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(54) Title: CONTROLLED RELEASE COMPOSITIONS OF DIVALPROEX SODIUM

(57) Abstract: The present invention pertains to a hydrophilic matrix tablet suitable for the once-a-day administration of valproate compounds such as divalproex sodium. The tablet comprises from about 30 weight percent to about 60 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide; from about 6 weight percent to about 16 weight percent of a pharmaceutically acceptable polymer preferably hydroxypropyl methylcellulose and from about 20 weight percent to about 50 weight percent of a filler; all weight percentages based upon the total weight of the tablet dosage form. Other aspects of the invention relate to the use of this formulation in the treatment of epilepsy and to methods for manufacturing this dosage form.



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CONTROLLED RELEASE COMPOSITIONS OF DIVALPROEX SODIUM.**FIELD OF THE INVENTION**

The present invention relates to a controlled release formulation of divalproex sodium, for once a day administration. The controlled release dosage form demonstrates improved pharmacokinetic profile by minimizing the variance between peak and trough plasma levels of the valproate salt, thus resulting in a reduction in the incidence of side effects. The invention significantly advances the existing art related to the controlled release formulations of divalproex sodium.

BACKGROUND OF THE INVENTION

Divalproex sodium is effective as an anti-epileptic agent used in the treatment of epilepsy, migraine and bipolar disorders. Though the exact three dimensional molecular structure of Divalproex is uncertain, it dissociates to the valproate ion, which itself is a known antiepileptic entity, within the gastrointestinal tract. Valproate is absorbed and produces the desired therapeutic effect. Divalproex sodium is described in more detail in US Patent Nos. 4,988,731 and 5,212,326.

Divalproex sodium was first introduced as a delayed release formulation, which may be administered twice a day. This dosage form comprises an enteric coat to minimize gastric irritation. However, within the gastrointestinal tract at higher pH conditions, the enteric coat dissolves resulting in faster release of the drug.

The need for a sustained release formulation of Divalproex sodium, and other valproate compounds permitting once-a-day dosing was felt, which would effectively maintain plasma concentrations of the drug at more constant levels over a 24 hours dosing period (i.e. minimize the variation between peak and trough plasma levels). More importantly, sustained release formulations were needed that would decrease the incidence of side effects associated with valproate therapy including incidence of nausea, vomiting, asthenia, somnolence, alopecia, weight gain, etc.

US Patent No. 4,913,906 to Friedman, et al. discloses a controlled release dosage form of valproic acid, its amide, or one of its salts or esters in combination with polymers and physiologically acceptable additives. The preferred additives are derivatives of cellulose such as carboxymethyl cellulose, ethylcellulose, methylcellulose, hydroxy propyl cellulose, polyvinyl alcohol, polyacrylamide, ethylene vinyl acetate copolymer,

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polyacrylate, polyurethane, polyvinylpyrrolidone, polymethylmethacrylate, polyvinyl acetate, polyhydroxyethyl methacrylate, and waxes such as paraffin. In addition combinations of these, or a combination of one these with a native protein may also be used. Sustained release formulations of valpromide were prepared with native proteins, such as soy protein, collagen, gelatin, ovalbumin, milk albumin, casein, etc. Tablets are formulated by applying a pressure of 1000 to 5000 kg/cm² under controlled atmospheric conditions.

US Patent No. 5,009,897 to Brinker, et al. discloses granules having sufficient hardness, suitable for pressing into tablets. The granule comprises a core of divalproex sodium and a coating of a mixture of a polymer and microcrystalline cellulose. Preferred polymer is selected from povidone, hydroxypropyl cellulose and hydroxypropyl methylcellulose. The polymer material functions as a binder and carrier for the microcrystalline cellulose, while the microcrystalline cellulose itself imparts the excellent compressibility properties to the granules.

US Patent No. 5,019,398 to Daste discloses a sustained-release tablet of divalproex sodium in a matrix of hydroxypropyl methylcellulose and hydrated silica. It has been shown that the standard lubricants such as talc or magnesium stearate do not prevent sticking on compression whereas 8 to 10 weight percent of hydrated silica, preferably mixed with 1 to 2 weight percent of colloidal silica, per 100 mg of complex suffice to form a compressible mixture giving a non-friable tablet.

US Patent Nos. 6,419,953 to Abbott Laboratories claim a hydrophilic matrix tablet suitable for once a day administration of Divalproex sodium comprising from about 40-80%w/w of active, 20 – 50% w/w of a hydrophilic polymer, 5 – 15%w/w lactose, 4-6%w/w microcrystalline cellulose and 1-5%w/w silicon dioxide.

US Patent No. 6,511,678 to Abbott Laboratories claims a controlled release tablet formulation releasing not more than about 30% valproate after 3 hours, 40 to about 70% after 9 hours, 55 to about 95% after 12 hours and not less than 85% after 18 hours, when measured in a type 2 dissolution apparatus, at 100 rpm, at a temperature of 37±0.5° C., in 500 ml of 0.1N HCl for 45 minutes, followed by 900 ml of 0.05M phosphate buffer containing 75 mM sodium lauryl sulfate, pH 5.5, for the remainder of the testing period.

US Patent No. 6,150,410 to Abbott achieves a controlled release of divalproex by using a mixture of neutral water-swellaable polymer and an acid soluble water swellaable polymer.

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US Patent No.6,528,090 to Abbott Laboratories claims a once -a-day formulation of divalproex sodium manufactured by using a hydrophilic polymer with a concentration of 20-50%w/w which gives statistically significant lower levels of $C_{\max}$ and $C_{\min}$ but a non-statistically significant AUC when determined in a healthy fasting population at steady state in comparison to a delayed release enteric coated divalproex formulation.

Ranbaxy Laboratories in PCT Application (WO 03/103635) has claimed a once a day tablet composition wherein, the hydrophilic matrix comprises 10-90% w/w of the drug, 7-65% w/w of hydroxy propyl methyl cellulose, 0.5-18%w/w of lactose and 0.5-5%w/w of colloidal silicon dioxide. They have also claimed an extended release composition of divalproex sodium with at least one extended release polymer manufactured under controlled atmospheric conditions of 27°C to 35°C and a relative humidity of less than about 40%. Based on disclosed examples the Ranbaxy composition did not make any major changes in the hydrophilic polymer, both qualitatively and quantitatively in comparison to the Abbott '090 patent, but differed in the use of other excipients, like diluents and in controlling the atmospheric conditions.

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to a controlled release tablet composition for once daily administration of a valproate salt. The composition comprises of divalproex sodium (30 – 50% w/w) as the active valproate salt, and a hydrophilic matrix-forming polymer system (less than 20% w/w) comprising preferably one or more cellulose polymers, and a water insoluble diluent (20 – 50% w/w). The said composition delivers the dose of divalproex sodium in a controlled manner such that when evaluated for “*in-vitro*” dissolution with an identical strength of a reference tablet formulation Depakote ER tablets, the test product shows a comparable dissolution profile.

