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(54) Title: SOLID FORMULATIONS OF VALACYCLOVIR HYDROCHLORIDE

(57) Abstract: Solid oral dosage forms of valacyclovir hydrochloride, particularly tablets, have been developed using wet granulation techniques that (i) are stable over time, (ii) meet demanding physical handling requirements, (iii) have optimal bioavailability, and (iv) allow for the integration of large proportions of valacyclovir hydrochloride in the total formulation.

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SOLID FORMULATIONS OF VALACYCLO VIR HYDROCHLORIDE

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations, and particularly to solid formulations of valacyclovir hydrochloride, such as tablets and granulates, and to methods of making and using such tablets and granulates.

BACKGROUND OF THE INVENTION

Valacyclovir hydrochloride is the hydrochloride salt of the L-valyl ester of the antiviral drug acyclovir. In vivo, valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV-I) and 2 (HSV-2) and varicella-zoster virus (VZV). In the United States, the drug is indicated for the treatment of herpes zoster (shingles), genital herpes, and cold sores (herpes labialis).

Valacyclovir hydrochloride is marketed as Valtrex® in the United States, and Zelitrex® in some countries outside the United States, by GlaxoSmithKline in 500 mg. and 1,000 mg. strength caplets for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir, and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated tablets are printed with edible white ink.

The drug is challenging from a formulation standpoint, especially when tablets are desired, because of the large amount of active drug ingredient required for antiviral activity and the low bioavailability of the active ingredient. Commercial tablets are formulated to contain 500 mg. and 1,000 mg. of valacyclovir, which translates into more than 1,100 mg. of valacyclovir hydrochloride. When combined with other inactive excipients, the resulting weight of a 1,000 mg. Valtrex® tablet is 1,425 mg.

Valacyclovir and its salts including the hydrochloride salt are disclosed in U.S. Patent No. 4,957,924, its counterpart European Patent No. 0308065 and Beauchamp

et al, Antiviral Chemistry and Chemotherapy, 3(3), 157 - 164 (1992). Tablets of valacyclovir are also generally disclosed in the U.S. Patent No. 4,957,924 and its counterpart European Patent No. 0308065.

U.S. Patent No. 5,879,706 (corresponding to EP 0806943 Bl), is owned by GlaxoSmithKline and discloses a tablet formulation of valacyclovir in which valacyclovir is granulated along with microcrystalline cellulose, crospovidone, and povidone, and the granulates are mixed with microcrystalline cellulose, crospovidone and silicon dioxide before being compressed into tablets. The alleged point of novelty in this patent is the use of silicon dioxide as an extra-granular excipient.

WO 2004/000265 is a PCT publication by Ranbaxy Laboratories that also discloses a tablet formulation of valacyclovir hydrochloride. The formulation replaces the silicon dioxide in the extra-granulate disclosed in the U.S. '706 patent with hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and magnesium stearate.

U.S. Patent No. 6,1 17,453 (corresponding to EP 0830129 Bl) is a United States patent owned by Pharma Pass, that also discloses a tablet formulation of valacyclovir hydrochloride. Granulates are prepared from valacyclovir and polyethylene oxide, and the granulates are mixed with excipients such as silicon dioxide, hydroxypropyl methyl cellulose and lactose before being compressed into tablets.

U.S. Patent No. 6,1 17,857 (corresponding to EP 0810865 Al) is owned by Astra Aktiebolag and discloses an antiviral topical or parenteral composition that includes valacyclovir hydrochloride in admixture with galactolipids and a polar solvent. European Patent No. 1146862 Bl (no corresponding granted U.S. patent) is owned by Disphar International and discloses a controlled release formulation that lists valacyclovir among the drugs suitable for use with the formulation. WO 03/022209 is owned by Teva Pharmaceutical, and discloses various polymorphs and pseudopolymorphs of valacyclovir, including valacyclovir hydrochloride monohydrate and valacyclovir hydrochloride dehydrate.

European Patent No. 1541 133 Bl (no corresponding granted U.S. patent) is a granted European patent owned by Helm AG that discloses the use of titanium dioxide in the production of valacyclovir hydrochloride tablets. The patent discloses a process in which valacyclovir, starch and lactose are mixed, added to a solution of povidone in alcohol, granulated, and mixed with magnesium stearate and titanium

dioxide before compression into a tablet. The patent teaches the desirability of using titanium dioxide in valacyclovir tablets to improve the density, compressibility and flowability of powders used to form the tablets. The patent also teaches that at least 1% povidone, based on the total weight of the formulation, should be used to bind the granulate together and improve tablet hardness.

The total weight of a 1,000 mg. valacyclovir hydrochloride tablet using the preferred formulation disclosed in EP 1541 133 would equal 1400 mg, which could be reduced somewhat to improve swallowability. What is needed is a formulation for valacyclovir that permits large amounts of valacyclovir to be incorporated into the dosage form, and still give excellent physical performance.

OBJECTS OF THE INVENTION

Therefore, it is an object of the invention to provide solid formulations of valacyclovir that are suitable for the production of tablets and granulates, especially valacyclovir hydrochloride tablets and granulates, and especially tablets and granulates that contain large proportions of valacyclovir hydrochloride.

It is also an object of the invention to provide methods of processing valacyclovir into solid formulations such as tablets and granulates, including wet granulation methods based on hydro-alcoholic solvents.

Still another object of the present invention is to provide methods and formulations for processing valacyclovir into tablets that meet demanding disintegration, dissolution, and bioavailability requirements.

SUMMARY OF THE INVENTION

Solid oral dosage forms of valacyclovir, particularly tablets of valacyclovir hydrochloride, have been developed using wet granulation techniques that (i) are stable over time, (ii) meet demanding physical handling requirements, (iii) have optimal bioavailability, and (iv) allow for the integration of large proportions of valacyclovir hydrochloride into the total formulation. In particular, the inventors have discovered that starch has intragranulate binding properties, and that valacyclovir hydrochloride can be manufactured into granulates using methylcellulose and starch in the granulate, based on a hydro-alcoholic granulation process. Granulates based on

the formulation can contain greater than even 90 wt.% of the active ingredient, while finished tablets can contain greater than even 85 wt.% valacyclovir hydrochloride. In one embodiment, the weight ratio of valacyclovir hydrochloride to methylcellulose is greater than 100:1 (giving rise to a formulation that contains less than 1 wt.% methylcellulose in the granulate and final formulation). In another embodiment, the granulate is substantially devoid of any fillers or binders other than starch and methylcellulose.

Therefore, in a first principal embodiment the invention provides a method of making a valacyclovir tablet comprising (a) wet granulating a mixture of valacyclovir hydrochloride, starch and methylcellulose to form a granulate; (b) mixing said granulate with a pharmaceutically acceptable excipient to form a blend; and (c) compressing said blend into a tablet. In a preferred embodiment the method is carried out by dissolving the methylcellulose in a hydro-alcoholic solution that comprises at least 50% water, and wet granulating the solution with valacyclovir hydrochloride and starch to form a granulate. When making tablets, the granulate may subsequently be mixed with one or more binders and other pharmaceutical excipients and compressed into tablets.

In another embodiment the invention provides a valacyclovir tablet comprising an intragranular portion and an extragranular portion, wherein: (a) said intragranular portion comprises valacyclovir hydrochloride, starch and methylcellulose; and (b) said extragranular portion comprises one or more binding agents. In still another embodiment the invention provides a granulate comprising valacyclovir hydrochloride, starch and methylcellulose. In each of the foregoing embodiments, the granulate preferably comprises less 1 wt.% methylcellulose or greater than 82 wt.% valacyclovir hydrochloride.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a plot of percent dissolution over time for test Formula IV made according to the invention, where the solution pH 1.2 at time zero.

FIG. 2 depicts a plot of dissolution over time for Film Coated tablets (1000 mg valacyclovir) Batch VALA 111/60 made according to the invention versus 1000 mg Zelitrex tablets.

FIG. 3 depicts a plot of dissolution over time for Film Coated tablets (500 mg valacyclovir) Batch VALA 111/62 made according to the invention versus 500 mg Zelitrex tablets.

FIG. 4 depicts the DSC curve of a mechanical mixture of all components present in the dosage form in 1:1 ratio, as made according to the invention.

FIG. 5 depicts the DSC curve of a mechanical mixture of all the components in proportions close to Formula IV, as made according to the invention.

FIG. 6 depicts the DSC curve of a mechanical mixture of all the components present in the dosage form, as made according to the invention.

FIG. 7 depicts the DSC curve for a mechanical mixture with all the components present in the dosage form, as made according to the invention.

FIG. 8 depicts the DSC curve for a VALA III /44 tablet (final formulation before film coating) made according to the invention.

FIG. 9 depicts the comparative acyclovir plasmatic concentrations for tablets of type T1 (1000 mg) and T2 (2x500 mg) made according to the invention, and the corresponding plasmatic concentrations for references R1 (1000 mg Valtrex ® tablets) and R2 (1000 mg Zelitrex ® tablets).

FIG. 10 depicts the mean and range of acyclovir plasmatic concentrations over time on linear and logarithmic scales for tablets of type T1 (1000 mg valacyclovir) made according to the invention.

FIG. 11 depicts the mean and range of acyclovir plasmatic concentrations over time on linear and logarithmic scales for tablets of type T1 (2x500 mg valacyclovir) made according to the invention.

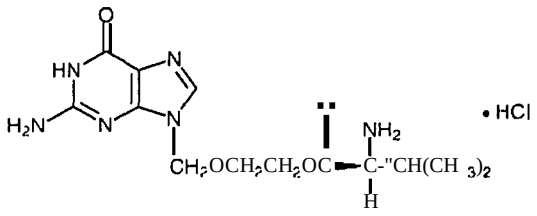
FIG. 12 depicts the mean and range of acyclovir plasmatic concentrations over time on linear and logarithmic scales for tablets of type R1 (Valtrex ® 1000 mg valacyclovir).

FIG. 13 depicts the mean and range of acyclovir plasmatic concentrations over time on linear and logarithmic scales for tablets of type R1 (Zelitrex® 1000 mg valacyclovir).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used in the specification and claims, the singular forms a, an and the include plural referents unless the context clearly dictates otherwise. For example, a pharmaceutical excipient may refer to one or more pharmaceutical excipients for use in the presently disclosed formulations and methods.

The present invention can be practiced with valacyclovir or any pharmaceutically acceptable salt thereof, but is preferably practiced with the hydrochloride salt. Valacyclovir hydrochloride is a white to off-white powder with the molecular formula $C_{13}H_{20}N_6O_4 \cdot HCl$ and a molecular weight of 360.80. The chemical name of valacyclovir hydrochloride is L-valine, 2-[(2-amino-l,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl ester, monohydrochloride. It has the following structural formula:



Valacyclovir hydrochloride for use in this invention can exist in any crystalline form that the molecule is known to assume. The term "valacyclovir hydrochloride" thus includes anhydrous forms, hydrates (e.g. the monohydrate, the sesquihydrate, or the dehydrate), solvates, and all crystalline forms (both polymorphs and pseudopolymorphs) of valacyclovir hydrochloride. Suitable forms are disclosed, for example, in U.S. Patent Nos. 4,957,924 and 6,107,302 of GlaxoSmithKline and WO 03/022209 of Teva Pharmaceuticals. A preferred form of valacyclovir hydrochloride contains water of hydration in an amount of from about 3 to about 9 wt.%.

The pharmaceutical formulation of the present invention may comprise any suitable amount of the active ingredient. The finished formulation preferably contains a high proportion of valacyclovir, such as at least 50 wt.%, and most preferably

contains at least 75%, 80%, 82% or 85 wt.% valacyclovir hydrochloride based on the total weight of the formulation. The granulates of the present invention preferably contain at least 75%, 80%, 85% or 90 wt.% valacyclovir hydrochloride.

