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(54) Title: EXTENDED RELEASE COMPOSITION OF DIVALPROEX

(57) Abstract: The present invention relates to an extended release pharmaceutical composition comprising divalproex sodium and lactose wherein the amount of lactose is less than 8% w/w of the total weight of the pharmaceutical composition.



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Description

EXTENDED RELEASE COMPOSITION OF DIVALPROEX

[1] Technical Field of the Invention

[2] The present invention relates to extended release pharmaceutical compositions that include valproic acid, a pharmaceutically acceptable salt, ester, or amide thereof, or divalproex sodium.

[3] Background of the Invention

[4] Valproic acid, valpromide, and pharmaceutically acceptable salts and esters of the acid are effectively used in the treatment of mania, migraine and epilepsy. After ingestion, they dissociate to the valproate ion within the gastrointestinal tract, which on absorption produces the desired therapeutic effect.

[5] Valproic acid and its derivatives are either liquid or liquefy rapidly and become sticky. Further, most of them are extremely hygroscopic in nature. These physicochemical properties can create serious problems during manufacture of pharmaceutical compositions.

[6] Valproic acid and its derivatives also suffer from another disadvantage of a relatively short elimination half-life. For example, a short half-life of between six to seventeen hours in adults and four to fourteen hours in children has been reported for valproic acid. Frequent dosing is thus necessary to maintain reasonably stable plasma concentrations. However, frequent dosing results in inconvenience to the patient, leading to reduced patient compliance. Moreover, widely fluctuating plasma concentrations of the drug also result in administration of erratic amounts of the drug.

[7] To overcome these disadvantages, a number of research endeavors have been directed towards preparing controlled release formulations that permit once a day dosing and thereby are useful in maintaining a reasonably stable plasma concentration.

[8] For example, U.S. 6,419,953 discloses a controlled release tablet dosage form containing a valproate compound. The controlled release tablet dosage form described has a hydrophilic matrix comprising a mixture of a valproate compound, hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, and silicon dioxide having an average particle size ranging between about one micron and about ten microns. The patent teaches that the addition of either 1% silicon dioxide or/and 5% microcrystalline cellulose to the hydrophilic matrix formulations of the invention increases tablet hardness. However the problem of sticking still persists when conventionally used grades of silicon dioxide are employed, and can be overcome only by the use of a special grade of silicon dioxide (Syloid™ 244) having a larger average particle size ranging from about one micron to about ten microns.

[9] Summary of the Invention

- [10] The present inventors have found out that it is necessary to control the amount of lactose present in the formulation as it affects the tablet matrix strength. As the concentration of lactose decreases strength of matrix increases, the increase in matrix strength influences the *in vitro* release and bioavailability of the divalproex sodium.
- [11] In one general aspect there is provided an extended release pharmaceutical composition that includes divalproex sodium, hydroxypropyl methylcellulose, lactose, and colloidal silicon dioxide. The amount of lactose is less than 8% w/w of the total weight of the pharmaceutical composition.
- [12] Embodiments of the extended release composition may include one or more of the following features. For example, the amount of lactose may be from about 0.5% to about 5% w/w of the total pharmaceutical composition weight. The amount of divalproex sodium may be from about 10% to about 90% w/w of the total pharmaceutical composition weight. The amount of hydroxypropyl methylcellulose may be from about 7% to about 65% w/w of the total pharmaceutical composition weight. The amount of colloidal silicon dioxide may be from about 0.5% to about 5% w/w of the total pharmaceutical composition weight.
- [13] When orally ingested by healthy human subjects, the extended release pharmaceutical composition produces a $C_{\max}$ and an $AUC_{0-\infty}$ which is comparable to the $C_{\max}$ and $AUC_{0-\infty}$ values generated by an equivalent dose of Depakote® divalproex sodium extended release tablet.
- [14] The pharmaceutical composition may be suitable for once a day dosing. The pharmaceutical composition may be selected from tablet, capsule or pill. The tablet may be further coated with one or more functional and/or non-functional layers.
- [15] The pharmaceutical composition may be prepared by a process that includes the steps of: (a) dry blending a mixture of divalproex sodium, lactose and hydroxypropyl methylcellulose; (b) wet granulating the blend of step a; (c) drying and sizing the wet granules; (d) lubricating the granules from step c; and (e) compressing into or filling into a suitable size solid dosage form.
- [16] The extended release pharmaceutical composition may include from about 10-90% w/w of divalproex sodium, from about 30-60% w/w of hydroxypropyl methylcellulose, from about 0.5-2.5% w/w of lactose, and from about 0.5-5% w/w of colloidal silicon dioxide. The extended release pharmaceutical composition may still further include from about 10-90% w/w of divalproex sodium, from about 7-20% w/w of hydroxypropyl methylcellulose, from about 0.5-2.5% w/w of lactose, and from about 0.5-5% w/w of colloidal silicon dioxide.
- [17] The extended release pharmaceutical composition may be manufactured at a temperature of from about 27°C to about 35°C and at a relative humidity of less than about 20%.