Divalproex sodium is a freely soluble drug substance in water. The controlled release tablet for once daily administration requires significant control of drug release so that the therapeutic benefit is extended satisfactorily throughout the period of 24 hours. Typical controlled formulations of Divalproex exhibit the variation between peak and trough plasma levels of valproate over a 24-hour dosing period. The US 6,528,090 patent uses a hydrophilic polymer matrix of a cellulose derivative namely hydroxy propyl methyl

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cellulose at a concentration of more than 20% w/w of the tablet, more preferably around 30% w/w. As a formulator, it is desirable that other excipients for controlling release of the active ingredient be used at a minimum so that the patient is exposed to ingredients other than the active at a minimum concentration. In addition use of high polymer concentrations like HPMC have significant limitations including deficient flow properties making direct tableting difficult and the dependence of the release of medicinal substance on the salt content and pH of the release medium. This is discussed in more detail in US Patent 6,579,953 awarded to BASF. In contrast, the present inventors have unexpectedly found that by employing a hydrophilic polymer at a concentration of less than 20%w/w, preferably less than 16%w/w in combination with a water insoluble diluent, they could obtain a similar and comparable control in drug release, to that achieved by the reference product, which uses 30%w/w of polymer. Comparative dissolution profiles showed a good level of similarity in drug release between identical strengths of the products under said invention and Depakote ER tablets that is the reference product.

The granules may be prepared either by dry or wet granulation process using a uniform admixture of the drug with hydrophilic polymers and a water insoluble diluent. The resulting granules are blended with required quantity of one or more lubricants and compressed into tablets. Divalproex sodium is hygroscopic and has been known to cause sticking to die and punch surfaces during compression. The tablet compression is carried out at a temperature of 15 – 27 °C and relative humidity above 40% such that there is minimal or no sticking of the granule material to die and punch surfaces. In contrast, the PCT application No. WO 03/103635, requires presence of controlled atmospheric conditions of 27 to 35 °C and a relative humidity of less than 40%, preferably less than 20%. In accordance with the present invention, a new oral polymeric controlled release formulation suitable for once-a-day administration of valproate compounds, such as divalproex sodium, has been achieved. This formulation exhibits significant advantages over the sustained release valproate formulations of the prior art. This formulation minimizes the variation between peak and trough plasma levels of valproate over a 24-hour dosing period. This formulation follows a zero-order release pattern thus producing essentially flat plasma levels of valproate, once steady-state levels have been achieved.

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This results in a significantly lower incidence of side effects for patients consuming such a formulation.

DETAILED DESCRIPTION OF THE INVENTION

The inventors have surprisingly found that the matrix formed by low proportions of hydrophilic polymers of less than 20%w/w, with the inclusion of an insoluble diluent gives adequate control for the release of a highly soluble drug like divalproex sodium. This formulation shows a drug release that is comparable to that obtained with a concentration of 30%w/w of hydrophilic polymer (Reference product). Initial dissolutions with formulations manufactured only with less than 20% w/w hydrophilic polymer revealed a faster drug release profile compared to the reference product. The similarity factor [(f 2)- factor] commonly used to compare *in-vitro* release was around 50 or even less. The incorporation of an insoluble diluent like dicalcium phosphate provided adequate hydrophobicity to the matrix and helped to slow down the drug release from the matrix to achieve a dissolution profile comparable to the reference formulation. The similarity factor [(f 2)- factor] values achieved from these formulations were well beyond 55, thus indicating a comparable dissolution release profile.

The term 'pharmaceutical composition' includes all dosage forms administered by the oral route. The product can be prepared by anyone skilled in the art and contains therapeutically effective amount of a valproate compound, together with other excipients as normally employed for forming such a dosage form.

The extended release composition as described includes a pharmaceutical polymer that can control drug release from the pharmaceutical composition. Water soluble or water swellable polymers that can be included in this composition include polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, vinyl acetate copolymers, polyvinyl alcohol, polysaccharides and gums like xanthan gum, cross-linked polyethylene oxide, methacrylic acid copolymers, maleic anhydride / methyl vinyl ether copolymers and derivatives and mixtures thereof.

Water-insoluble polymers were selected from methacrylates, acrylic acid copolymers, acrylamides, polyethylenes, polyvinyl alcohol and celluloses like cellulose mono-, di- and tri-acrylate, cellulose mono-, di-, and tri-acetate, ethyl cellulose, or cellulose acrylate. The composition under discussion also includes pharmaceutically acceptable inert excipients, like, fillers, binders, lubricants, glidants, and colorants, among others.

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Pharmaceutical fillers in the composition were selected from calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, cellulose, micro crystalline cellulose, dextrin, dextrose excipient, fructose, kaolin, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, among others. The fillers preferred for inclusion were the water insoluble materials, like, dibasic calcium phosphate.

Suitable binders included polyvinylpyrrolidone, carboxyvinyl polymer, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, dextrin, maltodextrin, gums like xanthan gum, tragacanth, acacia, and starch among others. The preferred binders were polyvinyl pyrrolidone and xanthan gum.

Lubricants included calcium stearate, glyceryl behenate, magnesium stearate, light mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, hydrogenated vegetable oil (Type I) and zinc stearate.

Glidants were selected from calcium silicate, magnesium silicate, silicon dioxide and talc. The examples below provide a summary of the experimental work that forms the basis of the pharmaceutical composition of the present invention.

Example 1:

Controlled release tablets were prepared using the following materials in the stated quantities:

Ingredient	Quantity (%w/w) of the composition
Divalproex sodium	50.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 100M)	4.5 %w/w
Hydroxypropyl methylcellulose (Methocel K 15M)	4.5 %w/w
Dibasic calcium phosphate	24.0 %w/w
Microcrystalline cellulose (Avicel PH102)	14.0 %w/w
Silica (Syloid 244 FP)	1.5 %w/w
Magnesium stearate	1.5 %w/w

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Procedure: Divalproex sodium was screened initially through 40-mesh ASTM and mixed intimately with hydroxypropyl methylcellulose, microcrystalline cellulose and dibasic calcium phosphate. Slugs were obtained on compression machine. Slugs were passed through suitable sieves to get final granules less than 18 mesh ASTM screen. The homogeneous granules thus obtained were mixed with silica and magnesium stearate and then compressed using oval shaped punches of size 18.8mm x 9.7 mm.

Example 2:

Controlled release tablets were prepared using the following materials in the stated quantities:

Ingredient	Quantity (%w/w) of the composition
Divalproex sodium	50.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 100M)	7.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 15M)	5.5 %w/w
Dibasic calcium phosphate	22.0 %w/w
Microcrystalline cellulose (Avicel PH102)	12.0 %w/w
Hydroxypropyl methylcellulose (6 cps)	2.0 %w/w
Silica (Syloid 244 FP)	1.5 %w/w
Purified water	q.s.
Isopropyl alcohol	q.s.

