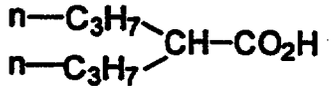
# PHARMACEUTICAL MICROSPHERES OF VALPROIC ACID FOR ORAL ADMINISTRATION

The present invention generally relates to new pharmaceutical microspheres for oral administration.

In particular, the invention relates to new pharmaceutical microspheres for oral administration containing valproic acid of formula:



and one of its pharmaceutically acceptable salts, in particular an alkali metal, such as sodium or potassium, or alkaline-earth metal, such as calcium or magnesium, salt.

Sodium valproate is an anti-epileptic medicament widely sold at the current time, in particular in the form of tablets assaying 500 mg per administration unit.

These tablets, which are provided with an enteric or programmed-release coating, are for this reason fairly large.

In consequence, such tablets will generally be disadvantageous, in particular for children or people experiencing difficulties in swallowing, for example elderly people.

For this type of patient, it thus appears desirable to have available administration forms which are better suited to their state or to their condition.

Moreover, sodium valproate has a rather unpleasant, bitter taste. It will consequently prove to be necessary to take into account this disadvantage in administration forms suitable for children, for example syrup forms or solutions to be taken orally, by masking this taste using various expedients.

However, administration forms such as syrups do not allow children to benefit from the advantages

resulting in some cases from the gastroresistance and the prolonged release of the active ingredient.

Moreover, the adjustment of the dose of active ingredient to the weight of the child, the child posology per kg of body weight being observed, represents an additional constraint in paediatrics.

A few years ago, a new pharmaceutical dosage presentation appeared which makes it possible to satisfy some of these requirements. It consists of a fine semolina composed of microspheres, in which microspheres the active ingredient is most often covered with an isolating film. This fine semolina, sprinkled over a spoonful of semi-solid food, for example purée, compote or yoghurt, is administered as is.

However, the so-called microsphere pharmaceutical form lends itself poorly to sustained release of the active ingredient. This is because, for equal masses, the surface area developed by these spheres will increase as their diameter becomes smaller, the consequence of which will be that these microspheres dissolve faster.

In order to overcome this disadvantage, it will generally be recommended to provide these spheres with an appropriate coating which makes possible the desired delayed release.

While it is industrially possible to coat pharmaceutical microspheres, it is however lengthy because it requires a large amount of polymer to be deposited.

Various methods for manufacturing these microspheres, sometimes known as "prills", are known and have been experimented with for various active ingredients.

One of them, applied to valproic acid, has been described in "Drug Development and Industrial Pharmacy", 21(7), pp. 793-807 (1995).

According to this process, a mixture composed of white beeswax in the molten form, valproic acid and a surface-active agent is stirred in an aqueous medium at pH = 4.5 while maintaining the mixture at a temperature greater than the melting temperature of the wax. On cooling, the spherical particles formed by dispersion solidify as microspheres.

However, the mean concentration of valproic acid in these microspheres does not exceed 17%, these microspheres having a certain concentration of the surfactant used, namely a mixture of ethoxylated or non-ethoxylated polysorbates.

Another technique for forming pharmaceutical microspheres resorts to the prilling technique.

According to this technique, described in particular in Patent DE 2,725,924, an excipient, the melting point of which is less than 120°C, is melted, the dissolved or dispersed active ingredient can be added thereto and then this molten dispersion is passed through a vibrating nozzle which causes the jet to break up and spherical droplets to form, which cool as microspheres in falling.

This process has been applied, for example, to pharmaceutical ingredients with an undefined crystallization point which melt in the excipient, as described in Patent EP 438,350. This excipient can be, for example, a fatty alcohol, such as stearyl alcohol, a fatty acid, such as stearic acid, a glycerol ester, a hydrogenated oil, a fatty acid salt, a polyol, a wax, a polyoxyethyleneglycol or an esterified polyoxyethylene. Moreover, stearic acid is exemplified therein as excipient.

However, it was specified therein that, in the specific case of ketoprofen, fatty acids and their salts, glycerol esters, hydrogenated oils, waxes or esterified polyoxyethylenes alone can be used.

Other pharmaceutical ingredients have also been experimented with in the prilling technique.