- [18] In another general aspect there is provided a process for preparing an extended release pharmaceutical composition. The process includes (a) preparing a blend of divalproex sodium, lactose and hydroxypropyl methylcellulose; (b) wet granulating the blend of step a; (c) drying and sizing the wet granules; (d) lubricating the granules from step c; and (e) compressing into, or filling into, a solid dosage form. The lactose includes less than 8% w/w of the total weight of the pharmaceutical composition.
- [19] The process may further include colloidal silicon dioxide. The pharmaceutical composition may include from about 10-90% w/w of divalproex sodium, from about 30-60% w/w of hydroxypropyl methylcellulose, from about 0.5-2.5% w/w of lactose, and from about 0.5-5% w/w of colloidal silicon dioxide.
- [20] The pharmaceutical composition may be manufactured at a temperature of from about 27°C to about 35°C and at a relative humidity of less than about 20%.
- [21] In another general aspect there is provided a method of treating epilepsy, migraine or bipolar disorders by administering an extended release pharmaceutical composition that includes divalproex sodium, hydroxypropyl methylcellulose, lactose, and colloidal silicon dioxide. The amount of lactose is less than 8% w/w of the total weight of the pharmaceutical composition.
- [22] The extended release pharmaceutical composition provides the drug over a prolonged period of time in such a manner as to provide substantial level of plasma concentrations of the drug following once-a-day dosing.
- [23] In another general aspect, there is provided an extended release tablet dosage form comprising a drug capable of dissociating to produce a valproate ion, and at least one extended release polymer, wherein the tablet is manufactured at a temperature of from about 27°C to about 35°C and a relative humidity of less than about 40% and, more particularly, less than about 20% and provides a low punch residue as compared to the tablet prepared under normal conditions. Normal conditions under which the tablets are generally manufactured are temperature of about 22°C-25°C and a relative humidity 50% or more.
- [24] In another general aspect, there is provided an extended release tablet comprising a drug capable of dissociating to produce a valproate ion, and at least one extended release polymer, wherein the average residue on the tablet punch is less than about 0.3% w/w of the active ingredient.
- [25] In another general aspect, there is provided an extended release tablet composition of divalproex sodium. The composition comprising divalproex sodium, equivalent to about 100 mg to about 1100 mg of valproic acid and at least one extended release polymer, wherein the total tablet weight is less than about 1500 mg.
- [26] In another general aspect, there is provided an extended release once a day tablet of divalproex sodium comprising divalproex sodium, and at least one extended release

polymer, wherein said tablet exhibits the following dissolution profile, when measured in a type 2 dissolution apparatus, paddle, at 100 rpm, at a temperature of $37 \pm 0.5^\circ\text{C}$, 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:

- [27] (a) no more than about 30% of total valproate is released after 3 hours of measurement in said apparatus;
- [28] (b) from about 40 to about 70% of total valproate is released after 9 hours of measurement in said apparatus;
- [29] (c) from about 50 to about 80% of total valproate is released after 12 hours of measurement in said apparatus, and;
- [30] (d) not more than 85% of total valproate is released after 18 hours of measurement in said apparatus.
- [31] In another general aspect, there is provided an extended release once a day tablet of divalproex sodium comprising divalproex sodium and sufficient quantity of at least one extended release polymer, so that said tablet when ingested orally by healthy human subjects produces C_{max} (Maximum plasma concentration) and $AUC_{0-\infty}$ (Area under the plasma concentration vs. time curve from 0 hours to infinity) that is comparable to the C_{max} and $AUC_{0-\infty}$ value produced by the equivalent dose of Depakote® ER divalproex sodium extended release tablets.
- [32] In another general aspect, there is provided a method of treating mania, migraine and epilepsy using an extended release pharmaceutical composition comprising a drug capable of dissociating to produce a valproate ion, and at least one extended release polymer, wherein the pharmaceutical composition is manufactured under controlled atmospheric conditions.
- [33] Pharmaceutically acceptable inert excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form.
- [34] Detailed Description of the Invention
- [35] It has been long known that successful formulation development depends on careful selection of excipients to obtain an optimum compressibility, fluidity, lubricity, hardness, and release profile. It was discovered by the inventors that optimum concentrations of lactose are required to obtain a formulation which is bioequivalent to Depakote® ER tablets.
- [36] The term 'about' as used herein includes temperature and relative humidity conditions up to $\pm 10\%$ of the indicated values.
- [37] The term 'pharmaceutical composition' as used herein includes solid dosage forms such as tablet, capsule, pill, and the like. The tablets can be prepared by techniques