The pharmaceutical formulation of the present invention is a solid, preferably oral composition, such as a tablet, capsule, granule, pellet or sachet, with the tablet dosage form being most preferred. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

The water content of the formulation (measured by the Karl Fischel Method) is preferably less than about 8, 7 or 6 wt.% and greater than about 3 or 4 wt.%. Other preferred physical properties for tablet dosage forms are as follows, based on testing methods described in greater detail in Example 2:

Hardness: greater than 235 or 250 N and less than 320, 300, 280 or 260 N

Friability: greater than 0.00, 0.01 or 0.03% and less than 0.15 or 0.10%

Disintegration Time: greater than 12, 15, 16 or 17 minutes and less than 25, 20 or 19 minutes as tested by USP 28 <701>.

In addition, the tablets preferably exhibit a dissolution profile substantially as shown in Figure 1 hereto, when tested according to USP 28 <71 1>.

The compositions are preferably prepared first by granulating valacyclovir along with starch and methylcellulose in a series of steps. The starch can constitute any commercially available grade of starch, including native starch, pregelatinized starch or a modified starch. The granulate is preferably prepared by (a) mixing valacyclovir and starch to form a blend, (b) dissolving or suspending methylcellulose in a liquid to form a methylcellulose solution or suspension, (c) mixing the blend with the methylcellulose solution or suspension to form a wet suspension or liquid slurry, and (d) drying the wet suspension or liquid slurry to form a granulate. The liquid is preferably a "hydro-alcohol" that contains at least 50 wt.% water, and more preferably comprises greater than 80 wt.% water, the balance preferably constituting ethanol.

In a preferred embodiment, the weight ratio of the valacyclovir hydrochloride to the methylcellulose in the granulate and/or finished tablet is greater than 100:1, 250:1 or even 500:1, and less than about 5,000:1 or 2,000:1. The weight ratio of the valacyclovir hydrochloride to the starch in the granulate and/or finished tablet is preferably greater than about 5:1, 8:1 or even 10:1, and less than about 100:1 or 30:1.

The weight ratio of starch to methylcellulose in the granulate and/or finished tablet is preferably from about 40:1 to about 100:1, and more preferably from about 50:1 to about 80: 1. The total weight of methylcellulose in the granulate or final formulation is preferably less than about 1.0%, 0.05%, or even 0.02% based on the weight of the granulate or formulation. The total weight of starch is preferably less than about 20%, 15% or 10%, based on the total weight of the granulate or final formulation.

After drying, the granulate is preferably mixed with one or more pharmaceutically acceptable excipients (i.e. extragranular excipients) such as fillers, binding agents, lubricants and disintegrating agents, depending on the final dosage form and the properties desired. In a preferred embodiment, the weight ratio of the intragranular component to the extragranular component is from about 1:5 to about 1:30,and more preferably is from about 1:10 to about 1:15. The intragranulaπextragranular weight ratio is preferably greater than about 5:1, 10:1 or even 12:1. As a total percentage of the dosage form, the extragranular portion preferably constitutes less than 15, 10 or even 8 wt.% of the total weight, whereas the intragranular portion preferably constitutes greater than 85, 90 or even 92 wt.% of the total weight.

Potentially suitable filler materials for the extragranulate are well-known to the art (see, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990), Mack Publishing Co., Easton, Pa., pp. 1635-1636), and include lactose and other carbohydrates, pregelatinized starch, e.g., starch 1500® (Colorcon Corp.), corn starch, dicalcium phosphate, cellulose, microcrystalline cellulose, sugars, sodium chloride, and mixtures thereof. Owing to its superior disintegration and compression properties, microcrystalline cellulose (Avicel®, FMC Corp., or Vivapur Type 12), and mixtures comprising microcrystalline cellulose and one or more additional fillers, e.g., corn starch, are particularly useful. The amount of the fillers present in the pharmaceutical formulation is not particularly limited and can be, for example, in the range of 0 to 30 wt.%, preferably 0.5 to 5 wt.% of the total weight of the formulation. An extragranular binding agent (e.g., gelatin, sugars, natural and synthetic gums, such as carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, hydroxypropylmethylcellulose), may also be used that serves, for example to bind the particles together and improve tablet hardness. Preferably the binding agent is present in an amount of 0.01 to 5 wt.%, more preferably at 0.1 to 2 wt.% of the total weight of the formulation. The extragranular binding agent can for example be methylcellulose

or more preferably povidone or crospovidone. The total amount of binding agent in the formulation, excluding starch, is preferably less than about 10, 5, 2 or even 1 wt.%.

A lubricant is suitably present in an amount of 0.1 to 10 wt.%, preferably from about 0.5 to about 5 wt.% of the total weight of the formulation. Although lubricants such as talc or sodium lauryl sulfate are suitable, as are alkali metal stearates such as magnesium stearate, in a preferred embodiment the lubricant is glyceryl behenate. Although valacyclovir is very soluble, especially in its salt form, it is preferable if an extragranular disintegrating agent is present in the pharmaceutical formulation, suitably in an amount of 0.1 to 20 wt.%, more preferably at about 1.0 to 10 wt.% of the total weight of the formulation. For example, crosscarmellose sodium may be used as disintegrating agent or any other suitable disintegrating agent known to the person skilled in the art. Other suitable disintegrants include, for example, cross-linked carboxymethylcellulose, crospovidone, and sodium starch glycolate.

It has been found that the formulations of the present invention do not require the presence of processing aids such as silicon dioxide or titanium dioxide, and in a preferred embodiment the formulations omit such processing aids.

EXAMPLES

EXAMPLE 1 FORMULATION DEVELOPMENT

Formulations of the current invention and comparative formulations were developed according to the following methods, to yield the formulations reported in Table 1.

Equipment

- Balances of various type (Al).
- High shear mixer lab scale (A2)
- Static oven (A3).
- Mixing: Ribbon mixer (A4).
- Sieving: sieve n° 10 (1,40 mm) (A5)
- Tabletting machine: alternated tabletting machine (A6)

Preparation of the Mixture for Granulation

Sieve all the ingredients, necessary for the preparation of the uncoated tablets, through a 1.40 mm sieve.(A5) Then weigh (Al) Valacyclovir HCl, Starch, mix in (A2) for 15 minutes. Add a solution composed with Methylcellulose (if any), Purified water, Ethanol under stirrer for 20 minutes. Unload the wet granulated on the tray of a static oven.

Dry (in A3) for 5 hours at 50°C

Preparation of the Mixture for the Tabletting of Uncoated Tablets

Load the mixing machine (A4) with the granulate and add microcrystalline cellulose, crospovidone, croscaramellose sodium and mix for 15 minutes.
Add glyceryl behenate and mix for 5 minutes.

Preparation of Uncoated Tablets

Compress (A6) the mixture using oblong punches with these dimensions: Length 19, Width 9 mm. Collect the finished uncoated tablets in brown coloured glass container. Store at room temperature.

Table 1

Names of ingredients	I	II	III	IV	V
Active ingredient					
Valacyclovir HCl	1112.0 mg	1112.0 mg	1112.0 mg	1112.0 mg	1112.0 mg
Matrix tablet excipients					
Microcrystalline cellulose (diluent)	15.0 mg	15.0 mg	15.0 mg	15.0 mg	15.0 mg
Crospovidone (binder)	6.0 mg	6.0 mg	6.0 mg	6.0 mg	6.0 mg
Croscaramellose Sodium (disintegrant)	46.0 mg	46.0 mg	46.0 mg	46.0 mg	46.0 mg
Methylcellulose (binder)	0	0	0.75 mg	1.5 mg	3 mg
Starch (binder/diluent)	50.0 mg	100.0 mg	100.0 mg	100.0 mg	100.0 mg
Glyceryl Behenate (lubricant)	25.0 mg	25.0 mg	25.0 mg	25.0 mg	25.0 mg
Total weight	1254.0 mg	1304.0 mg	1304.75 mg	1305.5 mg	1307.0 mg

EXAMPLE 2 TESTING OF PHYSICAL PROPERTIES OF FORMULATIONS I-V

Each of the formulations I-V was subsequently tested for various physical parameters, including hardness, friability, water content and disintegration time. The results of the testing are presented below in Table 2.

Table 2

	I	II[a]	III	IV	V
Appearance	Oblong white to light yellow tablet	Oblong white to light yellow tablet	Oblong white to light yellow tablet	Oblong white to light yellow tablet	Oblong white to light yellow tablet
Length	19 mm	na	19 mm	19 mm	19 mm
Width	9 mm	na	9 mm	9 mm	9 mm
Thickness	7.95 mm	na	8.09 mm	8,05 mm	7.89 mm
Hardness (Eur. Ph.)	194 N	na	231 N	251 N	321 N
Average weight	1231 mg	na	1286 mg	1336 mg	1335 mg
Friability (according Eur.Ph)	0,33 %	na	0,07 %	0,08 %	0,08 %
Water content (Karl Fisher)	4.98%	na	5.02%	4.95 %	5.32 %
Disintegration time (37^{0}C water) (Eur. Ph.)	2 min 14 sec.	na	2 min 23 sec	18 min	29 min

[a] -- Tablet not tested due to capping during tableting process and low hardness (40-60 N).

Hardness is determined on 10 finished product taken at random from different blisters, according to Eur. Ph. The instrument used to measure hardness for the finished product is Erweka TBH 30 HD. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The force is measured in Newtons (N).

Disintegration is measured in water (37^{0}C) on 6 finished product taken at random from different blisters, according to Eur. Ph.. The disintegration time must be not more than 30 minutes.

EXAMPLE 3 MANUFACTURING PROCESS FOR 500 MG. AND 1000 MG. COATED AND UNCOATED TABLETS

The ingredients of the drug product Valacyclovir 1000 Film Coated Tablet Batch VALA 111/60 and Uncoated Tablet Batch VALA 111/44 (without the coating agent) are listed below in table 3.

Table 3

Names of ingredients	Unit (mg)	Function	Reference to standards
Active ingredients			
Valacyclovir HCl	1112.0*	Antiviral	Eur. Ph.
Matrix tablet excipients			
Microcrystalline cellulose	15.0	Diluent	Eur. Ph.
Crospovidone	6.0	Binder	Eur. Ph.
Coscaramellose sodium	46.0	Disgregant agent	Eur. Ph.
Methylcellulose	1.5	Binder	Eur. Ph.
Pregelatinized Starch	100.0	Binder/Diluent	Eur. Ph.
Glyceryl behenate	25.0	Lubricant agent	Eur. Ph.
Film-coating excipients			
Opadry White	36.0	Coating agent	Int. standard
Total weight[1]	1341.5		

* Corresponding to Valacyclovir 1000 mg.

The ingredients of the drug product valacyclovir 500 mg. Film Coated Tablet Batch VALA 111/62 and 500 mg. Uncoated Tablet Batch VALA 111/46 (without the coating agent) are listed in Table 4.

Table 4

Names of ingredients	Unit (mg)	Function	Reference to standards
Active ingredients			
Valacyclovir HCl	556.0"	Antiviral	Eur. Ph.
Matrix tablet excipients			
Microcrystalline cellulose	7.5	Diluent	Eur. Ph.
Crospovidone	3.0	Binder	Eur. Ph.
Coscaramellose sodium	23.0	Disgregant agent	Eur. Ph.
Methylcellulose	0.75	Binder	Eur. Ph.
Pregelatinized Starch	50.00	Binder/Diluent	Eur. Ph.
Glyceryl behenate	12.5	Lubricant agent	Eur. Ph.
Film-coating excipients			
Opadry White	27.0	Coating agent	Int. standard
Total weight	679.75		

[a] Corresponding to Valacicloir 500 mg

The raw materials necessary for the production of a laboratory batch of 4627,74 g, corresponding to 3545 tablets (1305.5 *mgper* tablet w/o coating), for Valacyclovir 1000 Film Coated Tablet Batch VALA 111/60 are listed in Table 5.