Thus, tests on the manufacture of microspheres containing theophylline as active ingredient have been reported in the "Technical Bulletin", No. 83, pp 33-47 (1990) of the company Gattefossé, use being made, as matrix excipient, of combinations such as stearic acid/white wax or carnauba wax/glyceryl stearate (Precirol® WL 2155), optionally with addition of saturated polyglycolysed glyceride (Gelucire® 50-13), while taking into account the characteristics of these excipients with the process chosen.

However, problems of homogeneity were recorded which resulted, according to this publication, in so-called wax mixtures being dropped for the formation of theophylline microspheres.

In the context of the present invention, attempts were made to apply this technique to sodium valproate. However, the first tests carried out, starting with a matrix comprising a stearic derivative, demonstrated a number of problems, including crystallization of the sodium valproate in the mixture subjected to prilling and a viscosity unsuitable for the manufacture of microspheres.

These disadvantages were displayed in particular during the use of a 68/2/30 by weight mixture of stearyl alcohol/Gelucire® 50-13/sodium valproate.

Moreover, tests making use of sodium valproate and stearic acid as excipient showed a high degree of incompatibility, since precipitation brought about by contact of these ingredients is recorded.

It consequently appears illusory to transpose to sodium valproate the matrix excipients commonly used in the prior art for the preparation of pharmaceutical microspheres by the prilling technique.

In addition, the fruitless tests reported, on the one hand, in the state of the art and, on the other hand, in the context of the present invention convincingly show that there does not exist a standard

excipient which can be employed in a prilling process whatever the active pharmaceutical ingredient used.

Consequently, the development of an administration form for sodium valproate which is simultaneously easy to use in paediatrics and geriatrics, capable of masking the unpleasant taste of this active ingredient and preferentially possessed of a sustained-release profile remains of undeniable interest.

It has now been found, surprisingly, that it is possible to avoid the disadvantages reported above by using, as administration form, microspheres containing, as active ingredient, sodium valproate or any other pharmaceutically acceptable salt of valproic acid and valproic acid itself, in combination with a suitably chosen matrix vehicle.

In the majority of cases, these microspheres have additionally turned out to be suitable for sustained release of the active ingredient, without requiring them to be provided with a specific coating for this purpose.

Thus, a first subject of the invention relates to pharmaceutical microspheres containing, as active principle, a mixture of valproic acid and of one of its pharmaceutically acceptable salts, such as the sodium salt, in combination with a matrix vehicle selected from glycerol esters, hydrogenated oils, esterified polyethylene glycols, waxes and their mixtures.

Another subject of the invention relates to a process for the preparation of microspheres containing a mixture of valproic acid and of a pharmaceutically acceptable salt of this acid, in combination with a matrix vehicle.

Finally, the invention relates to a pharmaceutical form for oral administration containing microspheres according to the invention.

In the present context, both in the description and in the claims, "active principle" will denote the mixture of valproic acid and of pharmaceutically

acceptable salt of this acid used in the context of the present invention.

The microspheres of the invention can be obtained according to the prilling process mentioned above, which consists:

- in adding valproic acid and the pharmaceutically acceptable salt of this acid to the matrix vehicle in the molten form, so as to dissolve these active ingredients in the matrix, and maintaining the resulting mixture with stirring until a clear fluid is obtained,
- in forcing the mixture in the clear form thus obtained through a nozzle which is subjected to vibration, whereby droplets are formed at the outlet of the nozzle and are carried by gravity into a tower in which a cold gas, generally refrigerated air, moves in a counter-currentwise direction,
- in collecting the microspheres in the bottom of the tower.

If necessary, a fluidized bed can be added to this prilling tower, which bed makes it possible to keep the not yet completely solidified microspheres constantly fluidized.

In practice, the mixture used in the prilling can be obtained by heating the matrix vehicle to its melting temperature, then, when the mass is completely molten, by adding valproic acid and then a pharmaceutically acceptable salt of this acid, and by maintaining the combined mixture with stirring until a clear fluid is obtained.

Alternatively, it is also possible to prepare this mixture by adding, separately, the pharmaceutically acceptable salt of valproic acid to valproic acid itself and by then introducing the combined mixture into the molten matrix vehicle.

The microspheres of the invention contain, as active principle, a mixture in all proportions of

valproic acid and of one of its pharmaceutically acceptable salts.

This salt is generally an alkali metal salt, preferably the sodium salt, or an alkaline-earth metal salt, such as the calcium or magnesium salt.

