry. In appropriate instances, a solution can be
contacted with the zeolite compound or other substrate
which contains 2 or more drugs which are desired in the
resultant composition. Alternatively, a composition
containing two or more drugs can be made by contacting the
25 zeolite and/or pillared clay substrate in sequence with a
solution of each of the drugs of interest.

Zeolites are hydrated alumino-silicates, having
framework structures enclosing cavities and channels,
which can contain mobile cations and water molecules. As
30 is known, zeolites can undergo reversible ion exchange and
water loss reactions and they also have molecular seive
properties. The general formula of zeolites, both as
natural and synthetic forms, is as follows:



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1 where M^I and M^{II} are monovalent and divalent cations
respectively, n can have any value from 1 upwards and m
can have any integral or fractional value in the range
from 0 to 5. Modern synthetic techniques allow either or
5 both of the Al and Si atoms to be replaced by atoms of
other elements in the zeolite framework. Replacement can
also be effected by altering existing zeolite substances.
Elements introduced in this way include P, for Si, as in
AlPO compounds and many others, such as Be, Zn, Sn, Fe, B,
10 Ga, Ge, Zr and Ti. Another variant involves the substi-
tution of M^{III} , i.e. trivalent ions, for at least part of
the M^I and M^{II} in the general formula. M^I , N^{II} and M^{III}
can be selected from any desired inorganic and organic
cations. Thus the chemical modification of zeolites has
15 previously been concerned with ion replacement or the
physio-chemical attachment of ions or small molecules,
such as water.

Clays which have been treated in known manner so
that the individual platelets or other particles are more
20 widely spaced, namely pillared clays, are also useful as
substrates for the veterinary compositions of the
invention.

It has now surprisingly been discovered that
certain drug molecules can be associated with zeolites and
25 pillared clays and can be delivered to animal hosts, when
the resultant compositions are administered. The
mechanism involved in forming these compositions can be
internal, external or both, for instance by sorption
inside the zeolite or clay cavities, by adsorption upon
30 the zeolite crystal or clay particle surfaces or by both
internal sorption and external adsorption in the same
composition. It is surprising to find that even rela-
tively large drug molecules can be easily and specifically
taken up by these substrates, such as zeolites, from both
35 aqueous and polar solvents. Even more surprising is the

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1 discovery that such drug molecules can then be released,
when the resultant complexes or compositions are subse-
quently administered, e.g. to animals in carrying out a
worming or other veterinary treatment. From the previous
5 knowledge of the behaviour of zeolites, for instance, it
was not to be expected that such complexes would lead to a
release of the drug component. Moreover, a further aspect
of the surprising behaviour in use of compositions
according to the invention is that release of the one or
10 more drugs associated with the zeolite or pillared clay
component in a composition according to the invention
takes place slowly and in a largely even and regular
manner, so that release takes place in a most advantageous
manner. As will appear from the following part of this
15 description, it has been established that release of the
drug component is not only steady and very even, but is
initiated almost immediately when administration has
occurred.

The drug or drugs present in the therapeutic
20 composition do not lose their properties and can be
administered in any suitable way, for instance by mixing a
composition according to the invention, in powder form,
with animal feedstuffs or by forming the composition into
pellets and administering these as such or by addition to
25 feedstuffs. It has been suggested already that zeolites
are themselves beneficial, when given to animals, for
instance pigs, poultry, cattle, sheep and goats, for
instance in a ratio of 5% to 10% by weight of feedstuffs.
Thus the therapeutic compositions of the invention can be
30 used effectively to produce, by way of example, the known
beneficial effects of zeolites and the desired and known
beneficial effects of the therapeutic agents present in
the compositions of the invention and that these effects
are manifested at the same time and without either
35 component affecting the beneficial actions of the other.

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1 It has also been discovered that the compositions of the invention, when administered, allow the relatively slow and controlled release of the drugs into the gastric and circulatory systems of the animal.

5 In order to illustrate the invention and allow it to be fully appreciated and understood, various preferred techniques are described below, together with examples of the manufacture of therapeutic compositions according to the invention and test results given when
10 they are used. These techniques and examples are described in connection with zeolite substrates, for convenience, and it is to be understood that the same applies to the use of pillared clay substrates or to the use of both kinds of substrate materials in conjunction.