Table 5

Names of ingredients	Unit (g)
Active ingredients	
Valacyclovir HCl hydrate	3969.84
Matrix tablet excipients	
Microcrystalline cellulose	51.00
Crospovidone	20.40
Croscarmellose sodium	156.40
Methylcellulose	5.10
Starch	340.00
Glyceryl bhenate	85.00
Total weight	4627.74
Film-coating excipients	
Opadry White	154.00
Purified wateter	770.00

[a] The product contains about 5% of water

Equipment

- Balances of various type (Al).
- High shear mixer - DIOSNA - (A2)
- Static oven (A3).
- Mixing: Novinox ribbon mixer , 10 litres capacity (A4).
- Sieving: sieve n° 10 (1,40 mm) (A5)
- Tabletting machine: Ronchi ARl 8/23 rotating single layer tabletting press, equipped with 4 punches (23 mm x 9.5 mm) (A6)
- film-coating: film coating equipment GS Pellegnini (A7)

Operating Procedures

The equipment and the premises are of type suitable for pharmaceutical preparations and are air-conditioned at 25°C to 28^{0}C with 60% approximately relative humidity.

Preparation of the Mixture for Granulation

Sieve all the ingredients, necessary for the preparation of the uncoated tablets, through a 1.40 mm sieve.(A5) Then weight (Al) 3969,84 g of Valacyclovir HCl, 340 g of Starch, mix in (A2) for 15 minutes. Add a solution composed with 5,10 g of Methylcellulose, 616 g Purified water, 68 g Ethanol under stirrer for 20 minutes. Unload the wet granulated on the tray of a static oven.

Dry (in A3) for 7 hours at 50°C

Preparation of the Mixing for the Tablettins of Uncoated Tablets

Load the mixing machine (A4) with the granulate and add 51 g of Microcrystalline Cellulose, 20,4 g of Crosspovidone, 156,4 g Crosscaramellose Sodium and mix for 15 minutes.

Add 85 g of Glyceryl Behenate and mix for 5 minutes.

Preparation of Uncoated Tablets

Compress (A6) the mixture using oblong punches with these dimensions: Length 23 mm, Width 9,5 mm.

Collect the finish uncoated tablets in brown coloured glass container (batch VALAIII/44) and use a large part of them for the filming procedures.

Store at room temperature.

Preparation of the Aqueous Polymer Coating Suspension

Weigh 770 g of Purified water in a suitable vessel. Under mixing, add 154 g of Opadry White. Leave the Opadry suspension to swell for 1 hour under continuous mixing.

Film-Coating

Put the uncoated tablets (4400 g) into the automatic tablet coating pan (A7). Start rotation of the pan (rotation speed 6 rpm) and warm the uncoated tablets for 5 minutes (air inlet temperature of 70 °C).

Spray the uncoated tablets by the aqueous polymer coating suspension according to the following parameters:

- Air inlet temperature: Between 70.0°C and 75.O^{0}C
- Cores temperature: Between 38.0°C and 45.O^{0}C
- Pan rotation: about 13 rpm.
- Process time: About 1 hour (drying included).

After drying, collect the finished coated tablets (4500 g) in Brown coloured glass container (type III) suitable for pharmaceutical use (batch VALAIII/60).

Batch VALA 111/62 and Batch VALA 111/46

Batch VALA 111/62 and Batch VALA 111/46 500 mg. coated and uncoated tablets were prepared substantially as described for Batches VALA 111/44 and VALA 111/60, except that a smaller tablet punch was employed.

The results of testing for each batch are reported below in Table 6.

Table 6

	1000 Uncoated Tablet Batch VALA 111/44	1000 Film Coated tablet Batch VALA 111/60	500 Uncoated Tablet Batch VALA 111/46	500 Film Coated tablet Batch VALA 111/62
Appearance	Oblong white to light yellow tablet	Oblong white to light yellow tablet	Oblong white to light yellow tablet	Oblong white to light yellow tablet
Length	23,00 mm	23,00 mm	18,20 mm	18,20 mm
Width	9,50 mm	9,50 mm	7,14 mm	7,14 mm
Thickness	6,71 mm	6,82 mm	5,28 mm	5,38 mm
Hardness	314 N	312 N	262 N	281 N
Average weight	1307,91 mg	1340,17 mg	655,92 mg	684,62 mg
Friability	0,00 %		0,00 %	
Water content (Karl Fisher)	5,07 %	5,40 %	5,30 %	5,22 %
Uniformity of mass	Conform	Conform	Conform	Conform
Disintegration time (37°C water)	15'e 27"	18'e 28"	13'e 05"	16'e O4"
Identification (HPLC)	Positive	Positive	Positive	Positive
Assay	99,04%	101,90%	98,50%	101.90 %
Dissolution test		Figure 2 (vs Zelitrex 1000)		Figure 3 (vs Zelitrex 500)

EXAMPLE 4 DISSOLUTION TESTING

Dissolution testing of formulation IV, VaIa 111/60, VaIa 111/62, Zelitrex 500 and Zelitrex 100 were performed as described below and as set forth in USP 25 <71 1>. Dissolution profile results are depicted in Figures 1, 2 and 3.

Dissolution conditions

- Medium: 1000 ml of buffered pH=1.2 medium (8.3 ml/1 of HCl 0.1N of water)
- Apparatus: Paddle, 100 rpm
- Temperature: 37°C ± 0.5°C
- Sampling time: after 5, 10, 15, 20, 30, 45, and 60 minutes.
- Sampling amount: 0.5 ml

The dissolution test is performed by an Erweka DT800.

Spectrophotometer

UV Shimadzu controlled by Software UVProbe.

Sample solution

Transfer 1 tablet in each vessel. Take 0.5 ml from each vessel after 5, 10, 15, 20, 30, 45, and 60 minutes of agitation and dilute with medium into a 10 ml volumetric flask.

Standard solution

Weigh accurately about 60 mg of Valacyclovir HCL into a 100 ml volumetric flask. Dissolve with dissolution medium and sonicate for 5 minutes. Make up to volume. Transfer 1.0 ml of this solution into a 10 ml volumetric flask. Make up to volume with dissolution medium.

EXAMPLE 5 STABILITY TESTING OF FORMULATION

Experiments were also performed to evaluate the stability of SLS Batches VALA 111/60 and VALA 111/62 under various storage conditions of temperature and humidity, in amber glass bottles, the preferred container for storage. Results are reported below in Tables 7 - 12.

Table 7
Stability at 25^{0}C 60% HR in Amber Glass Bottles (VALA 111/60)

	Time 0	Time 1 month	Time 2 month	Time 3 month
Appearance	Oblong white to light yellow tablet	Conform	Conform	Conform
Assay	101.9%	105.1%	101.4%	100.1%
Purity -Aciclovir(%w/w) -Guanina (%w/w) -4.5min by area -7.6min by area	 0.49% 0.02% 0.019% 0.026%	 0.54% 0.02% 0.018% 0.025%	 0.51% 0.03% 0.018% 0.023%	 0.56% 0.03% 0.018% 0.026%
Hardness	312 N	382 N	355 N	373 N
Disint.Time pH=1.2	18 min	18 min	19 min	20 min
Dissolution pH=1.2*	Conform	Conform	Conform	Conform
Water content (KF)	5.36%	4.61%	5.15%	5.06%

*Not less than 85% after 40 min

Table 8
Stability at 30°C 65% HR in Amber Glass Bottles (VALA 111/60)

	Time 0	Time 1 month	Time 2 month	Time 3 month
Appearance	Oblong white to light yellow tablet	Conform	Conform	Conform
Assay	101.9%	100.7%	102.9%	99.2%
Purity -Aciclovir(%w/w) -Guanina (%w/w) -4.5min by area -7.6min by area	 0.49% 0.02% 0.019% 0.026%	 0.55% 0.02% 0.019% 0.025%	 0.54% 0.03% 0.018% 0.024%	 0.61% 0.03% 0.017% 0.025%
Hardness	312 N	374 N	367 N	368 N
Disint.Time pH=1.2	18 min	19 min	20 min	21 min
Dissolution pH=1.2*	Conform	Conform	Conform	Conform
Water content (KF)	5.36%	4.92%	4.98%	4.94%

*Not less than 85% after 40 min

Table 9
Stability at 40^{0}C 75% HR in Amber Glass Bottles (VALA 111/60)

	Time 0	Time 1 month	Time 2 month	Time 3 month
Appearance	Oblong white to light yellow tablet	Conform	Conform	Conform
Assay	101.9%	106.9%	100.9%	99.4%
Purity -Aciclovir(%w/w) -Guanina (%w/w) -4.5min by area -7.6min by area	 0.49% 0.02% 0.019% 0.026%	 0.64% 0.02% 0.018% 0.026%	 0.67% 0.03% 0.016% 0.024%	 0.80% 0.04% 0.016% 0.026%
Hardness	312 N	350 N	349 N	350 N
Disint.Time pH=1.2	18 min	24 min	23 min	24 min
Dissolution pH=1.2*	Conform	Conform	Conform	Conform
Water content (KF)	5.36%	4.96%	5.13%	5.03%

*Not less than 85% after 40 min

Table 10
Stability at 25^{0}C 60% HR in Amber Glass Bottles (VALA 111/62)

	Time 0	Time 1 month	Time 2 month	Time 3 month
Appearance	Oblong white to light yellow tablet	Conform	Conform	Conform
Assay	101.9%	104.25%	102.3%	103.1%
Purity -Aciclovir(%w/w) -Guanina (%w/w) -4.5min by area -7.6min by area	 0.49% 0.02% 0.019% 0.026%	 0.55% 0.02% 0.017% 0.025%	 0.54% 0.03% 0.018% 0.024%	 0.60% 0.03% 0.017% 0.026%
Hardness	280 N	331 N	326 N	360 N
Disint.Time pH=1.2	16 min	16 min	16 min	18 min
Dissolution pH=1.2*	Conform	Conform	Conform	Conform
Water content (KF)	5.22%	5.73%	4.41%	5.09%

*Not less than 85% after 40 min

Table 11
Stability at 30°C 65% HR in Amber Glass Bottles (VALA 111/62)

	Time 0	Time 1 month	Time 2 month	Time 3 month
Appearance	Oblong white to light yellow tablet	Conform	Conform	Conform
Assay	101.9%	105.1%	100.8%	102.8%
Purity -Aciclovir(%w/w) -Guanina (%w/w) -4.5min by area -7.6min by area	 0.49% 0.02% 0.019% 0.026%	 0.59% 0.02% 0.018% 0.026%	 0.59% 0.03% 0.018% 0.024%	 0.65% 0.03% 0.017% 0.027%
Hardness	280 N	337 N	336 N	346 N
Disint.Time pH=1.2	16 min	19 min	18 min	22 min
Dissolution pH=1.2*	Conform	Conform	Conform	Conform
Water content (KF)	5.22%	5.00%	5.02%	4.93%

*Not less than 85% after 40 min

Table 12
Stability at 40°C 75% HR in Amber Glass Bottles (VALA 111/62)

	Time 0	Time 1 month	Time 2 month	Time 3 month
Appearance	Oblong white to light yellow tablet	Conform	Conform	Conform
Assay	101.9%	100.7%	103.9%	104.4%
Purity -Aciclovir(%w/w) -Guanina (%w/w) -4.5min by area -7.6min by area	 0.49% 0.02% 0.019% 0.026%	 0.71% 0.02% 0.015% 0.025%	 0.87% 0.03% 0.016% 0.024%	 0.96% 0.03% 0.015% 0.025%
Hardness	280 N	330 N	318 N	320 N
Disint.Time pH=1.2	16 min	19 min	19 min	23 min
Dissolution pH=1.2*	Conform	Conform	Conform	Conform
Water content (KF)	5.22%	5.13%	4.70%	5.03%

*Not less than 85% after 40 min

EXAMPLE 6 COMPATABILITY TESTING OF FORMULATION EXCIPIENTS BY DIFFERENTIAL SCANNING CALORIMETRY

Compatability between Valacyclovir HCl, excipients and film coating components were investigated by differential scanning calorimetry to assess the

compatibility among drug substance and excipients. Thermal events were recorded for each component and for various mixtures of components, and analyses were carried out comparing peaks recorded by DSC for various mixtures to individual peaks observed for valacyclovir HCl and the excipients under investigation.

The formulation and ingredients under investigation are reported in Table 13.