Preferentially, but not exclusively, use is made as active principle of mixtures containing at least 5% by weight either of valproic acid or of one of its pharmaceutically acceptable salts, the surplus being composed of at most 95% by weight of a pharmaceutically acceptable salt of valproic acid or of valproic acid respectively.

In particular, the active principle is composed of mixtures of 15% to 60% by weight of valproic acid and of 40% to 85% by weight of pharmaceutically acceptable salt of this acid.

Mixtures containing from 25% to 35% by weight of valproic acid and from 65% to 75% by weight of salt in question represent mixtures which are particularly preferred for the purposes of the invention.

As a general rule, the viscosity of the composition formed by the pharmaceutical ingredient and the matrix excipient is a limiting factor in making use of the prilling process suited to the preparation of pharmaceutical microspheres.

In the present case and for this reason, the microspheres of the invention will contain at most 35% by weight of active principle, as described above, preferably from 30% to 35% by weight.

Indeed, it has been noticed that a concentration by weight of active principle greater than 35% would require a higher temperature of the matrix mass in order to maintain a sufficient viscosity of the latter for the purpose of preparing the microspheres. Moreover, a concentration of active principle greater than 35% causes difficulties of dissolution of the latter in the matrix vehicle.

This matrix vehicle, which is composed of one or of several excipients of the class of glycerol esters, hydrogenated oils, esterified polyethylene glycols, or waxes, is selected such that its melting point is between 50°C and 120°C, generally between 70°C and 90°C.

This matrix vehicle does not contain any additional contribution of surface-active agents, such as those of the ethoxylated or non-ethoxylated polysorbate type.

Excipients capable of melting at a temperature of the order of 80°C, the latter corresponding to the temperature which allows the active principle to be dissolved in the matrix vehicle and to the maximum temperature which can be used for good preservation of the microspheres formed, are preferably selected. Moreover, an excessively high temperature would require an excessively high drop height for the microspheres in order to achieve complete solidification, with the risk of causing the active principle to degrade.

On taking into consideration this recommended melting temperature range, the excipients in question can be selected from:

- saturated or unsaturated fatty acid glycerides, in particular glycerides containing up to 80 carbon atoms, such as, for example, glyceryl tribehenate, glyceryl palmitate/stearate, glyceryl monostearate, glyceryl monooleate or caprylic/capric glycerides, such as glyceryl tricaprylate/caprate
- saturated polyglycolysed glycerides, such as mixtures of glycerol monoesters, diesters and triesters and of polyethylene glycol mono- and diesters
- hydrogenated oils, such as hydrogenated castor oil
- a wax, such as natural beeswax or synthetic beeswax.

By way of example, matrix excipients capable of forming microspheres according to the invention can be selected from:

- glyceryl tribehenate, such as sold under the trademark Compritol® 888
- glyceryl palmitate/stearate, such as sold under the trademark Precirol® ATO5
- a hydrogenated castor oil, such as sold under the trademark Cutina® HR
- glyceryl monostearate, such as sold under the trademark Monomuls® 90/25
- glyceryl monooleate, such as sold under the trademark Myverol® 18/99
- glyceryl tricaprylate/caprate, such as sold under the trademark Labrafac® lipophile
- saturated polyglycolysed glycerides, such as sold under the trademarks Gelucire® 50-02 or Labrafil® 2130CS
- a natural beeswax or a synthetic beeswax, such as sold under the trademark Cutina® BW
- a paraffin.

The excipients used in the context of the invention will furthermore be selected while taking into account the hydrophilic, lipophilic (or hydrophobic) or amphiphilic nature which they may possess and according to the kinetics desired for the release of the active principle.

In particular, and in a non-limiting way, mixtures of excipients of the type:

<u>either</u> glyceryl tribehenate (Compritol® 888)/surfactant Labrafil® 2130CS

<u>or</u> glyceryl tribehenate (Compritol® 888)/glyceryl monooleate (Myverol® 18/99)

<u>or</u> synthetic beeswax (Cutina® BW)/hydrogenated castor oil (Cutina® HR)/glyceryl monostearate (Monomuls® 90/25)

have proved to be suitable for fairly immediate release of the active principle.

By way of example, **in vitro** dissolution tests were carried out at pH = 6.8 for 6 hours according to the method described in the monograph "Dissolution tests for solid oral forms" of the European Pharmacopoeia II in the part General Directions V. 5.4, pp. 1-9 (1995).