known in the art and contain a therapeutically effective amount of the valproate compound and such excipients as are necessary to form the tablet by such techniques. Tablets and pills can additionally be prepared with enteric coatings and other release-controlling coatings for the purpose of acid protection, easy swallowing, etc.

- [38] The term 'drug capable of dissociating to produce a valproate ion' includes a compound which dissociates within the gastrointestinal tract, to produce a valproate ion including, but not limited to, valproic acid, the sodium salt of valproate, divalproex sodium, any of the various salts of valproic acid described below, and any of the prodrugs of valproic acid described below.
- [39] Valproic acid is known for its activity as an antiepileptic compound as described in the Physician Desk Reference, 55th Edition, page 422 (2001). Upon oral ingestion within the gastrointestinal tract, the acid moiety dissociates to form a carboxylate moiety (i.e., a valproate ion).
- [40] The sodium salt of valproic acid is also known in the art as an anti-epileptic agent. It is also known as sodium valproate and is described in The Merck Index, 12 Edition, page 1691 (1996).
- [41] Divalproex sodium is effective as an antiepileptic agent and is also used for migraine and bipolar disorders. It is a stable co-ordination compound of sodium valproate and valproic acid in a 1:1 ratio and is formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. The amount of drug may vary from about 10% to about 90% by weight of the total pharmaceutical composition weight. Like valproic acid, divalproex sodium also dissociates within the gastrointestinal tract to form a valproate ion.
- [42] In addition to these specific compounds, one of ordinary skill in the art would readily recognize that the carboxylic moiety of the valproate compound might be functionalized in a variety of ways. This includes forming compounds that readily metabolize in vivo to produce valproate, such as valproate amide (valpromide), as well as other pharmaceutically acceptable amides and esters of the acid (i.e., prodrugs). Functionalizing also includes forming a variety of pharmaceutically acceptable salts.
- [43] Suitable pharmaceutically acceptable basic addition salts include, but are not limited to cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.
- [44] Other possible compounds include pharmaceutically acceptable amides and esters.

'Pharmaceutically acceptable ester' refers to those esters that retain, upon hydrolysis of the ester bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. The alcohol component of the ester will generally comprise (i) a C2-C12 aliphatic alcohol that optionally contains one or more double bonds and optionally contains branched carbons or (ii) a C7-C12 aromatic or heteroaromatic alcohols. This invention also contemplates the use of those compositions which are both esters as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

[45] 'Pharmaceutically acceptable amide' refers to those amides that retain, upon hydrolysis of the amide bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. This invention also contemplates the use of those compositions which are both amides as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

[46] The term 'extended release pharmaceutical composition' as used herein includes any pharmaceutical composition that achieves the slow release of drug over an extended period of time, and includes both prolonged and controlled release compositions. This term includes matrix systems, osmotic systems and membrane-controlled systems.

[47] The extended release polymer may be a water-soluble polymer, or a water insoluble polymer (including waxes). Examples of water-soluble polymers include polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropyl methylcellulose, methylcellulose, vinyl acetate copolymers, polysaccharides (such as alginate, xanthan gum, etc.), polyethylene oxide, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof. Examples of water-insoluble polymers include acrylates such as methacrylates and acrylic acid copolymers; cellulose derivatives such as ethylcellulose or cellulose acetate; polyethylene; and high molecular weight polyvinylalcohols. Examples of suitable waxes include fatty acids and glycerides.

[48] The extended release pharmaceutical composition may be prepared by processes known in the art for example, by comminuting, mixing, granulating, melting, sizing, filling, drying, molding, immersing, coating, compressing, etc.

[49] In one general aspect, the extended release tablets may be prepared by a wet granulation technique that includes the steps of blending a drug capable of dissociating to produce a valproate ion, one or more extended release polymers, and, optionally, one or more pharmaceutically inert excipients; granulating with a granulating fluid or solution/dispersion of one or more binders; drying and sizing the granules; optionally blending with one or more pharmaceutically inert extragranular excipients; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets; and optionally coating with film forming polymer and coating additives.