Procedure: Divalproex sodium was sifted initially through 40 mesh ASTM sieve and mixed intimately with hydroxypropyl methylcellulose, microcrystalline cellulose and dibasic calcium phosphate in a suitable mixer. The solution of hydroxy propyl methyl cellulose 6cps in IPA: Water in ratio of 9:1 was prepared separately, and was used for granulating the previously obtained powder mixture. The resultant homogeneous mass was passed through an 8 mm mesh ASTM screen and then dried overnight in tray drier at 50° C to 55° C to obtain dried granules. These dried granules were then passed through

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18mm mesh ASTM screen. The homogeneous granulate thus obtained was mixed with the silica and then compressed using oval shaped punches of size 18.8 mm x 9.7 mm. Dissolution was carried out in 900 ml of pH 6.8 phosphate buffer at 100 rpm using USP type II apparatus with sinkers. Comparative profiles for Depakote ER 500 mg Tablets and tablets as per example (2) has been shown in Figure 1.

Example 3:

Controlled release tablets were prepared using the following materials in the stated quantities:

Ingredient	Quantity (%w/w) of the composition
Divalproex sodium	50.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 100M)	8.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 15M)	6.0 %w/w
Dibasic calcium phosphate	20.0 %w/w
Microcrystalline cellulose (Avicel PH102)	12.0 %w/w
Polyvinyl pyrrolidone (PVPK30)	2.0 %w/w
Silica (Syloid 244 FP)	2.0 %w/w
Purified water	q.s.

Procedure: Divalproex sodium was sifted initially through 40 mesh ASTM sieve and mixed intimately with hydroxypropyl methylcellulose, microcrystalline cellulose and dibasic calcium phosphate in a suitable mixer. The solution of polyvinyl pyrrolidone in purified water was prepared separately, and was used for granulating the previously obtained powder mixture. The resultant homogeneous mass was passed through an 8mm mesh ASTM screen and then dried overnight in tray drier at 50° C to 55° C to obtain dried granules. These dried granules were then passed through 18mm mesh ASTM screen. The homogeneous granulate thus obtained was mixed with the silica and then compressed using Oval shape punches of size 18.8mm x 9.7 mm.

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Dissolution was carried out in 900 ml of pH 6.8 phosphate buffer at 100 rpm using USP type II apparatus with sinkers. Comparative profiles for Depakote ER 500 mg Tablets and tablets as per example (3) has been shown in Figure 2.

Example 4:

Controlled release tablets were prepared using the following materials in the stated quantities:

Ingredient	Quantity (%w/w) of the composition
Divalproex sodium	43.5 %w/w
Hydroxypropyl methylcellulose (Methocel K 100M)	8.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 15M)	6.0 %w/w
Dibasic calcium phosphate	33.5 %w/w
Microcrystalline cellulose (Avicel PH102)	5.0 %w/w
Xanthan Gum	2.0 %w/w
Silica (Syloid 244 FP)	2.0 %w/w
Purified water	q.s.

Procedure: Sifted Divalproex sodium through 40 mesh ASTM screen and blended with hydroxypropyl methylcellulose and dibasic calcium phosphate in a suitable mixer. Colloidal solution of xanthan gum in purified water was used for wet granulation of the powder mixture. The resulting homogeneous mass was passed through 8mm mesh ASTM screen and then dried overnight in tray drier at 50° C to 55° C to obtain dried granules, which were then passed through 18 mm mesh ASTM screen. Extragranular silica was blended with the granules and compressed using Oval shape punches of size 18.8 mm x 9.7 mm. Dissolution was carried out in 900 ml of pH 6.8 phosphate buffer at 100 rpm using USP type II apparatus with sinkers. Comparative profiles for Depakote ER 500 mg tablets and tablets as per example (4) has been shown in Figure 3.

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Example 5:

Controlled release tablets were prepared using the following materials in the stated quantities:

Ingredient	Quantity (%w/w) of the composition
Divalproex sodium	50.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 100M)	8.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 15M)	6.0 %w/w
Dibasic calcium phosphate	33.5 %w/w
Xanthan Gum	0.5 %w/w
Silica (Syloid 244 FP)	2.0 %w/w
Purified water	q.s.

Procedure: Passed divalproex sodium through 40 mesh ASTM screen, followed by mixing with hydroxypropyl methylcellulose and dibasic calcium phosphate in a suitable blender. The blend was granulated using solution of xanthan gum in purified water. The resultant wet mass was sifted through 8mm mesh ASTM screen and then dried overnight in tray drier at 50° C to 55° C to obtain dried granules. The dried granules were sifted using 18mm ASTM mesh screen. The dried granules were mixed with the silica and compressed using Oval shape punches of size 18.8mm x 9.7 mm. Dissolution was carried out in 900 ml of pH 6.8 phosphate buffer at 100 rpm using USP type II apparatus with sinkers. Comparative profiles for Depakote ER 500 mg Tablets and tablets as per example (5) has been shown in Figure 4.

Example 6:

Controlled release tablets were prepared using the following materials in the stated quantities:

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Ingredient	Quantity (%w/w) of the composition
Divalproex sodium	43.5 %w/w
Hydroxypropyl methylcellulose (Methocel K 100M)	8.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 15M)	6.0 %w/w
Dibasic calcium phosphate	40.0 %w/w
Xanthan Gum	0.5 %w/w
Silica (Syloid 244 FP)	2.0 %w/w
Purified water	q.s.

Procedure: Divalproex sodium was first sifted through 40-mesh ASTM screen and then mixed with hydroxypropyl methylcellulose and dibasic calcium phosphate in a suitable blender. The solution of Xanthan gum in purified water was prepared separately, and was used for granulating the previously obtained powder mixture. The resultant wet material was passed through 8mm ASTM mesh screen and then dried overnight in tray drier at 50° C to 55° C to obtain dried granules. These dried granules were then passed through 18mm mesh ASTM screen. The homogeneous granulate thus obtained was mixed with the silica and then compressed using oval shape punches of size 18.8mm x 9.7 mm. Dissolution was carried out in 900 ml of pH 6.8 phosphate buffer at 100 rpm using USP type II apparatus with sinkers. Comparative profiles for Depakote ER 500 mg Tablets and tablets as per example (6) has been shown in Figure 5.