Microspheres comprising from 55% to 60% by weight of product Compritol® 888 or of product Precirol® ATO5, from 30% to 35% by weight of active principle (valproic acid/sodium valproate) and from 10% to 15% by weight of surfactant Labrafil® 2130CS were used for this purpose.

After 1 hour, 100% of dissolved active principle was recorded in the case of the formulation including the product Precirol® ATO5 and 85% was recorded for that comprising the product Compritol® 888.

Likewise, dissolution tests carried out under the same conditions with microspheres containing from 20% to 25% by weight of product Cutina® HR, 20% to 25% by weight of product Cutina® BW, 20% to 25% by weight of product Monumuls® 90/25 and 30% to 35% by weight of active principle (valproic acid/sodium valproate) showed 100% dissolution of the active principle after 1 hour.

Moreover, an analogous test carried out with 55% to 60% by weight of product Compritol® 888, 30% to 35% by weight of active principle (valproic acid/sodium valproate) and 10% by weight of product Myverol® 18/99 also revealed an immediate release profile.

Following these tests, it could be concluded that none of the formulations tested and exemplified above exhibits a profile of delayed release of the active principle over a period of 6 hours.

In contrast, other microsphere formulations involving the product Compritol® 888 as sole matrix excipient have proved to be fairly suitable for delayed release of the active principle.

The addition of certain hydrophobic substances, such as hydrogenated castor oil (Cutina® HR), beeswax, paraffin, product Gelucire® 50-02 or product Labrafac® lipophile, has furthermore made it possible to accentuate the delayed release of the active principle.

By way of example, microspheres containing from 65 to 70% by weight of product Compritol® 888 and from 30% to 35% by weight of active principle (valproic acid/sodium valproate) have revealed, during dissolution tests, a slow dissolution profile. Analogous results were recorded from microspheres comprising from 55% to 60% by weight of product Compritol® 888, 10% to 15% by weight of product Cutina® HR, beeswax, paraffin, product Gelucire® 50-02 or product Labrafac® lipophile and 30% to 35% by weight of active principle.

In particular, microspheres with the following formulations were subjected to dissolution tests at pH = 6.8 for 9 hours according to the method of the European Pharmacopoeia II described above, namely:

| | % by weight |
|---|---|
| Compritol® 888 | 58.37 |
| Adjuvants | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

the adjuvants corresponding to the products Cutina® HR, Cutina® BW, paraffin, Gelucire® 50-02 and Labrafac® lipophile.

The dissolution profiles obtained are reproduced in the appended Figure I, in which figure:

a) the curve denoted "formula 1" represents the percentages of dissolution of the valproate anion as a function of the time from above microspheres, in which microspheres the adjuvant is the product Cutina® HR

b) the curve denoted "formula 2" represents analogous percentages to the curve "formula 1", the adjuvant being the product Cutina® BW

c) the curve denoted "formula 3" represents analogous percentages to the curve "formula 1", the adjuvant being paraffin

d) the curve denoted "formula 4" represents analogous percentages to the curve "formula 1", the adjuvant being the product Gelucire® 50-02

e) the curve denoted "formula 5" represents analogous percentages to the curve "formula 1", the adjuvant being the product Labrafac® lipophile.

The results obtained show delayed-release kinetics for the active principle. It can be deduced therefrom that the formulations containing paraffin, hydrogenated castor oil (Cutina® HR) and synthetic beeswax (Cutina® BW) appear as the most advantageous.

As the active principle used in the present invention is composed of a hydrophobic component, namely valproic acid, and of a hydrophilic component, that is to say a pharmaceutically acceptable salt of this acid, it seems that the most suitable matrix excipients should be amphiphilic substances, in order, by their hydrophobic part, to provide for the delayed release of the active principle and, by their hydrophilic part, to provide for the regulation of the rate of release of this active principle from the excipient.

It has been found, unexpectedly, that a matrix excipient formed solely of natural beeswax, a typically hydrophobic fatty substance, makes possible a release profile of the active principle which is entirely compatible with a retard pharmaceutical formulation. In addition, this profile proved to be fairly similar to the release profile recorded with known tablets containing a valproic acid/sodium valproate mixture as active ingredient.