- [50] In another general aspect, the extended release tablets may be prepared by a dry granulation technique that includes the steps of blending a drug capable of dissociating to produce a valproate ion, one or more extended release polymers, and optionally one or more pharmaceutically inert excipients; dry granulating the blend by roller compactor or slugging; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets; and optionally coating with film forming polymer and coating additives.
- [51] In another general aspect, the extended release tablets may be prepared by a direct compression technique that includes the steps of blending a drug capable of dissociating as a valproate ion, one or more extended release polymers, and optionally one or more pharmaceutically inert excipients; lubricating the blend; directly compressing the lubricated blend into suitable sized tablets; and optionally coating with film forming polymer and coating additives.
- [52] In another general aspect, the extended release tablets may be prepared by a melt extrusion technique that includes the steps of blending a drug capable of dissociating as valproate ion, one or more extended release polymers, and optionally one or more pharmaceutically inert excipients; melting the blend followed by solidifying into a compact mass; breaking the compact mass into granules; optionally blending with one or more pharmaceutically inert extragranular excipients; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets; and optionally coating with film forming polymer and coating additives.
- [53] The term 'pharmaceutically acceptable inert excipients' as used herein includes all excipients used in the art of manufacturing solid dosage forms. Common excipients include binders, diluents, surfactants, lubricants/glidants, coloring agents, and the like.
- [54] Examples of suitable binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.
- [55] Examples of suitable diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrans, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like.
- [56] Examples of suitable surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include polyethoxylated fatty acids and its derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol-20 dioleate, polyethylene glycol 4-150 mono dilaurate, polyethylene glycol-20 glyceryl stearate; alcohol-oil transesterification

products, for example, polyethylene glycol-6 corn oil; polyglycerized fatty acids, for example, polyglyceryl-6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monocaprylate; mono and diglycerides, for example, glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example, polyethylene glycol-20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol-20 cetyl ether, polyethylene glycol-10-100 nonyl phenol; sugar esters, for example, sucrose monopalmitate; polyoxyethylene-polyoxypropylene block copolymers known as 'poloxamer'; ionic surfactants, for example sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl camitine; and the like.

[57] Examples of suitable lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like.

[58] Coloring agents include any FDA approved colors for oral use.

[59] The pharmaceutical composition may optionally be coated with functional and/or non-functional layers comprising film-forming polymers, if desired.

[60] Examples of film-forming polymers include ethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethyl cellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate; waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit.TM RL and RS; and the like. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as OpadryTM may also be used for coating.

[61] The following examples are provided to enable one of ordinary skill in art to prepare dosage forms of the invention and should not be construed as limiting the scope of invention. In the following examples, the divalproex sodium tablets were prepared under controlled conditions (temperature from about 27°C to about 35°C and relative humidity less than about 20%) using the procedures as described below.

[62] Divalproex sodium, lactose and hydroxypropyl methylcellulose were blended in a rapid mixer granulator. The granules were prepared by adding the granulation fluid (purified water) to a mixture of drug/polymer/lactose. The resulting granules were dried in a fluidized bed drier and sieved through suitable sieves. The dried granules were blended with talc and magnesium stearate and compressed into suitable sized tablets and coated with an aqueous dispersion of PEG 400 and Opadry.

[63] EXAMPLES 1-6

[64]

Wt/tablet (mg)						
Ingredients	1	2	3	4	5	6
Divalproex sodium	272.3	272.3	544.6	538.2	1076.4	1076.4
Lactose	10	10	125.4	131.8	10	25
Hydroxypropyl methylcellulose	300	350	270	300	245	275
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium Stearate	5	5	5	5	10	10
Talc	7.7	7.7	15	15	28.6	28.6
Colloidal Silicon Dioxide	5	5	10	10	10	10

[65] **EXAMPLE 7**

[66] Tablets were prepared as per the composition of Example 6 using the following procedure: divalproex sodium, hydroxypropyl methylcellulose and lactose were blended in a rapid mixer granulator. The granules were prepared by adding the granulation fluid (dispersion of 0.5 mg/ml hydroxypropyl methylcellulose in purified water) to a mixture of drug/polymer/lactose. The resulting granules were dried in a fluidized bed drier and sieved through suitable sieves. The dried granules were blended with talc and magnesium stearate and compressed into suitable sized tablets and coated with an aqueous dispersion of PEG 400 and Opadry.

