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(54) **PROCESS FOR PREPARING NON-HYGROSCOPIC SODIUM VALPROATE COMPOSITION**

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(57) **ABSTRACT**

The invention provides a process for preparing a non-hygroscopic, highly stable, oral pharmaceutical composition of a salt of valproic acid. The pharmaceutical composition is prepared by blending ingredients including a hygroscopic salt of valproic acid, carbomer, and a non-hygroscopic additive such as dibasic calcium phosphate. Such a composition forms non-hygroscopic, highly moisture stable solid dosage form.

PROCESS FOR PREPARING NON-HYGROSCOPIC SODIUM VALPROATE COMPOSITION

FIELD OF THE INVENTION

[0001] The present invention relates to a process for preparing non-hygroscopic, highly stable, pharmaceutical composition of a salt of valproic acid. More particularly, the invention relates to preparation of a pharmaceutical composition which includes a mixture of a hygroscopic salt of valproic acid, carbomer and a non-hygroscopic additive such as dibasic calcium phosphate. Such a composition forms non-hygroscopic, highly moisture stable solid dosage form.

BACKGROUND OF THE INVENTION

[0002] Valproic acid and its pharmaceutically acceptable salts are useful for treating various forms of epilepsy. Valproic acid is considered a first line therapy for treating petit mal, monoclonic seizures, generalized and partial motor seizures, absence and infantile spasms. Recently valproic acid was also approved for the treatment of partial epilepsy, bipolar disorders (psychotic disorders) and migraine.

[0003] The effective blood concentrations of the drug generally range from 50 to 100 μg/ml. Because sodium valproate has a short biological half life, the drug must be administered three times a day to maintain an effective blood concentration. Since such a short dose interval reduces patient compliance, there have been many efforts to develop sustained release preparations of sodium valproate.

[0004] Although valproic acid or its salts have known utility as anti-convulsants, a number of problems are associated in formulating them in a solid form. According to the Merck Index valproic acid is a liquid and therefore suffers from the difficulty attendant any liquid formulation; that is, it is inconvenient to use since the precise volume necessary to result in administration of the proper dose must be measured for each administration and it is less easily portable than solid dosage forms. Efforts have been made to address the problems of administering valproic acid by converting it to its salt forms. However, as taught in U.S. Pat. No. 4,301,176, the sodium salt of valproic acid is hygroscopic. This precludes production of a compacted tablet formulation which is a serious disadvantage.

[0005] Various attempts have been made to formulate moisture-stable solid valproic acid and valproic acid salt formulations. U.S. Pat. No. 5,049,586 teaches conventional (immediate-release) formulations of valproic acid containing fillers, disintegrants, binders and lubricants. The lubricated granulate taught is claimed to be a dry, non-hygroscopic mixture which is suitable for use in forming compacted tablets or for filling capsules. The formulation was found to be moisture stable and to need no protective coating. However, the production of the tablets mentioned above is disadvantageous since it requires a wet granulation step and is more complicated compared to the procedure described in the present invention.

[0006] U.S. Pat. Nos. 5,017,613 and 5,185,159 teach a pharmaceutical composition based on valproic acid and one of the pharmaceutically acceptable salts thereof. According to these teachings, the granules for compression are formed directly by simply mixing suitable proportions of valproic acid and one of the pharmaceutically acceptable salts thereof in the absence of any binder or granulating solvent. Valproic acid was added slowly, either directly or by spraying, to the valproic acid salt, with the granular agglomeration occurring automatically in few minutes. The granules thus obtained were passed through a screen for calibration. This operation could be carried out in an atmosphere of 55-60% relative humidity, without risk of any uptake of moisture. The compressibility of these granules was found to be very good and moreover the valproic acid acted as a lubricant.

[0007] Similarly EP0133110 discloses an oral tablet pharmaceutical composition of aproximately 25-35% by weight of valproic acid and about 65-75% by weight of sodium valproate. The granules for compression are formed directly by mixing suitable proportions of valproic acid and one of the pharmaceutically acceptable salts thereof in the absence of any binder or granulating solvent.

[0008] U.S. Pat. Nos. 4,988,731 and 5,212,326 teach a highly stable non-hygroscopic, solid entity prepared from valproic acid and its salts. The new compound represents a single crystalline entity consisting of one molecule each of valproic acid or diethylacetic and sodium valproate salt. It was shown that the new material has equal or better physiological properties than either valproic acid or sodium valproate. Since the new compound has far superior physical characteristics than either monomer from which it is made, it greatly facilitates the preparation of solid pharmaceutical dosage forms.

[0009] The method disclosed in U.S. Pat. Nos. 5,017,613, 5,185,159, 4,988,731, 5,212,326 and EP0133110 is disadvantageous since it requires a reaction between valproic acid and its salt to produce a new entity. Moreover the production of the new entity according to U.S. Pat. Nos. 4,988,731 and 5,212,326 includes steps involving cooling and filtration which complicates the production of the new formed entity.

[0010] The production of the granules according to U.S. Pat. Nos. 5,017,613, 5,185,159 and EP0133110 is disadvantageous. Since valproic acid is a viscous liquid which is hard to handle and the granules for compression are formed in the absence of a granulating solvent this might lead to a technological difficulty in forming an homogeneous mixture of valproic acid and valproic acid salt.

