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(57) Abstract

Tablet formulations for oral administration comprising a first layer which includes amoxycillin and/or clavulanate, and a second layer which includes amoxycillin and/or clavulanate. The overall tablet contains amoxycillin and the relative rate of release of amoxycillin and/or clavulanate from the first and second layers differs. The tablet formulations of the invention provide sustained release of amoxycillin and optionally also clavulanate.

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BILAYERED AMOXICILLIN TABLETS

This invention relates to novel tablet formulations for oral administration of amoxycillin optionally together with clavulanic acid.

Amoxycillin and clavulanic acid are respectively a known β-lactam antibiotic and a known β-lactamase inhibitor. Their use together in antibiotic formulations is disclosed in for example GB 2005538, which discloses formulations comprising amoxycillin trihydrate and potassium clavulanate. In oral formulations amoxycillin is generally used in the form of its trihydrate, and clavulanic acid is generally used in the form of a pharmaceutically acceptable salt (hereinafter "clavulanate") in particular potassium clavulanate.

It is desirable to provide oral pharmaceutical formulations which release their active material content at a controlled rate after oral administration, so that for example release of the active material into the stomach or intestine occurs over a period of several hours after ingestion of the formulation. This can allow unit doses of the formulation to be taken at widely separated intervals, for example twice daily, whilst maintaining a therapeutically effective plasma level of the active material content, such as amoxycillin and clavulanate.

Among various ways of achieving a controlled rate of release are layered tablets. For example GB 1346609 discloses three layer tablets having two drug-containing layers located one on each side of an inert disintegrable intermediate layer. The only drug substance mentioned in GB 1346609 is Mepyrizole. US 4122157 discloses a controlled release nitrofurantoin tablet which comprises two adjacent layers, one being a rapid release layer, the other being a slow release layer. US 4,839,177 discloses controlled release tablets comprising a deposit-core containing an active drug substance, with a support platform applied to this deposit core.

Particular problems are encountered with making controlled-release formulations which include clavulanate in combination with antibiotics such as amoxycillin. Amoxycillin trihydrate and clavulanate differ substantially in their solubility in water. Potassium clavulanate is very water soluble and amoxycillin trihydrate is relatively insoluble, so it is difficult to avoid rapid leaching out of potassium clavulanate from formulations containing these two in admixture. Also clavulanate is relatively sensitive to hydrolysis, so degradation of clavulanate may occur on contact with aqueous gastrointestinal contents during the relatively long periods between oral administration of controlled-release formulations.

According to this invention a tablet formulation for oral administration comprises a first layer which includes amoxycillin and/or clavulanate, and a second

layer which includes amoxycillin and/or clavulanate, provided that the overall tablet contains amoxycillin, wherein the relative rate of release of amoxycillin and/or clavulanate from the first and second layers differs.

Amoxycillin may suitably be used in the form of amoxycillin trihydrate, and clavulanate may be used in the form of potassium clavulanate. The tablet formulation may contain other antibacterial agents in addition to amoxycillin and clavulanate. Amoxycillin, clavulanate and any such other antibacterial agents which may be present are herein singly and collectively referred to as "active material content" unless otherwise specifically identified.

Tablet formulations of this invention may provide extended plasma levels of their active material content, for example of amoxycillin and clavulanate after ingestion.

When the formulation of the invention contains amoxycillin and clavulanate the overall weight ratio of amoxycillin : clavulanate (expressed as the free acid equivalent) may vary between broad limits, for example between 30 : 1 to 1 : 1. Suitably the ratio may be between 8 : 1 to 1 : 1, for example between 7 : 1 to 1 : 1, typically around 4 : 1, eg between 3.5 : 1 and 4.5 : 1. When both of the layers comprise amoxycillin and clavulanate the amoxycillin : clavulanate ratio in each layer may be the same as the overall tablet ratio or there may be different ratios in each of the layers, making up the ratio in the overall tablet. For example one layer may contain amoxycillin without clavulanate and the other layer may contain amoxycillin plus clavulanate, making up the ratio in the overall tablet. For example one layer may contain clavulanate without amoxycillin and the other layer may contain amoxycillin plus clavulanate, making up the ratio in the overall tablet. For example one layer may contain amoxycillin without clavulanate and the other layer may contain clavulanate without amoxycillin, making up the ratio in the overall tablet.

Suitably the tablet formulations of the invention may contain up to the maximum permitted daily dose of amoxycillin and clavulanate per unit dose. The formulations may for example contain nominally around 875 mg of amoxycillin and around 250 mg of clavulanate. Suitably unit dose tablets of the invention may contain the following nominal weights (mg) of amoxycillin: clavulanate (expressed as free acid equivalent); 875 : 125, 500 : 250, 500 : 125; 250 : 125 and 250 : 62.5.

The differing relative rate of release of active material content from the first and second layers of the tablet may be achieved in various ways.

For example differing rates of release may be achieved by a first layer which is a rapid release layer, ie which releases the bulk of its active material content within a relatively short time, for example within 1 hour, eg within 30 minutes after

oral injestion, and a second layer which is a slow release layer, ie which releases the bulk of its active material content during a relatively long period after oral ingestion or is a delayed release layer which releases the bulk of its active material content after a period of delay after oral ingestion, either in the stomach or in the intestine.

Rapid release layers may for example be rapid disintegrating layers having a composition similar to that of known rapid-disintegrating tablets. For example, the composition may comprise principally active material content, binders such as plasdone K29-32 (trade mark), compression aids, fillers or diluents such as mannitol, microcrystalline cellulose, and silicon dioxide, eg Syloid (trade mark), disintegrants, eg Explotab (trade mark), Avicel (trade mark) lubricants such as talc, magnesium stearate etc. Suitably such a rapid release layer may comprise around 30 - 70 % (all percentages given herein are on a weight percentage basis unless otherwise stated) eg 50-60% of active material content, around 10 - 30% of fillers/compression aids, and conventional amounts of disintegrants and lubricants etc.

An alternative type of rapid-release layer may be a swellable layer having a composition which incorporates polymeric materials which swell rapidly and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass. Active material content may be rapidly leached out of this mass.

Slow release layers may have a composition which comprises active material content together with a release retarding material. Suitable release retarding materials include pH sensitive polymers, e.g. the known Eudragit (trade mark) polymers, for example Eudragit L (trade mark), i.e polymers based upon methacrylic acid copolymers, used either alone or with a plasticiser, release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents, polymeric materials which form a gel on contact with water or aqueous media, and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

Polymers which have a high degree of swelling include, inter alia, cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols etc. Gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone etc. Polymers

simultaneously possessing swelling and gelling properties include medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinylalcohols.

Examples of such polymers include Methocel K4M (Trade Mark), Methocel E5 (Trade Mark), Methocel E5O (Trade Mark), Methocel E4M (Trade Mark), Methocel K15M (Trade Mark) and Methocel K100M (Trade Mark). An example of a suitable polymer mixture is a mixture of Methocel E5 and K4M, for example1:1, w:w.

Other known release-retarding polymers which may be incorporated include hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, proteinaceous substances such as acacia, gum tragacanth, locust bean gum, guar gum, agar, pectin, carageenam, soluble and insoluble alginates, carboxypolymethylene, gelatin, casein, zein, Veegum (trade mark) and the like.

Such a slow release layer may contain polymers which rapidly swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not rapidly discharged from the stomach into the intestine.

Suitably such a slow release layer may contain around 30-70% eg 40 - 60%, of active material content, around 15 - 45% of release-retarding polymers, around 0-30% of fillers/compression aids, conventional quantities of disintegrants and lubricants, and some 5 - 20% of soluble excipients.

Alternative types of slow- or delayed- release layer are those in which the active material content is mixed with, coated with, or embedded in a matrix of a poorly soluble or practically insoluble excipient (e.g. calcium phosphate etc) and/or a hydrophobic excipient (e.g. fats or waxes). Poorly soluble or practically insoluble excipients can yield a very hard tablet which would slowly dissolve or erode from the surface without substantial diffusion of surrounding liquid into the body of the tablet. Hydrophobic excipients similarly hinder moisture ingress and release of active material content occurs through erosion and enzymatic digestion. Examples of such waxes include Compritol (trade mark), for example Compritol HD5 and Compritol 888 (trade marks). Compritol wax remains intact in aqueous solutions at all pH, but is digested by lipase enzymes at pH 5-7. Thus active material content such as clavulanate protected with Compritol wax as described above may be released primarily in the small intestine due to the action of intestinal lipase. Typically when the slow- or delayed- release layer includes such a wax, the wax may suitably comprise 10-80% of the layer, e.g. around 20-40%, e.g. 30% ± 5% by weight.

