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CA 2147759 C 2004/08/10

(11)(21) 2 147 759

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 1993/10/25
(87) Date publication PCT/PCT Publication Date: 1994/05/11
(45) Date de délivrance/Issue Date: 2004/08/10
(85) Entrée phase nationale/National Entry: 1995/04/24
(86) N° demande PCT/PCT Application No.: EP 1993/002954
(87) N° publication PCT/PCT Publication No.: 1994/010129
(30) Priorité/Priority: 1992/10/26 (P 42 36 074.9) DE

(51) Cl.Int.^{6}/Int.Cl.^{6} C07C 229/48, A61K 31/215

(72) Inventeurs/Inventors:
HERRMANN, WOLFGANG, DE;
KNAPP, ARMIN, DE;
KLAUSMANN, HANS, DE;
WITZKE, JOACHIM, DE

(73) Propriétaire/Owner:
GODECKE AKTIENGESELLSCHAFT, DE

(74) Agent: SMART & BIGGAR

(54) Titre : DIHYDROGENOORTHOPHOSPHATE DE TILIDINE; METHODE DE PREPARATION ET PREPARATIONS PHARMACEUTIQUES A BASE DE CE COMPOSE

(54) Title: TILIDIN DIHYDROGEN ORTHOPHOSPHATE, METHOD OF PREPARING IT AND PHARMACEUTICAL PREPARATIONS CONTAINING IT

(57) Abrégé/Abstract:
Described is a tilidine salt, tilidine dihydrogen othophosphate, which, owing to its stability, is particularly suitable for use in the preparation of solid, in particular delayed-action, drugs in tablet, pill or capsule form.

ABSTRACT

Described is a tilidine salt, tilidine dihydrogen othophosphate, which, owing to its stability, is particularly suitable for use in the preparation of solid, in particular delayed-action, drugs in tablet, pill or capsule form.

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PD-6360

TILIDIN DIHYDROGEN ORTHOPHOSPHATE, METHOD OF PREPARING IT AND PHARMACEUTICAL PREPARATIONS CONTAINING IT

Tilidine dihydrogen orthophosphate, a process for the preparation thereof and pharmaceutical compositions containing it

Tilidine [(±)-ethyl trans-2-dimethylamino-1-phenyl-3-cyclohexene-trans-1-carboxylate)] is an analgesic which is enterally resorbed very quickly and is especially suitable for the treatment of very severe pains. For galenical compositions, there are preferably used salts of the basic active material since the base as such does not have a sufficient stability over a comparatively long period of time. Hitherto, however, also for reasons of stability, even with the use of salts, it has not been possible to develop solid pharmaceutical forms, for example tablets or suppositories. Hitherto, only the hydrochloride semihydrate (DE-PS 1 518 959 and 1 793 571) has, in practice, proved to be useful as a salt for stable liquid compositions. It is commercially available in the form of a solution or of a portioned suspension in soft gelatine capsules under the Trade Mark Valoron N. Because of its outstandingly favourable properties in combatting pain, Valoron N has, in the meantime, become one of the leading analgesics. However, all endeavours to make available useful solid pharmaceutical forms of the active material tilidine have hitherto been unsuccessful because of the above-mentioned stability problems. The desire for a usable solid galenical form of tilidine exists especially because only by way of such a solid formulation can a controllable retarding of tilidine be realised. Since tilidine acts for a relatively short period of time and a uniform treatment of pain for a comparatively long period of time, for example overnight, with a single dosage of active material in the case of normal liberation, such as is quite generally provided by liquid compositions, is problematical, the making available of such a retarded form would be a very great advance in the field of analgesics and especially there where a uniform, high level of active material over long periods of time is required, for example for combatting chronic and severe painful conditions in the case of cancerous diseases and in the case of burns.

Thus, it is an object of the present invention to provide a tilidine salt which is also stable in solid and retarded pharmaceutical compositions, especially in tablets, coated tablets and suppositories, and also a process for the production of especially solid and retarded pharmaceutical compositions with this new salt.