Example 7:

Controlled release tablets were prepared using the following materials in the stated quantities:

Ingredient	Quantity (%w/w) of the composition
Divalproex Sodium	44.83 %w/w
Hydroxypropyl methylcellulose (Methocel K 100M)	8.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 15M)	6.0 %w/w

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Dibasic calcium phosphate	36.67 %w/w
Xanthan Gum	0.5 %w/w
Silica (Syloid 244 FP)	2.0 %w/w
Talc	1.5 %w/w
Glyceryl behenate (Compritol)	0.5 %w/w
Opadry II 85G52272 Yellow	1.25 %w/w
Purified water	q.s

Procedure: Divalproex sodium was first sifted through 40-mesh ASTM screen and then mixed with hydroxypropyl methylcellulose and dibasic calcium phosphate in a suitable blender. The solution of Xanthan gum in purified water was prepared separately, and was used for granulating the previously obtained powder mixture. The resultant wet material was passed through 8mm ASTM mesh screen and then dried overnight in tray drier at 50° C to 55° C to obtain dried granules. These dried granules were then passed through 18mm mesh ASTM screen. The homogeneous granulate thus obtained was mixed with the talc, compitrol and silica and then compressed using oval shape punches of size 18.8mm x 9.7 mm. Aqueous coating was carried out on core tablets. Dissolution was carried out in 900 ml of pH 6.8 phosphate buffer at 100 rpm using USP type II apparatus with sinkers. Comparative profiles for Depakote ER 500 mg Tablets and tablets as per example (7) has been shown in Figure 6.

Example 8:

Controlled release tablets were prepared using the following materials in the stated quantities:

Ingredient	Quantity (%w/w) of the composition
Divalproex Sodium	35.86 %w/w
Hydroxypropyl methylcellulose (Methocel K 100M)	8.0 %w/w
Hydroxypropyl methylcellulose (Methocel K 15M)	6.0 %w/w
Dibasic calcium phosphate	45.14 %w/w
Xanthan Gum	0.5 %w/w
Silica (Syloid 244 FP)	2.0 %w/w
Talc	1.5 %w/w
Glyceryl behenate (Compritol)	1.0 %w/w
Opadry II 85F18378 White	1.25 %w/w
Purified water	q.s.

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Procedure: Divalproex sodium was first sifted through 40-mesh ASTM screen and then mixed with hydroxypropyl methylcellulose and dibasic calcium phosphate in a suitable blender. The solution of Xanthan gum in purified water was prepared separately, and was used for granulating the previously obtained powder mixture. The resultant wet material was passed through 8mm ASTM mesh screen and then dried overnight in tray drier at 50° C to 55° C to obtain dried granules. These dried granules were then passed through 18mm mesh ASTM screen. The homogeneous granulate thus obtained was mixed with the talc, compitrol and silica and then compressed using oval shape punches of size 16.0 mm x 8.0 mm. Aqueous coating was carried out on core tablets. Dissolution was carried out in 900 ml of pH 6.8 phosphate buffer at 100 rpm using USP type II apparatus with sinkers. Comparative profiles for Depakote ER 250 mg Tablets and tablets as per example (8) has been shown in Figure 7.

While there have been shown and described what are the preferred embodiments of the invention, one skilled in the pharmaceutical formulation art will appreciate that various modifications in the formulations and process can be made without departing from the scope of the invention as it is defined by the appended claims.

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CLAIMS:

We claim:

1. An oral controlled release composition comprising from about 20 – 80% w/w of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium and valpromide, not more than 20% w/w of a pharmaceutically acceptable polymer and 10 – 50% w/w of filler; all weight percentages are based upon the total weight of the tablet dosage form.
2. An oral controlled release composition of claim 1 comprising -
 - a. from about 30 – 60% w/w of divalproex sodium, in admixture with;
 - b. about 6 – 16% w/w of a pharmaceutically acceptable polymer, and
 - c. from about 20 – 50% w/w of a filler;all weight percentages are based upon the total weight of the tablet dosage form.
3. An oral controlled release composition of claim 1, wherein said active ingredient is divalproex sodium.
4. An oral controlled release composition of claim 1, wherein the pharmaceutically acceptable polymer is preferably a hydrophilic polymer.
5. An oral controlled release composition of claim 4, wherein said hydrophilic polymer is selected from the group consisting of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, vinyl acetate copolymers, methacrylic acid copolymers polysaccharides, polyethylene oxide and maleic anhydride/methyl vinyl ether copolymers
6. An oral controlled release composition of claim 5, wherein said hydrophilic polymer is hydroxypropyl methylcellulose.
7. An oral controlled release composition of claim 1, wherein the filler is preferably water insoluble.
8. An oral controlled release composition of claim 7, wherein said filler is selected from microcrystalline cellulose, dibasic calcium phosphate, calcium carbonate, calcium sulfate, and starch.
9. An oral controlled release composition of claim 8, wherein the filler is dibasic calcium phosphate.

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10. An oral controlled release composition of claim 9, wherein said dibasic calcium phosphate is from about 15 to about 45 weight percent based upon total weight of the tablet dosage form.

11. An oral controlled release composition of claim 1, wherein the divalproex sodium, hydrophilic polymer, filler and other ingredients are granulated by either wet or dry granulation techniques.

12. An oral controlled release composition of claim 11, wherein wet granulation is carried out using a binder selected from polyvinylpyrrolidone, carboxyvinyl polymer, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, dextrin, maltodextrin, gums like xanthan gum, starch, acacia, and tragacanth.

13. A method of preparing a controlled release tablet dosage form of divalproex sodium comprising the steps of:

a) dry blending a mixture of from about 35 to about 55% w/w of divalproex sodium, from about 10 to about 15% w/w of hydroxypropyl methylcellulose and from about 20 to about 45% w/w of dibasic calcium phosphate to form a uniform mixture of the dry ingredients;

b) wet granulating the dry uniform mixture from step a) by aqueous solution of xanthan gum having pH more than 6.0 or aqueous PVP solution

c) drying and sizing the wet granules from step b) to select granules having an average size below about 0.84 mm; and

d) dry blending the granules from about 3 to about 6 weight percent of suitable pharmaceutically acceptable lubricants, including silica having an average particle size ranging between about 1 micron and about 10 micron.

e) compressing the blend of step d) optionally under controlled atmospheric conditions.

14. A method of preparing a controlled release tablet dosage form of divalproex sodium comprising the steps of:

a) dry blending a mixture of from about 30 to about 55% w/w of divalproex sodium, from about 10 to about 15% w/w of hydroxypropyl methylcellulose and from about 20 to about 45% w/w of dibasic calcium phosphate to form a uniform mixture of the dry ingredients;

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- b) Wet granulating the dry uniform mixture from step a) by hydro alcoholic solution of hydroxypropyl methylcellulose;
- c) drying and sizing the wet granules from step b) to select granules having an average size below about 0.84 mm; and
- d) dry blending the granules with about 3 to about 6 weight percent of suitable pharmaceutically acceptable lubricants, including silica having an average particle size ranging from about 1 micron and to about 10 micron.
- e) compressing the blend of step d) optionally under controlled atmospheric conditions.