Delayed-release layers may use the known properties of enteric polymers to delay release of active material content until the whole or part of the tablet is discharged by the stomach into the intestine after oral ingestion. Enteric polymers

are insoluble or only slightly soluble in the stomach contents, but relatively soluble in the higher pH intestinal environment. Individual particles, e.g. granules of active material content may be coated with a layer of or made up with an enteric polymer, and embedded or dispersed within a soluble or disintegrable matrix. Alternatively a delayed release layer may comprise a matrix of enteric polymer within which are dispersed granules comprising active material content, and these granules may themselves be coated with an enteric polymer layer. Such granules may include conventional granulating materials. Examples of suitable enteric polymer materials include the known Eudragit (trade mark) polymers discussed above.

Such a slow-or delayed-release layer may also include fillers/compression aids such as microcrystalline cellulose, eg Avicel (trade mark), desiccants, such as silicon dioxide, eg Syloid (trade mark), disintegrants, eg Explotab (trade mark) and polyvinyl-pyrrolidone, eg polyvidon K30 (trade mark), lubricants such as talc or magnesium stearate, pH-controlling agents such as potassium dihydrogen phosphate or substantially insoluble ion-exchange resins, and soluble excipients such as mannitol or other soluble sugars.

Differing rates of release may also be achieved by having a first layer which is a slow or delayed release layer, and a second layer which is also a slow or delayed release layer. Such first and second layers may for example differ in their composition, so that they comprise different quantities, combinations or types of release-retarding materials and/or soluble excipients etc. Additionally or alternatively such first and second layers may for example differ in the relative amounts of active material content in the first and second layers.

Due to the difference in solubility of amoxycillin and clavulanate, the former may be only slowly dissolved out of a layer, whereas the latter, unless the layer is very impervious or hydrophobic, may be dissolved out relatively rapidly. Therefore if a layer contains both amoxycillin and clavulanate it may be at the same time a slow- or delayed- release amoxycillin layer but a rapid-release clavulanate layer. For example such a layer may comprise amoxycillin trihydrate, potassium clavulanate and the erodable polymer Methocel E5 (trade mark).

In this above-described tablet having two slow or delayed release layers, one or both of the first and second layers may for example be slow release layers comprising active material together with release retarding materials as described above. Alternatively one or both of the first or second layers may be a delayed release layer using enteric polymers as described above.

The tablet formulations of the invention may also include one or more barrier layers, which may be located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers, for

example the end faces of the layers of a substantially cylindrical tablet. Such barrier layers may for example be composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media. Suitably the barrier layer should be such that it retains these characteristics at least until complete or substantially complete transfer of the active material content to the surrounding medium.

Suitable polymers for the barrier layer include acrylates, methacrylates, copolymers of acrylic acid, celluloses and derivatives for the barrier layer such as ethylcelluloses, cellulose acetate propionate, polyethylenes and polyvinyl alcohols etc. Alternatively barrier layers may comprise enteric polymers. Barrier layers comprising polymers which swell in contact with water or aqueous media may swell to such an extent that the swollen layer forms a relatively large swollen mass, the size of which delays its rapid discharge from the stomach into the intestine. The barrier layer may itself contain active material content, for example the barrier layer may be a slow or delayed release layer. Barrier layers may typically have an individual thickness of 2mm to 10 microns.

Suitable polymers for barrier layers which are relatively impermeable to water include the Methocel (trade mark) series of polymers mentioned above, e.g. Methocel K100M, Methocel K15M, Methocel E5 and Methocel E50, used singly or combined, or optionally combined with an Ethocel (trade mark) polymer. Such polymers may suitably be used in combination with a plasticiser such as hydrogenated castor oil. The barrier layer may also include conventional binders, fillers, lubricants and compression acids etc such as Polyvidon K30 (trade mark) magnesium stearate, and silicon dioxide, e.g. Syloid 244 (trade mark).

The tablet formulation of the invention may be wholly or partly covered by a coating layer, which may be a protective layer to prevent ingress of moisture, or damage to the tablet, or may be an enteric coating layer, for example of the known Eudragit (trade mark) polymers described above. The coating layer may itself contain active material content, and may for example by a rapid release layer, which rapidly disintegrates in contact with water or aqueous media to release its active material content for example of amoxycillin, or amoxycillin plus clavulanate combined.

As well as active material content etc, the tablet of the invention may also include a pH modifying agent, such as a pH buffer, which may be contained in either rapid-, slow-, or delayed release layers, or in a coating around all or part of the tablet. A suitable buffer is calcium hydrogen phosphate.

The various first and second layers, barrier layers and coating layers may be

combined in various ways to form embodiments of tablet formulations of the present invention, as described below.

One embodiment comprises a tablet having a rapid disintegrating first layer which contains amoxycillin and/or clavulanate as active material, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release-retarding polymers such as Methocel E5, E50, E4M, K4M, K15M and K100M and mixtures thereof, with a barrier layer of either a substantially completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate. Suitably the rapid disintegrating and slow release layers may both contain only amoxycillin as active material, or the rapid disintegrating and slow release layers may both contain amoxycillin plus clavulanate, or only the rapid disintegrating layer may contain clavulanate and the slow release layer may contain only amoxycillin as active material content.

Typically the first layer in such a tablet contains around 20-35%, eg around 25-30% of the overall tablet active material content. Suitably the first layer comprises 15-35%, the second layer comprises 50-70%, and the barrier layer comprises 5 - 30% of the overall tablet weight.

A further embodiment comprises a tablet having a rapid-disintegrating first layer which contains amoxycillin and/or clavulanate as active material, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers such as Methocel E5, E50, E4M, K4M, K15M or K100M or mixtures thereof, but without a barrier layer, the overall tablet containing amoxycillin or amoxycillin plus clavulanate. Suitably the first layer in such a tablet contains some 20 - 35%, eg 25 - 30% of the overall active material content.

A further embodiment comprises a slow-release first layer which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a second layer which is also a slow-release layer and which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate.

Suitably in this embodiment the first layer may contain amoxycillin without clavulanate and the second layer may contain amoxycillin plus clavulanate, or the first and second layers may both contain amoxycillin plus clavulanate, or the first layer may contain amoxycillin without clavulanate and the second layer may contain clavulanate without amoxycillin. Suitable release-retarding polymers include

Methocel E5, E50, E4M, K4M, K15M and K100M or mixtures thereof. Suitably the first and second layers in such a tablet may each contain some 30 - 60% of the active material content making up the overall tablet content of 100%. Suitably the first layer comprises 30 - 60%, the second layer comprises 30-60% and the barrier layer comprises 5-20%, of the overall tablet weight.

A further embodiment comprises a slow-release first layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a substantially completely impermeable polymer or a slowly erodable polymer located on one of the end faces of the tablet.

Suitably the first layer may contain amoxycillin without clavulanate as its active material and the second layer may contain amoxycillin plus clavulanate (eg in a 1 : 1 ratio) as its active material, with the barrier layer located on the end face of the second layer, the overall tablet containing amoxycillin or amoxycillin plus clavulanate. Suitable release-retarding polymers are Methocel E5, E50, E4M, K4M, K15M and K100M or mixtures thereof. Suitably the first layer and second layers may respectively contain some 35 - 70% and 20 - 50% of the active material content. Suitably the first layer comprises 35 - 70%, the second layer 20 - 50% and the barrier layer 5 - 20% of the overall tablet weight.

A further embodiment comprises a rapid release first layer which is a swellable layer as described above containing amoxycillin, and a slow-release or delayed release second layer as described above containing amoxycillin, or clavulanate, or amoxycillin plus clavulanate, having a barrier layer of either a substantially or completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers.

A further embodiment comprises a slow-release first layer comprising amoxycillin optionally together with clavulanate as active material, and a second layer which is a delayed release layer comprising a disintegrable or soluble matrix within which are dispersed enteric polymer coated granules which comprise clavulanate, optionally together with amoxycillin, with a barrier layer sandwiched between the first and second layers. Suitably the first layer may comprise amoxycillin and a Methocel (trade mark) polymer such as Methocel E5, and the second layer may comprise granules of a mixture of amoxycillin and clavulanate, together with a suitable granulating material such or a Methocel (trade mark) polymer such as Methocel K4M, coated with a Eudragit polymer such as Eudragit L.

A further embodiment comprises a first layer which is a slow release layer

containing polymers which rapidly swell in contact with water or aqueous media so that the swollen mass is not rapidly discharged from the stomach containing amoxycillin or amoxycillin plus clavulanate as active material, and a second layer which is a slow release layer containing amoxycillin or amoxycillin plus clavulanate as active material, with a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers. The tablet of this embodiment may optionally be surrounded by a coating layer which is a rapidly disintegrating composition containing amoxycillin and clavulanate as active material.