15 According to one preferred embodiment of the method of the invention, contact between the agent and the zeolite component involves use of a solution of the agent; this can either be passed through a column of the zeolite component in powder or pellet form or can be slurried with
20 a quantity of it in powder, aggregate or pellet form. In another preferred embodiment, an agent capable of vaporisation is contacted in vapour form with the zeolite component while contained in an enclosure.

In the following part of the description, X and
25 Y designate synthetic faujasite, used in the Na, Ba and Cs forms, Z 900 indicates a synthetic mordenite, in its Na form while NaA indicates the sodium form of zeolite A. Therapeutic compositions according to the invention have been made with all of these zeolites and all of the
30 following anthelmintic drugs:

Dichlorovos (DDVP)

Fenbendazole (FEN)

Levamisole (LEVA)

Tetramisole (TETRA).

35 Manufacture of therapeutic compositions using

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1 the zeolites and drugs mentioned above, has mainly been
based upon contacting solutions containing the drug with
the zeolite in powder or pellet form or by stirring the
zeolite, in powder, aggregate or pellet form, into such a
5 solution to form a slurry. Zeolites can be aggregated, in
order to form suitable sized pellets, or they can be
pelletized by mixing them with a clay-based mineral.
Commercially, zeolites are obtainable in powder, aggregate
("self-bound") or pellet form. Solutions of the drugs have
10 been used, in concentrations in the preferred range from
0.1 to 10% by weight, using water, carbon tetrachloride,
methanol, dimethylformamide, tetrahydrofuran or mixtures
thereof, as indicated in the following Table. It has been
found preferable to use a solution of DDVP in water and
15 CCl_4 in the range from 0.1 to 10%, a solution of FEN in
dimethylformamide and tetrahydrofuran in the range from
0.1 to 1% and a solution of LEVA or TETRA in methanol in
the range from 0.1 to 1%. After preparation of the
compositions, all the solvents are recoverable by normal
20 methods.

A loading solution of the drug, in the concen-
tration indicated in the Table below, in a suitable
solvent, is placed with a predetermined weight of the
selected zeolite in a glass vessel and the vessel contents
25 are stirred for 72 hours, using a PTFE stirrer. The
zeolite is then filtered off and air-dried for four hours.
The zeolite composition is then dried for 24 hours at 60°C
in a vacuum oven.

Methods of preparation of the compositions have
30 also been used, which are essentially the same as above,
but with increased temperature of the use of reflux
conditions in the temperature range stated.

A further technique involves filling a glass or
other column with, e.g., 1 to 5 grams of the zeolite in
35 the form of powder, pellets or aggregate and allowing a

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1 solution containing a predetermined concentration of the
selected drug to percolate through the column.

A fourth technique involves exposing a predeter-
mined quantity of the selected zeolite in an enclosure and
5 subjecting it to contact with the drug in vapour form.

Uptake of the drug on and/or into the zeolite
carrier can be monitored by measuring the disappearance of
the drug from the loading solution, using gas-liquid
chromatography, UV spectrometry or radio-labelling, to
10 determine the concentration of the drug left in solution.
Thermal analysis (DTA, DSC or TG) can be used to determine
drug loading levels on the zeolite carrier.

See Table on following page.

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TABLE

Zeolite	Solvent	Drug	Zeolite wt. g	Vol of loading solution	% Drug in solution	Loading of zeolite. mg drug per g zeolite
NaY	H ₂ O	DDVP	5	500	0.9	5
NaY	CCl ₄	DDVP	5	500	10.0	115
NaY	CCl ₄	DDVP	5	500	1.0	215
NaY	Vapour phase	DDVP	5	20	vapour	269
NaY	CCl ₄	DDVP	5	500	1.0	80
NaY	CCl ₄	DDVP	5	500	4.0	75
NaY	CCl ₄	DDVP	5	500	2.0	75
NaY	CCl ₄	DDVP	5	500	0.9	60
NaY	CCl ₄	DDVP	5	500	0.5	55
NaY	CCl ₄	DDVP	5	500	0.1	12.5
NaY	CCl ₄	DDVP	5	502	0.05	7.5
Na Mordenite	vap	DDVP	5	20	vapour	90
Z900	H ₂ O	DDVP	15	30	10	33
NaX(Pellets)	CCl ₄	DDVP	0.1	10	1.0	~ 20
NaA(Pellets)	H ₂ O	DDVP	0.1	10	1.0	~ 15
NaY	MeOH	Tetra	5	500	1.0	33
NaY	DMF	Fen	5	500	1.0	10
NaY	THF	Fen	1	100	0.5	10
NaY	MeOH	Leva	5	500	0.1	10
NaY	MeOH	Leva	5	100	1.0	30