Surprisingly, we have now found that tilidine dihydrogen orthophosphate has an outstanding stability and is suitable as the hitherto only salt for the production of solid pharmaceutical compositions because, in solid form, i.e. in combination with solid adjuvants, it suffers practically no decomposition. Furthermore, the new salt has surprising pharmaceutical-technological properties which are superior to the properties of all other comparable tilidine salts, for example tilidine hydrogen sulphate or tilidine hydrogen fumarate, so that, for example, without special requirements for the climatising of the working rooms and for the corrosion protection of the apparatus and tools used, granulates, tablets and suppositories can be produced which are storage stable not only chemically but also physically over a very long period of time.

In DE-PS 1 923 619, it is admittedly mentioned in passing that basically-substituted cyclohexenes can form salts with a number of organic and inorganic acids, inter alia also with phosphoric acid (see column 4, line 19) which can possibly be considered for working up to give pharmaceutical compositions but no phosphate is described and especially not tilidine dihydrogen orthophosphate. In particular, the above-mentioned stability problems and especially those of tilidine are not described. Hitherto, there has been no indication in the literature regarding the difficulties concerning the storage stability of this active material or of the technical problems when it is worked up to give solid pharmaceutical compositions. Therefore, hitherto the expert has had no reasons to have any thoughts regarding selection criteria and, in particular, the known state of the art gave no indication that precisely tilidine dihydrogen orthophosphate is especially suitable for solving the mentioned problems.

In addition it has been found that the production of the phosphate is critical and has to be carried out under very special conditions if a crystalline product of high purity is to be obtained. The salt formation is started with 80-90%, preferred 85-88% orthophosphoric acid, which is dissolved in an amount of water containing isopropanol (water content 4-10% bei weight, preferred 6%) which is suitable for a complete solution. This solution is combined at a temperature of 30-50°C, preferred 40±5°C with a solution of 0.8-1.2 mol, preferred 1 mol of tilidine base in isopropanol of the above given water content under stirring in about stoechiometric amounts and the suspension obtained is slowly (over several hours) cooled under stirring. After washing with isopropanol of the above given water content there is obtained tilidine dihydrogen orthophosphate of 99.5% purity in a yield of more than 90%. Both of the parameters water content and reaction temperature are insofar important as there will be obtained at temperatures below 35°C and differing water content products with impurities of the solvents and bad crystallisation behavior, which are not completely dryable and retain persistent isopropanol.

Therefore, the present invention provides tilidine dihydrogen orthophosphate and a process for the preparation thereof. The present invention also provides a solid and especially a retarded solid galenical pharmaceutical composition consisting of conventional solid pharmaceutical adjuvants, as well as possibly retarding agents, which is characterised by a content of tilidine dihydrogen orthophosphate as active material, as well as process for the production thereof. The present invention is also

concerned with the use of tilidine dihydrogen orthophosphate for the production of solid and especially of retarded pharmaceutical compositions. The present invention is also concerned with the use of tilidine dihydrogen orthophosphate for the production of an analgesic. The present invention is also concerned with the use of tilidine dihydrogen orthophosphate, or a pharmaceutical composition containing it, as an analgesic. The present invention is further concerned with a commercial package comprising a pharmaceutical composition containing tilidine dihydrogen orthophosphate as described herein, and a written matter describing instructions for the use thereof for treating pain.

For the production of retarded solid pharmaceutical compositions containing tilidine, there can be used all conventional retarding processes which do not have a negative influence on the stability of the active material on the basis of their composition. A tablet retarded by a melt process according to EP-PS 0 043 254 is especially useful. However, quite generally, as retarding agents there can be used sparingly soluble materials, for example lipid or lipoid substances, such as stearic acid and especially

hydrogenated castor oil (Cutina HR) (DE-A 1 617 657, US-A 4,123,753) or hydrophilic polymers, which, as swelling materials, delay the liberation of the active material (see J. Pharm. Sci., p. 974/1966). For the objective control of the rate of liberation, there can also be used the process according to EP-PS 0 068 446 in which the rate of liberation of the active material from an active material composition retarded by means of sparingly-soluble substances is adjusted by the viscosity of an added hydrophilic polymer, for example methyl cellulose or carboxymethyl cellulose, starting from the knowledge that the speed of liberation increases with increasing viscosity.