A further embodiment is a tablet comprising three layers tablet in which all the three layers include an active material content. Suitably such a tablet may comprise a slow-or delayed-release first layer which comprises amoxycillin, optionally together with clavulanate, a rapid-release second layer which comprises amoxycillin, optionally together with clavulanate, and a third layer, sandwiched between the first and second layers, and being a slow- or delayed-release layer comprising calvulanate, optionally together with amoxycillin. Suitably in such a tablet the first layer may include amoxycillin without clavulanate, the second layer may comprise a mixture of amoxycillin plus clavulanate, and the third layer may comprise clavulanate or a mixture of clavulanate and amoxycillin. The first layer may suitably comprise amoxycillin and a release-retarding polymer such as Methocel E5 (trade mark) optionally together with a swellable material, the second layer may comprise a mixture of amoxycillin and clavulanate together with conventional fillers, binders, disintegrants etc, and the third, intermediate layer may comprise amoxycillin, clavulanate and a release retarding polymer such as Methocel K100M.

Each of the above-mentioned embodiments of the invention may be coated with a polymer layer, for example an enteric polymer such as the Eudragit (trade mark) polymers mentioned above, or a coating layer which contains active material content, such as a rapid-release layer which includes amoxycillin and/or clavulanate.

Suitably the tablet formulations of the invention may be formed by known compression tabletting techniques for example using a known multi-layer tabletting press. Suitably a dry densification process may be used, e.g. briquetting. Typically the active material content, pH modifiers, buffers, fillers and/or diluent, release retarding agents, disintegrants and binders, when used are mixed, then lubricants and compression aids are added. The complete mixture may then be compressed under high pressure in the tablet press. Roller compaction may be used to form granulates for compaction. Alternatively wet granulation may be used,

isopropanol being a suitable solvent. A suitable wet granulating aid is Polyvidon K-30 (trade mark).

For making up layers which include a wax, e.g. Compritol (trade mark) dry compression or wet granulation may be used. Typically for wet granulation a colloidal solution or suspension of the wax in a solvent such as dichloromethane may be used. Typically the solution or suspension may be mixed with the layer ingredients and the wet cake sieved and dried. This can be repeated until the required amount of wax has been incorporated.

The barrier layer may typically be made up by a wet granulation technique, or by dry granulation techniques such as roller compaction. Typically the barrier material, e.g. Methocel (trade mark) is suspended in a solvent such as ethanol containing a granulation acid such as Ethocel or Polyvidon K-30 (trade mark), followed by mixing, sieving and granulation. Typically a first layer may be formed, then a barrier layer deposited upon it, eg by compression, spraying or immersion techniques, then the second layer may be formed so that the barrier layer is sandwiched between the first and second layers. Additionally or alternatively the first and second layers may be formed and a barrier layer may then be formed, eg by compression, spraying or immersion, on one or more of the end faces of the tablet. An enteric polymer coating may be applied to the whole or part of the tablet formulation of the invention by conventional spraying or immersion techniques.

For applying an enteric coating to particles used to make up the layers of the tablet of the invention, typically a solution or suspension of the enteric polymer, e.g. Eudragit (Trade Mark), is mixed with the active material content, e.g. powders or granules e.g. make up as described above, and the wet cake is sieved and dried. This procedure may be repeated until the required amount of the polymer is incorporated. Alternatively the granule ingredients or the granules themselves may be coated with enteric polymer by means of a fluid bed granulator, for example spray-coating the ingredients with a solution of the polymer e.g. in isopropanol.

Clavulanic acid and its derivatives are known to be extremely water sensitive, potassium clavulanate being the most stable pharmaceutically acceptable derivative. Therefore formulations which contain derivatives of clavulanic acid, such as potassium clavulanate, should be made up in dry conditions, preferably at 30% relative humidity or less, and the ingredients of the formulation should be pre-dried where appropriate. Formulations of the invention which include derivatives of clavulanic acid should be stored in containers which are sealed against the ingress of atmospheric moisture.

The invention also provides a method for the manufacture of a tablet formulation as described above comprising the steps of forming said first and

second layers, and any barrier layers and coating layer(s) which may be present.

The invention further provides a formulation as described above for use as a therapeutic substance for oral administration for the treatment of bacterial infections.

The invention further provides a method of use of a formulation as described above, in the manufacture of a medicament for the treatment of bacterial infections.

The invention further provides a method of treatment of bacterial infections in humans or animals which comprises the administration thereto of a therapeutically effective amount of active material content included in a formulation as described herein.

The invention will now be described by way of example only with reference to the accompanying drawings, in which:

Fig. 1 shows the structure of various types of tablet formulation of the present invention.

Figs. 2, 3, 4, 5 and 6 show *in vitro* and *in vivo* release characteristics from tablet 6-1.

Referring to Fig 1, substantially cylindrical compressed tablets of the present invention are shown in longitudinal section. In Fig 1A, the tablet comprises a first layer (1) and a second layer (2), without any barrier layer or coating layer. In Fig 1B the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) sandwiched between the first and second layers (1) and (2). In Fig 1C, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) located on the end face of the second layer (2). In Fig 1D the tablet comprises a first layer (1), a second layer (2), a barrier layer (3) sandwiched between the first and second layers (1) and (2), and a coating layer (4) which partly covers the tablet. The dotted line shows the possibility of the coating layer (4A) covering the entire tablet. In Fig. 1E the tablet comprises a first layer (1) a second layer (2), and a third layer (3) intermediate between the first and second layers (1) and (2). All three of these layers (1), (2) and (3) include active material content.

(In the examples and figures below "AMX" is an abbreviation for amoxycillin, and "KCA" is an abbreviation for potassium clavulanate).

Barrier Layers

In the Examples below, barrier layers L1, S2, S6 and RSB1 are referred to. The composition of these layers and the method for preparing them was as follows:

	Amounts in %			
	L1	**S2**	**S6**	**RSB1**
Methocel K100M	79.75%	--	--	--
Methocel K15M	--	--	--	38.20%
Methocel E5	--	75.50%	--	--
Methocel E50	--	--	76.50	--
Mannitol	--	--	--	38.20%
Hydrogenated castor oil	13.50%	18.80%	18.40%	18.50%
Yellow FCF aluminium lake	0.25%	--	--	--
Eudralak green	--	0.10%	0.10%	0.10%
Ethocel	5.00%	--	--	--
Polyvidon K30	--	2.80%	3.50%	3.50%
Mg-Stearate	1.00%	1.90%	1.00%	1.00%
Syloid 244	0.50%	0.90%	0.50%	0.50%
Total:	100.00%	100.00%	100.00%	100.00%

The binding ingredient (Ethocel or Polyvidon K-30) was dissolved in Ethanol (94%). Methocel, Cutina HR and dye were mixed for 5 minutes in a Lödige MGT 30P at 150 r.p.m. after which the granulation solution was added. Mixing was continued for another 5 minutes. The wet granulate was dried at 45°C. The dry granulate was passed through a 1 mm sieve. Mg-stearate and Syloid 244, which had been passed through a 0.71 mm sieve, were added and the whole was mixed in the Lödige during 1 min at 150 r.p.m. to homogeneity

Preparation of Tablets

The active ingredients, fillers and diluents (mannitol), release controlling agents (Methocels) or disintegrants (Avicel, Explotab) and binders (Plasdone K29-32) were mixed during 5 minutes in a Stefan Mixer at speed level 11. Lubricants (talc, Mg-stearate) and colloidal silicon dioxide (Syloid 244) were added, and mixing at level 1 was continued for another minute. The complete mixture was slugged on a Kilian tablet press (briquetting step), followed by size reduction (Frewitt) and passage through an oscillatory 1 mm sieve. If the flow properties were unsatisfactory, the briquetting step was repeated. The tablets of Examples 1 to 4 were prepared in this way.

The tablets of subsequent Examples were prepared by non-aqueous wet granulation. In most cases, isopropanol was chosen as the most appropriate non-aqueous solvent. In the formulations with Compritol, dichloromethane was used. In the non-aqueous granulation step an isopropanolic solution of polyvidon K-30

was mixed with a powder mixture of active ingredients and methocels (and fillers, buffers, etc.). The wet cake was pressed through a 0.5 mm sieve, the mixing was repeated and followed by sieving through a 2 mm sieve. After drying at 40°C the dry material was passed through a 1 mm sieve. Magnesium stearate and talc were added and mixed.

This granulate possessed good flow properties. In some cases, where the bulk density was rather low a densifying step (pre-tabletting and sieving as in the briquetting method) was still required in order to achieve the nominal weight of a particular layer.

Coating particles and granules with Eudragit L was performed in a similar manner. A solution of Eudragit in isopropanol was mixed with the active ingredients or with a granulate (without talc and Mg-stearate) prepared in the aforementioned wet granulation manner. The wet cake was pressed through a 0.5 mm sieve, the mixing was repeated and followed by sieving though a 2 mm sieve. After drying at 40°C the dry material was passed through a 1 mm sieve. The treatment with Eudragit, sieving and drying was repeated until the nominal amount of Eudragit L according to the recipe was contained within the granulate. Then Mg-stearate and talc were added and mixed.