In particular, dissolution tests and pharmacokinetic tests were carried out from:

- either microspheres formed of 68.37 g of natural beeswax as matrix vehicle and of 31.63 g of active principle, namely 9.63 g of valproic acid and 22 g of sodium valproate, hereinafter denoted "Composition A microspheres".
  The active principle consequently corresponds to a 30.45%/69.55% by weight valproic acid/sodium valproate mixture.
- or a scored retard tablet formulated with 478 mg of a valproic acid/sodium valproate mixture, namely 145 mg of acid and 333 mg of salt, this tablet comprising in particular methacrylic acid polymers as excipient.

The active ingredients of this commercial tablet consequently correspond to a 30.33%/69.67% by weight valproic acid/sodium valproate mixture or to 500 mg of active ingredient expressed as sodium valproate.

**I. - Dissolution tests**

These tests were carried out **in vitro** at pH = 6.8 according to the method cited above.

The dissolution profiles obtained are reproduced in the appended Figure II, in which figure :

a) the curve denoted "microspheres" represents the percentages of dissolution of the valproate anion as a function of the time from the above Composition A microspheres
b) the curve denoted "tablet" represents the percentages of dissolution of the valproate anion as a function of the time from the above scored retard tablet.

The results obtained clearly show that the dissolution profile of the Composition A microspheres is close to and resembles the dissolution profile of the tablet, since a difference of only 10% separates

them after the first hour, a difference which remains constant for at least 5 hours.

**II. - Pharmacokinetic tests**

Tests were carried out on three series of 24 healthy subjects, to whom were administered:

- Composition A microspheres in water
- Composition A microspheres in yoghurt
- a scored retard tablet such as above

so that each subject receives a dose of active ingredient (valproic acid/sodium valproate) equivalent to 500 mg expressed as sodium valproate.

The blood concentration of valproate anion and in particular the maximum blood concentration (C max), the time after administration at which this maximum concentration occurs (T max) and the residual blood concentration 24 hours after administration were then recorded every hour, from administration, for each subject.

The results obtained are reproduced in the appended Figure III, in which figure:

a) the curve denoted "Composition A/water" represents the mean blood concentration obtained with the Composition A microspheres in water

b) the curve denoted "Composition A/yoghurt" represents the mean blood concentration obtained with the Composition A microspheres in yoghurt

c) the curve denoted "tablet" represents the mean blood concentration obtained with the scored retard tablet.

These results show that the C max of the Composition A microspheres is slightly greater than that of the scored retard tablet, i.e. approximately 16% for the microspheres in water and approximately 22% for the microspheres in yoghurt, whereas the T max values prove to be slightly shorter for the microspheres with respect to the tablet.

Finally, the results of the analyses of variance show that there is no significant difference between the areas under the curves (AUC).

In other words, these tests enable it to be concluded that there exists no significant difference in bioavailability between the Composition A microspheres and the scored retard tablet.

Consequently, microspheres containing from 30% to 35% of active principle in combination with a matrix vehicle entirely composed of beeswax represent microspheres of vital importance.

Likewise, microspheres of this type, in which the active principle is formed of 25% to 35% of valproic acid and of 65% to 75% of a pharmaceutically acceptable salt of this acid, such as sodium valproate, are particularly preferred for the purposes of the invention.

Unlike other technologies for the production of spheroids, prilling makes it possible to obtain a so-called monodisperse particle size distribution with the advantage of producing spheres which are regular in size. Consequently, during the administration of the medicament containing them, the amount of such microspheres received by the patient will be constant.

The pharmaceutical microspheres of the invention possess this advantage, in that they exhibit such a regular spherical shape, with a diameter of between 250 µm and 500 µm, generally of the order of 400 µm.

If necessary, these microspheres can be covered with a film-forming agent, so as to form, for example, a gastroresistant film.

In addition, they can be packaged in various pharmaceutical forms, unitary or otherwise, suitable for oral administration. Such pharmaceutical forms can be, for example, a tablet, scored or otherwise, a capsule, including a hard gelatin capsule, or a powder packaged, for example, in a chartula or in a system for

dispensing unit doses, in particular a dispensing/measuring bottle or a container furnished with an adjustable-volume measuring spoon, for example for adjusting doses to the weight of the patient.