Table 13

Commercial name	Chemical Name	Tablets of 1000	Tablets of 500
		mg	mg
Valacyclovir HCl		1112*	556*
Vivapur 102	Cellulose	15	7,5
Kollidon CL	1-Ethenyl-2-pyrrodinone homopolymer	6	3
Ac-Di-Sol	Cellulose, carboxymethyl ether, sodium salt, crosslinked	46	23
Methocel A4C	Cellulose methyl ether	1,5	0,75
UNI PURE DW	Starch	100	50
Compritol 888 ato	Docosanoic acid, monoester whit glycerin	25	12,5
	Docosanoic acid, diester whit glycerin		
	Docosanoic acid, triester whit glycerin		

Preparation of samples for analysis

Three methods were used to prepare mixtures for analysis.

Dry solids —Aliquots of Valacyclovir HCl and excipient under investigation were weighed in a ratio of 1:1 or in the method ratio and ground in an agate mortar. Homogeneous powder was used for the analysis.

Wet granulation —aliquots of mixtures were wetted with water or with EtOH and water mixture (1:9); after mixing the wet powder was left to dry at room temperature.

Film coated —The investigation was also done with film coating components (Opadry white) in a mixture with the final formulation in the ratio 1:1

In order to assure the consistency of the data, analyses carried out on a final mixture prepared in the lab were compared with data collected with the final tablet VALA 111/44 before film coating

Differential Scanning Calorimetry (DSC)

DSC heating curves were obtained using a TA 821 DSC Mettler instrument under the following conditions:

- heating rate: 10 °C/min
- ambient: Nitrogen 30 mL/min
- sample holder: normal open aluminium pan
- temperature range: from 25 to 250 °C
- instrument calibration: Indium sample purity 99.999 %

DSC Curves were first generated for each of the single ingredients, and subsequently for various mixtures. Curves generated for the mixtures are reproduced in Figures 4 - 8. The results of the DSC investigation are discussed below.

Figure 4 depicts the DSC curve of a mechanical mixture of all components present in the dosage form in 1:1 ratio. A peak for the gliceril benehate can be observed at 70°C, a reduced peak for the valacyclovir hydrochloride is observed at 195^0C, and one other peak corresponding to the sodium lauryl sulphate is observed at $23O^0$C.

Figure 5 depicts the DSC curve of a mechanical mixture of all the components in proportions close to Formula IV. A peak for the valacyclovir hydrochloride is readily evident in the upper curve at 195°C and a peak for gliceril benehate is evident at at $7O^0$C. The lower DSC curve in figure 5 was generated after granulated this mixture with water. The valacyclovir hydrochloride peak is visible, and there is a broad endothermic effect in the temperature range of 100-120 ^{0}C probably due to the aggregation of the celluloses.

Figure 6 depicts the DSC curve of a mechanical mixture of all the components present in the dosage form. A mixture was made of valacyclovir hydrochloride and mais starch; then the solid mixture was wetted with a hydro-alcoholic solution 1:9 in methocel.. All the components were kneaded and left in ambient conditions to be dried. In the DSC curve produced from this mixture, valacyclovir hydrochloride shows a peak at 195°C with low intensity probably due to partial decreasing of

crystallinity. There is a broad endothermic effect in the temperature range of 100-120°C probably due to the interaction of celluloses with water (inclusion water).

Figure 7 depicts the DSC curve for a mechanical mixture with all the components present in the dosage form. In the upper DSC curve in figure 7, a valacyclovir hydrochloride peak is evident at 195°C and a gliceril benehate peak is evident at 70°C. No interaction peaks are evident. After the mixture is granulated with water and analysed by DSC, the lower curve in figure 7 is generated. The valacyclovir hydrochloride peak is visible, but with lower intensity, and there is a broad endothermic effect in the temperature range of 100-120°C probably due to the aggregation of the celluloses. Once again, no interactions among valacyclovir hydrochloride and excipients are detected.

Figure 8 depicts the DSC curve for a VALA III /44 tablet (final formulation before film coating). In the upper DSC curve in figure 8, a peak for valacyclovir hydrochloride is evident at 195°C and one for gliceril benehate is evident at 70°C. No interaction peaks are observed. The mixture was then granulated with water and analysed by DSC to produce the lower curve in figure 8. The valacyclovir hydrochloride peak is very visible, but with lower intensity, and there is a broad endothermic effect in the temperature range of 100-120°C probably due to the aggregation of the celluloses, or due to the Opadry effect.

In summary, it can be concluded based on the DSC data that there is no detectable interaction between the excipients and valacyclovir hydrochloride during the formulation steps, but only a very low reduction of valacyclovir hydrochloride crystallinity. The wet granulation step, in relation to the amount of solvent used, induces little decrease in valacyclovir hydrochloride crystallinity. The film coating step of the core tablet with Opadry-white product does not induce interaction between valacyclovir hydrochloride and excipients.

EXAMPLE 7 BIOAVAILABILITYTESTS

The study here was a pilot, four periods, four sequences, cross-over, controlled, block randomized, single dose bioequivalence study, and employed 77 healthy fasting volunteer patients. The two test formulations were Valacyclovir 1000 mg coated tablets and 2x500 mg coated tablets, and were compared to Zelitrex® (U.S. product) and Valtrex® (European product) tablets as reference 1000 mg formulations.

5 ml blood samples were drawn before valacyclovir administration (time 0.0), and at 0.5; 0.75; 1.0; 1.33; 1.67; 2.0; 2.5; 3.0; 4.0; 6.0; 8.0; 10.0; 12.0; 16.0; and 24 hours past dose.

Based on the results, the following pharmacokinetic parameters were calculated for Acyclovir: AUCo-$_{m}$f = (from time 0 to infinite) area under the concentration-time curve integrated from the plasma concentrations extrapolating the terminal elimination phase; AUC_{0-t} = area under the concentration-time curve integrated, by the trapezoidal rule, from plasma concentrations between time 0 to the last quantifiable sample; $C_{ma}\chi$ = peak plasma drug concentration, obtained directly from the data, without interpolation; T_{max} = time of peak drug concentration, obtained directly from the data, without interpolation; AUC%extra = percent of extrapolated AUC = the ratio 100*(AUC_{0-}j$_{n}$f - AUC_{0-t})/ AUCo-jnf, where the percent of extrapolated AUC cannot exceed 20%; th$_{a}$if = plasma half-life, calculated as 0.693/ k_{el}, where kei, = elimination rate constant; MRT = mean residence time, calculated as AUMCinf/AUCinf, where AUMCinf = area under the moment curve. All pharmacokinetic and statistical calculations were performed using SAS (Ver. 9.1) software.

The statistical analysis of pharmacokinetic data obtained in this study found that the 1000 mg coated test tablets formulated according to the invention are fully bioequivalent with both the Zelitrex ® and Valtrex ® tablets, and this was true for both the extent and rate of absorption of Acyclovir in the body.

Table 14

Mean Concentration Values by Sampling Time

Time in Body (Hours)	Mean T1 1000mg test (ng/ml)	Std Dev T1 1000mg test	Mean T2 500mg test (ng/ml)	Std Dev T2 500mg test	Mean R1 1000mg Valtrex® (ng/ml)	Std Dev R1 1000mg Valtrex®	Mean R2 1000mg Zelitrex® (ng/ml)	Std Dev R2 1000mg Zelitrex®
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
5.000	2377.581	1211.850	3455.614	1859.876	2183.561	982.040	2749.369	1687.766
0.750	3251.742	1050.491	4502.166	1502.708	3071.468	912.169	3670.546	1735.502
1.000	3612.985	1187.936	4689.207	1203.892	3285.880	790.375	3596.816	1215.125
1.333	4169.216	1308.922	4589.723	872.515	3507.491	755.649	4001.446	1483.134
1.667	4261.531	1608.747	4770.787	1021.550	3759.221	766.952	4134.966	1184.992
2.000	4321.116	1231.711	4465.357	626.420	4066.645	1038.015	4187.980	1243.200
2.500	3888.327	762.103	3721.204	870.269	4598.475	1334.088	4353.057	1147.630
3.000	3209.470	518.984	2972.906	874.541	3807.494	1145.655	3503.131	990.264
4.000	1965.756	407.249	1955.067	549.374	2383.491	674.523	2300.246	720.500
6.000	943.551	231.274	992.996	236.266	1066.654	190.890	1059.064	220.281
8.000	519.826	156.584	542.845	143.992	572.155	111.179	569.406	139.517
10.000	310.037	100.832	308.994	87,160	328.669	70.009	335.740	87.209
12.000	186.518	63.533	183.589	73.550	196.482	52.130	199.794	64.435
16.000	84.415	34.203	78.381	36.508	85.019	27.991	85.619	34.097
24.000	32.011	23.103	23.778	23.323	31.152	16.472	24.558	24.255

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

1) A method of making a valacyclovir tablet comprising:
   a) wet granulating a mixture of valacyclovir hydrochloride, methylcellulose, and starch to form a granulate;
   b) mixing said granulate with an extragranulate composition comprising pharmaceutically acceptably excipient to form a blend; and
   c) compressing said blend into a tablet;
   wherein the granulate comprises less than 1.0 wt.% methylcellulose or greater than 82 wt.% valacyclovir hydrochloride.
2) The method of claim 1 wherein said starch is pregelatinized starch.
3) The method of claim 1 wherein said valacyclovir tablet comprises greater than 85 wt.% of said tablet.
4) The method of claim 1 wherein said tablet comprises less than about 5 wt.% binding agent other than starch.
5) The method of claim 1 wherein the weight ratio of said valacyclovir hydrochloride to said methylcellulose is greater than 500:1.
6) The method of claim 1 wherein the weight ratio of said valacyclovir hydrochloride to said starch is from about 5:1 to about 30:1.
7) The method of claim 1 wherein said wet granulating comprises preparing said granulate in a solvent that comprises greater than about 50 wt.% water.
8) The method of claim 1 wherein said wet granulating comprises:
   a) dissolving or suspending said methylcellulose in a solvent comprising greater than about 50 wt.% water to form a liquid methylcellulose suspension or solution;
   b) mixing said valacyclovir hydrochloride with said starch to form a blend;
   c) mixing said blend with said liquid methylcellulose suspension or solution to form a wet suspension or liquid slurry; and
   d) drying said wet suspension or liquid slurry to form a granulate.
9) The method of claim 1 wherein said valacyclovir hydrochloride comprises from about 3 to about 9 wt.% water of hydration.
10) A valacyclovir tablet comprising an intragranular portion and an extragranular portion, wherein:

a) said intragranular portion comprises valacyclovir hydrochloride, starch and methylcellulose;

b) said extragranular portion comprises one or more binding agents; and

c) said granulate comprises less than 1.0 wt.% methylcellulose or greater than 82 wt.% valacyclovir hydrochloride.

11) The tablet of claim 10 wherein said tablet does not contain titanium dioxide.

12) The tablet of claim 10 wherein said tablet does not comprise silicon dioxide.

13) The tablet of claim 10 comprising less than about 8 wt.% water.

14) The tablet of claim 10 wherein said tablet has a hardness of from about 235 to about 300 N.

15) The tablet of claim 10 wherein said tablet has a friability of from about 0.03% to about 0.15%.

16) The tablet of claim 10 wherein said tablet has a disintegration time of from about 15 to about 25 minutes when tested according to USP 28 <701>.

17) The tablet of claim 10 wherein said tablet has a dissolution profile substantially as shown in Figure 1, when tested according to USP 28 <71 1>.

18) The tablet of claim 10 comprising greater than about 70 wt.% valacyclovir hydrochloride.

19) A granulate comprising valacyclovir hydrochloride, starch and methylcellulose, wherein the granulate comprises less than 1.0 wt% methylcellulose or greater than 82 wt.% valacyclovir hydrochloride.