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1 In order to evaluate the rate of release of the
 drug from a therapeutic composition according to the
 invention, these were contacted with artificial gastric
 juice at room temperature. The amount of the drug
 5 released into solution was measured as a function of time.
 Analyses were carried out by radio labelling, gas-liquid
 chromatography and chemical methods. The accompanying
 drawings show examples of the release profiles obtained in
 graphical form.

10 Animal Trials on Rat (6 rats per group).

Drug - tetramisole

Rats infected with 500 larva

Fed as follows:

Group A - Control fed no drug and no zeolite.

15 Group B - zeolite only at level in subsequent groups.

Group C - tetramisole at 15 mg/kg body weight (no zeolite)

Group D - zeolite loaded with drug dosed at 15 mg/kg body
 weight.

20 Group E - zeolite loaded with drug at 7.5 mg/kg body
 weight.

RESULTS

	<u>GROUP</u>	<u>LARVA DETECTED</u>
	A	269 ± 27.4
	B	274 ± 20.1
25	C	62 ± 18
	D	5.2 ± 3.6
	E	26.8 ± 10.3

Student Test

	<u>Group Pairing</u>	<u>P</u>
30	A : B	No significant difference
	A : C	<0.001
	A : D	<0.001
	A : E	<0.001
	C : D	p = 0.01
35	C : E	No significant difference

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1 D : E No significant difference.

D has significantly less worms than C so zeolite + drug is more effective than drug alone.

5 In order to demonstrate the behaviour of typical complexes according to the invention upon administration, reference is made to the accompanying drawings; each shows graphically a release profile, obtained by plotting wt/wi against time in minutes; Fig. 1 shows the release profile
10 for DDVP from Z900 at room temperature and Fig. 2 shows the release profile for DDVP from NaY at 80°C. It will be noted, in Fig. 1, that the rate of release rapidly increases over the first 60 minutes, reaching a value of 0.10 wt/wi at that time and then attaining a steady rate
15 of about 0.12 wt/wi after another 30 minutes and maintaining this steady rate of release for the remaining 210 minutes of the test. Fig. 2 shows an almost instantaneous attainment of a rate of over 0.20 wt/wi, followed by a period of much slower rate increase, until
20 the rate generally levels out at about 0.28 wt/wi after around 160 minutes and maintaining this rate for the remainder of the test. Neither example shows any reduction in the rate of release.

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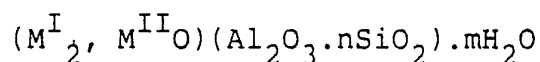
1 CLAIMS:

1. A therapeutic composition comprising at least one veterinary therapeutic agent, characterised in that

5 the composition comprises at least one substrate selected from zeolites and pillared clays with which the therapeutic agent is associated by internal sorption and/or external adsorption.

2. A therapeutic composition comprising at least one veterinary therapeutic agent, characterised in that the composition includes a substrate comprising at least one zeolite, with which the therapeutic agent is associated by internal sorption and/or external adsorption.

15 3. A composition according to claim 1 or 2, wherein the substrate comprises at least one zeolite compound of the general formula:



20 wherein M^I and M^{II} respectively represent monovalent and divalent cations or together represent at least in part a trivalent cation M^{III} , M^I , M^{II} and M^{III} each being selected from inorganic and organic cations, n has a value from 1 upwards and m has an integral or fractional value in the range from 0 to 5 and wherein either or both of the Al and Si atoms may be at least partly replaced within the zeolite framework structure with atoms of another element.