[67] The extended release tablets prepared according to Examples 1-6 were then evaluated for hardness and friability. The hardness of extended release tablets of divalproex sodium prepared as per the compositions of Examples 1-6 was determined using Scheulinger Tablet hardness tester (for Examples 3-6) and Vankel Hardness tester (for Examples 1 and 2), the results of which are listed in Table 1.

[68] **Table 1**

[69]

Hardness and friability of extended release tablets of divalproex sodium						
	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
Hardness (kP)	12-14	12-14	15-17	15-17	16-18	18-20
Friability (% loss)	0.02	0.22	0.12	0.08	0.7	0.11

[70] The tablet of Example 4 and preferred tablet formulation B of U.S. 6,419,953 were prepared and evaluated for stickiness. These tablets were made on a rotary press with punch of dimensions 19.2X9.3 mm and at a hardness of about 13-15 kP. After 50 tablets, the tablet material was extracted from the punches using about 7.5 ml of acetonitrile and sonicated. The volume was then made up to 10 ml with water; this procedure was repeated for runs of 100, 150, 200, and 250 tablets. The extracts, together with valproic acid calibration samples, were measured by HPLC for content of valproic acid. The amount of valproic acid in the samples obtained from tablet formulation B was calculated from the standard curve and the total amount of valproic acid extracted from both the upper and lower punch was plotted against the amount of tablets made. An average value for stickiness was calculated from the slope of the regression line by forcing the y-intercept of the line through zero. The weight residue obtained from tablet formulation B of U.S. 6,419,953 with respect to valproic acid was 0.0189 mg/tablet.

[71] On the other hand, a constant weight residue of 0.010 mg/tablet (0.1% w/w of active ingredient) was obtained from the first 50 tablets made according to Example 4. Further, no increase in punch residue was observed irrespective of the number of tablets produced. The constant residue weight clearly indicates almost negligible sticking of the composition to the punches when manufacturing was done under the conditions described herein. The above data also indicates that divalproex sodium tablets when manufactured under controlled temperature and humidity conditions produce tablets with less friability.

[72] Table 2 provides comparative dissolution data for the marketed Depakote® ER (500 mg) and the extended release tablets of divalproex sodium of Example 4. The testing was performed using type 2 USP dissolution apparatus operating at 37°C with a paddle rotation speed of 100 rpm. The tablets were tested in 500 ml of 0.1 N hydrochloric acid for the first 45 min, followed by 900 ml of 0.05M phosphate buffer containing 75 mM sodium lauryl sulphate at pH 5.5.

[73] **TABLE 2**

[74]

Comparative Dissolution profile of Divalproex Sodium Extended Release Tablets (equivalent to 500 mg valproic acid) of Example 4 and Depakote® (500 mg) ER tablets		
	Cumulative percentage (%) release of valproic acid	
Time (h)	Example 4	Depakote® (500 mg) ER tablets
1	9	8

3	22	19
5	33	29
9	49	44
12	59	60
18	79	102

[75] Table 3 provides comparative dissolution data for the marketed Depakote® ER (2X500 mg) and the extended release tablets of divalproex sodium of Examples 5 and 6. The testing was performed using type 2 USP dissolution apparatus with a paddle speed of 100 rpm. The tablets were tested in 900 ml phosphate buffer (pH 6.8) with 1% sodium lauryl sulphate. The tablets were kept in a sinker basket of 10# and the height of paddle was 4.5 cm from the bottom.

[76] **TABLE 3**

[77]

Comparative Dissolution profile of Divalproex sodium extended release tablets (equivalent to 1000 mg valproic acid) of Example 5-6 and Depakote® (2X500 mg) ER tablets			
	Cumulative percentage (%) release of valproic acid		
Time (h)	Example 5	Example 6	Depakote® (500 mg) ER tablets
1	16	15	17
2	26	22	24
4	39	34	35
8	59	53	50
12	75	64	61
16	88	75	69
20	98	94	83
24	105	98	96

[78] Table 4 provides comparative dissolution data for the marketed Depakote® ER (250 mg) and the extended release tablets of divalproex sodium of Example 2. The testing was performed using type 2 USP dissolution apparatus, operating at 37°C with a paddle rotating speed of 100 rpm. The tablets were tested in 500 ml of 0.1 N hydrochloric acid for the first 45 min, followed by 900 ml of 0.05M phosphate buffer containing 75 mM sodium lauryl sulphate at pH 5.5.