15. A method of preparing a controlled release tablet dosage form of divalproex sodium comprising the steps of:

- a) dry blending a mixture of from about 30 to about 55% w/w of divalproex sodium, from about 10 to about 15% w/w of hydroxypropyl methylcellulose and from about 20 to about 45% w/w of dibasic calcium phosphate to form a mixture of the dry ingredients;
- b) obtaining slugs on compression machine.
- c) sizing the slugs from step b) to get granules having an average size below about 0.84 mm; and
- d) dry blending the granules with from about 3 to about 6 weight percent of suitable pharmaceutically acceptable lubricants, having an average particle size ranging between about 1 micron and about 10 micron.
- e) compressing the blend of step d) optionally under controlled atmospheric conditions.

16. An oral controlled release tablet dosage form of divalproex sodium according to claim 13-15, manufactured under optional control of atmospheric conditions.

17. A controlled release tablet dosage form of divalproex sodium of claim 16, wherein the temperature is from about 15 to about 27°C.

18. A controlled release tablet dosage form of divalproex sodium according to claim 16 wherein the relative humidity is more than 40%.

19. A method of treating epilepsy comprising administering once daily, to a patient in need of such treatment, a controlled release tablet dosage form according to claim 1.

20. A method of treating epilepsy comprising administering once daily, to a patient in need of such treatment, a controlled release tablet dosage form prepared according to claims 13-15.