When they are put into pharmaceutical form, the microspheres in question can receive agents which facilitate flow, as well as lubricants, inorganic fillers, such as silicas, talc or aluminium oxide, or alternatively sweeteners, such as aspartame.

These pharmaceutical forms can advantageously comprise, per administration unit, from 50 to 500 mg of active principle in the form of microspheres according to the invention, in particular from 50 to 250 mg.

The following non-limiting Examples illustrate the invention:

**EXAMPLE 1**

Preparation of microspheres containing valproic acid/sodium valproate in beeswax

Microspheres with the following composition are prepared:

| | % by weight |
|---|---|
| White beeswax | 68.424 |
| Valproic acid | 9.576 |
| Sodium valproate | 22 |
| | 100.00 |

the preparation being carried out in the following way.

68.424 g of white beeswax are introduced into the jacketed vessel of a melting device thermostatically adjusted to 95°C and then the wax is melted at a temperature of 90°C to 93°C while monitoring that the product has completely melted.

9.576 g of valproic acid and then 22.000 g of sodium valproate are then dispersed, with slow stirring, in the molten wax maintained at 90°C and it is confirmed that the two ingredients have dissolved

when the mixture becomes clear (no appearance of crystals).

The mixture is then prilled, at a temperature of 90°C, through 200 µm injectors maintained at a temperature of 87°C to 91°C and under a pressure of 0.5 bar. The frequency of the vibrator of the device ($5.75 \times 10^3$ to $6.70 \times 10^3$ Hz) is adjusted, so as to individualize the droplets formed, under stroboscopic monitoring at a frequency of 25,000 Hz.

Microspheres solidified by cooling during their fall in air (drop height: approximately 2.5 m) refrigerated by a countercurrent of cold air or by a liquid nitrogen bath are thus collected at the base of the device. These microspheres have a mean diameter of 400 µm.

Microspheres were prepared in the same way, but by using other matrix excipients, from the following formulations, which all proved to be clear after dissolution of the active principle (no appearance of crystals):

**EXAMPLE 2**

| | % by weight |
|---|---|
| Cutina® HR | 34.185 |
| Cutina® BW | 34.185 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 3**

| | % by weight |
|---|---|
| Cutina® HR | 29.185 |
| Cutina® BW | 29.185 |
| Monomuls® 90-25 | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 4**

| | % by weight |
|---|---|
| Compritol® 888 | 58.37 |
| Labrafil® 2130 CS | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 5**

| | % by weight |
|---|---|
| Precirol® ATO 5 | 58.37 |
| Labrafil® 2130 CS | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 6**

| | % by weight |
|---|---|
| Cutina® HR | 24.185 |
| Cutina® BW | 24.185 |
| Monomuls® 90-25 | 20 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 7**

| | % by weight |
|---|---|
| Compritol® 888 | 68.37 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 8**

| | % by weight |
|---|---|
| Compritol® 888 | 58.37 |
| Cutina® HR | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 9**

| | % by weight |
|---|---|
| Compritol® 888 | 58.37 |
| Beeswax | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 10**

| | % by weight |
|---|---|
| Compritol® 888 | 58.37 |
| Paraffin | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 11**

| | % by weight |
|---|---|
| Compritol® 888 | 58.37 |
| Gelucire® 50-02 | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 12**

| | % by weight |
|---|---|
| Compritol® 888 | 58.37 |
| Labrafac® lipophile | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 13**

| | % by weight |
|---|---|
| Compritol® 888 | 58.37 |
| Myverol® 18/99 | 10 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 14**

| | % by weight |
|---|---|
| Compritol® 888 | 34.185 |
| Beeswax | 34.185 |
| Valproic acid | 9.63 |
| Sodium valproate | 22 |
| | 100.00 |

**EXAMPLE 15**

Pharmaceutical forms containing microspheres

1) Chartula

756.7 mg of microspheres as prepared in Example 1 are introduced into a chartula, so as to form an oral administration unit containing 238.96 mg of active principle composed of 30.4%/69.6% by weight valproic acid/sodium valproate, which corresponds to 250 mg of active principle expressed as sodium valproate.

2) Dispenser/measuring bottle

24 g of microspheres prepared in Example 1, i.e. 8 g of active principle per packaged unit, are introduced into a bottle with a working volume of approximately 45 ml which allows unit doses to be dispensed.