Other coating work with Eudragit L involved the use of a fluid bed granulator. The active ingredients were spray-coated with an isopropanolic solution of Eudragit L in a Glatt fluid bed granulator to 20% Eudragit L of the weight of the active ingredients. Samples were taken at the 5, 10, 15 and 20% Eudragit weight level. In addition, a granulate of active ingredients with Methocels was prepared in the Glatt employing an isopropanolic solution of polyvidon K-30. This granulate was then spray-coated with Eudragit L on the Glatt.

The formulation work with Compritol either involved dry compression or a wet granulation step with a colloidal solution of Compritol in dichloromethane. The wet granulation was analogous to the Eudragit wet granulation. The treatment with the Compritol solution, sieving and drying was repeated until the nominal amount of Compritol according to the recipe was contained within the granulate. Then Mg-stearate and talc were added and mixed.

Dissolution Testing Methods

The release of amoxycillin and clavulanate from tablets into static media was measured using the USP Dissolution Test Method II.

The release of amoxycillin and clavulanate from tablets into flowing water and other media was measured using the USP Method IV Dissolution , using large (22.6 mm, 8.3 ml/min) and small (12 mm 8.3 ml/min) cells.

The test was performed according to USP XXXII <724>, apparatus 4.

Dissolution apparatus:

Dissolution apparatus:	SOTAX CE6 flow cell
	SOTAX CY7-50 pump

Test specifications:

Temperature:	37.0 ± 0.5°C
Test medium:	0 - 2h: HCl 0.01 M (pH 2.0)
	2 - 8h: phosphate buffer 0,05 M; pH = 6.6
Flow rate:	8.3 ml/min (500 ml/h)
Flow cell:	22.6 mm diameter

Solutions:

- 0.05 M phosphate buffer solution 3 (pH 6.6): Dissolve 544g potassium dihydrogenphosphate in 20.0L water and adjust to pH 6.6 with NaOH 40% (m/v).
- 0.05 M phosphate buffer solution 4 (pH 6.6): Dissolve 408g potassium dihydrogenphosphate and 39g sodium hydroxide pellets p.a. in 60L water.

Method:

Three tablets were tested each as follows. A 5 mm diameter ruby bead was placed at the bottom of the cone of the flow cell and the cone was filled with 1 mm diameter glass beads. A tablet was introduced into the cell and fixed vertically using a holder. The filter head was assembled and the parts fixed together by means of a clamping device. The dissolution medium warmed to 37.0 ± 0.5°C was introduced through the bottom of the cell at a flow rate of 8.3 ml/min. 0.01 M HCl from the beginning to 2 hours was used, then changed to buffer solution 4 until the end of the run.

The drug release after 30 min, 60 min 2 h 3 h, 4 h, 5 h, 6 h, 7 h and 8 h was determined.

As Potassium Clavulanate is very unstable at low pH values, the fractions for the time from 0 to 2 hours (medium 0.01 M HCL) were collected directly in a buffer solution and were mixed well with this buffer in a ratio of about 1:1.

Example 1

Tablets 1.1, 1.2 and 1.3, each having a structure as shown in Fig 1B were prepared using an oval biconvex punch 21 x 10 mm, having a rapid-disintegrating first layer and a slow-release second layer, with a barrier layer between. The composition of these tablets is as follows:

	Amounts in mg		
	1.1	**1.2**	**1.3**
First Layer			
AMX.$3H_2O$	160.7	160.7	160.7
(= AMX f.a.)	(138.8)	(138.8)	(138.8)
Avicel PH 102	44.8	44.8	44.8
Explotab	11.2	11.2	11.2
Talc	22.3	22.3	22.3
Mg-Stearate	8.4	8.4	8.4
Syloid 244	5.6	5.6	5.6
weight of layer	253.0	253.0	253.0
Barrier Layer	L1	L1	S2
weight of layer	180.0	180.0	180.0
Second Layer			
AMX.$3H_2O$	413.3	413.3	413.3
(= AMX f.a.)	(357.1)	(357.1)	(357.1)
Methocel K4M	72.0	72.0	72.0
Methocel E5	72.0	72.0	72.0
Mannitol	72.0	26.0	72.0
KH_2PO_4	-	46.0	-
Polyvidon K30	28.6	28.6	28.6
Talc	7.2	7.2	7.2
Mg-Stearate	2.9	2.9	2.9
weight of layer	668.0	668.0	668.0
Total tablet weight	**1101.0**	**1101.0**	**1101.0**
Total content AMX f.a.	495.9	495.9	495.9

Example 2

Tablets 2.1 and 2.2 each having a structure as shown in Fig. 1B were prepared using an oval biconvex punch 21 x 10mm, having a first layer which is a rapid disintegrating layer, a second layer which is a slow-release layer, and a barrier layer sandwiched between them. These tablets had the following composition:

	Amounts in mg	
First Layer	**2.1**	**2.2**
AMX.3H_2O	118.7	118.7
(= AMX f.a.)	(102.6)	(102.6)
AMX.3H_2O : KCA 1:1*	83.4	83.4
(= AMX f.a.)	(35.1)	(35.1)
(= CA f.a.)	(36.3)	(36.3)
Avicel PH 102	45.1	45.1
Explotab	11.4	11.4
Talc	22.4	22.4
Mg-Stearate	8.4	8.4
Syloid 244	5.6	5.6
weight of layer	295.0	295.0
Barrier Layer	L1	L1
weight of layer	160.0	160.0
Second Layer		
AMX.3H_2O	305.27	305.27
(= AMX f.a.)	(263.75)	(263.75)
AMX.3H_2O : KCA 1:1*	214.40	214.40
(= AMX f.a.)	(90.26)	(90.26)
(= CA f.a.)	(93.26)	(93.26)
Methocel K4M	62.00	62.00
Methocel E5	62.00	62.00
Mannitol	46.00	-
KH_2PO_4	-	46.00

Polyvidon K30	10.03	10.03
Talc	5.00	5.00
Mg-Stearate	20.30	20.30
weight of layer	725.00	725.00

Total tablet weight	**1180.00**	**1180.00**
Total content AMX f.a.	491.7	491.7
Total content CA f.a.	129.6	129.6

* **Note:** Potassium clavulanate was used in the form of a commercially available 1 : 1 mixture of potassium clavulanate and amoxycillin trihydrate.

Example 3

Tablets 3.1 and 3.2 each having a structure as shown in Fig 1C were prepared, using respectively oval biconvex punch 18 x 8 mm and 21 x 10 mm, having a first layer which is a slow release layer, a second layer which is also a slow release layer and a barrier layer located on the end face of the second layer. These tablets had the following composition:

	Amounts in mg	
First Layer	**3.1**	**3.2**
AMX.$3H_2O$	305.27	327.52
(= AMX f.a.)	(263.75)	(282.98)
Methocel K4M	53.18	57.06
Methocel E5	53.18	57.06
Mannitol	53.18	57.06
Polyvidon K30	18.03	19.34
Talc	5.31	5.70
Mg-Stearate	5.85	6.26
weight of layer	494.00	530.00

Second Layer		
AMX.3H_2O : KCA 1:1	202.04	214.40
(= AMX f.a.)	(85.06)	(90.26)
(= CA f.a.)	(87.89)	(93.26)
Methocel K4M	35.20	37.35
Methocel E5	35.20	37.35
Mannitol	35.20	37.35
Polyvidon K30	11.99	12.72
Talc	3.52	3.73
Mg-Stearate	3.85	4.10
weight of layer	327.00	347.00
Barrier Layer	S6	S6
weight of layer	150.00	180.00
Total tablet weight	**971.00**	**1057.00**
Total content AMX f.a.	348.8	373.3
Total content CA f.a.	87.9	93.3

Example 4

Tablets 4.1, 4.2, 4.3, 4.4, 4.5 and 4.6, each having a structure as shown in Fig 1B were prepared, using oval biconvex punches 21 x 10 mm, having a first layer which is a slow-release layer, a second layer which is also a slow-release layer, and a barrier layer sandwiched between the first and second layers. These tablets had the following compositions.