[0011] Hasegawa et al. [Hasegawa, A. et al., YAKUZAIGAKU, 47: 86-92, 1987] describes a solid dispersion of water insoluble carriers and sodium valproate. This composition inhibits moisture absorption when saturated fatty acid such as stearic acid or other organic acids such as citric acid, succinic acid or tartaric acid are employed. Although it was shown that these solid dispersions inhibit the moisture uptake, such compositions are disadvantageous since relatively high concentrations of the acids are required (about 20% by weight of sodium valproate). Moreover, part of these reactions (especially the reaction with citric acid) are exothermic and require cooling of the mixture. The reaction of sodium valproate with citric acid is highly exothermic and leads to melting of the mixture, which is a serious disadvantage.

[0012] Other attempts have been made to develop controlled release pharmaceutical compositions of valproic acid. U.S. Pat. No. 4,913,906 teaches a controlled release

dosage form of valproic acid, sodium valproate, valproamide and other derivatives of therapeutic value. The controlled release oral dosage form comprises homogeneous admixture of an active ingredient and a physiologically acceptable polymer or a native protein. Although the formulations described were found to provide sustained release action, the production of the tablets requires that such dosage form should be performed in dry atmosphere cabinet, at less than 30% R.H which is a serious disadvantage.

[0013] None of these prior art references taught or disclosed a process for preparing a non-hygroscopic, highly stable composition of a salt of valproic acid which can be produced under normal to high relative humidity conditions by combining a hygroscopic salt of valproic acid (sodium valproate) with a polymeric agent (carbomer) and a non-hygroscopic additive.

[0014] There is thus a widely recognized need for and it would be highly advantageous to have an effective sodium valproate formulation, which is non-hygroscopic, highly stable, simplified in production, lower in cost and yet which is suitable for treatment of epilepsy, psychotic disorders and migraine headaches as described in the present invention.

SUMMARY OF THE INVENTION

[0015] The present invention provides a process for preparing a non-hygroscopic, highly stable pharmaceutical formulation of a salt of valproic acid. More particularly, the invention relates to a composition comprising a mixture of a hygroscopic salt of valproic acid, carbomer and a non hygroscopic additive, preferably dibasic calcium phosphate, which can be produced under normal to high relative humidity conditions to form a non-hygroscopic, highly stable solid dosage form.

[0016] According to one aspect of the present invention there is provided a process for preparing a non-hygroscopic highly stable oral pharmaceutical composition of a salt of valproic acid, the process comprising the single step of blending ingredients including a hygroscopic salt of valproic acid, carbomer, and a non-hygroscopic additive.

[0017] According to further features in preferred embodiments of the invention described below, the hygroscopic salt of valproic acid is sodium valproate.

[0018] According to still further features in the described preferred embodiments the process further comprises the step of adding at list one excipient.

[0019] According to still further features in the described preferred embodiments the process further comprises the step of compressing the ingredients into a solid dosage form after the step of blending.

[0020] According to still further features in the described preferred embodiments a single dose of the solid dosage form contains from about 50 to about 1200 mg of sodium valproate.

[0021] According to still further features in the described preferred embodiments sodium valproate is present in an amount of from about 5% to about 99% of the weight of the final composition.

[0022] According to still further features in the described preferred embodiments a single dose of the solid dosage form contains from about 0.2 mg to about 500 mg of carbomer.

[0023] According to still further features in the described preferred embodiments the carbomer is present in an amount of from about 0.2% to about 30% of the weight of the final composition.

[0024] According to still further features in the described preferred embodiments the carbomer is present in an amount such that the weight ratio of carbomer to sodium valproate is in the range of from about 0.3:99.7 to about 35:65.

[0025] According to still further features in the described preferred embodiments the non-hygroscopic additive is selected from the group consisting of dibasic calcium phosphate anhydrous, calcium silicate, microcrystalline cellulose and mixtures thereof.

[0026] According to still further features in the described preferred embodiments the dibasic calcium phosphate anhydrous is present in an amount of from about 10% to about 40% of the weight of the final composition.

[0027] According to still further features in the described preferred embodiments the dibasic calcium phosphate anhydrous is present in an amount such that the weight ratio of dibasic calcium phosphate anhydrous to carbomer is in the range of from about 99.95:0.05 to about 40:60.

[0028] According to still further features in the described preferred embodiments the excipient is selected from the group consisting of lubricants, disintegrators, glidents, adsorbents, and mixtures thereof

[0029] According to still further features in the described preferred embodiments the lubricant is selected from the group consisting of stearic acid, a salt of stearic acid, talc, sodium lauryl sulfate, sodium stearyl fumarate and mixtures thereof.

[0030] According to still further features in the described preferred embodiments the lubricant is present in an amount of from about 0.25% to about 5% of the weight of the final composition.

[0031] According to still further features in the described preferred embodiments the disintegrator is selected from the group consisting of crosscarmelose sodium, sodium starch glycolate, starch, magnesium aluminum silicate, colloidal silicon dioxide, carboxymethyl cellulose, microcrystalline cellulose, and mixtures thereof.

[0032] According to still further features in the described preferred embodiments the disintegrator is present in an amount of from about 0.5% to about 25% of the weight of the final composition.

[0033] According to still further features in the described preferred embodiments the glident is selected from the group consisting of colloidal silicon dioxide, talc and mixtures thereof.

[0034] According to still further features in the described preferred embodiments the glident is present in an amount of from about 0.1% to about 10% of the weight of the final composition.

[0035] According to still further features in the described preferred embodiments the adsorbent is selected from the group consisting of colloidal silicon dioxide, microcrystalline cellulose, calcium silicate and mixtures thereof.

[0036] According to still further features in the described preferred embodiments the adsorbent is present in an amount of from about 0.05% to about 42% of the weight of the final composition.

[0037] According to still further features in the described preferred embodiments the solid dosage form is selected from the group consisting of a tablet, a caplet, a pellet, a capsule, a tablet which disintegrates into granules, and a pill.