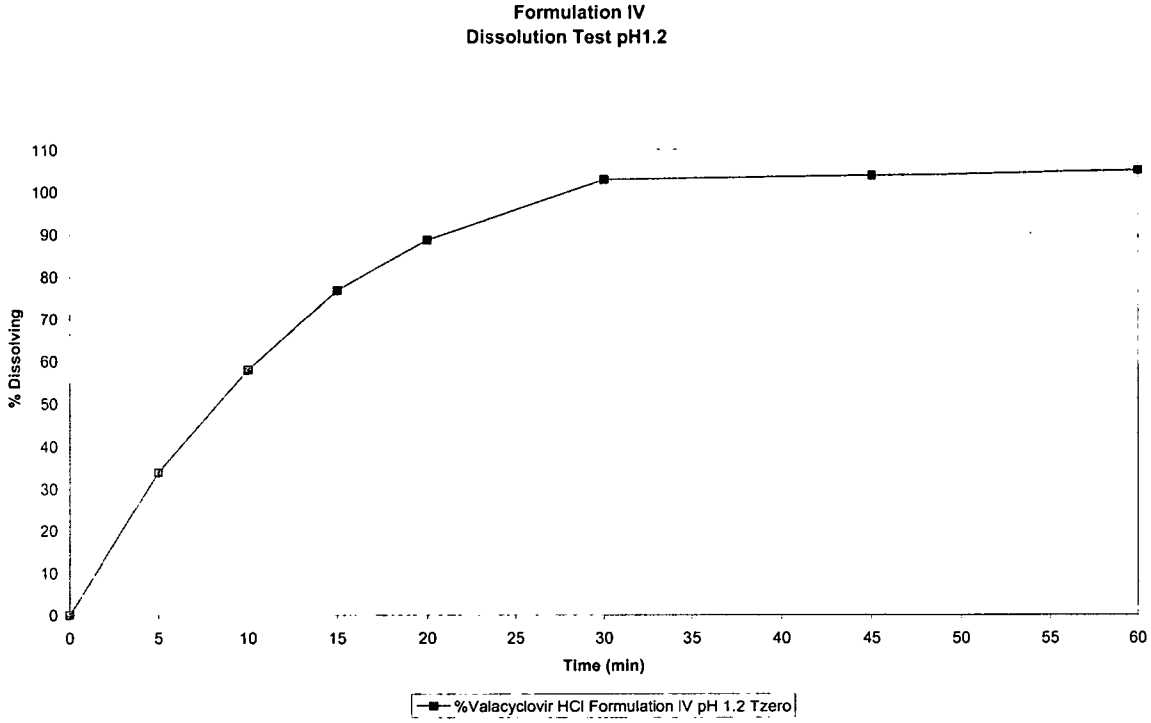


FIGURE 1

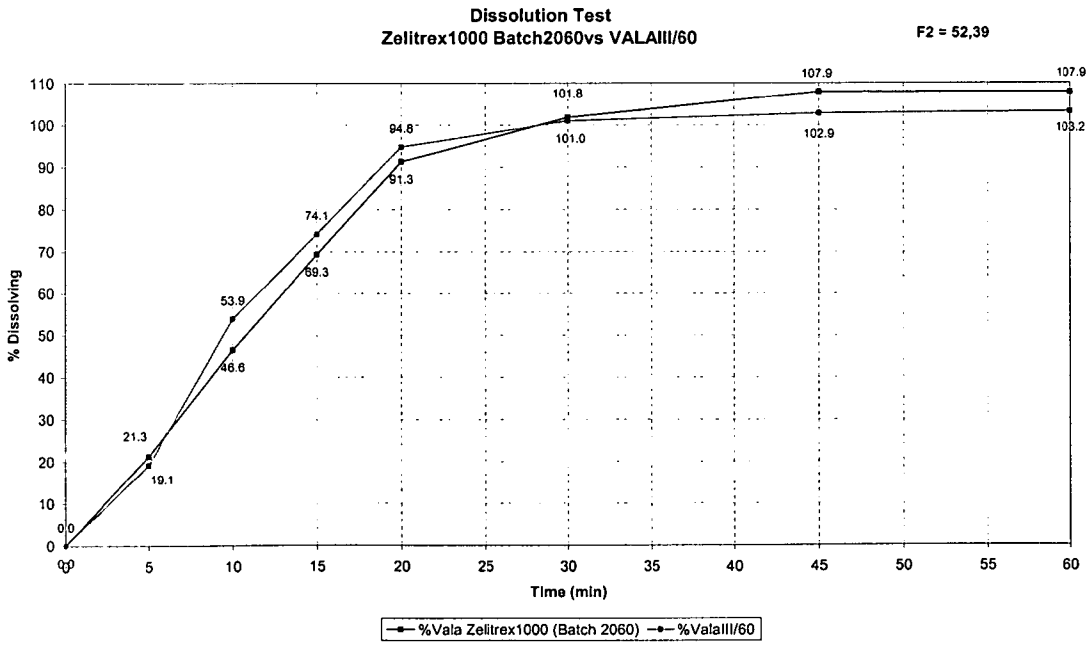


FIGURE 2

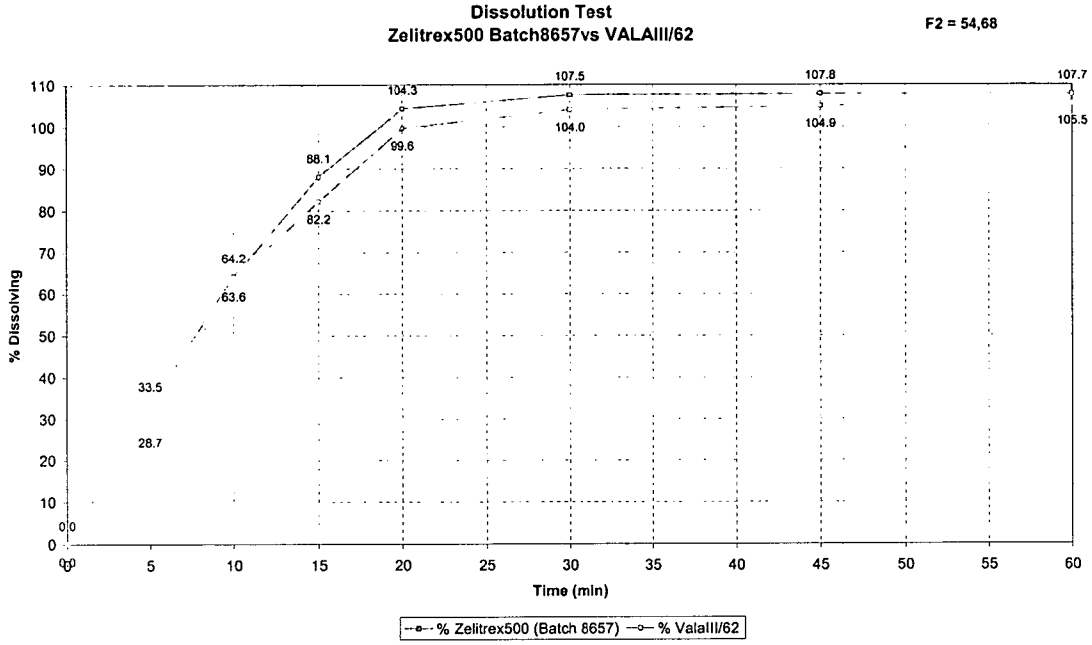


FIGURE 3

DSC heating curve relative to the mechanical mixture of all components (1:1)

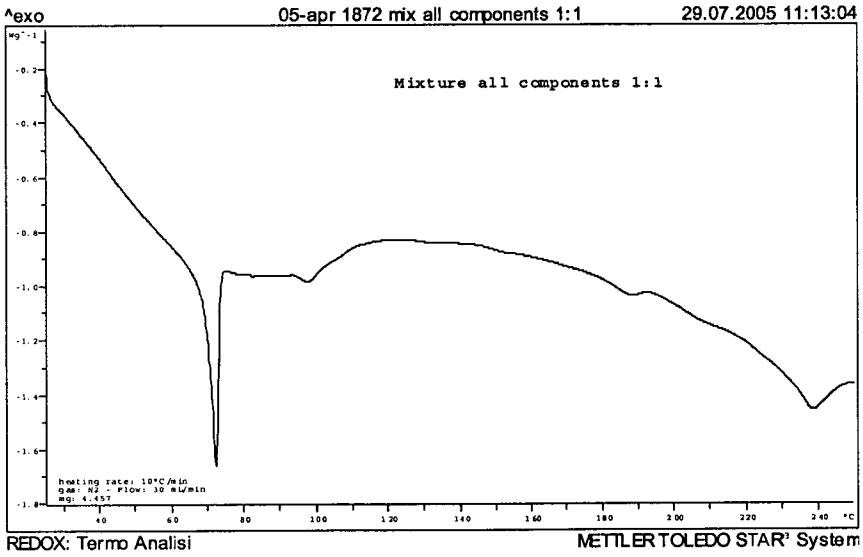


FIGURE 4

DSC heating curve relative to the mechanical and granulated mixture of all components in the ratio to close the formula.

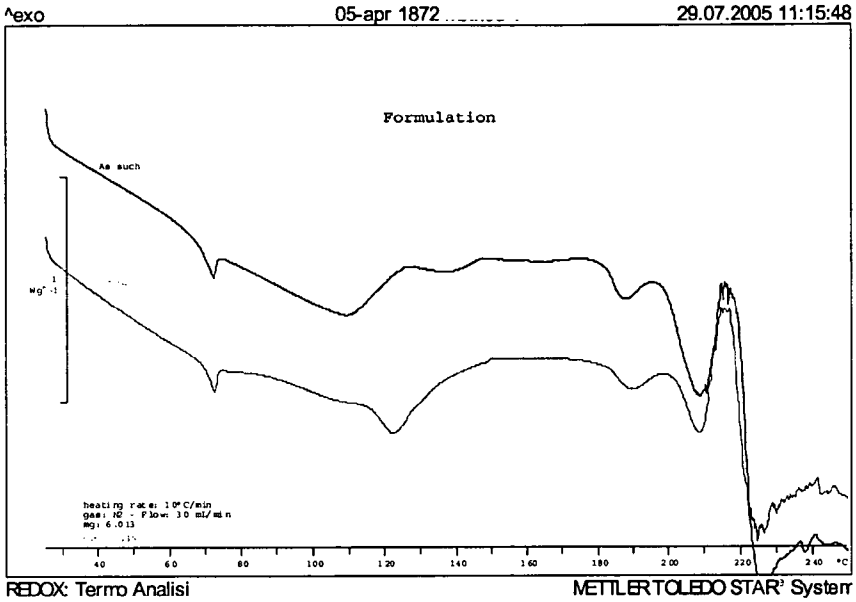


FIGURE 5

DSC heating curve relative to the mechanical mixture of all components (wet granulation).