Amounts in mg						
First Layer	4.1	4.2	4.3	4.4	4.5	4.6
AMX.$3H_2O$	305.27	305.27	305.27	305.27	305.27	305.27
(=AMX f.a.)	(263.75)	(263.75)	(263.75)	(263.75)	(263.75)	(263.75)
Methocel K4M	35.42	35.42	35.42	35.42	35.42	35.42
Methocel E5	70.94	70.94	70.94	70.94	70.94	70.94
Mannitol	88.53	88.53	88.53	88.53	88.53	88.53
Polyvidon K30	18.03	18.03	18.03	18.03	18.03	18.03
Talc	5.31	5.31	5.31	5.31	5.31	5.31
Mg-Stearate	6.50	6.50	6.50	6.50	6.50	6.50
weight of layer	530.00	530.00	530.00	530.00	530.00	530.00

Barrier Layer	L1	L1	L1	L1	L1	L1
weight of layer	180.00	180.00	180.00	180.00	180.00	180.00

Second Layer	4.1	4.2	4.3	4.4	4.5	4.6
AMX.3H_2O:KCA 1:1	214.90	214.90	214.90	214.90	214.90	214.90
(=AMX f.a.)	(90.47)	(90.47)	(90.47)	(90.47)	(90.47)	(90.47)
(=CA f.a.)	(93.48)	(93.48)	(93.48)	(93.48)	(93.48)	(93.48)
Methocel E5	120.00	--------	-------	-------	120.00	-------
Methocel E50	--------	120.0	-------	-------	-------	120.00
Methocel E4M	--------	--------	120.00	120.00	-------	-------
Methocel K4M	--------	--------	30.00	-------	-------	-------
Methocel K15M	--------	--------	-------	-------	30.00	30.00
Methocel K100M	30.00	30.00	-------	30.00	-------	-------
Mannitol	67.86	67.86	67.86	67.86	67.86	67.86
Polyvidon K30	16.86	16.86	16.86	16.86	16.86	16.86
Talc	4.94	4.94	4.94	4.94	4.94	4.94
Mg-Stearate	5.44	5.44	5.44	5.44	5.44	5.44
weight of layer	460.00	460.00	460.00	460.00	460.00	460.00
Total tablet weight	1170.00	1170.00	1170.00	1170.00	1170.00	1170.00
Total AMX f.a.	354.3	354.3	354.3	354.3	354.3	354.3
Total CA f.a.	93.5	93.5	93.5	93.5	93.5	93.5

Example 5

Tablets 5.1, 5.2, 5.3, and 5.4 were prepared having a structure as shown in Fig. 1B.

	Amounts			
First Layer	5.1	5.2	5.3	5.4
AMX.$3H_2O$(mg)	320	215	320	210
Methocel K4M%	8.2	8.2	8.2	8.2
Methocel E5%	16.4	16.4	16.4	16.4
Barrier Layer	L1	L1	L1	L1
Second Layer				
AMX.$3H_2O$ (mg)	121	121	121	121
KCA (mg)	125	125	125	125
Methocel K4M %	10	30	-------	-------
Methocel K100M %	--------	--------	10	20

Example 6

Tablets 6.1 and 6.2 were prepared having a structure as shown in Fig. 1C.

	Amounts in mg	
First Layer	**6.1**	**6.2**
AMX.$3H_2O$	438.71	438.71
(= AMX f.a.)	(379.05)	(379.50)
AMX.$3H_2O$/K-CA 1:1	103.45	103.45
(= AMX f.a.)	(43.55)	(43.55)
(= CA f.a.)	(45.0)	(45.0)
Methocel K4M	26.91	26.91
Methocel E5	107.63	107.63
Polyvidon K30	25.20	25.20
Talc	9.36	9.36
Mg-Stearate	8.64	8.64
weight of layer 1	719.90	719.90

Second Layer		
AMX.3H_2O/K-CA 1:1	183.91	183.91
(= AMX f.a.)	(77.4)	(77.4)
(CA f.a.)	(80.0)	(80.0)
Methocel K15M	32.04	-------
Methocel K100M	--------	32.04
Methocel E50	32.04	32.04
Polyvidon K30	8.75	8.75
Talc	3.30	3.30
Mg-Stearate	3.05	3.05
weight of layer 2	263.09	263.09

Barrier layer	S6	S6
weight of layer	180.00	180.00
Total tablet weight	**1162.99**	**1162.99**

Example 7

Tablets 7.1, 7.2 and 7.3 were prepared having a structure as shown in Figs 1B (7.1) and 1E (7.2, 7.3).

	Amounts in mg
First Layer	**7.1**
AMX.3H_2O	438.71
(= AMX f.a.)	(379.05)
AMX.3H_2O/K-CA 1:1	103.45
(= AMX f.a.)	(43.55)
(= CA f.a.)	(45.00)
Methocel E5	134.64
Polyvidon K30	25.20
Talc	9.36
Mg-Stearate	8.64
weight of layer 1	720.00

Barrier layer	L1
weight of layer	180.00

Second Layer	
AMX.3H_2O/K-CA 1:1	183.91
(= AMX f.a.)	(77.4)
(= CA f.a.)	(80.0)
Methocel K100M	49.71
Polyvidon K30	8.70
Talc	3.23
Mg-Stearate	2.98
weight of layer 3	248.53
Total tablet weight	**1148.53**

In tablet 7.1 the potassium clavulanate in the first layer is a rapid release component, as the erodable polymer Methocel E5 allows rapid dissolution of soluble potassium clavulanate.

	Amounts in mg	
First Layer	**7.2**	**7.3**
AMX.3H_2O	319.96	319.96
(= AMX f.a.)	(276.45)	(276.45)
Methocel E5	100.00	100.00
Mannitol	50.04	50.04
Polyvidon K30	17.50	17.50
Talc	6.50	6.50
Mg-Stearate	6.00	6.00
weight of layer 1	500.00	500.00

Third Layer		
$AMX.3H_2O$/K-CA 1:1	203.91	203.91
(= AMX f.a.)	(85.85)	(85.85)
(= CA f.a.)	(88.70)	(88.70)
Methocel K100M	55.12	80.01
$CaHPO_4$	--------	92.08
Polyvidon K30	9.65	14.01
Talc	3.58	5.20
Mg-Stearate	3.30	4.79
weight of layer 2	275.56	400.00

Second Layer		
$AMX.3H_2O$	118.7	118.7
(= AMX f.a.)	(102.6)	(102.6)
$AMX.3H_2O$/K-CA 1:1	83.4	83.4
(= AMX f.a.)	(35.1)	(35.1)
(= CA f.a.)	(36.3)	(36.3)
Avicel PH 102	45.1	45.1
Explotab	11.4	11.4
Polyvidon K30	10.0	10.0
Talc	12.4	12.4
Mg-Stearate	8.4	8.4

Syloid 244	5.6	5.6
weight of layer 3	295.0	295.0
Total tablet weight	1070.56	1195.00

In tablets 7.2 and 7.3 all three of the layers contain active material content, first and second layers being slow-release layers, and the intermediate third layer being a rapid-release layer.

Example 8

Tablets 8.1 and 8.2 were prepared having a structure as shown in Fig. 1B.

	Amounts in mg	
First Layer	**8.1**	**8.2**
AMX.3H_2O	118.7	118.7
(= AMX f.a.)	(102.6)	(102.6)
AMX.3H_2O/K-CA 1:1	83.4	83.4
(= AMX f.a.)	(35.1)	(35.1)
(= CA f.a.)	(36.3)	(36.3)
Avicel PH 102	45.1	45.1
Explotab	11.4	11.4
Polyvidon K30	10.0	10.0
Talc	12.4	12.4
Mg-Stearate	8.4	8.4
Syloid 244	5.6	5.6
weight of first layer	295.0	295.0

Barrier layer	S6	RSB1
weight of layer	180.00	180.00

Second Layer		
$AMX.3H_2O$	320.02	320.02
(= AMX f.a)	(276.5)	(276.5)
$AMX.3H_2O$/K-CA 1:1	(203.91)	203.91
(= AMX f.a.)	(85.8)	(85.8)
(=CA f.a.)	(88.7)	(88.7)
Methocel K4M	62.00	62.00
Methocel E5	62.00	62.00
Mannitol	31.74	31.74
Polyvidon K30	20.03	20.03
Talc	5.00	5.00
Mg-Stearate	20.30	20.30
weight of second layer	725.00	725.00
Total tablet weight	1200.00	1200.00

Example 9

Tablets 9.1 and 9.2 were prepared having a structure as shown in Figs 1B (9.1) and 1C (9.2).

	Amounts in mg	
First Layer	**9.1**	**9.2**
$AMX.3H_2O$	329.05	329.05
(= AMX f.a.)	(248.3)	(248.3)
Methocel E5	102.84	102.84
Mannitol	51.46	51.46
Polyvidon K30	18.00	18.00
Talc	6.68	6.68
Mg-Stearate	6.17	6.17
weight of first layer	514.20	514.20

	9.1	**9.2**
Barrier layer	L1	Second layer of 9.1
weight of layer 2	180.00	374.82

Second Layer 9.2	9.1	
AMX.3H$_2$O/K-CA 1:1	215.52	Barrier L1
(= AMX f.a.)	(90.73)	
(= CA f.a.)	(93.75)	
Methocel K4M	74.96	
Eudragit L*	56.22	
Dibutylphthalate*	5.62	
Polyvidon K30	13.12	
Talc	4.87	
Mg-Stearate	4.50	
weight of layer3	374.81	
Total tablet weight	1069.01	1069.01

* In these tablets the Eudragit L and plasticiser were coated directly onto the active material content by repeated steps of wet granulation. Two further examples of tablets (9.3 and 9.4) were prepared to the formula for 9.1 and 9.2 by first preparing a granulate of amoxycillin plus potassium clavulanate plus Methocel K4M, then coating the granulate with the Eudragit L.