[0038] According to still further features in the described preferred embodiments the pharmaceutical composition exists in a form selected from the group consisting of a capsule, a sachet, a powder and a granule.

[0039] According to still further features in the described preferred embodiments the process comprises the additional step of maintaining relative humidity in the range of about 30% to about 75% during the step of blending of the ingredients.

[0040] According to another aspect of the present invention there is provided a non-hygroscopic highly stable orally deliverable pharmaceutical composition for release of a salt of valproic acid into the bloodstream at a physiologically effective level, the composition comprising a pharmaceutically effective amount of a hygroscopic salt of valproic acid, a carrier, a non-hygroscopic additive, and at least one excipient.

[0041] According to further features in preferred embodiments of the invention described below, the hygroscopic salt of valproic acid is sodium valproate.

[0042] According to still further features in the described preferred embodiments the carrier is selected from the group consisting of a polymeric carrier, a non-polymeric carrier and mixtures thereof

[0043] According to still further features in the described preferred embodiments the polymeric carrier is carbomer.

[0044] According to still further features in the described preferred embodiments the carbomer is present in an amount of from about 0.2% to about 30% of the weight of the final composition.

[0045] According to still further features in the described preferred embodiments the non-polymeric carrier is selected from the group consisting of a sugar, a protein, a biologically inert material, elemental carbon and mixtures thereof.

[0046] According to still further features in the described preferred embodiments the pharmaceutically effective amount is selected from the group consisting of:

[0047] (a) less than 10% by weight of the total formulation; and

[0048] (b) more than 80% by weight of the total formulation.

[0049] According to yet another aspect of the present invention there is provided a method of treating a medical condition in a human patient, the method comprising the step of orally administering a non-hygroscopic highly stable pharmaceutical composition for release of a salt of valproic acid into the bloodstream at a physiologically effective level;

[0050] wherein the composition comprises a pharmaceutically effective amount of a hygroscopic salt of valproic acid, a carrier, a non-hygroscopic additive, and at least one excipient.

[0051] According to further features in preferred embodiments of the invention described below, the medical condition is selected from the group consisting of epilepsy, a psychotic disorder and a migraine headache.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0052] The present invention provides a process for preparing a non-hygroscopic, highly stable, oral pharmaceutical composition of a salt of valproic acid. The product is preferably in a tablet form and production is simplified by the procedure of the present invention.

[0053] For purposes of this specification and the accompanying claims, the term "tablet" refers equally to a tablet, a caplet or any other solid dosage form which is suitable for oral administration.

[0054] The structure features a compressed admixture containing a hygroscopic salt of valproic acid, carbomer, a non-hygroscopic additive, preferably dibasic calcium phosphate and optionally at least one additional excipient. The additional excipients include pharmaceutical lubricants, disintegrators, glidents, adsorbents, or mixtures thereof.

[0055] Preferably, the process for preparing a non-hygroscopic highly stable oral pharmaceutical composition of a salt of valproic acid includes the single step of blending ingredients including a hygroscopic salt of valproic acid, carbomer, and a non-hygroscopic additive.

[0056] The hygroscopic salt of valproic acid may be for example sodium valproate.

[0057] Preferably, the process further includes the step of adding at list one excipient.

[0058] Preferably, the process further includes the step of compressing the ingredients into a solid dosage form after the step of blending.

[0059] Preferably, a single dose of the solid dosage form contains from about 50 to about 1200 mg of sodium valproate and more preferably, from about 100 to about 650 mg of sodium valproate.

[0060] Preferably, sodium valproate is present in an amount of from about 5% to about 99% of the weight of the final composition, more preferably from about 10% to about 90%, and most preferably from about 40% to about 65% of the weight of the final composition.

[0061] Although sodium valproate is used in the present invention as the active agent, any other hygroscopic salt or derivative of valproic acid, or mixtures of valproic acid salts and derivatives can be used.

[0062] In contrast to expectations, it was found that carbomer in combination with a non-hygroscopic additive prevent the liquefaction of sodium valproate as a result of moisture uptake and indeed prevents the finished composition from absorbing significant amounts of water. Carbomer serves as the dissolution retarding agent of the composition which enable the formation of a non-hygroscopic, highly stable composition of sodium valproate. Carbomer can be mixed with sodium valproate in regulated amounts to attain the desired drug release characteristics.

[0063] Preferably any acceptable pharmaceutical grade of carbomer may be used. Preferred pharmaceutical grades of carbomer are carbomer 971P or carbomer EX-507. Carbomer is obtained from B.F. Goodrich Inc., but any other pharmaceutically acceptable grade of carbomer from other sources can be used.

[0064] Preferably, a single dose of the solid dosage form contains from about 0.2 mg to about 500 mg of carbomer and more preferably from about 0.2 mg to about 250 mg of carbomer.

[0065] Preferably, carbomer is present in an amount of from about 0.2% to about 30% of the weight of the final composition and more preferably from about 0.2% to about 20% of the weight of the final composition.

[0066] Preferably, carbomer is present in an amount such that the weight ratio of carbomer to sodium valproate is in the range of from about 0.3:99.7 to about 35:65 and more preferably from about 0.3:99.7 to about 25:75.

[0067] In general, the weight ratio of carbomer to sodium valproate is varied depending on the size and shape of the tablet or the drug amount. Typically, when the shape of the tablet is flatter, i.e. when the ratio of tablet diameter to width is higher drug release is faster.