For the demonstration of the surprising superiority of the dihydrogen orthophosphate,

a) tilidine hydrochloride semihydrate
b) tilidine hydrogen fumarate
c) tilidine hydrogen sulphate and
d) tilidine dihydrogen orthophosphate

were, in each case, triturated with naloxone hydrochloride dihydrate and conventionally employed adjuvants. Naloxone hydrochloride semihydrate is an effective morphine antagonist which commercially available tilidine compositions contain. Already after storage for 28 days at 60°C, distinct differences are shown between the four salts: whereas mixtures a) to c) were substantially discoloured, mixtures of d) showed no change of colour and thus no decomposition phenomena.

In a further experiment, three different salts of tilidine were, in each case, worked up with naloxone hydrochloride dihydrate, hydrogenated castor oil, lactose, hydroxyethyl cellulose, stearic acid, tablettose and magnesiulm stearate to give melt granulate tablets. With tilidine hydrogen fumarate, even in the case of the production of the melt granulate, there was shown a strong green coloration. The tablets with tilidine hydrochloride semihydrate already showed orange-grey discolorations after two days storage in brown glass containers at 22°C. On the other hand, the tablets with tilidine dihydrogen orthophosphate showed no discolorations under the same conditions even after storage for six months.

In the case of the production of the samples, the new dihydrogen orthophosphate also proved to be extremely good with regard to the working up properties.

Thus, it is in no way hygroscopic, does not react with metallic materials and is inert towards electrostatic charging. At a relative humidity of 63%, the hydrochloride semihydrate already takes up considerable amounts of water and acts corrosively on tools which are not specially protected against corrosion. In the case of a relative atmospheric humidity of 58%, the sulphuric acid salt already takes up water and exceeds the hydrochloride semihydrate in its aggressive corrosion behaviour. This can lead to imprecise weighed amounts and the partial demixing of the adjuvant and active materials.

It is to be understood that the expression "retarding agent" as used throughout this specification is equivalent to, and is used interchangeably with, the expression "sustained-release agent". It is also to be understood that the expression "retarded pharmaceutical composition(s)" as used throughout this specification is equivalent to, and is used interchangeably with, the expression "sustained-release pharmaceutical composition(s)".

The following Examples are given for the purpose of illustrating the present invention:

Example 1

Preparation of tilidine dihydrogen orthophosphate 27.091 kg

(99.10 mol) tilidine base are dissolved in 99 l of 94% isopropanol (6% water) with warming to about 40°C (±5°C).

While stirring, a solution of 11.54 kg of 85-88% orthophosphoric acid (corresponding to 9.844 kg = 100.46 mol of 100%, acid) is added thereto at 40°C in the course of 3 hours. For improved crystallisation, seed crystals are continuously added thereto. The suspension is slowly cooled overnight to ambient temperature, while stirring. The crystals are centrifuged off and washed twice with 10 l of 94% isopropanol. The white salt obtained is dried at 50 to 60°C. Yield: 33.89 kg (92.09% of theory). The salt has an analytical purity (HPLC) of 99.5%. M.p. 137.0°C. Molecular weight: 371.37. The IR spectrum of the salt is shown in Fig. 1 of the accompanying drawing.