4. A composition according to claim 1, 2 or 3, wherein the substrate is a zeolite component in powder, aggregate or pellet form and is selected from synthetic faujasite in any of the Na, Ba and Cs forms, synthetic mordenite in the Na form or the Na form of zeolite A and the therapeutic agent is an anthelmintic drug selected from Dichlorovos, Fenbendazole, Levamisole and Tetramisole.

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1 5. A composition according to any preceding
claim, wherein the therapeutic agent comprises at least
one anthelmintic agent.

5 6. A composition according to any preceding
claim, wherein the therapeutic agent is present in an
amount in the range from 5 to 30 mg per gram of substrate.

7. A method of manufacture of a therapeutic
composition comprising at least one veterinary therapeutic
agent,
10 characterised in that
the therapeutic agent in solution or vapour form is
brought into contact with at least one substrate selected
from zeolites and pillared clays for a time sufficient to
allow a significant amount of the therapeutic agent to
15 become associated by internal sorption and/or external
adsorption with the substrate component and, if required,
the resultant composition is caused or allowed to dry.

8. A method of manufacture of a therapeutic
composition comprising at least one veterinary therapeutic
20 agent,
characterised in that
the therapeutic agent in solution or vapour form is
brought into contact with a substrate comprising at least
one zeolite for a time sufficient to allow a significant
25 amount of the therapeutic agent to become associated by
internal sorption and/or external adsorption with the
substrate and, if required, the resultant composition is
caused or allowed to dry.

9. A method according to claim 7 or 8, wherein
30 contact between the therapeutic agent and the substrate is
effected by passing a solution of the agent through a
column of the substrate in powder or pellet form.

10. A method according to claim 7 or 8, wherein
contact between the therapeutic agent and the substrate is
35 effected by slurring a solution of the agent with a

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1 quantity of the substrate in powder, aggregate or pellet
form.

11. A method according to claim 9 or 10, wherein
the solution of the therapeutic agent has a concentration
5 in the range from 0.1 to 10% by weight in a solvent
selected from water, carbon tetrachloride, methanol,
dimethylformamide, tetrahydrofuran or mixtures thereof.

12. A method according to claim 7, wherein an
agent capable of vaporisation is contacted in vapour form
10 with the substrate while contained in an enclosure.

13. A method according to any of claims 7 to 12,
wherein the substrate is a zeolite component in powder,
aggregate or pellet form and is selected from synthetic
faujasite in any of the Na, Ba and Cs forms, synthetic
15 mordenite in the Na form or the Na form of zeolite A and
the therapeutic agent is an anthelmintic drug selected
from Dichlorovos, Fenbendazole, Levamisole and Tetramisole.

14. A method according to any of claims 7 to 13,
wherein the therapeutic agent comprises at least one
20 anthelmintic agent.

15. A method according to any of claims 7 to 14,
wherein contact between the therapeutic agent and the
substrate is maintained so that the agent is present in
the resultant composition in an amount in the range from 5
25 to 30 mg per gram of substrate.