Example 10

Tablets 10.1 and 10.2 having a structure as shown in Fig. 1C were prepared

	Amounts in mg	
First Layer	**10.1**	**10.2**
AMX.3H$_2$O	438.68	438.68
(= AMX f.a.)	(379.0)	(379.0)
Methocel E5	53.00	53.00
Mannitol	6.52	6.52
Polyvidon K30	18.55	18.55
Talc	6.89	6.89
Mg-Stearate	6.36	6.36
weight of first layer 1	530.00	530.00

Second Layer		
AMX.3H_2O/K-CA 1:1	287.36	287.36
(= AMX f.a.)	(121.0)	(121.0)
(= CA f.a.)	(125.0)	(125.0)
Methocel K4M	34.50	-------
Methocel K100M	-----	34.50
Mannitol	2.44	2.44
Polyvidon K30	12.08	12.08
Talc	4.48	4.48
Mg-Stearate	4.14	4.14
weight of layer 2	345.00	345.00

Barrier layer	S6	S6
weight of layer 2	180.00	180.00
Total tablet weight	1055	1055

Two further examples of tablets (10.3 and 10.4) were prepared by coating tablets 10.1 and 10.2 with Eudragit L.

Example 11

Tablets 11.1 having a structure as shown in Fig. 1B were prepared

	Amounts in mg
First Layer	**11.1**
AMX.3H_2O	270.85
(= AMX f.a.)	(234.0)
AMX.3H_2O/K-CA 1:1	(206.90)
(= AMX f.a.)	(87.1)
(= CA f.a.)	(90.0)
Compritol 888	225.00
Polyvidon K30	26.25
Talc	9.75
Mg-Stearate	11.25
weight of first layer 1	750.00

Barrier layer	S2
weight of layer 2	120

Second Layer	
AMX.3H_2O	167.86
(= AMX f.a.)	(145.0)
AMX.3H_2O/K-CA 1:1	80.46
(= AMX f.a.)	(33.9)
(= CA f.a.)	(35.0)
Avicel PH 102	53.21
Explotab	14.19
Talc	14.19
Polyvidon K-30	12.42
Syloid 244	7.09
Mg-Stearate	5.32
weight of layer 3	345.74
Total tablet weight	1224.74

Potassium clavulanate was embedded in Compritol 888 by repeated steps of wet granulation. The first layer was a slow-release layer, and the second layer was a rapid-release layer.

In Vitro and In Vivo Test Results

In vitro dissolution tests were carried out in a dual system, e.g. flowing media 2 hours at pH 2.2 followed by 6 hours at pH 6.6. Fig 2 shows results for tablet 6.1 from which amoxycillin and clavulanate were released with completion of release being almost reached within 8 hours.

In vivo tests using tablet 6.1 were carried out on fed (milk) volunteers, and as shown in Fig 3 showed a prolonged amoxycillin plasma level. Similarly as shown in Fig 4 a prolonged release of clavulanate was also experienced. The tablet 6.1 consequently shows a prolonged release profile of amoxycillin and clavulanate.

Fig.5 shows *in vitro* dissolution test results for tablet 9.1, and Fig.6 shows results for tablet 11.1, both showing prolongation of the release of clavulanate.

Claims:

1. A tablet formulation for oral administration, comprising a first layer which includes amoxycillin and/or clavulanate, and a second layer which includes amoxycillin and/or clavulanate, provided that the overall tablet contains amoxycillin, wherein the relative rate of release of amoxycillin and/or clavulanate from the first and second layers differs.

2. A tablet formulation according to claim 1 wherein the amoxycillin is in the form of amoxycillin trihydrate, and clavulanate is in the form of potassium clavulanate.

3. A tablet formulation according to claim 1 or 2 wherein one layer contains amoxycillin without clavulanate and the other layer contains amoxycillin plus clavulanate, making up the ratio in the overall tablet.

4. A tablet formulation according to claim 1 or 2 wherein one layer contains clavulanate without amoxycillin and the other layer contains amoxycillin plus clavulanate, making up the ratio in the overall tablet.

5. A tablet formulation according to claim 1 or 2 wherein one layer contains amoxycillin without clavulanate and the other layer contains clavulanate without amoxycillin, making up the ratio in the overall tablet.

6. A tablet formulation according to any one of the preceding claims wherein differing rates of release are achieved by a first layer which is a rapid release layer which releases the bulk of its active material content within a relatively short time, and a second layer which is a slow release layer which releases the bulk of its active material content during a relatively long period after oral ingestion or a delayed release layer which releases the bulk of its active material content after a period of delay after oral ingestion, either in the stomach or in the intestine.

7. A tablet formulation according to claim 6 wherein the rapid release layer is a rapid disintegrating layer.

8. A tablet formulation according to claim 6 wherein the rapid-release layer is a

swellable layer having a composition which incorporates polymeric materials which swell rapidly and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass.

9. A tablet formulation according to any one of the preceding claims wherein the slow release layer has a composition which comprises active material content together with a release retarding material.

10. A tablet formulation according to claim 9 wherein the release retarding material is selected from pH sensitive polymers, release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents, polymeric materials which form a gel on contact with water or aqueous media, and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

11. A tablet formulation according to claim 9 wherein the slow release layer contains polymers which rapidly swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not rapidly discharged from the stomach into the intestine.

12. A tablet formulation according to claim 9 wherein the slow- or delayed-release layer is a layer in which the active material content is mixed with, coated with, or embedded in a matrix of a poorly soluble or practically insoluble excipient, and/or a hydrophobic excipient.

13. A tablet formulation according to claim 9 wherein the delayed release layer uses the known properties of enteric polymers to delay release of active material content until the whole or part of the tablet is discharged by the stomach into the intestine after oral ingestion.

14. A tablet formulation according to any one of the preceding claims wherein differing rates of release are achieved by having a first layer which is a slow or delayed release layer, and a second layer which is also a slow or delayed release layer.

15. A tablet formulation according to claim 14 wherein one or both of the first

and second layers are slow release layers comprising active material together with release retarding materials.

16. A tablet formulation according to claim 14 wherein one or both of the first or second layers is a delayed release layer using enteric polymers.

17. A tablet formulation according to any one of the preceding claims wherein the tablet includes one or more barrier layers.

18. A tablet formulation according to claim 17 wherein the barrier layer is located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers.

19. A tablet formulation according to claim 17 or 18 wherein the barrier layer(s) is/are composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media.

20. A tablet formulation according to any one of the preceding claims wherein the tablet is wholly or partly covered by a coating layer.

21. A tablet formulation according to any one of the preceding claims which comprises a tablet having a rapid disintegrating first layer which contains amoxycillin and/or clavulanate as active material, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release-retarding polymers, with a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate.

22. A tablet formulation according to any one of claims 1 - 20 which comprises a tablet having a rapid-disintegrating first layer which contains amoxycillin and/or clavulanate as active material, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, but without a barrier layer, the overall tablet containing

amoxycillin or amoxycillin plus clavulanate.

23. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a second layer which is also a slow-release layer and which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate.

24. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a completely impermeable polymer or a slowly erodable polymer located on one of the end faces of the tablet.

25. A tablet formulation according to any one of claims 1-20 which comprises a rapid release first layer which is a swellable layer containing amoxycillin, and a slow-release or delayed release second layer as described above containing amoxycillin, or clavulanate, or amoxycillin plus clavulanate, having a barrier layer of either a substantially or completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers.

26. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer comprising amoxycillin optionally together with clavulanate as active material, and a second layer which is a delayed release layer comprising a disintegrable or soluble matrix within which are dispersed enteric polymer coated granules which comprise clavulanate, optionally together with amoxycillin, with a barrier layer sandwiched between the first and second layers.

27. A tablet formulation according to any one of claims 1-20 which comprises a first layer which is a slow release layer containing polymers which rapidly swell in contact with water or aqueous media so that the swollen mass is not rapidly

discharged from the stomach containing amoxycillin or amoxycillin plus clavulanate as active material, and a second layer which is a slow release layer containing amoxycillin or amoxycillin plus clavulanate as active material, with a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers.

28. A tablet formulation according to any one of claims 1-20 which comprises a three-layer tablet in which all three of the layers include an active material content.

29. A tablet formulation according to claim 28 which comprises a slow-or delayed-release first layer which comprises amoxycillin, optionally together with clavulanate, a rapid-release second layer which comprises amoxycillin, optionally together with clavulanate, and a third layer, sandwiched between the first and second layers, and being a slow- or delayed-release layer comprising calvulanate, optionally together with amoxycillin.

30. A method for the manufacture of a tablet formulation according to any one of the preceding claims comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

31. A tablet formulation according to any one of claims 1-29 for use as a therapeutic substance for oral administration for the treatment of bacterial infections.