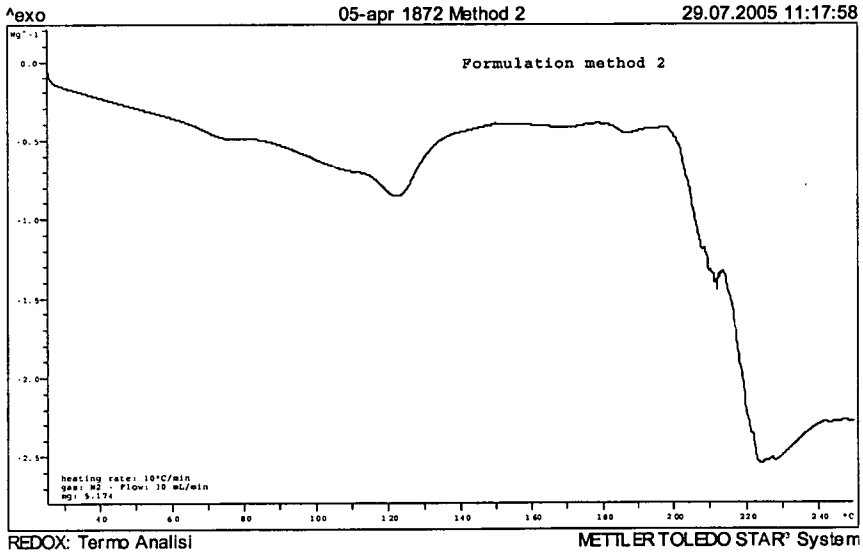


FIGURE 6

DSC heating curve relative to the mechanical mixture of all components

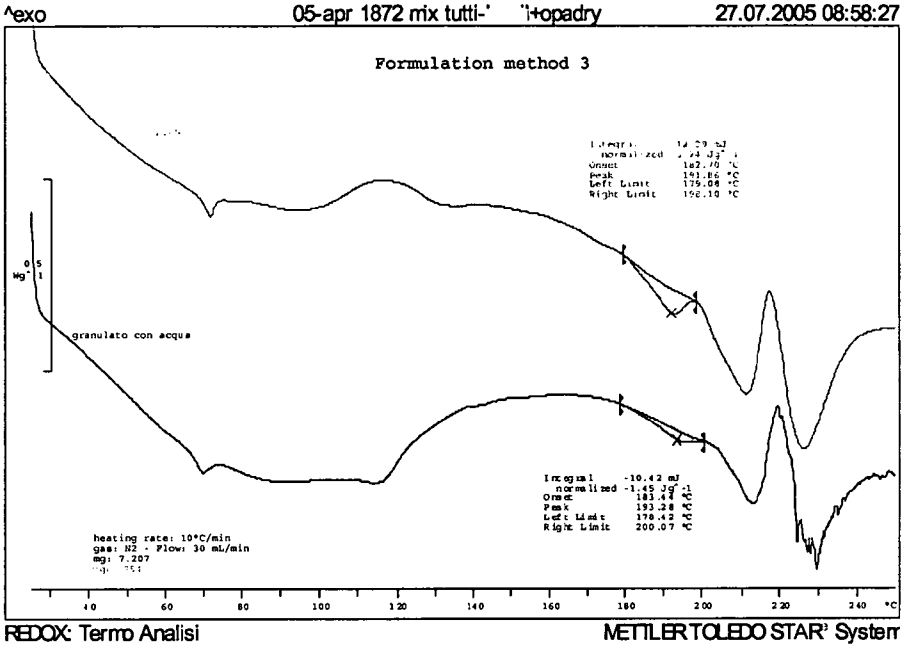


FIGURE 7

DSC heating curve relative to the tablet VALA III/ 44 before film coating

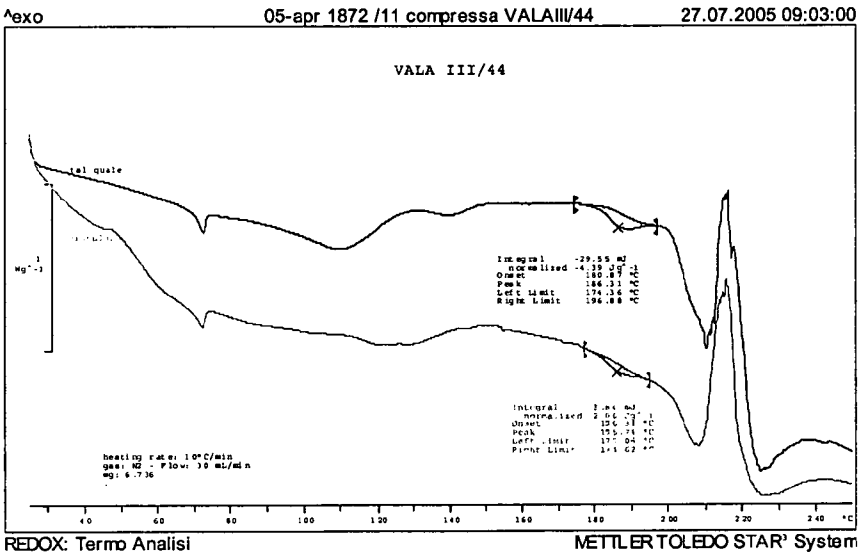


FIGURE 8

Mean ACYCLOVIR plasmatic concentrations for T1 vs. T2 vs. R1 vs. R2

T1 = 1000 mg test tablets R1 = 1000 mg Valtrex® tablets

T2 = 2x500 mg test tablets R2 = 1000 mg Zelitrex® tablets

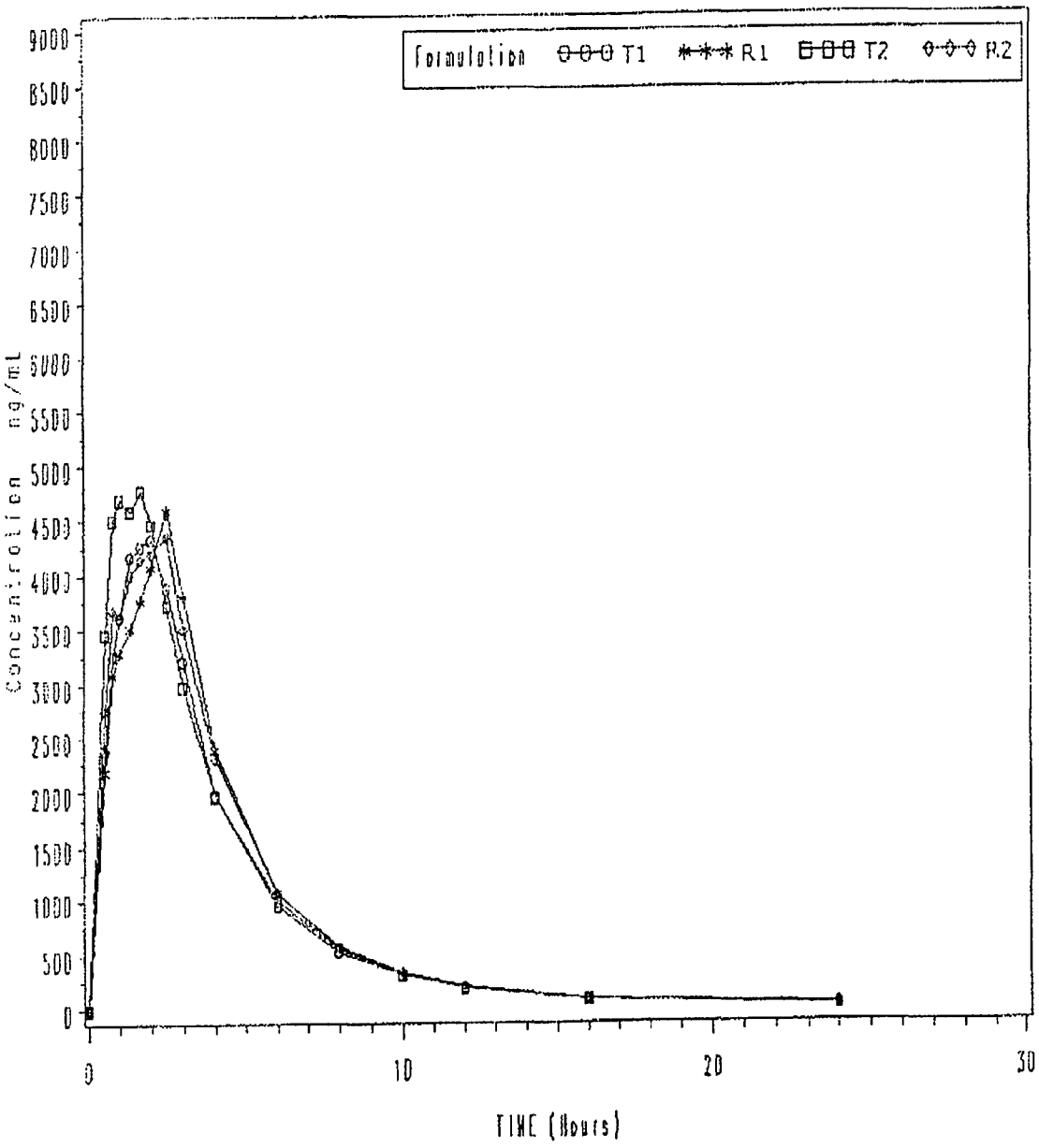
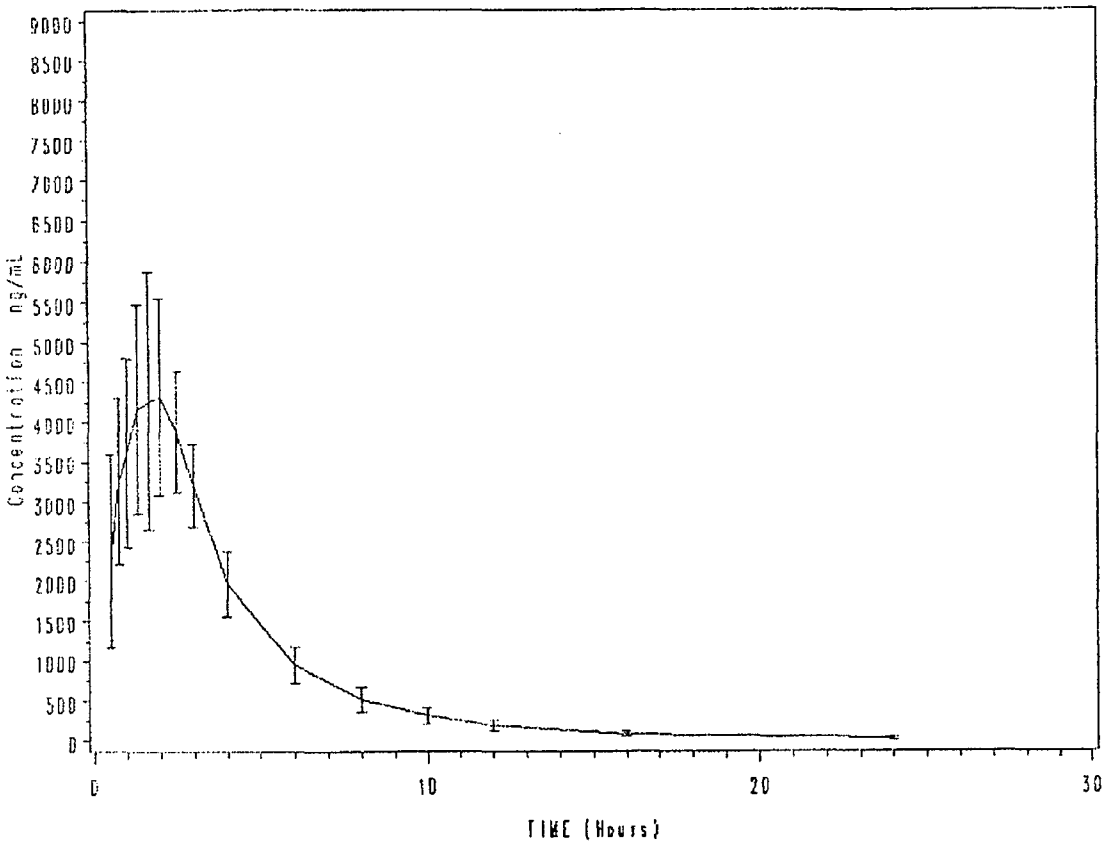


FIGURE 9

Mean ACYCLOVIR plasmatic concentration from T1 (1000 mg test tablets)