This bottle makes it possible to dispense approximately 50 unit doses containing 150 mg of active principle composed of 30.4%/69.6% by weight valproic acid/sodium valproate.

**CLAIMS**

1. Pharmaceutical microspheres, containing, as active principle, a mixture of valproic acid and of one of its pharmaceutically acceptable salts in combination with a matrix vehicle selected from glycerol esters, hydrogenated oils, esterified polyethylene glycols or waxes and their mixtures.

2. Pharmaceutical microspheres according to Claim 1, wherein the pharmaceutically acceptable salt is an alkali metal salt or an alkaline-earth metal salt.

3. Pharmaceutical microspheres according to Claim 1 or 2, wherein the alkali metal salt is the sodium salt.

4. Pharmaceutical microspheres according to Claim 1 or 2, wherein the alkaline-earth metal salt is the calcium or magnesium salt.

5. Pharmaceutical microspheres according to one of Claims 1 to 4, wherein the active principle is composed of at least 5% by weight either of valproic acid or of pharmaceutically acceptable salt of this acid.

6. Microspheres according to one of Claims 1 to 5, wherein the active principle is composed of a mixture of 15% to 60% by weight of valproic acid and of 40% to 85% by weight of pharmaceutically acceptable salt of this acid.

7. Microspheres according to one of Claims 1 to 6, wherein the active principle is composed of a mixture of 25% to 35% by weight of valproic acid and of 65% to 75% by weight of pharmaceutically acceptable salt of this acid.

8. Microspheres according to one of Claims 1 to 7, containing at most 35% by weight of active principle.

9. Microspheres according to one of Claims 1 to 8, containing from 30% to 35% by weight of active principle.

10. Pharmaceutical microspheres according to one of Claims 1 to 9, wherein:



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* C L M S *

- the glycerol esters are saturated or unsaturated fatty acid glycerides containing up to 80 carbon atoms
- the esterified polyethylene glycols are saturated polyglycolysed glycerides.

11. Pharmaceutical microspheres according to Claim 10, wherein the saturated polyglycolysed glycerides are mixtures of glycerol monoesters, diesters and triesters and of polyethylene glycol mono- and diesters.

12. Pharmaceutical microspheres according to one of Claims 1 to 11, wherein:

- the glycerol ester is glyceryl tribehenate, glyceryl palmitate/stearate, glyceryl monostearate, glyceryl monooleate or caprylic/capric glycerides,
- the hydrogenated oil is hydrogenated castor oil
- the wax is natural beeswax or synthetic beeswax or a paraffin.

13. Pharmaceutical microspheres according to one of Claims 1 to 12, wherein the matrix vehicle is natural beeswax.

14. Pharmaceutical microspheres according to one of Claims 1 to 13, wherein the melting point of the matrix vehicle is between 50°C and 120°C.

15. Pharmaceutical microspheres according to Claim 14, wherein the melting point of the matrix vehicle is between 70°C and 90°C.

16. Pharmaceutical microspheres according to one of Claims 1 to 15, containing from 30% to 35% of active principle in combination with a matrix vehicle composed of beeswax.

17. Pharmaceutical microspheres according to Claim 16, wherein the active principle is formed of 25% to 35% of valproic acid and of 65% to 75% of a pharmaceutically acceptable salt of valproic acid.

18. Pharmaceutical microspheres according to Claim 16 or 17, wherein the pharmaceutically acceptable salt is the sodium salt.



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19. Process for the preparation of pharmaceutical microspheres according to one of Claims 1 to 18, wherein:

- valproic acid and the pharmaceutically acceptable salt of this acid are added to the matrix vehicle in the molten form and the resulting mixture is maintained with stirring until a clear fluid is obtained,
- the mixture in the clear form thus obtained is forced through a nozzle which is subjected to vibration, whereby droplets are formed at the outlet of the nozzle and carried by gravity into a tower in which a cold gas moves in a counter-currentwise direction,
- the microspheres are collected in the bottom of the tower.

20. Pharmaceutical forms for oral administration, containing microspheres according to one of Claims 1 to 18.

21. Pharmaceutical forms according to Claim 20, corresponding to tablet, capsule, including hard gelatin capsule, or powder packaged in a chartula or in a system for dispensing unit doses.

22. Pharmaceutical forms according to Claim 20 or 21, containing agents which facilitate flow, lubricants, inorganic fillers and/or sweeteners.

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