Example 2

Retarded tablets containing 120 mg of tilidine dihydrogen orthophosphate

960 g tilidine dihydrogen orthophosphate, prepared according to Example 1, are premixed with 70.4 g naloxone hydrochloride dihydrate, 740 g lactose and 700 g hydrogenated castor oil and then slowly heated with continuing mixing to a product tentperature of 83°C. The resultant melt mass is removed from the mixing vessel and passed through a sieve of 2.5 mm size. After cooling to ambient temperature, the product is passed through a further sieve of 1 mm mesh size. Subsequently, 273.6 g ammonio methacrylate copolymer, 32 g magnesium stearate and 24 g silicon dioxide are sieved and uniformly mixed with the granulate. The mixture is then pressed with an eccentric press to give round, slightly domed tablets of 10 mm diameter, 11 mm dome radius and 350 mg nominal weight. The tablets obtained have the following composition:

tilidine dihydrogen orthophosphate	120.0 mg
naloxone hydrochloride dihydrate USP	8.8 mg
lactose	92.5 mg
hydrogenated castor oil	87.5 mg
aznmonio methacrylate copolymer	34.2 mg
magnesium stearate	4.0 mg
silicon dioxide	3.0 mg

The following product properties were determined for the tablets obtained:
weight average value: 351 mg , minimum 340 mg , maximum 362 mg, S_{rel} 1.8%
breaking strength: average value 82 N, minimum 64 N, maximum 90 N, S_{rel} 8.4%
friability: 0.23%
breakdown: more than 3 hours.

Example 3

Suppositories containing 59.93 mg tilidine dihydrogen orthophosphate
9700 g hard fat with a hydroxyl number of 40 - 50 (Witepsol W 35 (R)) or an alternative hard fat with a hydroxyl number of up to 2 (massa estarinum R 299) is melted at 45°C in a heatable vessel equipped with a stirrer until completely clear. After cooling to

36 to 38°C, 300 g tilidine dihydrogen orthophosphate are dispersed in the molten fat base with the help of an Ultra-Turrax (R) mixer. The product temperature is thereby maintained at 36 to 38°C, possibly with cooling of the mantle of the vessel. The melt ready for casting is then poured out in a shaping, filling and closing machine into suppository blisters made of triple-laminate film. The casting temperature at the dosing plant is maintained at 37°C. During the casting, the temperature of the vessel is 37°C. The dosage amount per filling station is 2.0 g ± 5%. The suppositories are cooled during transport through a cooling tunnel in which a temperature of 20 to 22°C prevails and thereby solidified. The blisters are subsequently heat-sealed and stamped out. In this way, up to 9000 suppositories can be produced per hour. The batch used in the present Example gives 4850 suppositories each containing 59.93 mg tilidine dihydrogen orthophosphate (corresponding to 50 mg tilidine hydrochloride).

CLAIMS:

1. Tilidine dihydrogen orthophosphate.

2. A process for the preparation of tilidine dihydrogen orthophosphate, comprising the steps of:

a) reacting tilidine base with 80-90% orthophosphoric acid in isopropanol with a water content of 4-10% by weight at a temperature of 30-50°C; and

b) isolating the tilidine dihydrogen orthophosphate.

3. The process according to claim 2, wherein the temperature is 40±5°C.

4. A pharmaceutical composition comprising a tilidine salt and a conventional adjuvant, wherein the tilidine salt is present as the dihydrogen orthophosphate.

5. The pharmaceutical composition according to claim 4, wherein it is present in solid form.

6. The pharmaceutical composition according to claim 4 or 5, further comprising a sustained-release agent.

7. The pharmaceutical composition according to claim 4, 5 or 6, which is a tablet, coated tablet, capsule, suppository or granulate.

8. The use of tilidine dihydrogen orthophosphate for the production of a solid pharmaceutical composition.

9. The use of tilidine dihydrogen orthophosphate according to claim 8 for the production of a sustained-release pharmaceutical composition.

10. The use of tilidine dihydrogen orthophosphate as an analgesic.

11. The use of the pharmaceutical composition of claim 4, 5, 6 or 7 as an analgesic.

12. The use of tilidine dihydrogen orthophosphate for the production of an analgesic.

13. A commercial package, comprising:

a) the pharmaceutical composition of claim 4, 5, 6 or 7; and

b) a written matter describing instructions for the use thereof for treating pain.