[0068] The non-hygroscopic additive is preferably any material which assists in preventing the moisture absorption of sodium valproate and retains the non-hygroscopic properties of the composition. Preferably the non-hygroscopic additive includes, but is not limited to dibasic calcium phosphate anhydrous, calcium silicate, microcrystalline cellulose or mixtures thereof and more preferably dibasic calcium phosphate anhydrous.

[0069] Preferably, dibasic calcium phosphate anhydrous is present in an amount of from about 10% to about 40% of the weight of the final composition and more preferably from about 15% to about 35% of the weight of the final composition.

[0070] Dibasic calcium phosphate anhydrous is used in the present invention to enhance the non-hygroscopic properties of the composition. Dibasic calcium phosphate anhydrous is a non hygroscopic ingredient which does not pick up significant moisture over a wide range of relative humidities. Dibasic calcium phosphate anhydrous serves also as a direct compression agent in the present invention.

[0071] The combination of sodium valproate, carbomer and dibasic calcium phosphate anhydrous is particularly advantageous since such a combination prevents the liquefaction of sodium valproate and forms a non-hygroscopic mixture which is highly compressible and have optimal flow properties, thereby providing the tablets excellent physical properties.

[0072] Preferably, dibasic calcium phosphate anhydrous is present in an amount such that the weight ratio of dibasic calcium phosphate anhydrous to carbomer is in the range of from about 99.95:0.05 to about 40:60 and more preferably from about 99.5:0.5 to about 60:40.

[0073] For purposes of this specification and the accompanying claims, the phrase "closed conditions" indicates that the experiment was done in a closed bottle.

[0074] Preferably, the pharmaceutical composition is stable under relative humidity of from about 30% to about 75% at 40° C. in closed conditions and more preferably from about 30% to about 60% at 25° C. in closed conditions, when the carbomer is present in an amount such that the weight ratio of carbomer to sodium valproate is in the range of from about 0.3:99.7 to about 25:75 and the weight ratio of carbomer to dibasic calcium phosphate is in the range of from about 0.5:99.5 to about 40:60.

[0075] The additional excipients may be for example lubricants, disintegrators, glidents, adsorbents, or mixtures thereof.

[0076] The excipients give the desired flow of the granules, prevent the adhesion of material to the punches and dies, modify the dissolution profile, improve the non-hygroscopic properties of the tablets and provide the desired compressibility properties of the composition.

[0077] The lubricant includes, but is not limited to stearic acid, a salt of stearic acid, talc, sodium lauryl sulfate, sodium stearyl fumarate or mixtures thereof.

[0078] Preferably, the lubricant is present in an amount of from about 0.25% to about 5% of the weight of the final composition and more preferably from about 0.5 to about 1.5% of the weight of the final composition.

[0079] Preferably the disintegrator includes, but is not limited to crosscarmelose sodium, sodium starch glycolate, starch, magnesium aluminum silicate, colloidal silicon dioxide, carboxymethyl cellulose, microcrystalline cellulose, or mixtures thereof and more preferably sodium starch glycolate.

[0080] Preferably, the disintegrator is present in an amount of from about 0.5% to about 25% of the weight of the final composition and more preferably from about 1% to about 15% of the weight of the final composition.

[0081] The glidents may be for example colloidal silicon dioxide, talc or mixtures thereof.

[0082] Preferably, the glident is present in an amount of from about 0.1% to about 10% of the weight of the final composition and more preferably from about 0.1% to about 5% of the weight of the final composition.

[0083] The adsorbent may be, for example colloidal silicon dioxide, microcrystalline cellulose, calcium silicate or mixtures thereof.

[0084] Preferably, the adsorbent is present in an amount of from about 0.05% to about 42% of the weight of the final composition and more preferably from about 0.05% to about 37% of the weight of the final composition.

[0085] If desired, other ingredients, such as diluents, stabilizers and antiadherants, conventionally used for pharmaceutical formulations may be included in the present formulations.

[0086] Optional ingredients include coloring and flavoring agents which are well known in the art.

[0087] The present invention further provides a non-hygroscopic highly stable orally deliverable pharmaceutical composition for release of a salt of valproic acid into the bloodstream at a physiologically effective level, the composition including a pharmaceutically effective amount of a

hygroscopic salt of valproic acid, a carrier, a non-hygroscopic additive, and at least one excipient.

[0088] The hygroscopic salt of valproic acid may be for example sodium valproate.

[0089] The carrier may be, for example polymeric, preferably carbomer, or non-polymeric for example a sugar, a protein, a biologically inert material, elemental carbon or mixtures thereof.

[0090] Preferably carbomer is present in an amount of from about 0.2% to about 30% of the weight of the final composition and more preferably from about 0.2% to about 20% of the weight of the final composition.

[0091] The non-hygroscopic additive may be, for example, dibasic calcium phosphate anhydrous, calcium silicate, microcrystalline cellulose or mixtures thereof and more preferably dibasic calcium phosphate anhydrous.

[0092] Preferably the pharmaceutically effective amount is less than 10% by weight of the total formulation or more than 80% by weight of the total formulation.

[0093] The present invention further provides a method of treating a medical condition in a human patient, the method including the step of orally administering a non-hygroscopic highly stable pharmaceutical composition for release of a salt of valproic acid into the bloodstream at a physiologically effective level, wherein the composition includes a pharmaceutically effective amount of a hygroscopic salt of valproic acid, a carrier, a non-hygroscopic additive, and at least one excipient.

[0094] The medical condition may be, for example, epilepsy, a psychotic disorder or a migraine headache.

[0095] The pharmaceutical composition described in the present invention is formulated to release sodium valproate in a controlled release or an immediate release manner. The in-vitro and in-vivo drug release profile depends mainly on carbomer and dibasic calcium phosphate concentrations.