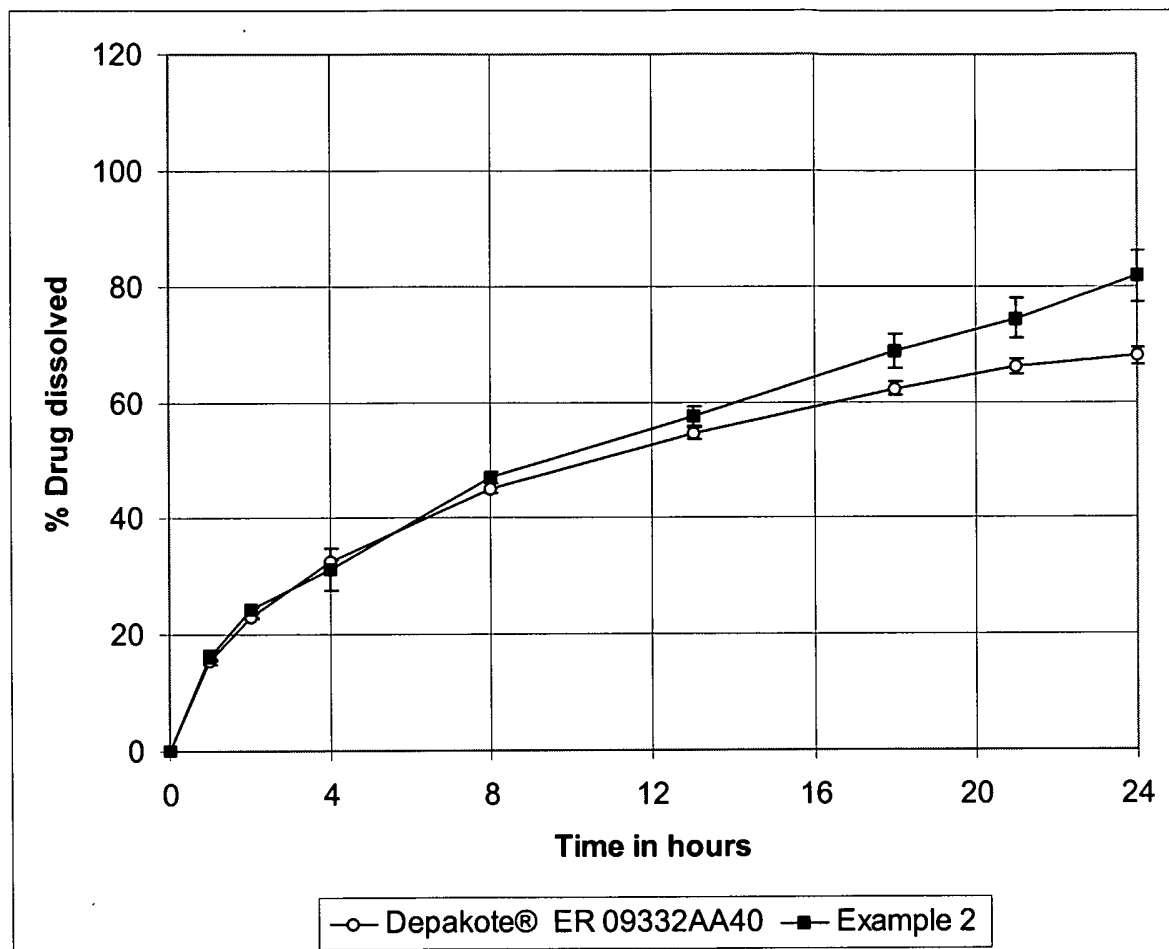
Figure 1

Figure 2

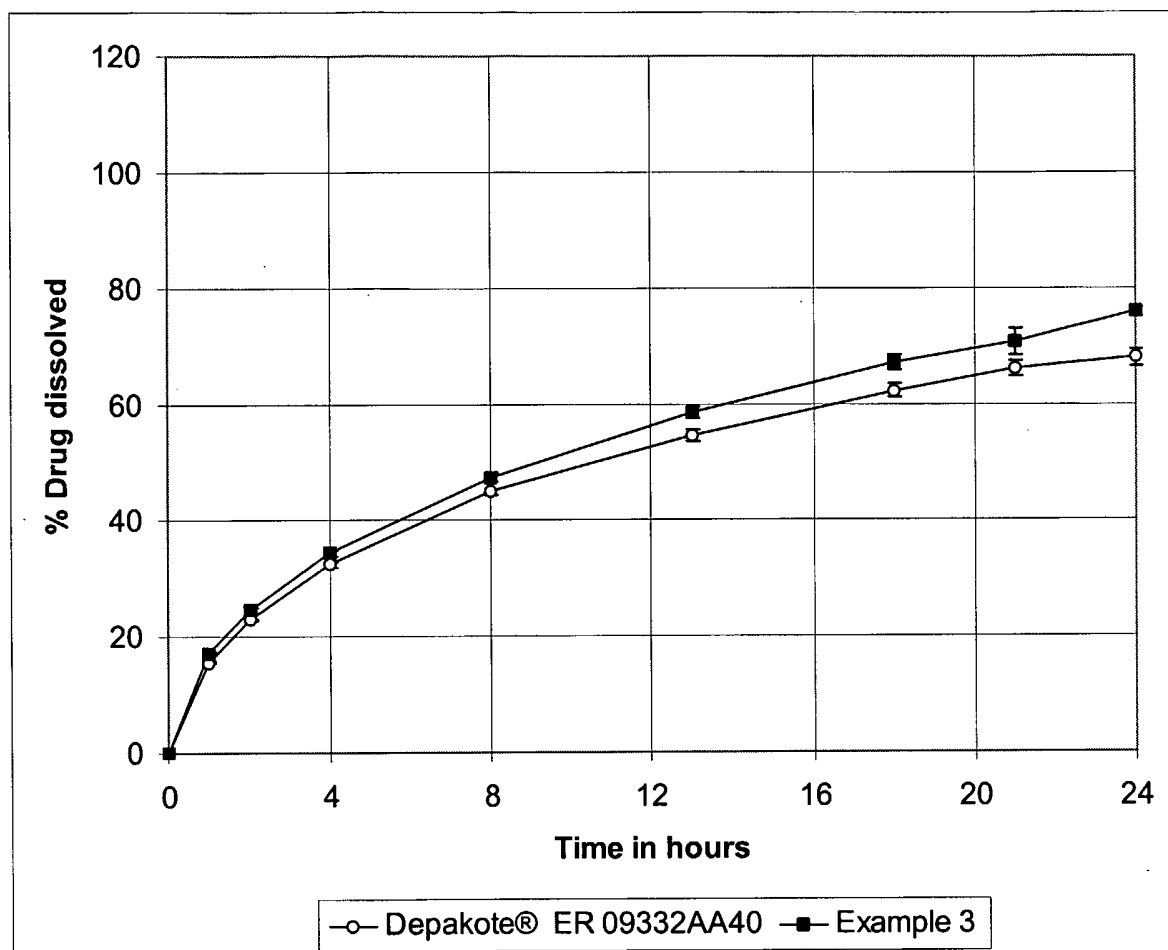


Figure 3

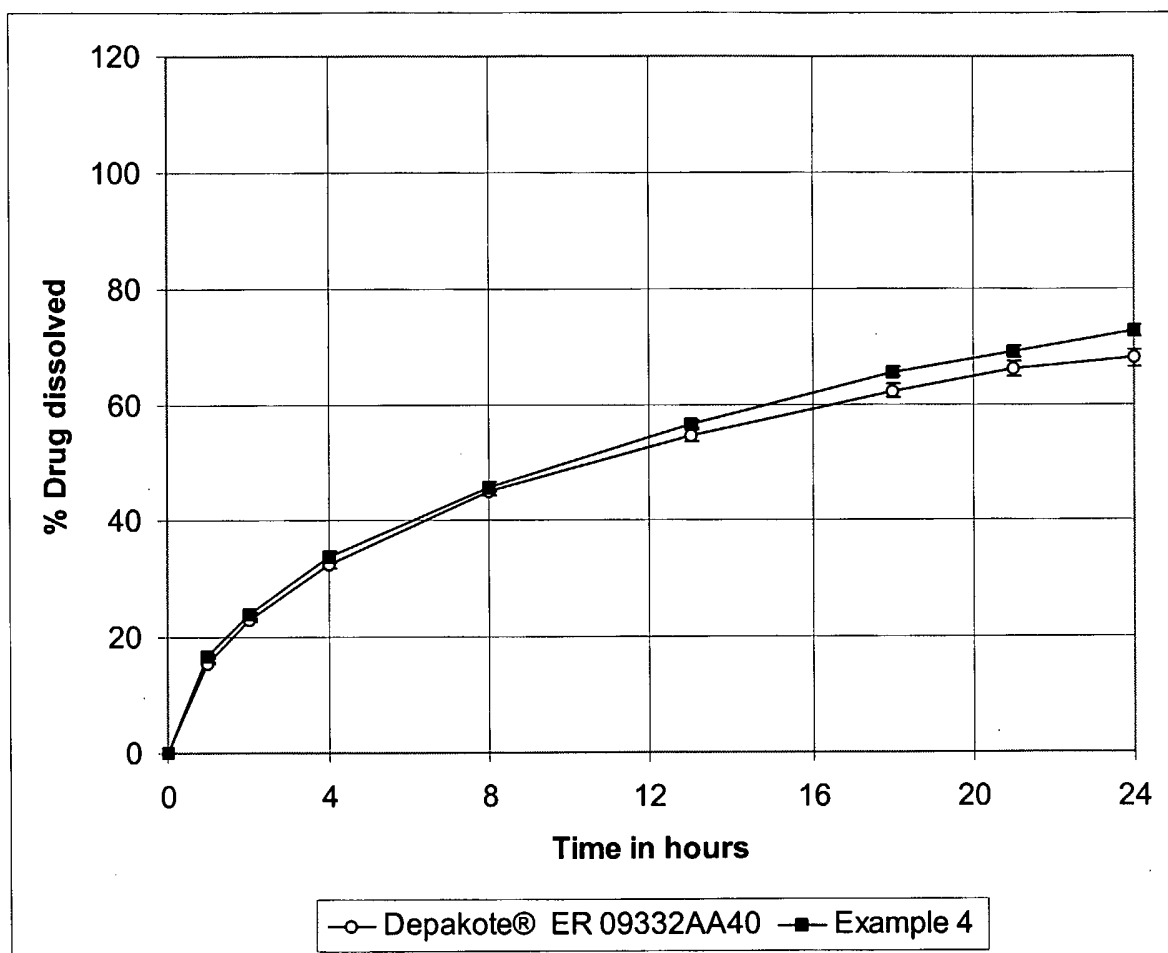


Figure 4

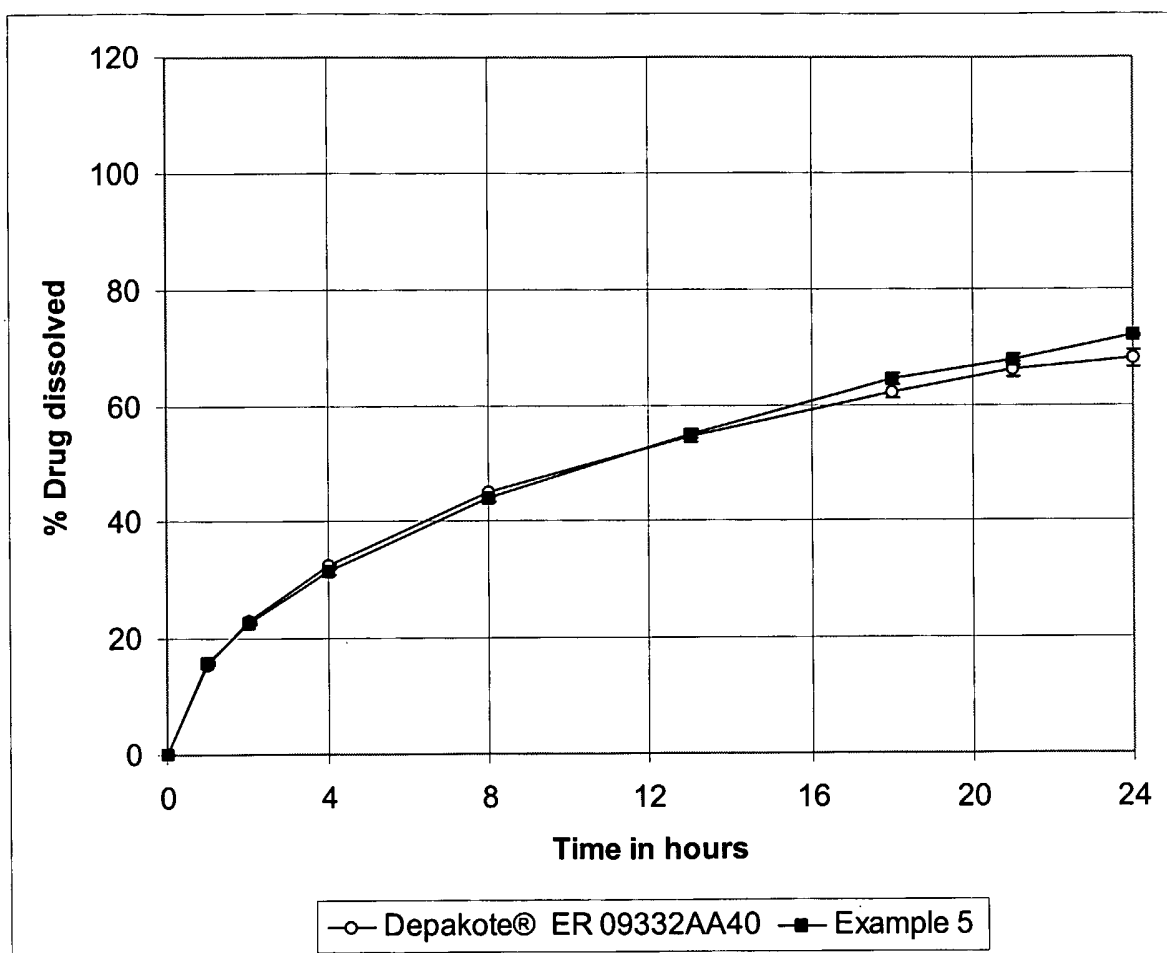


Figure 5

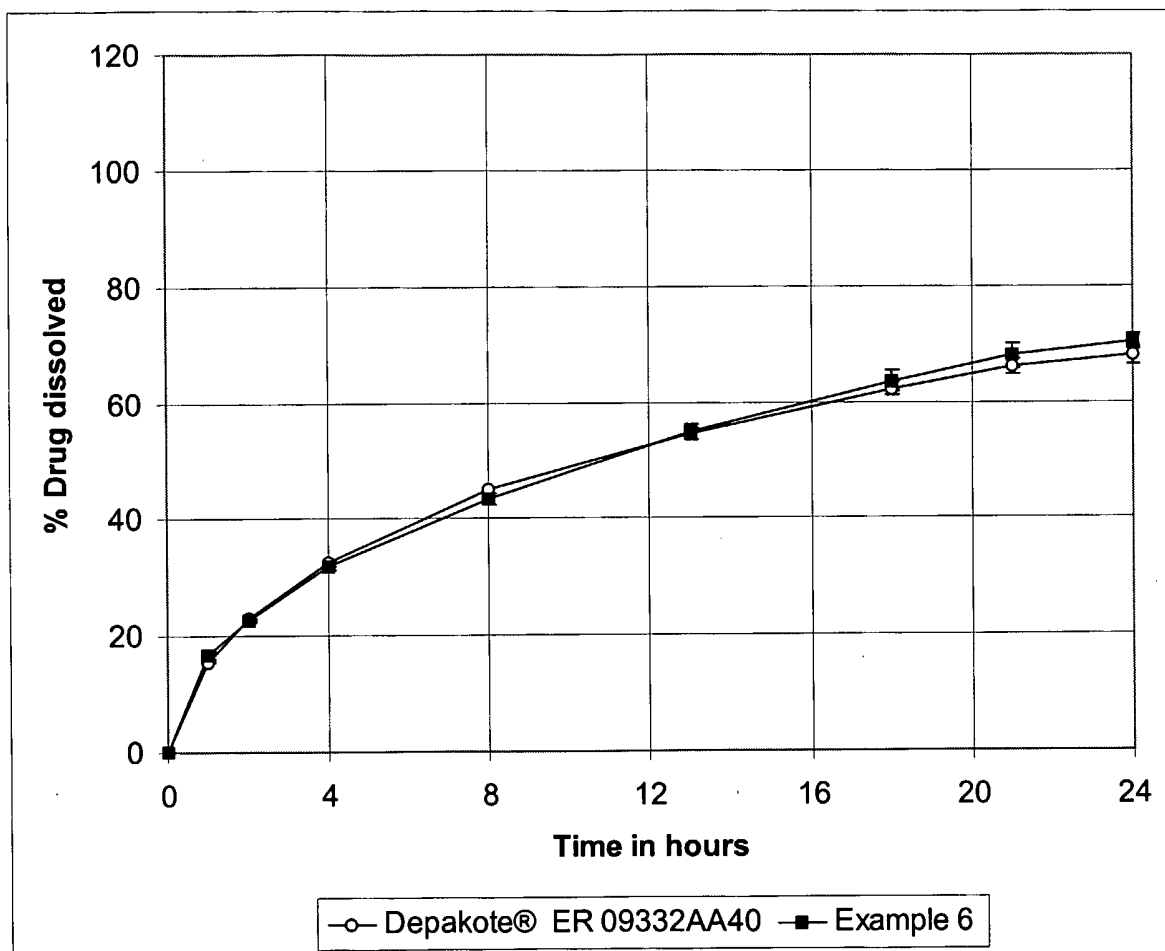


Figure 6

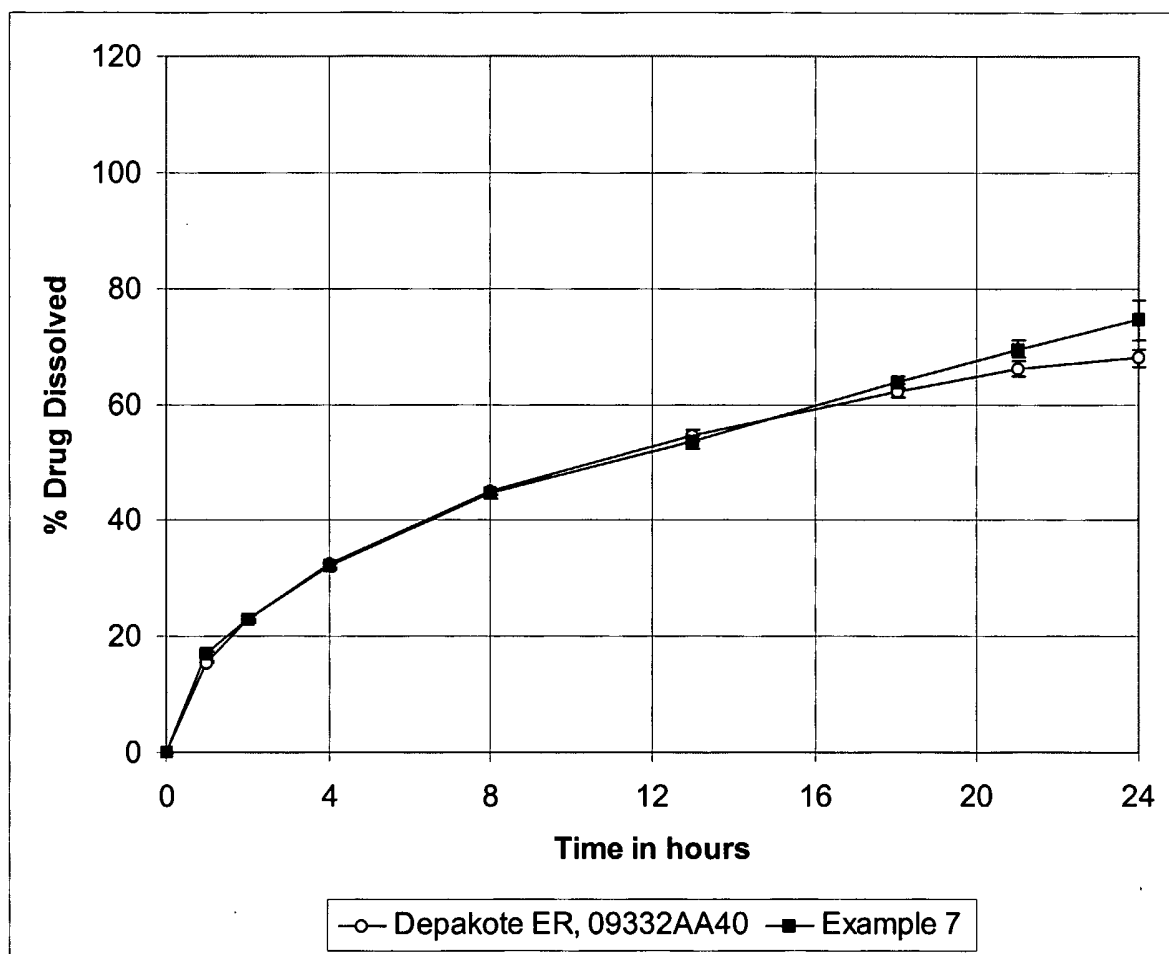
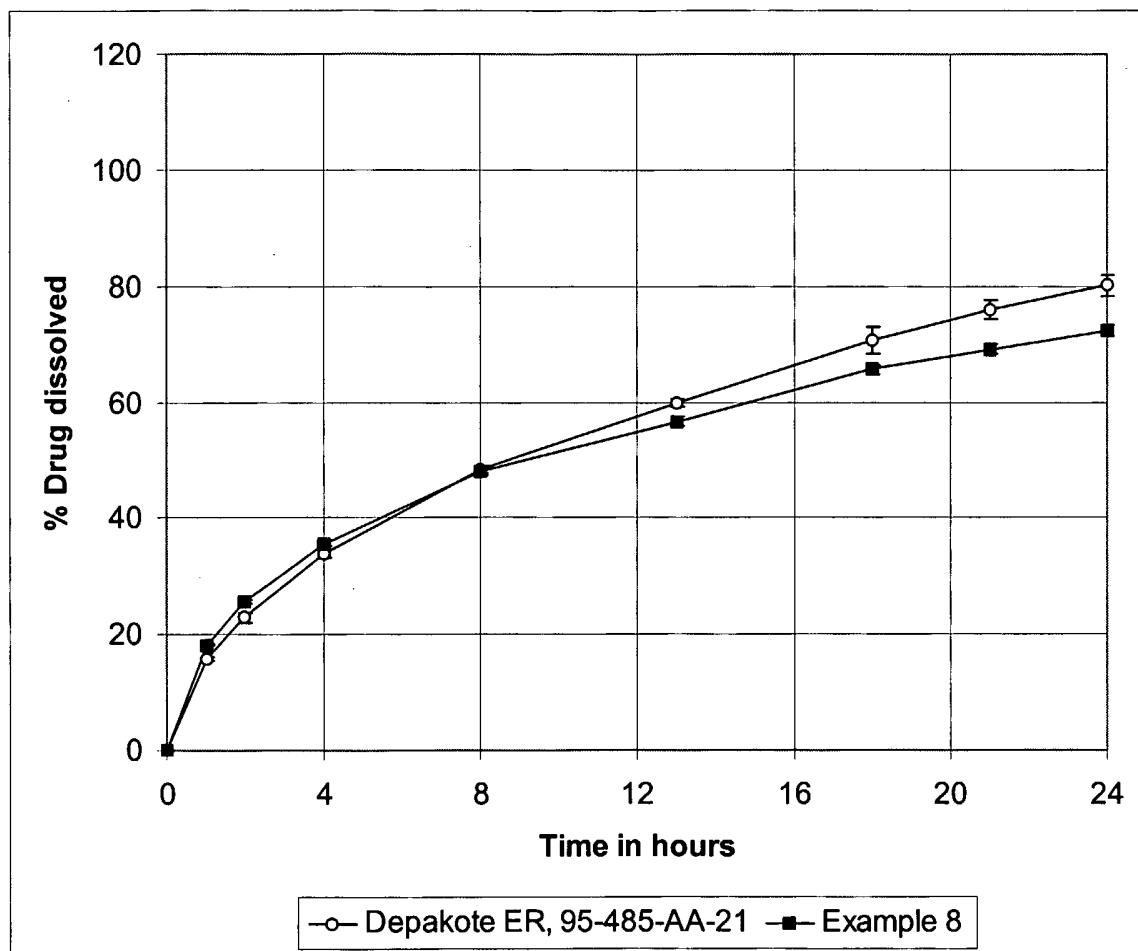


Figure 7



INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB04/02568

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/22, 9/20

US CL : 424/468, 464

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)

U.S. : 424/468, 464

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 practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,212,326 A (MEADE) 18 May 1993 (18.05.1993), see entire document.	1-21
A	US 4,913,906 A (FRIEDMAN et al) 03 April 1990 (03.04.1990), see entire document.	1-21
A	US 5,019,398 A (DASTE) 28 May 1991 (28.05.1991), see entire document.	1-21



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search

17 February 2005 (17.02.2005)

Date of mailing of the international search report

31 MAR 2005

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB04/02568

Continuation of B. FIELDS SEARCHED Item 3:

WEST

(valproic acid, valpromide, divalproex sodium, hydroxypropylmethylcellulose, tablet, epilepsy)