32. A method of use of a formulation as claimed in any one of claims 1-29, in the manufacture of a medicament for the treatment of bacterial infections.

33. A method of treatment of bacterial infections in humans or animals which comprises the administration thereto of a therapeutically effective amount of active material content included in a formulation as claimed in any one of claims 1-29.

34. A tablet formulation according to any one of claims 1-29 substantially as hereinbefore described with reference to the accompanying drawings.

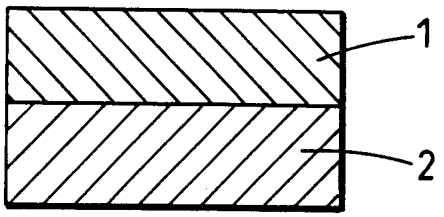


Fig. 1A

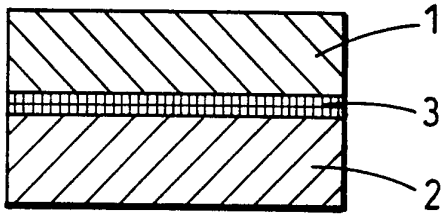


Fig. 1B

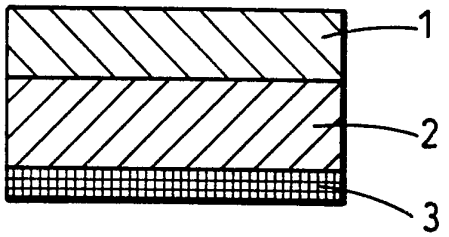


Fig. 1C

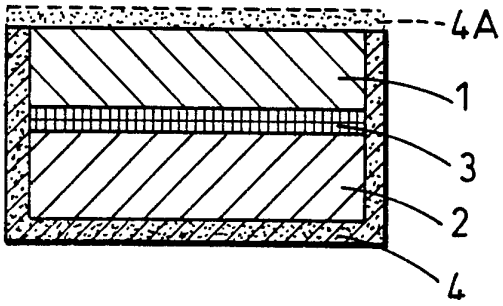


Fig. 1D

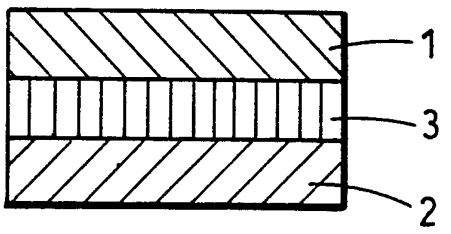


Fig. 1E

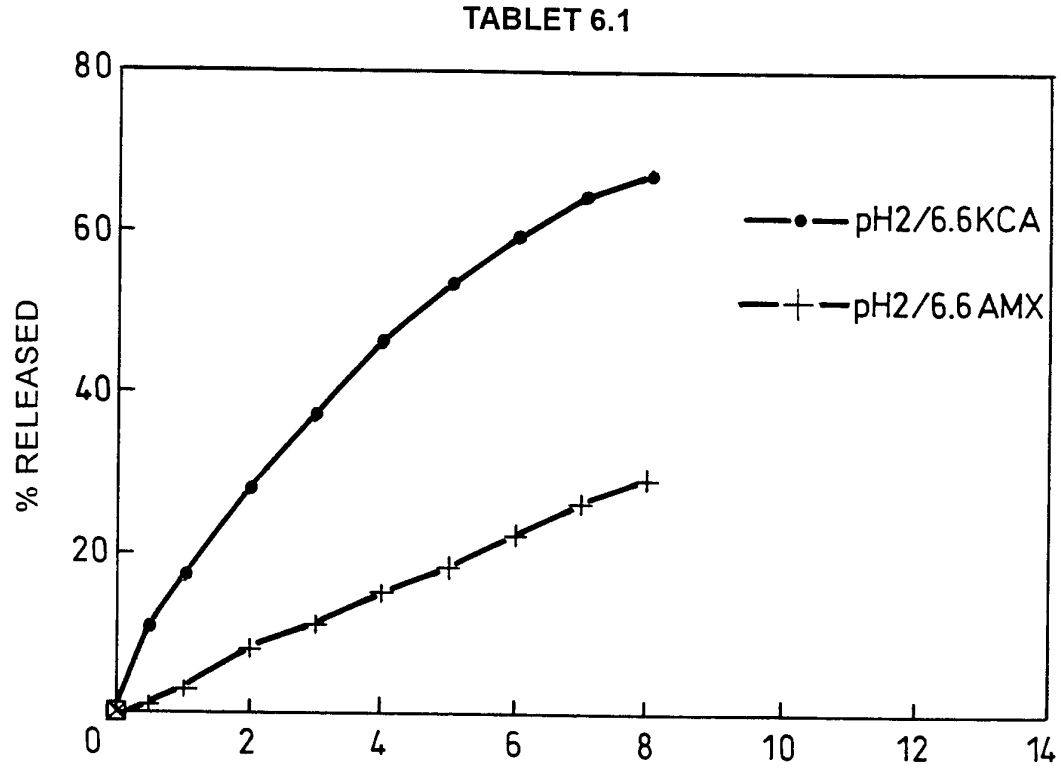

TABLET 6.1
80
60
40
20
0
% RELEASED
pH2/6.6KCA
pH2/6.6 AMX
2
4
6
8
10
12
14
TIME IN HOURS

Fig. 2

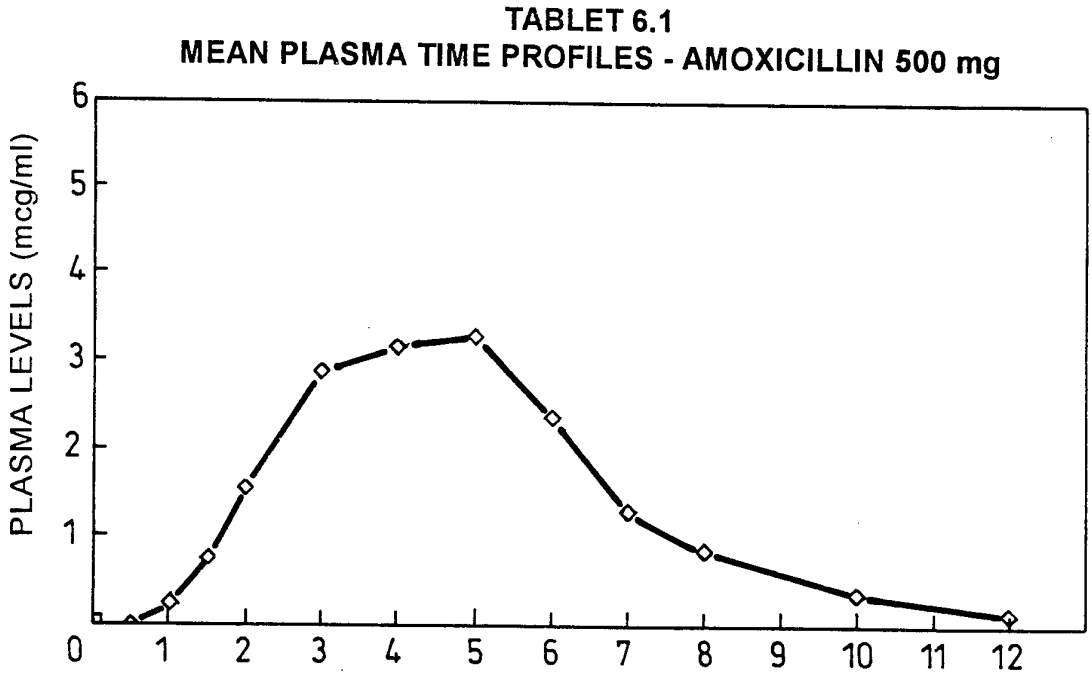

TABLET 6.1
MEAN PLASMA TIME PROFILES - AMOXICILLIN 500 mg
6
5
4
3
2
1
0
PLASMA LEVELS (mcg/ml)
1
2
3
4
5
6
7
8
9
10
11
12
TIME IN HOURS