[0096] Controlled release compositions are formulated such that in vitro preferably from about 5% to about 40% of the drug is released after 2 h, preferably from about 10% to about 50% is released after 6 h, approximately from about 30% to about 90% is released after 8 h and approximately from about 50% to about 100% is released within 12 to 24 h.

[0097] Immediate release compositions are formulated such that in vitro approximately between about 30% to about 60% of the drug is released after 2 h, approximately from about 40% to about 90% is released after 6 h, approximately from about 70% to about 95% is released after 8 h and approximately at least 95% is released within 12 h.

[0098] Enteric coated compositions may exhibit an initial time delay before drug release.

[0099] The pharmaceutical composition may be, for example, in the form of a tablet, a caplet, a pellet, a capsule, a granule, a tablet which disintegrates into granules, a pill, a powder or a sachet. Preferably the pharmaceutical composition is in the form of a tablet or a caplet, more preferably the caplet is oval shaped. The capsule may contain a powder, a compressed powder or a granule.

[0100] The pharmaceutical compositions of the present invention are administered orally.

[0101] The pharmaceutical composition may further be coated with a moisture barrier film, an enteric-coating film or a combination thereof to improve the non-hygroscopic properties of the composition.

[0102] Preferably, the process for preparing non-hygroscopic, highly moisture stable composition of sodium valproate is carried out at relative humidity of from about 30% to about 75% and more preferably from about 30% to about 50%.

[0103] The amount of sodium valproate in the formulation varies depending on the desired dose for efficient drug delivery. The actual amount of the used drug is dependent on the patient's age, weight, sex, disease and on any other medical criteria, and is determined according to intended medical use by techniques known in the art. The pharmaceutical dosage forms of the invention may be administered once or more times per day, as determined by the attending physician.

[0104] Typically, to treat seizure disorders, sodium valproate is formulated in a tablet or other dosage form in amounts of 10-40 mg/kg body weight per day, preferably 15-30 mg/kg body weight per day. For adults, the daily dose is typically 20 mg/kg body weight per day. For children and infants, the daily dose is typically 25 mg/kg body weight per day.

[0105] When a controlled release dosage form is to be administered, the daily dosage of sodium valproate is formulated in a controlled release composition to be released slowly to maintain therapeutic levels of sodium valproate in patients blood between about 50 to about 100 μg/ml. Above this concentration, patients may experience adverse effects.

[0106] The daily dose can be formulated in a single tablet, or more than one tablet, depending on the daily dose of sodium valproate, the final weight of the composition and the number of times the formulation is to be administered.

[0107] It is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description. The invention includes other embodiments and can be practiced or implemented in various ways. Also it is to be understood that the phraseology and terminology employed herein is for the purpose of description only and should not be regarded as limiting.

Definitions

[0108] For purposes of this specification and the accompanying claims, the term "Cab-O-Sil" refers to colloidal silicon dioxide or aerosil.

[0109] For purposes of this specification and the accompanying claims, the term "A-tab" refers to dibasic calcium phosphate anhydrous or dibasic calcium phosphate.

[0110] For purposes of this specification and the accompanying claims, the term "Explotab" refers to sodium starch glycolate.

[0111] For purposes of this specification and the accompanying claims, the term "Avicel" refers to microcrystalline cellulose

[0112] For purposes of this specification and the accompanying claims, the term "Ac-Di-Sol" refers to crosscarmelose sodium.

EXAMPLES

[0113] Reference is now made to the following examples, which together with the above descriptions, illustrate the invention in a non limiting fashion.

[0114] Generally, the nomenclature used herein and the laboratory procedures in the pharmaceutical technology described below are those well known and commonly employed in the art. Standard techniques are used for tablet preparation and drug release measurement. Generally tablet preparation is performed using the direct compression method. Measurement of drug release from the tablet is performed using the USP basket method I. These techniques and various other techniques are generally performed according to The United States Pharmacopoeia XXI, pp. 1243-1244, 1985; A. Osol (Ed.) Remington's Pharmaceutical Sciences, 16th Edition, Tablets Capsules and Pills, pp. 1553-1584, 1980.

[0115] Various formulations of sodium valproate according to the present invention were prepared as specified in the Examples given below.

[0116] Reference is now made to a general manufacturing process for sodium valproate tablets. This process is employed in examples disclosed hereinbelow. The process for preparing non-hygroscopic, sodium valproate tablets involves blending a formulation of dry ingredients including sodium valproate, carbomer and dibasic calcium phosphate anhydrous. The formulation may further include one or more excipients such as disintegrators, lubricants, glidents, adsorbents, or combinations thereof Compression of the blended ingredients forms tablets.

[0117] The following example serves to illustrate the preparation method of the tablets

Example 1

Preparation of Sodium Valproate Tablets Using the Direct Compression Procedure

[0118] (a) Sodium valproate, colloidal silicon dioxide, talc, dicalcium phosphate anhydrous and Carbomer 971P are admixed and blended in V-blender for 5 minutes.

[0119] (b) The blend from step (a) is comminuted through a 0.250" screen

[0120] (c) The mixture from step (b) is passed through 20 mesh vibrating sieve

[0121] (d) The sifted material from step (c) is blended in a V-blender for an additional 15 minutes.

[0122] (e) Magnesium stearate is passed through a 50-mesh sieve

[0123] (f) The sieved magnesium stearate from step (e) is added to the resulting granulate from step (d) and blended for 5 minutes.

[0124] (g) The blend from step (f) is compressed into caplets.

[0125] The present invention may be better understood with reference to the Examples and the accompanying description. The formulation of each tablet is given below in Example 2.