[79] **TABLE 4**

[80]

Comparative Dissolution profile of Divalproex sodium extended release tablets (equivalent to 250 mg valproic acid) of Example 2 and Depakote® (250 mg) ER tablets		
	Cumulative percentage (%) release of valproic acid	
Time	Example 2	Depakote® (250 mg) ER tablets
45 min	2.88	4.36
3 h	16.31	17.75
9 h	41.50	41.63
18 h	77.09	81.13

[81] Further, a bioavailability study of the divalproex sodium extended release tablet (500 mg) of Example 4 was carried out on healthy male volunteers (n=12) taking Depakote® ER tablet (500 mg) as the reference, the results of which are presented in Table 5.

[82] An open randomized, 2 treatment, 2 period, 2 sequence, single dose crossover protocol was used for a comparative bioavailability study of divalproex sodium 500 mg extended release tablets against Depakote® ER tablets-500 mg of Abbott laboratories under fed conditions:

[83] **TABLE 5**

[84]

Pharmacokinetic parameters obtained through the bioavailability studies of divalproex sodium extended release tablets and Depakote® ER tablets (500 mg).				
Pharmacokinetic parameter	C _{max} * (ng/ml)	AUC _{0-t} ** (ng.h/ml)	AUC _{0-infinity} *** (ng.h/ml)	T _{max} (h)
Divalproex sodium extended release tablet of Example 4 (Test)	50.7	1592.31	1811.54	18.67
Depakote® ER 500 mg tablet (Ref.)	47.75	1599.74	1940.07	20
Test/Ref. (90% confidence interval)	106.91 (99.63-114.72)	99.21 (87.41-112.61)	92.21 (81.76-104)	-

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- [85] *C_{max} = Maximum plasma concentration,
- [86] **AUC_{0-t} = Area under the plasma concentration vs time curve from 0 hrs to the time of last sample collected,
- [87] ***AUC_{0-infinity} = Area under the plasma concentration vs. time curve from 0 hrs to infinity,
- [88] ****T_{max} = Time to attain maximum plasma concentration.
- [89] As can be seen in Table 5, the AUC_{0-infinity} for Divalproex sodium was within 80-125% as per FDA guidelines on bioequivalence. The above results show that divalproex sodium 500 mg extended release tablets prepared as per Example 4 have a bioavailability comparable to the reference product, Depakote® ER tablet 500 mg.
- [90] The extended release tablet formulations of the present invention thus provide an effective delivery system for the once daily administration of valproic acid (divalproex sodium) to patients in need of such treatment.
- [91] A bioavailability study of the Divalproex sodium (1000 mg) ER tablet prepared according to the composition of Example 6 was carried out on healthy male volunteers (n=11) taking Depakote® ER tablet (2X500 mg) as the reference, the results of which are presented in Table 6. The objective of this study was to show that a formulation of Example 6 provides an activity and safety profile that is similar to or better than one obtained with the equivalent product in the market.
- [92] An open randomized, 2 treatment, 2 period, 2 sequence, single dose crossover, comparative bioavailability study of Divalproex sodium extended release tablets against 2X500 mg ER tablets of Depakote® ER tablets was performed under fed conditions. The comparative pharmacokinetic parameters thus obtained are listed in Table 6.
- [93] **TABLE 6**
- [94]

Comparative pharmacokinetic parameters for tablets of Divalproex Sodium ER and Depakote® ER tablets (500 mgX2).				
Pharmacokinetic parameter	C _{max} * (ng/ml)	AUC _{0-t} ** (ng.h/ml)	AUC _{0-infinity} *** (ng.h/ml)	T _{max} (h)
Divalproex sodium extended release tablet of Example 6 (Test)	70.31	1827.86	1981.31	9.91
Depakote® ER 500	63.61	1899.77	2099.67	14.36

mg tablet (Ref.)				
Test/Ref. (90% confidence interval)	110.02 (99.61-121.52)	95.41 (86.08-105.76)	93.81 (83.99-104.78)	-

[95] *C_{max} = Maximum plasma concentration,

[96] **AUC_{0-t} = Area under the plasma concentration vs time curve from 0 hours to the time of last sample collected,

[97] ***AUC_{0-infinity} = Area under the plasma concentration vs. time curve from 0 hours to infinity, and

[98] ****T_{max} = Time to attain maximum plasma concentration

[99] The AUC_{0-infinity} for Divalproex sodium was within 80-125% as shown in Table 6. The results show that Divalproex Sodium 1000 mg extended release tablets prepared as per the examples described herein have a bioavailability comparable to the reference product, Depakote® ER tablet (500X2 mg).