SMART & BIGGAR

OTTAWA, CANADA

PATENT AGENTS

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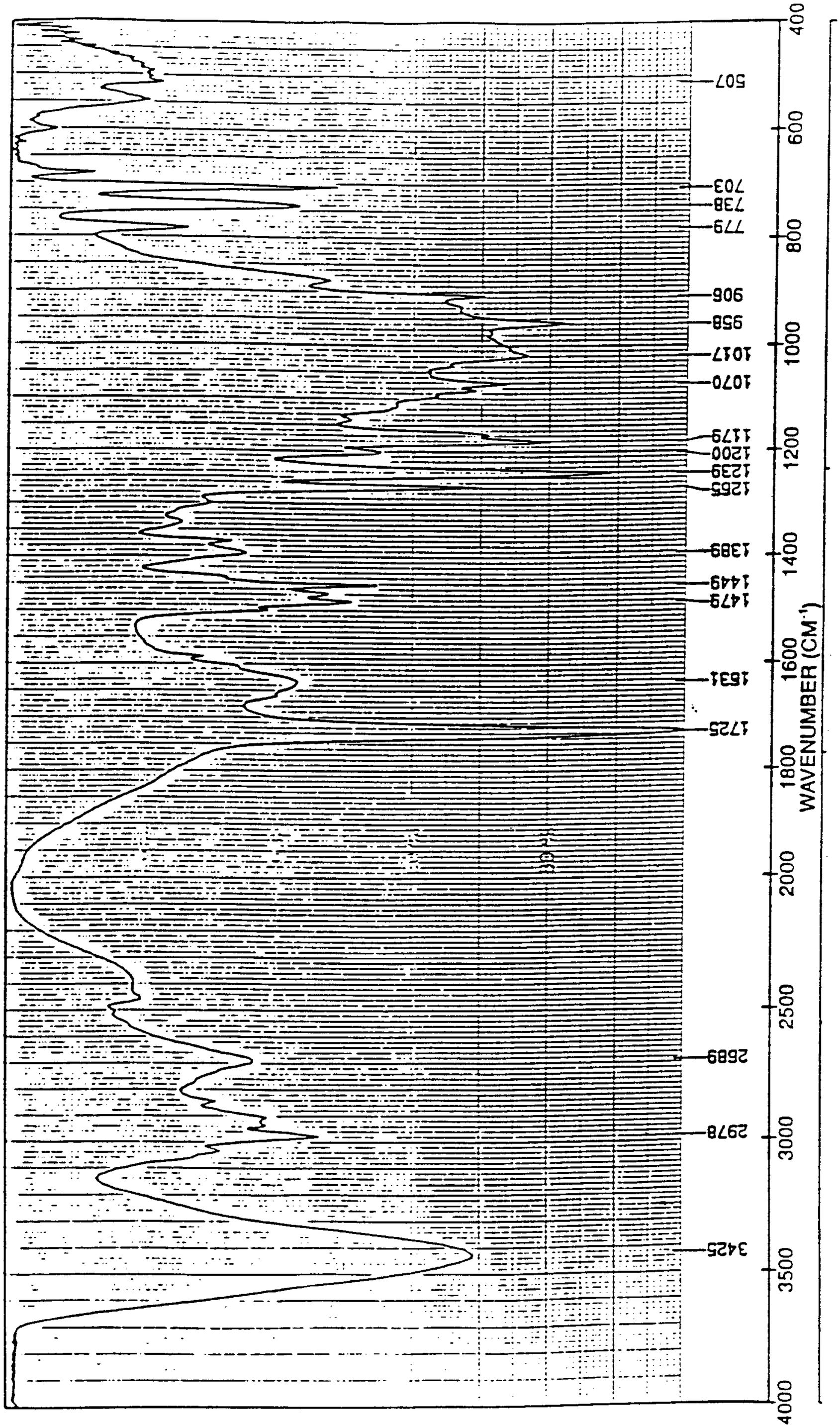

Figur 1

Patent Agents

Smart & [illegible]