Example 2

[0126] Sodium valproate (576 mg) tablets were prepared using various combinations of additional materials as described hereinabove and detailed in Tables I, II , Il, IV and V. The values in parenthesis present the percentage of the ingredient from the total weight of the tablet (% w/w).

TABLE I

Ingredient	RD-0276 mg/tablet (%, w/w)	RD-0293 mg/tablet (%, w/w)	RD-0294 mg/tablet (%, w/w)	RD-0296 mg/tablet (%, w/w)	RD-0297 mg/tablet (%, w/w)	RD-0314 mg/tablet (%, w/w)
Sodium Valproate	576 (56.14%)	576 (56.14%)	576 (56.14%)	576 (56.14%)	576 (65.56%)	576 (56.14%)
Cab-O-Sil	20 (1.95%)	15 (1.46%)	15 (1.46%)	20 (1.95%)	15 (1.71%)	20 (1.95%)
A-tab	266 (25.93%)	324.5 (31.63%)	343 (33.43%)	297 (28.95%)	193 (21.96%)	358 (34.89%)
Carbomer 971P	154 (15.01%)	100.5 (9.80%)	82 (8.00%)	123 (11.99%)	86 (9.79%)	62 (6.04%)
Mg Stearate	10 (0.97%)	10 (0.97%)	10 (0.97%)	10 (0.97%)	8.6 (0.98%)	10 (0.98%)

[0127]

TABLE II

Ingredient	RD-0315 mg/tablet (%, w/w)	RD-316 mg/tablet (%, w/w)	RD-0331 mg/tablet (%, w/w)	RD-0332 mg/tablet (%, w/w)	RD-0334 mg/tablet (%, w/w)	RD-0335 mg/tablet (%, w/w)
Sodium Valproate	576 (64.00%)	576 (62.61%)	576 (55.85%)	576 (56.14%)	576 (55.82%)	576 (58.78%)
Cab-O-Sil	20 (2.22%)	39.6 (4.30%)	20 (1.94%)	20 (1.95%)	10 (0.97%)	10 (1.02%)
A-Tab	241 (26.78%)	240 (26.09%)	358 (34.71%)	337.9 (32.93%)	338 (32.75%)	292.9 (29.89%)
Carbomer 971P	54 (6.00%)	55.2 (6.00%)	62 (6.01%)	82.1 (8.00)	82.4 (7.99%)	78.4 (8.00%)
Talc	—	—	—	—	10 (0.97%)	8 (0.81%)
Mg Stearate	9 (1.00%)	9.2 (1.00%)	15.4 (1.49%)	10 (0.98%)	15.5 (1.50%)	14.7 (1.50%)

[0128]

TABLE III

Ingredient	RD-0336 mg/tablet (%, w/w)	RD-0340 mg/tablet (%, w/w)	RD-0341 mg/tablet (%, w/w)	RD-0342 mg/tablet (%, w/w)	RD-0343 mg/tablet (%, w/w)
Sodium Valproate	576 (58.78%)	576 (58.78%)	576 (58.78%)	576 (58.78%)	576 (58.78%)
Carbomer 971P	78.4 (8.00%)	68.6 (7.00%)	58.8 (6.00%)	93.1 (9.50%)	58.8 (6.00%)
Cab-O-Sil	10 (1.02%)	10 (1.02%)	10 (1.02%)	10 (1.02%)	10 (1.02%)
Talc	8 (0.81%)	8 (0.81%)	8 (0.81%)	8 (0.81%)	8 (0.81%)
A-Tab	292.9 (29.89%)	302.7 (30.89%)	312.5 (31.89%)	278.2 (28.39%)	273.3 (27.89%)
Explotab	—	—	—	—	39.2 (4.00%)
Mg Stearate	14.7 (1.50%)	14.7 (1.50%)	14.7 (1.50%)	14.7 (1.50%)	14.7 (1.50%)

[0129]

TABLE IV

Ingredient	RD-0419 mg/tablet (%, w/w)	RD-376 mg/tablet (%, w/w)	RD-0393 mg/tablet (%, w/w)
Sodium Valproate	576 (57.27%)	576 (52.36%)	576 (56.47%)
Carbomer 971P	2 (0.20%)	20 (1.82%)	5 (0.49%)
Avicel PH112	187 (18.59%)	—	—
A-Tab	—	169 (15.36%)	164 (16.08%)
Calcium Silicate	80 (7.95%)	200 (18.18%)	160 (15.69%)
Ac-Di-Sol	140 (13.92%)	110 (10.00%)	—
Starch 1500	—	—	100 (9.80%)
Talc	—	10 (0.91%)	—
Mg. Stearate	20.8 (2.07%)	15 (1.37%)	15 (1.47%)

[0130]

TABLE V

Ingredient	B.N. 780277 mg/tablet (%, w/w)	B.N. 780278 mg/tablet (%, w/w)	B.N. 780279 mg/tablet (%, w/w)	B.N. 780280 mg/tablet (%, w/w)
Sodium Valproate	576 (58.78%)	576 (58.78%)	576 (58.78%)	576 (58.78%)
Carbomer 971 P	58.8 (6.00%)	93.1 (9.50%)	78.4 (8.00%)	68.6 (7.00%)
Cab-O-Sil	10 (1.02%)	10 (1.02%)	10 (1.02%)	10 (1.02%)
Talc	8 (0.81%)	8 (0.81%)	8 (0.81%)	8 (0.81%)
A-tab	312.5 (31.89%)	278.2 (28.39%)	292.9 (29.89%)	302.7 (30.89%)
Mg Stearate	14.7 (1.50%)	14.7 (1.50%)	14.7 (1.50%)	14.7 (1.50%)
% Relative Humidity				
Blending Stage	40–43%	29–42%	26–42%	41–44%
Packaging Stage	44–48%	46–48%	—	46–48%

[0131] All the formulations presented in Tables I-V may optionally be coated with an anti-moisture barrier, for example aqueous Opadry AMB (Colorcon, England).