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RELEASE PROFILE FOR DDVP FROM NAY (DRIED) TO WATER AT 80° C

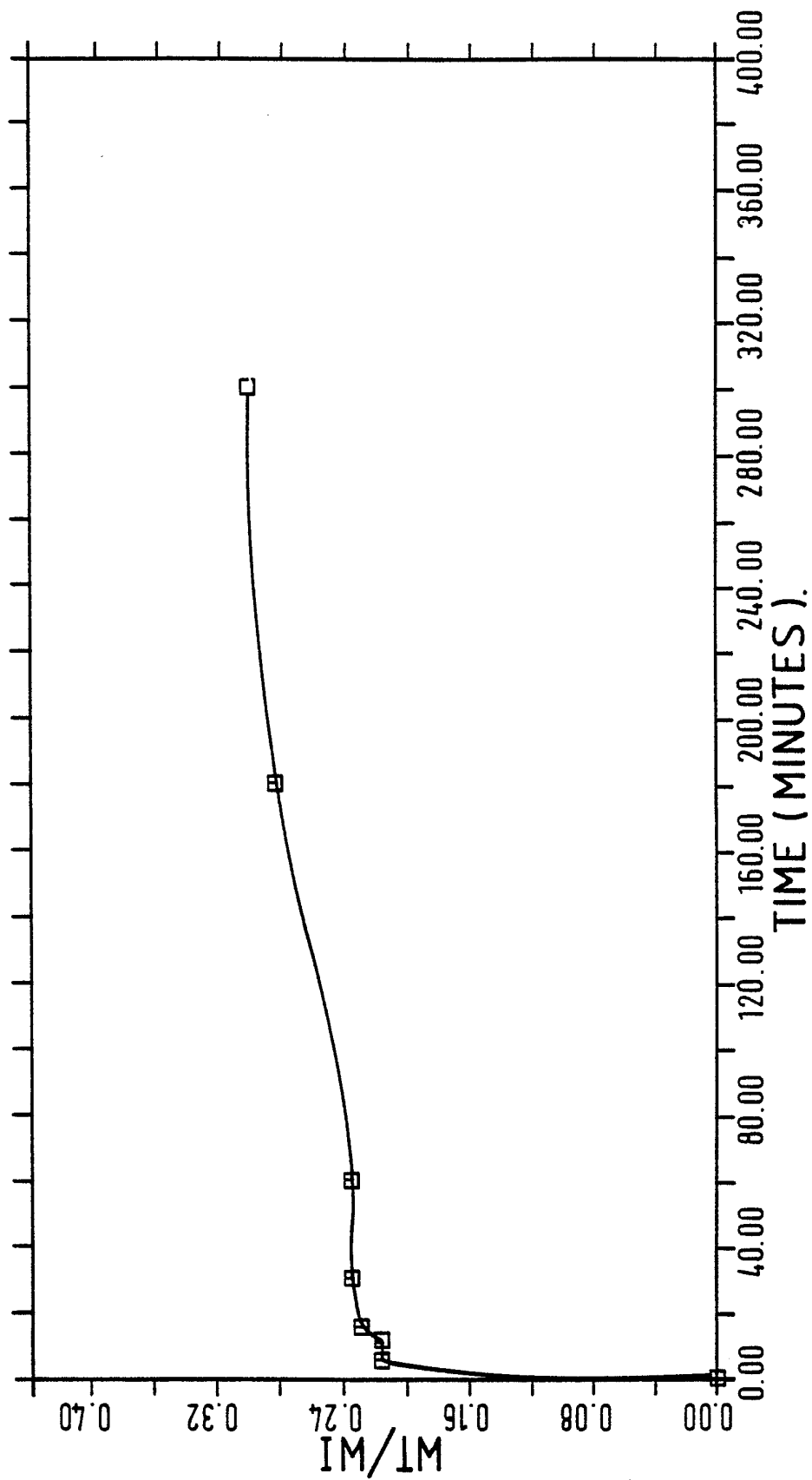


FIG.1.

SUBSTITUTE SHEET

2 / 2

RELEASE PROFILE FOR DDVP FROM Z900 (DRIED) TO WATER AT ROOM TEMP.