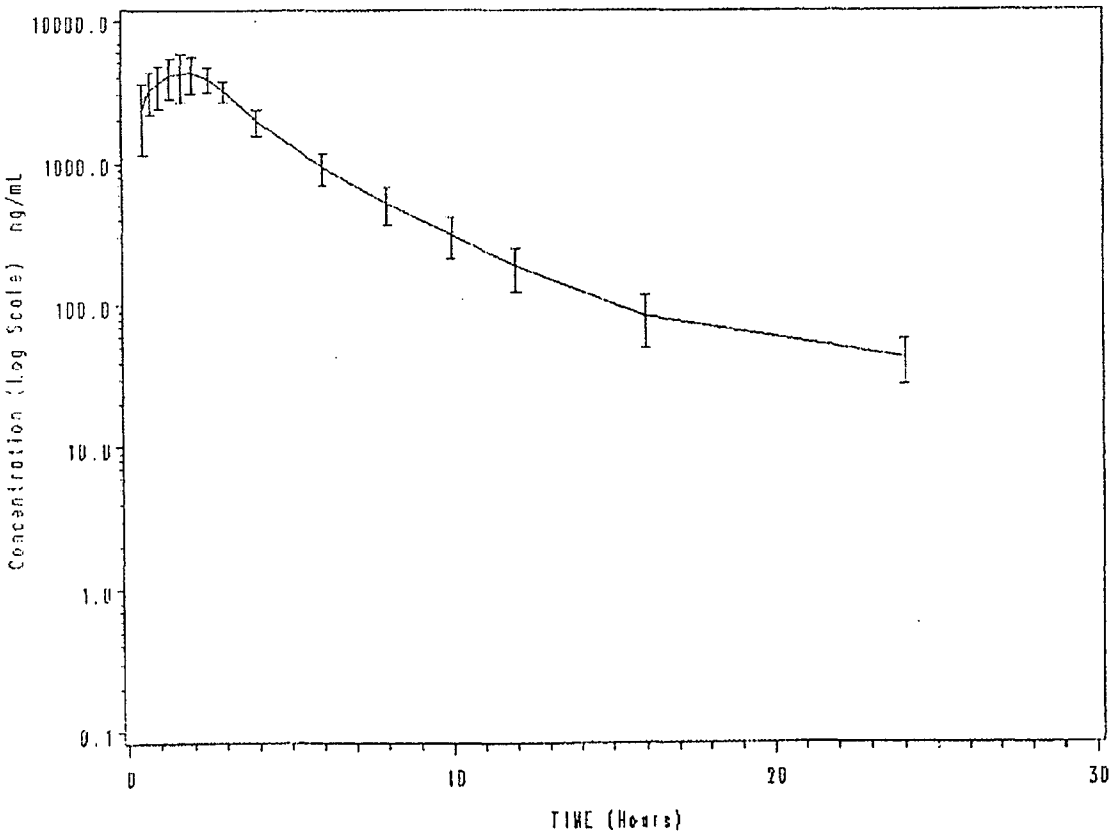
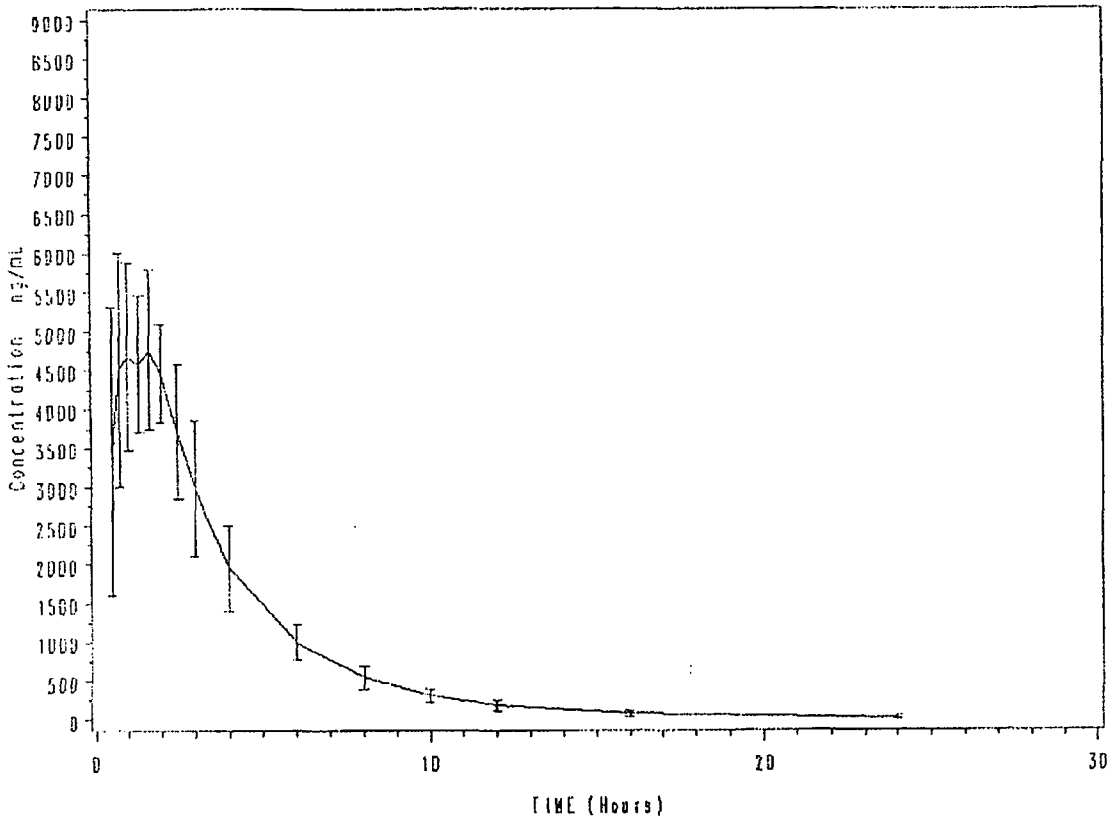


FIGURE 10

Mean ACYCLOVIR plasmatic concentration from T2 (2x500 mg test tablets)



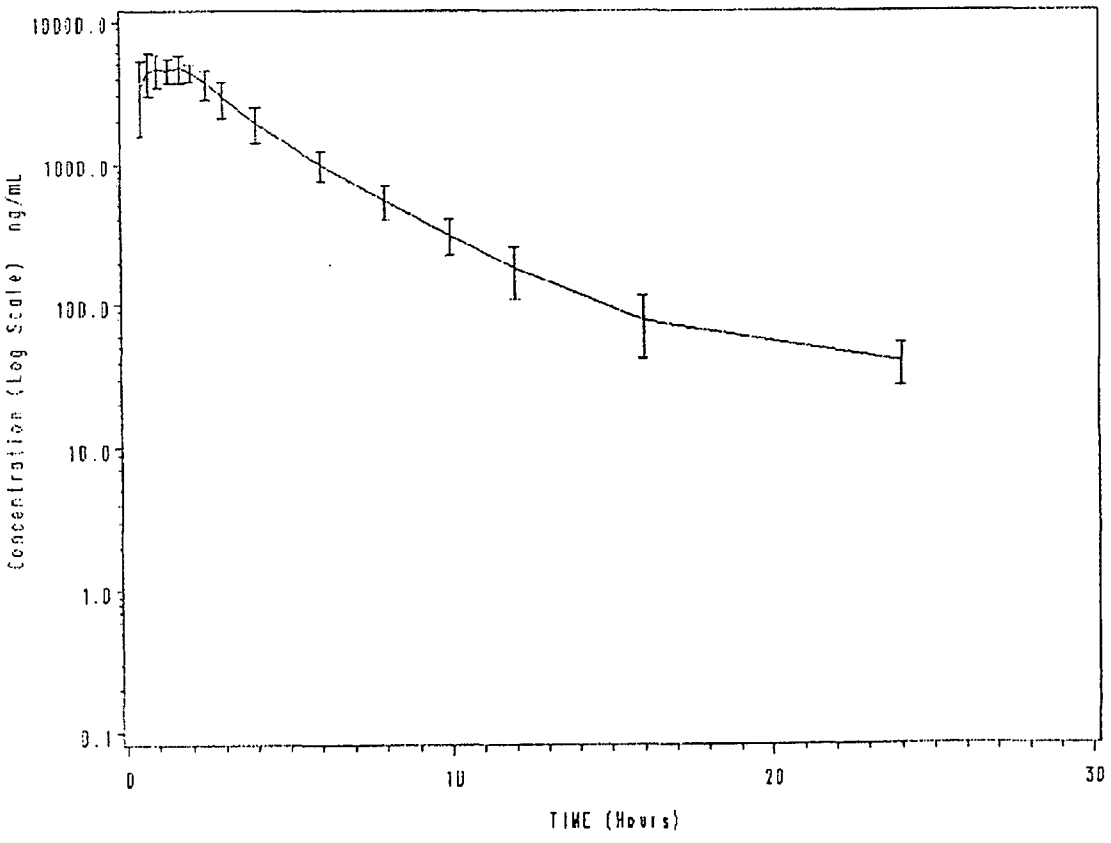
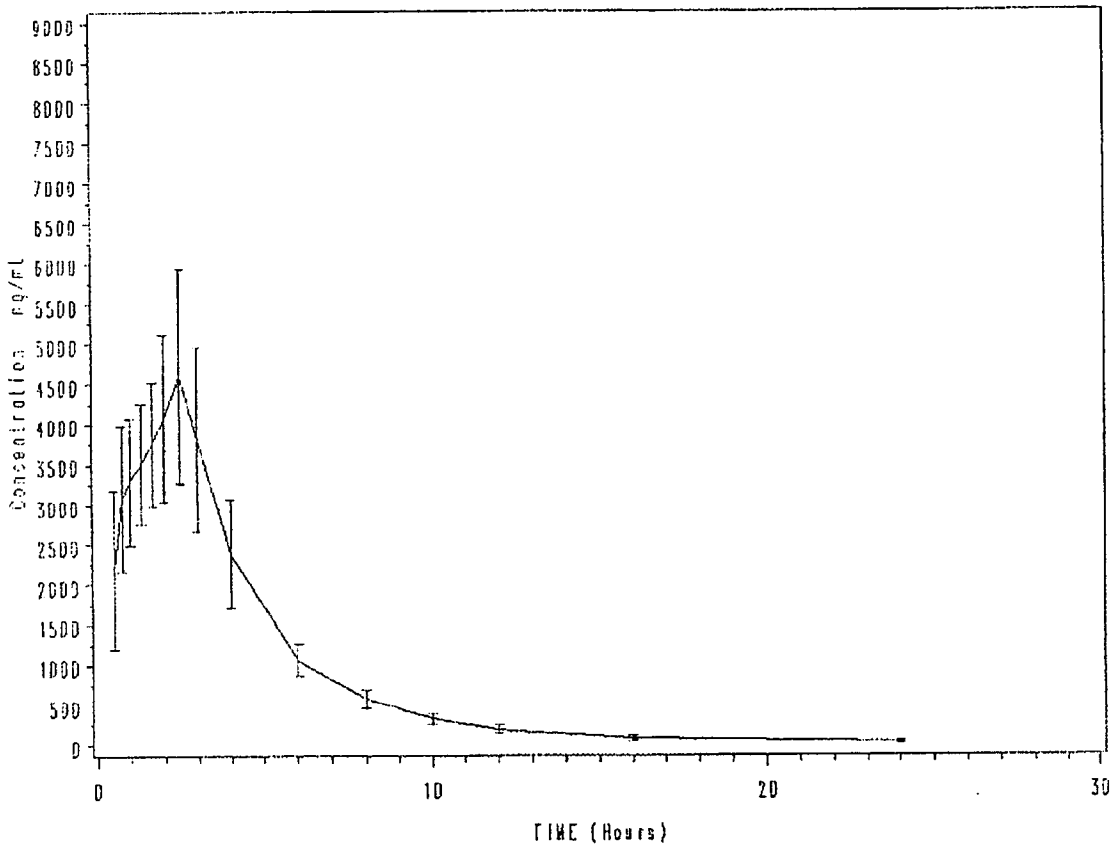


FIGURE 11

Mean ACYCLOVIR plasmatic concentration from R1 (1000 mg Valtrex®)