[0132] All the formulations presented in Tables I-V were highly stable (non-hygroscopic) during all stages of tablet preparation. The blend did not uptake moisture under relative humidity of 30-50%. The final tablets had very good physical properties and exhibited excellent hardness and friability as presented in table VI.

TABLE VI

Finished product physical properties.

Friability	Hardness (Kp)	% Carbomer	Batch No.
0.08%	19.09	7%	780280
0.043%	20.8	8%	780279
0.027%	20.57	9.5%	780278
0.05%	19.12	6%	780277

[0133] The formulations presented in tables I-V demonstrate that the combination of sodium valproate, carbopol and dibasic calcium phosphate anhydrous prevents the liquefaction of sodium valproate and forms non-hygroscopic highly stable dosage form. The most preferred formulations providing such effect are those wherein the weight ratio of carbomer to sodium valproate is in the range from about 0.3:99.7 to about 25:75 and the weight ratio of dibasic calcium phosphate anhydrous (A-tab) to carbomer is in the range from about 95.95:0.05 to about 60:40.

TABLE VII

Stability test results of loss on drying for 100. Tablets/Pack and bulk containers(*)

B.N.	0 M	1 M Acc[a]	2 M Acc	3 M Acc	3 M RT	1 M RT Bulk[b]	3 M RT Bulk
780277	0.3%	0.2%	0.23%	0.2%	0.3%	0.2%	0.2%
780280	0.3%	0.2%	0.18%	0.2%	0.2%	0.2%	0.2%
780279	0.2%	0.1%	0.15%	0.2%	0.2%	0.2%	0.6%
780278	0.3%	0.1%	0.16%	0.2%	0.2%	02%	0.6%

[a]Accelerated stability
[b]Bulk containers

[0134] The results of the three months room temperature (RT) and accelerated stability (40° C., 75% RH) of the above four batches, packaged in HDPE (high density polyethylene) bottles containing 100 tablets each and a desiccant, and the room temperature stability (25° C., 60%RH) of the bulk containers (double polyethylene bags with desiccant) are summarized in table VII.

[0135] The results presented in table VII show that the finished product (tablets) is stable. It can be seen that the final product had excellent physical properties as indicated by the loss on drying test which was unchanged during the stability period. This is indicative of the non-hygroscopic properties of the formulations.

[0136] (*) Specifications:

[0137] Loss on drying: Not more than 2.0%

[0138] Package Type for 100 tablets: 200 mLHDPE white bottle, Polypropylene safety cap, Heat Seal Aluminum liner.

[0139] Desiccant type: 3 Sorb-It-Can Desiccants containing 1 g each.

[0140] Package type for 1 Kg of tablets per pack bulk: double polyethylene bag with desiccant in between two layers placed in a plastic container.

Example 3

[0141] Sodium Valproate Release Kinetics of Example 2 Formulations as Assayed by the Dissolution Studies

[0142] The dissolution kinetics of tablets prepared as described in examples 1 and 2 were monitored using a commercially available tablet dissolution tester (Vankel VK7000 with sampler VK8000). The USP basket method I [The United States Pharmacopoeia XXI, pp. 1243-1244, 1985] was used. Rotation speed was 100 rpm. The dissolution profile was examined in 900 ml buffer pH 2.0 for 3 hours after which the medium was exchanged to 900 ml phosphate buffer pH 6.8 for an additional 5 hours. The dissolution medium was maintained at 37±0.5° C. The dissolution studies were performed using 12 tablets for each composition tested. Results are summarized in tables VIII and IX.

[0143] At specified time intervals samples were taken from the dissolution medium and sodium valproate levels were monitored using HPLC. The following conditions were used for HPLC analysis of sodium valproate:

Instrument:	Suitable chromatograph with a variable wavelength UV detector (HP1100 or Waters Alliance)
Column	
Manufacturer's name:	Hypersil Elite
Type:	C18
Dimensions:	150 x 2.1 mm
Particle size:	5 μm
Detection:	UV at 220 nm
Flow rate:	0.3 mL/min
Injection volume:	20 μL
Run time:	6 minutes
Mobile Phase:	45:55 Buffer pH 3/Acetonitrile

[0144]

TABLE VIII

Sodium valproate release kinetics

Amount Released (%)

Time (hrs)	RD0336 (8% Carbomer)	RD0341 (6% Carbomer)	RD0340 (7% Carbomer)	RD0342 (9.5% Carbomer)
0	0	0	0	0
1	23	31	27	20
2	33	43	37	28
3	40	50	45	34
4	48	63	55	42
5	55	71	63	48
6	60	77	69	54
7	65	81	74	59
8	70	85	78	64

[0145]

TABLE IX

Sodium valproate release kinetics

Amount Released (%)

Time (hrs)	780280 (7% Carbomer)	780279 (8% Carbomer)	780278 (9.5% Carbomer)	780277 (6% Carbomer)
0	0	0	0	0
1	27	24	20	31
2	37	34	29	42
3	44	42	37	49
4	56	51	43	62
5	64	59	50	71
6	71	65	56	77
7	75	69	61	82
8	80	73	65	86

[0146] The results summarized in Tables VIII and IX indicate that carbomer is able to retard sodium valproate release from the tablets and to provide controlled release properties.