Fig. 3

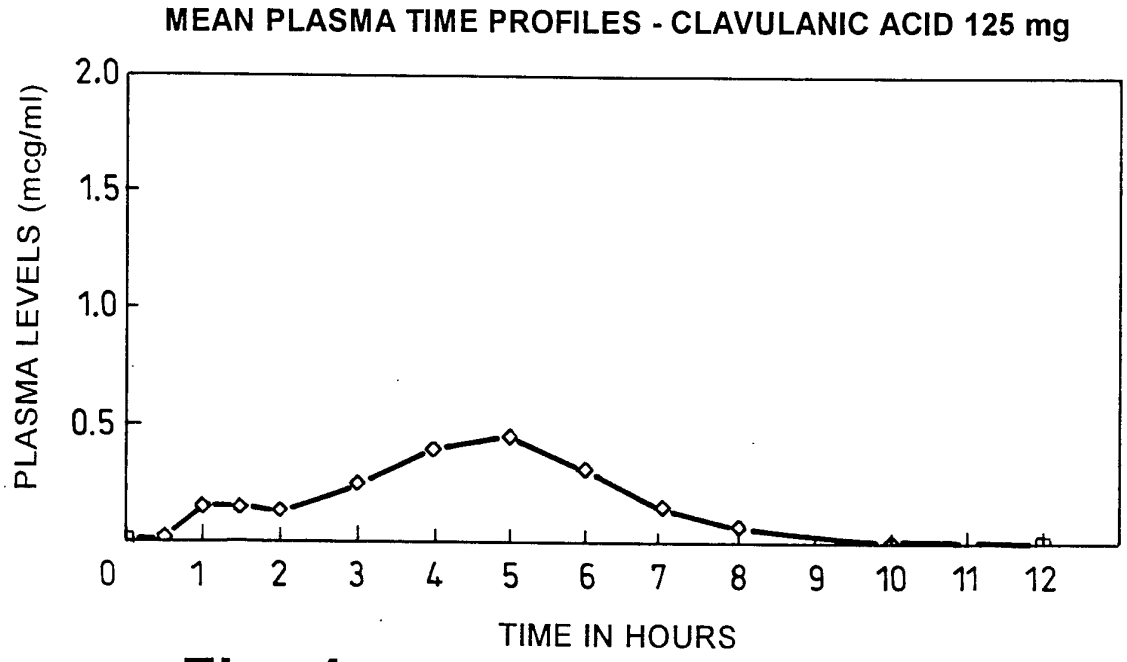

MEAN PLASMA TIME PROFILES - CLAVULANIC ACID 125 mg
PLASMA LEVELS (mcg/ml)
2.0
1.5
1.0
0.5
0
1
2
3
4
5
6
7
8
9
10
11
12
TIME IN HOURS

Fig. 4

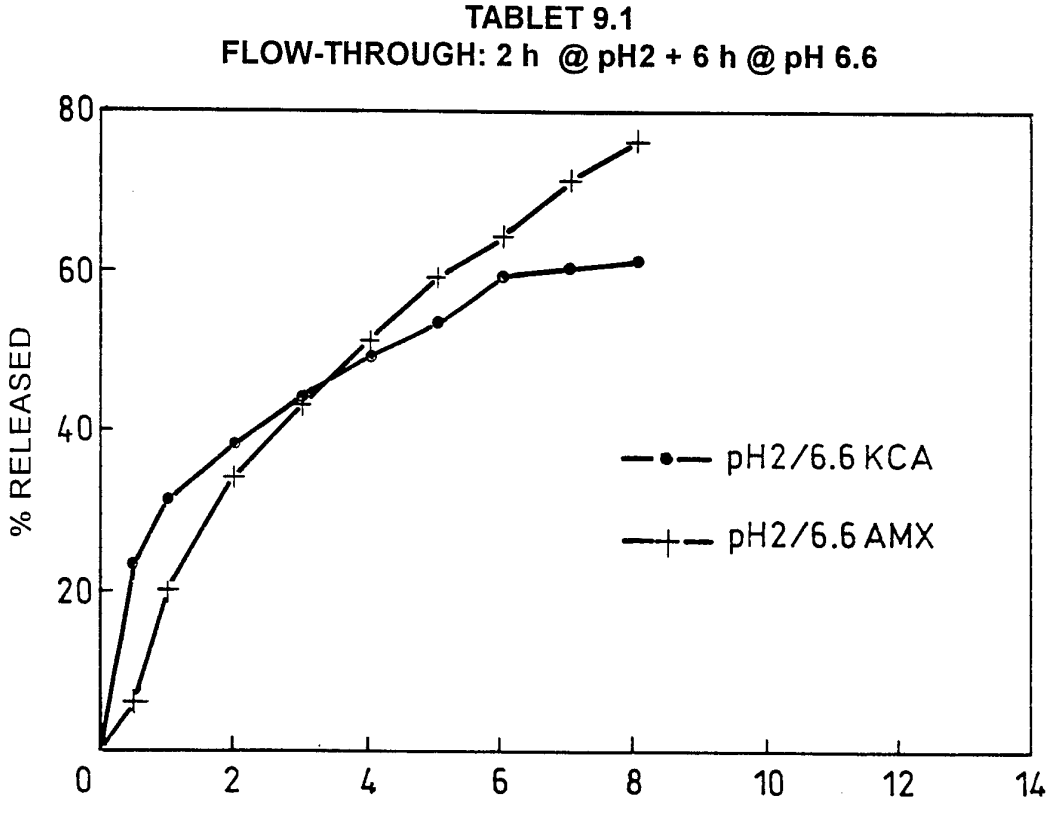

TABLET 9.1
FLOW-THROUGH: 2 h @ pH2 + 6 h @ pH 6.6
% RELEASED
80
60
40
20
0
2
4
6
8
10
12
14
pH2/6.6 KCA
pH2/6.6 AMX
TIME IN HOURS

Fig. 5

TABLET 11.1
FLOW-THROUGH: 2 h @ pH 2 + 6 h @ pH 6.6

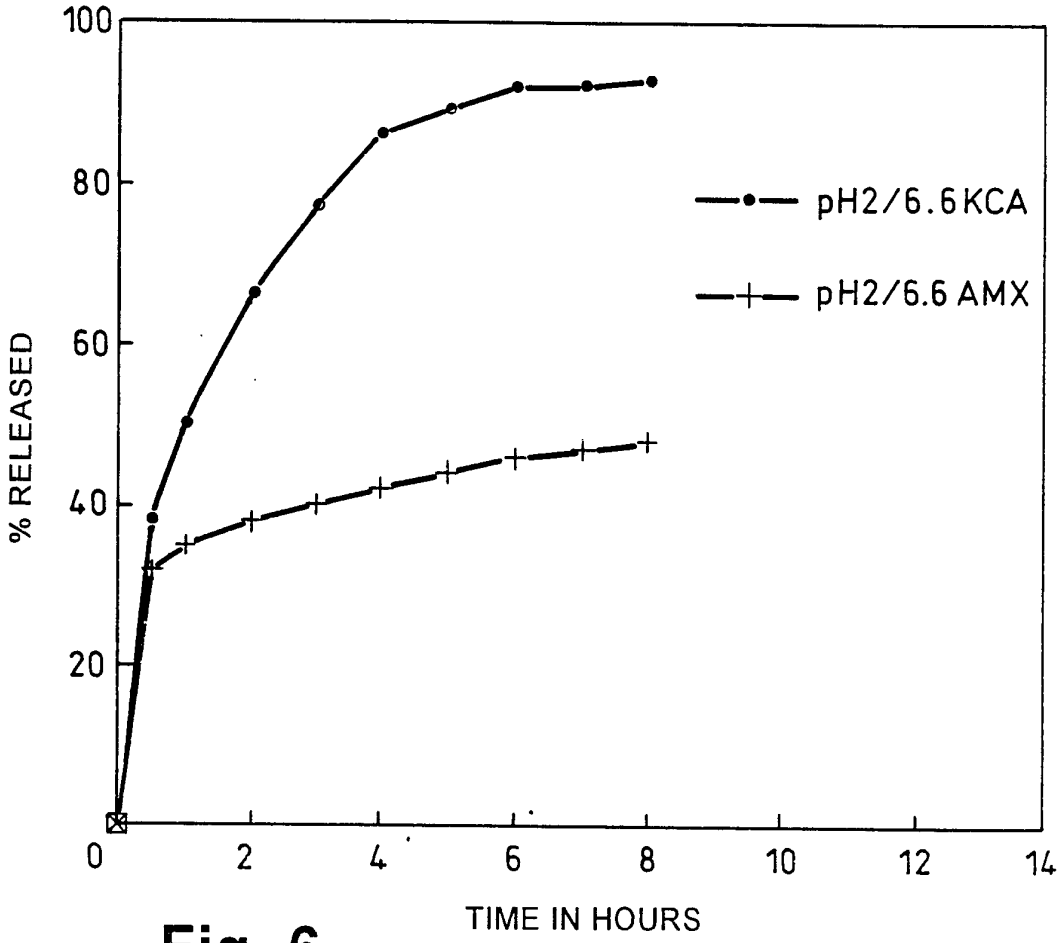


Fig. 6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/00343

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K31/43

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)
IPC 6 A61K

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 practical, 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.
P,X	WO,A,94 27557 (SMITHKLINE BEECHAM CORPORATION) 8 December 1994 see the whole document ---	1-34
P,X	WO,A,94 06416 (JAGOTEC AG) 31 March 1994 see the whole document -----	1-34

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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

1

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 1995	04. 07. 95

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 95/00343

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9427557	08-12-94	AU-B- 7096294	20-12-94
WO-A-9406416	31-03-94	AU-B- 4818293	12-04-94