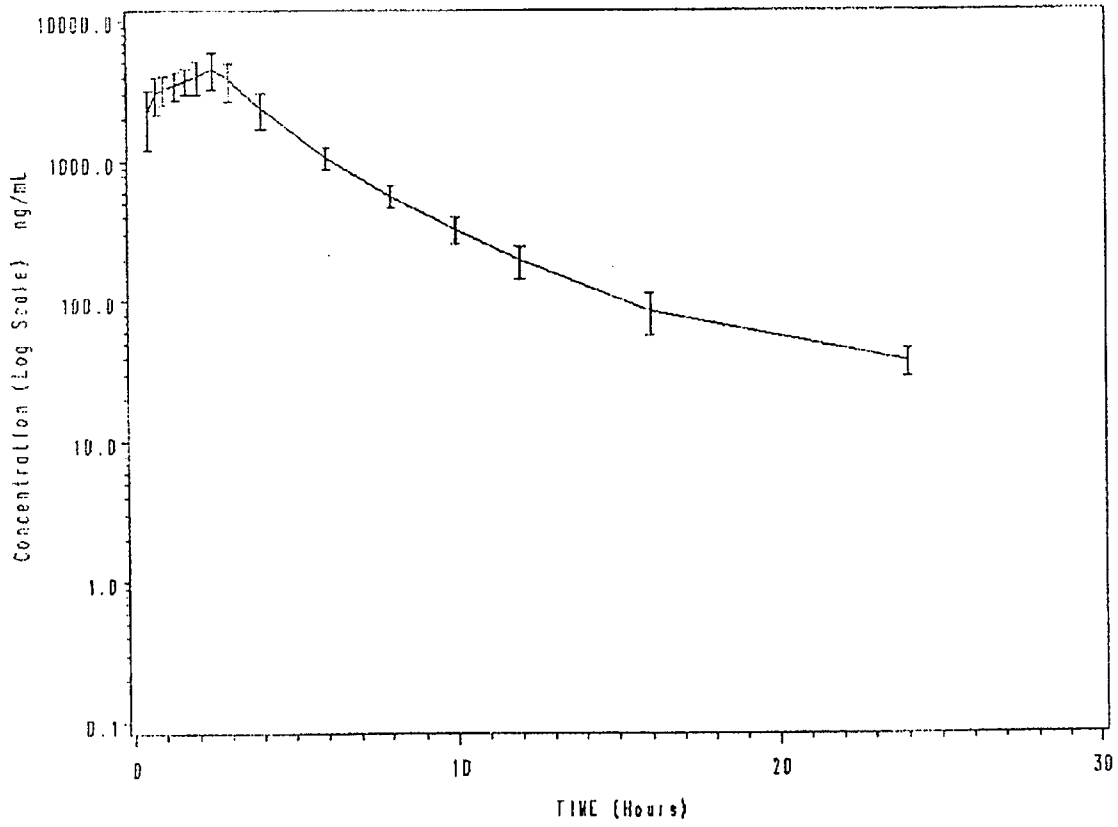
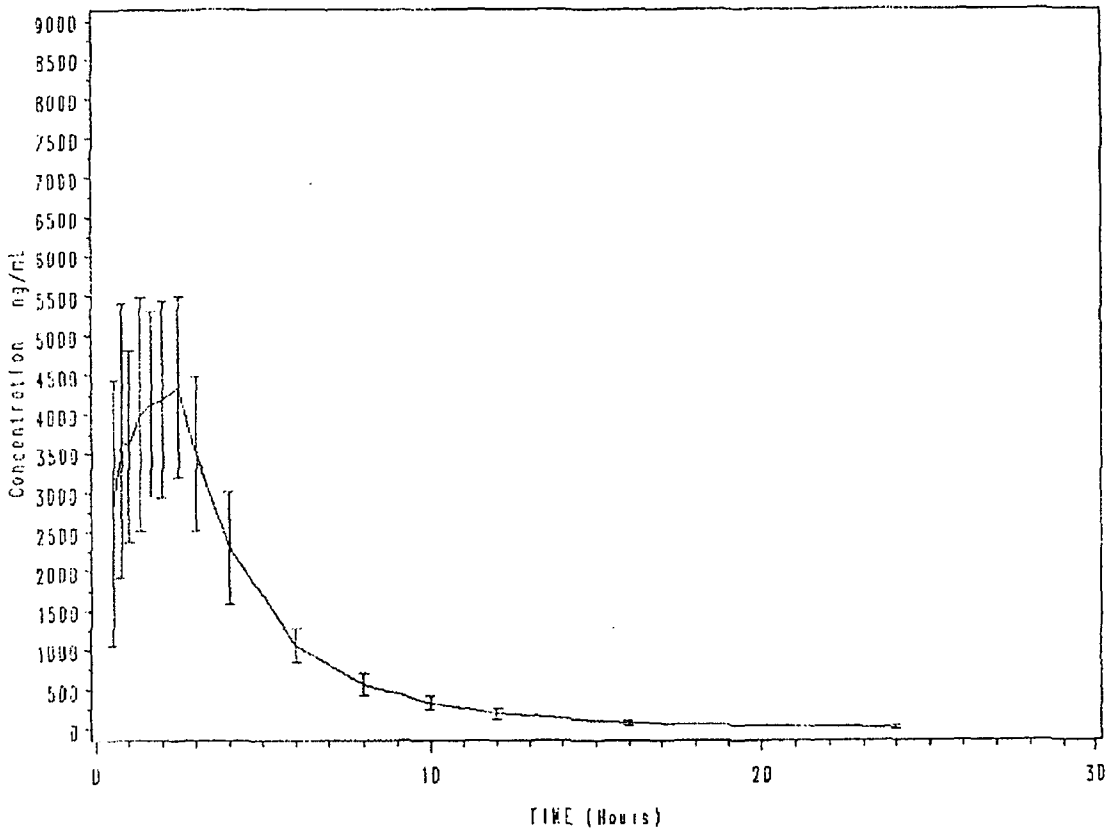


FIGURE 12

Mean ACYCLOVIR plasmatic concentration from R2 (1000 mg Zelitrex®)



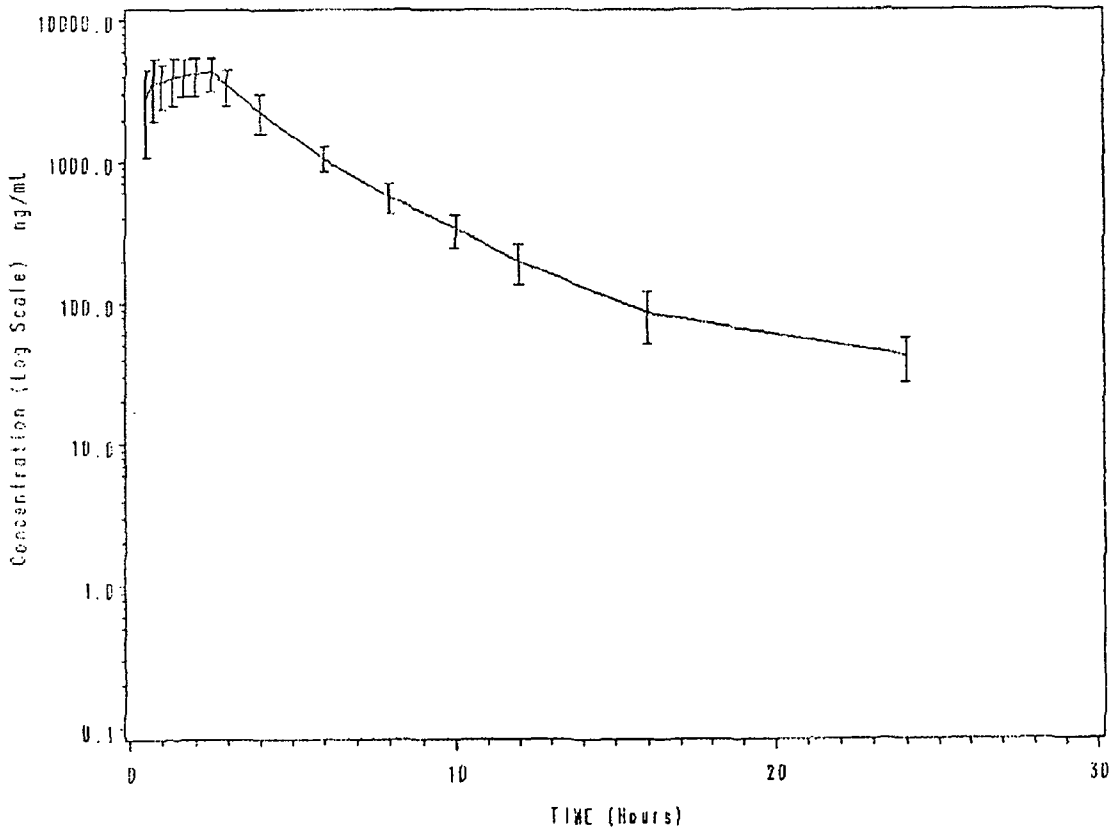


FIGURE 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/000966

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/522

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)
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)

EPO-Internal , WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	EP 1 541 133 A (HELM AG) 15 June 2005 (2005-06-15) claims examples paragraphs [0015] - [0025]	1-19
Y	WO 96/22082 A (WELLCOME) 25 July 1996 (1996-07-25) claims examples	1-19
Y	WO 97/25989 A (GLAXO) 24 July 1997 (1997-07-24) claims examples	1-19

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[X] Further documents are listed in the continuation of Box C

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* Special categories of cited documents

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Date of the actual completion of the international search	Date of mailing of the international search report
17 Apri l 2007	07/05/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rljswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi , Ugo

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/000966

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/000265 A (RANBAXY) 31 December 2003 (2003-12-31) claims examples	1-19
Y	WO 2004/037263 A (RANBAXY) 6 May 2004 (2004-05-06) claims examples	1-19
Y	WO 03/017981 A (RANBAXY) 6 March 2003 (2003-03-06) claims example 3	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/000966

Patent document cited In search report	Publication date	Patent family member(s)	Publication date
EP 1541133 A	15-06-2005	AT 301455 T	15-08-2005
		DE 60301277 Dl	15-09-2005
		DE 60301277 T2	30-03-2006
		ES 2246034 T3	01-02-2006
		US 2005123607 Al	09-06-2005
WO 9622082 A	25-07-1996	AP 666 A	24-08-1998
		AT 190483 T	15-04-2000
		AU 710823 B2	30-09-1999
		AU 4453496 A	07-08-1996
		BG 63187 Bl	29-06-2001
		BG 101831 A	30-04-1998
		BR 9606769 A	30-12-1997
		CA 2210891 Al	25-07-1996
		CN 1179100 A	15-04-1998
		CN 1494898 A	12-05-2004
		CY 2182 A	23-08-2002
		CZ 9702292 A3	18-02-1998
		DE 69607146 Dl	20-04-2000
		DE 69607146 T2	21-09-2000
		DK 806943 T3	24-07-2000
		EA 276 Bl	25-02-1999
		EE 3336 Bl	15-02-2001
		EP 0806943 Al	19-11-1997
		ES 2145425 T3	01-07-2000
		FI 973062 A	18-09-1997
		GR 3033677 T3	31-10-2000
		HK 1002851 Al	08-09-2000
		HU 9801872 A2	28-10-1999
		IL 116830 A	29-02-2000
		IN 181318 Al	09-05-1998
		JP 3350055 B2	25-11-2002
		Jp 10512564 T	02-12-1998
		NO 973327 A	16-09-1997
		NZ 298846 A	26-06-1998
		OA 10500 A	10-04-2002
		PL 321361 Al	08-12-1997
		PT 806943 T	31-08-2000
		RO 118175 Bl	28-03-2003
		SK 96497 A3	14-01-1998
		TR 9700657 Tl	21-02-1998
		UA 68325 C2	16-08-2004
		US 5879706 A	09-03-1999
		ZA 9600448 A	07-08-1996
WO 9725989 A	24-07-1997	AT 254463 T	15-12-2003
		AU 722304 B2	27-07-2000
		AU 1443497 A	11-08-1997
		CA 2243237 Al	24-07-1997
		CY 2512 A	23-12-2005
		DE 69726255 Dl	24-12-2003
		DE 69726255 T2	26-08-2004
		DK 874631 T3	22-03-2004
		EP 0874631 Al	04-11-1998
		ES 2210490 T3	01-07-2004
		Jp 2000503310 T	21-03-2000
		PT 874631 T	30-04-2004
		ZA 9700400 A	13-11-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/000966

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004000265 A	31-12-2003	AU 2003240213 A1	06-01-2004
		EP 1517678 A2	30-03-2005
		US 2006147519 A1	06-07-2006
WO 2004037263 A	06-05-2004	AU 2003274410 A1	13-05-2004
		EP 1556050 A1	27-07-2005
		US 2006189565 A1	24-08-2006
WO 03017981 A	06-03-2003	US 2003175341 A1	18-09-2003