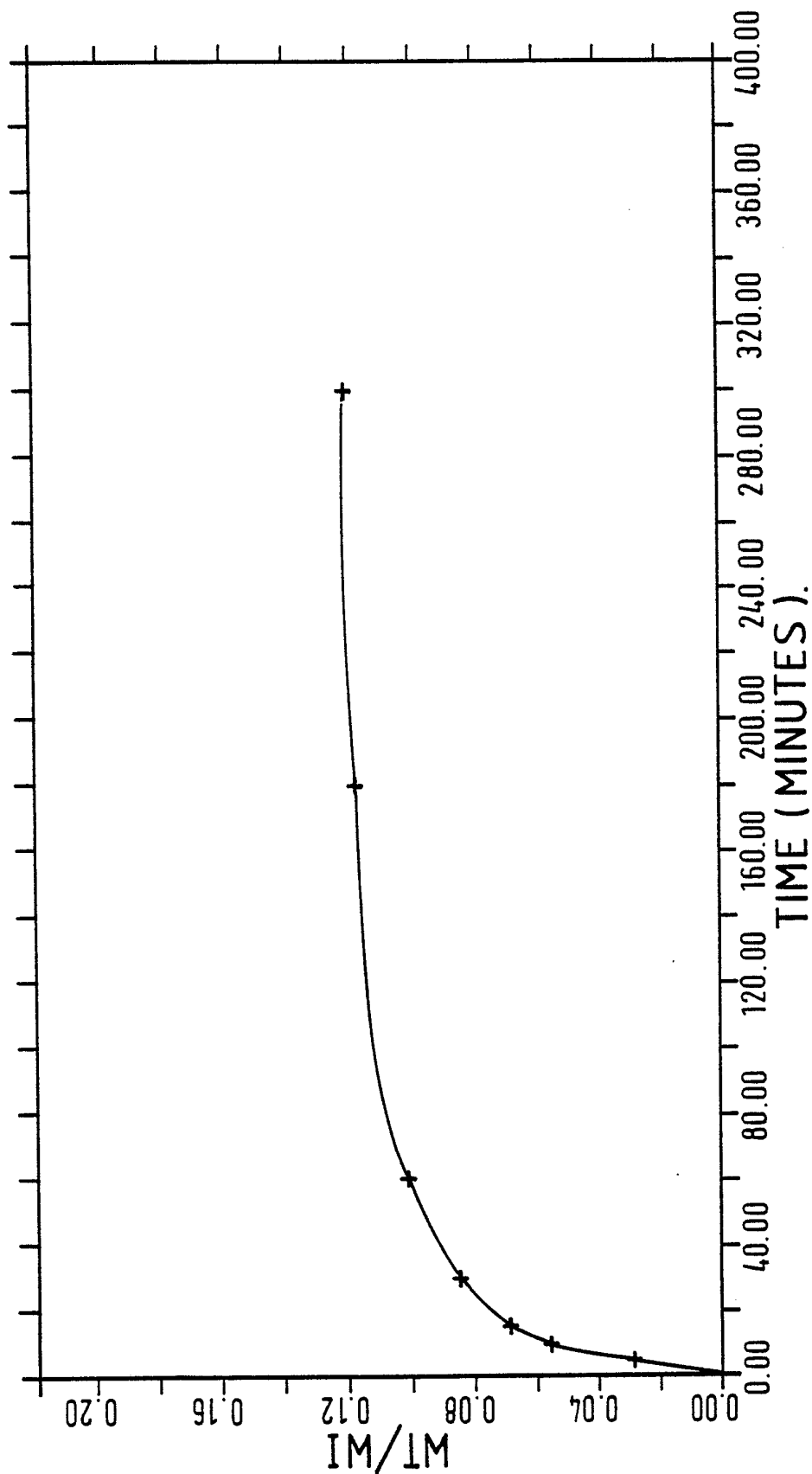


FIG. 2.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 87/00147

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁴ : A 61 K 9/18; A 61 K 9/22; A 61 K 47/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁴	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X,Y	FR, A, 1255314 (UNION CARBIDE CORPORATION) 30 January 1961, see page 1, column 1, lines 8-11; claims	1-15
A	US, A, 3119738 (R.E. NICHOLS et al.) 28 January 1964, see column 2, lines 37-68; claims	1
X	FR, A, 2117728 (R. ARIES) 28 July 1972, see page 1, lines 35-38; page 2, lines 7-14; page 7, lines 32-33; claims 1,12,18-19	1-15
X	Journal of Pharmaceutical Sciences, volume 73, no. 10, October 1984, (Washington, US), M.S. Stul et al.: "In vitro adsorption-desorption of phenethylamines and phenylimidazoles by a bentonite and a resin", pages 1372-1375, see the whole article	1-15
A	US, A, 4145429 (C.D. CLARKE) 20 March 1979, see claims	1-15
* Special categories of cited documents: ¹⁰ "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 "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		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1st June 1987	17 JUL 1987	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	M. VAN MOL	

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
Y	FR, A, 2461495 (A.E.L. EDMOND) 6 February 1981, see page 3, lines 24-30; claims 1,2,4 -----	4,5,13,14

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 87/00147 (SA 16362)

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 01/07/87

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 1255314		None	
US-A- 3119738		None	
FR-A- 2117728	28/07/72	None	
US-A- 4145429	20/03/79	BE-A- 833432	15/03/76
		NL-A- 7511059	23/03/76
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		SE-B- 426909	21/02/83
		SE-A- 7510365	22/03/76
FR-A- 2461495	06/02/81	None	

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82