[0147] Therefore, Sodium valproate release kinetics from the tablets can be controlled by changing the carbomer concentration in the tablet composition. Specifically, increasing carbomer concentration in the tablets decreases sodium valproate release rate.

[0148] Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

[0149] All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

What is claimed is:

1. A process for preparing a non-hygroscopic highly stable oral pharmaceutical composition of a salt of valproic acid, said process comprising the single step of blending ingredients including a hygroscopic salt of valproic acid, carbomer, and a non-hygroscopic additive.

2. The process of claim 1, wherein said hygroscopic salt of valproic acid is sodium valproate.

3. The process of claim 1, further comprising the step of adding at list one excipient.

4. The process of claim 1, further comprising the step of compressing said ingredients into a solid dosage form after said step of blending.

5. The process of claim 4, wherein a single dose of said solid dosage form contains from about 50 to about 1200 mg of sodium valproate.

6. The process of claim 2, wherein said sodium valproate is present in an amount of from about 5% to about 99% of the weight of the final composition.

7. The process of claim 4, wherein a single dose of said solid dosage form contains from about 0.2 mg to about 500 mg of carbomer.

8. The process of claim 1, wherein said carbomer is present in an amount of from about 0.2% to about 30% of the weight of the final composition.

9. The process of claim 1, wherein said carbomer is present in an amount such that the weight ratio of carbomer to sodium valproate is in the range of from about 0.3:99.7 to about 35:65.

10. The process of claim 1, wherein said non-hygroscopic additive is selected from the group consisting of dibasic calcium phosphate anhydrous, calcium silicate, microcrystalline cellulose and mixtures thereof.

11. The process of claim 10, wherein said dibasic calcium phosphate anhydrous is present in an amount of from about 10% to about 40% of the weight of the final composition.

12. The process of claim 10, wherein said dibasic calcium phosphate anhydrous is present in an amount such that the weight ratio of dibasic calcium phosphate anhydrous to carbomer is in the range of from about 99.95:0.05 to about 40:60.

13. The process of claim 3, wherein said excipient is selected from the group consisting of lubricants, disintegrators, glidents, adsorbents, and mixtures thereof.

14. The process of claim 13, wherein said lubricant is selected from the group consisting of stearic acid, a salt of stearic acid, talc, sodium lauryl sulfate, sodium stearyl fumarate and mixtures thereof.

15. The process of claim 13, wherein said lubricant is present in an amount of from about 0.25% to about 5% of the weight of the final composition.

16. The process of claim 13, wherein said disintegrator is selected from the group consisting of crosscarmelose sodium, sodium starch glycolate, starch, magnesium aluminum silicate, colloidal silicon dioxide, carboxymethyl cellulose, microcrystalline cellulose, and mixtures thereof.

17. The process of claim 13, wherein said disintegrator is present in an amount of from about 0.5% to about 25% of the weight of the final composition.

18. The process of claim 13, wherein said glident is selected from the group consisting of colloidal silicon dioxide, talc and mixtures thereof.

19. The process of claim 13, wherein said glident is present in an amount of from about 0.1% to about 10% of the weight of the final composition.

20. The process of claim 13, wherein said adsorbent is selected from the group consisting of colloidal silicon dioxide, microcrystalline cellulose, calcium silicate and mixtures thereof.

21. The process of claim 13, wherein said adsorbent is present in an amount of from about 0.05% to about 42% of the weight of the final composition.

22. The process of claim 4, wherein said solid dosage form is selected from the group consisting of a tablet, a caplet, a pellet, a capsule, a tablet which disintegrates into granules, and a pill.

23. The process of claim 1, wherein said pharmaceutical composition exists in a form selected from the group consisting of a capsule, a sachet, a powder and a granule.

24. The process of claim 1, comprising the additional step of maintaining relative humidity in the range of about 30% to about 75% during said step of blending of said ingredients.

25. A non-hygroscopic highly stable orally deliverable pharmaceutical composition for release of a salt of valproic acid into the bloodstream at a physiologically effective level, said composition comprising a pharmaceutically effective amount of a hygroscopic salt of valproic acid, a carrier, a non-hygroscopic additive, and at least one excipient.

26. The pharmaceutical composition of claim 25, wherein said hygroscopic salt of valproic acid is sodium valproate.

27. The pharmaceutical composition of claim 25, wherein said carrier is selected from the group consisting of a polymeric carrier, a non-polymeric carrier and mixtures thereof.

28. The pharmaceutical composition of claim 27, wherein said polymeric carrier is carbomer.

29. The pharmaceutical composition of claim 28, wherein said carbomer is present in an amount of from about 0.2% to about 30% of the weight of the final composition.

30. The pharmaceutical composition of claim 27, wherein said non-polymeric carrier is selected from the group consisting of a sugar, a protein, a biologically inert material, elemental carbon and mixtures thereof.

31. The pharmaceutical composition of claim 25, wherein said pharmaceutically effective amount is selected from the group consisting of:

(a) less than 10% by weight of the total formulation; and

(b) more than 80% by weight of the total formulation.

32. A method of treating a medical condition in a human patient, the method comprising the step of orally administering a non-hygroscopic highly stable pharmaceutical composition for release of a salt of valproic acid into the bloodstream at a physiologically effective level;

wherein said composition comprises a pharmaceutically effective amount of a hygroscopic salt of valproic acid, a carrier, a non-hygroscopic additive, and at least one excipient.

33. The method of claim 32, wherein said medical condition is selected from the group consisting of epilepsy, a psychotic disorder and a migraine headache.

* * * * *