[100] A bioavailability study of the Divalproex sodium (250 mg) ER tablet of Example 2 was carried out on healthy male volunteers (n=39) taking Depakote® ER tablet (250 mg) as the reference under fasting conditions, the results of which are presented in Table 7.

[101] An open randomized, 2 treatment, 2 period, 2 sequence, single dose crossover protocol was used for a comparative bioavailability study of divalproex sodium 250 mg extended release tablet against Depakote® ER tablets 250 mg of Abbott laboratories under fasting conditions:

[102] **TABLE 7**

[103]

Comparative pharmacokinetic parameters for tablets of Divalproex Sodium ER and Depakote® ER tablets under fasting conditions (250 mg).				
Pharmacokinetic parameter	C _{max} * (ng/ml)	AUC _{0-t} ** (ng.h/ml)	AUC _{0-infinity} *** (ng.h/ml)	T _{max} (h)
Divalproex sodium extended release tablet of Example 2 (Test)	20.66	530.06	643.95	12.78
Depakote® ER 250 mg tablet (Ref.)	20.70	524.08	640.31	14.27
Test/Ref. (90% confidence interval)	99.60 (88.77-111.76)	101.01 (89.38-114.15)	100.60 (90.88-111.37)	-

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[104] *C_{max} = Maximum plasma concentration,

[105] **AUC_{0-t} = Area under the plasma concentration vs time curve from 0 hours to the time of last sample collected,

[106] ***AUC_{0-infinity} = Area under the plasma concentration vs. time curve from 0 hours to infinity, and

[107] ****T_{max} = Time to attain maximum plasma concentration

[108] The bioavailability study of the Divalproex sodium (250 mg) ER tablet of Example 2 was carried out on healthy male volunteers (n=33) taking Depakote® ER tablet (250 mg) as the reference under fed conditions, the results of which are represented in Table 8.

[109] An open randomized, 2 treatment, 4 period, 2 sequence, single dose crossover protocol was used for comparative bioavailability study of divalproex sodium 250 mg extended release tablet against Depakote® ER tablets 250 mg of Abbott laboratories under fed conditions:

[110] **TABLE 8**

[111]

Comparative pharmacokinetic parameters for tablets of Divalproex Sodium ER and Depakote® ER tablets under fed conditions (250 mg).				
Pharmacokinetic parameter	C _{max} * (ng/ml)	AUC _{0-t} ** (ng.h/ml)	AUC _{0-infinity} *** (ng.h/ml)	T _{max} (h)
Divalproex sodium extended release tablet of Example 2 (Test)	16.44	515.23	646.07	21.65
Depakote® ER 250 mg tablet (Ref.)	16.22	512.32	632.15	21.46
Test/Ref. (90% confidence interval)	101.20 (95.42-107.33)	100.51 (93.90-107.58)	102.23 (96.10-108.75)	-

[112] *C_{max} = Maximum plasma concentration,

[113] **AUC_{0-t} = Area under the plasma concentration vs time curve from 0 hours to the time of last sample collected,

[114] ***AUC_{0-infinity} = Area under the plasma concentration vs. time curve from 0 hours to infinity, and

[115] **** $T_{\max}$ = Time to attain maximum plasma concentration

[116] The objective of these studies was to show that a formulation of Example 2 provides an activity and safety profile that is similar to one obtained with an equivalent product in the market.

[117] $AUC_{0-\infty}$ for Divalproex sodium was within 80-125% as shown in Table 7 and 8. The results show that Divalproex Sodium 1000 mg extended release tablets prepared as per the examples described herein have bioavailability comparable to the reference product, Depakote® ER tablet (250 mg), under fasting and fed conditions.

[118] EXAMPLES 8 and 9

[119]

Ingredients	8	9
Wt/tablet (mg)		
Divalproex sodium	538.1	807.15
Lactose	68.60	18.90
Methocel K-15 MCR	360.00	-
Methocel K-100 MCR	-	254.00
Methocel E-5	8.00	6.00
Water	q.s.	q.s.
Magnesium Stearate	3.00	3.00
Talc	7.30	10.95
Colloidal Silicon Dioxide	15.00	22.50

[120]

1. Divalproex sodium, lactose, Methocel K-15M CR and Methocel E-5 were blended in a rapid mixer granulator.
2. The granules were prepared adding the granulation fluid (purified water) to above blend.
3. The resulting granules were dried in a fluidized bed drier and sieved through suitable sieves.
4. The dried granules were blended with talc and magnesium stearate and compressed into suitable sized tablets.
5. The tablets so obtained were coated with an aqueous dispersion of PEG 400 and Opadry.

[121] While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the

invention. Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

Claims

- [1] An extended release pharmaceutical composition comprising:
(a) divalproex sodium,
(b) hydroxypropyl methylcellulose,
(c) lactose, and
(d) colloidal silicon dioxide;
wherein the amount of lactose is less than 8% w/w of the total weight of the pharmaceutical composition.
- [2] The extended release composition according to claim 1 wherein the amount of lactose comprises from about 0.5% to about 5% w/w of the total pharmaceutical composition weight.
- [3] The extended release composition according to claim 1 wherein the amount of divalproex sodium comprises from about 10% to about 90% w/w of the total pharmaceutical composition weight.
- [4] The extended release composition according to claim 1 wherein the amount of hydroxypropyl methylcellulose comprises from about 7% to about 65% w/w of the total pharmaceutical composition weight.
- [5] The extended release composition according to claim 1 wherein the amount of colloidal silicon dioxide comprises from about 0.5% to about 5% w/w of the total pharmaceutical composition weight.
- [6] The extended release composition according to claim 1 which when orally ingested by healthy human subjects produces a $C_{\max}$ and an $AUC_{0-\infty}$ which is comparable to the $C_{\max}$ and $AUC_{0-\infty}$ values generated by equivalent dose of Depakote® divalproex sodium extended release tablet.
- [7] The extended release composition according to claim 1 wherein the pharmaceutical composition is suitable for once a day dosing.
- [8] The extended release composition according to claim 1 wherein the pharmaceutical composition is selected from tablet, capsule or pill.
- [9] The extended release composition according to claim 8 wherein the tablet is further coated with one or more functional and/or non-functional layers.
- [10] The extended release pharmaceutical composition according to claim 1 wherein the pharmaceutical composition is prepared by a process comprising the steps of:
(a) dry blending a mixture of divalproex sodium, lactose and hydroxypropyl methylcellulose;
(b) wet granulating the blend of step a;
(c) drying and sizing the wet granules;
(d) lubricating the granules from step c; and

- (e) compressing into or filling into a suitable size solid dosage form.
- [11] The extended release pharmaceutical composition according to claim 1 wherein the pharmaceutical composition comprises:
- (a) from about 10-90% w/w of divalproex sodium,
 - (b) from about 30-60% w/w of hydroxypropyl methylcellulose,
 - (c) from about 0.5-2.5% w/w of lactose, and
 - (d) from about 0.5-5% w/w of colloidal silicon dioxide.
- [12] The extended release pharmaceutical composition according to claim 1 wherein the pharmaceutical composition comprises:
- (a) from about 10-90% w/w of divalproex sodium,
 - (b) from about 7-20% w/w of hydroxypropyl methylcellulose,
 - (c) from about 0.5-2.5% w/w of lactose, and
 - (d) from about 0.5-5% w/w of colloidal silicon dioxide.
- [13] The extended release pharmaceutical composition according to claim 1 wherein the pharmaceutical composition is manufactured at a temperature of from about 27°C to about 35°C.
- [14] The extended release pharmaceutical composition according to claim 1 wherein the pharmaceutical composition is manufactured at a relative humidity of less than about 20%.
- [15] A process for preparing an extended release pharmaceutical composition, the process comprising:
- (a) preparing a blend of divalproex sodium, lactose and hydroxypropyl methylcellulose;
 - (b) wet granulating the blend of step a;
 - (c) drying and sizing the wet granules;
 - (d) lubricating the granules from step c; and
 - (e) compressing into, or filling into, a solid dosage form,
- wherein the lactose comprises less than 8% w/w of the total weight of the pharmaceutical composition.
- [16] The process of claim 15, further comprising colloidal silicon dioxide.
- [17] The process of claim 16 wherein the pharmaceutical composition comprises:
- (a) from about 10-90% w/w of divalproex sodium,
 - (b) from about 30-60% w/w of hydroxypropyl methylcellulose,
 - (c) from about 0.5-2.5% w/w of lactose, and
 - (d) from about 0.5-5% w/w of colloidal silicon dioxide.
- [18] The process of claim 15 wherein the pharmaceutical composition is manufactured at a temperature of from about 27°C to about 35°C.
- [19] The process of claim 15 wherein the pharmaceutical composition is man-

ufactured at a relative humidity of less than about 20%.

- [20] A method of treating epilepsy, migraine or bipolar disorders by administering an extended release pharmaceutical composition according to claim 1.