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(54) Title: CONTROLLED RELEASE COMPOSITIONS OF DIVALPROEX SODIUM

(57) Abstract: The present invention pertains to a hydrophilic matrix tablet suitable for the once-a-day administration of valproate compounds such as divalproex sodium. The tablet comprises from about 10 weight percent to about 90 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide; from about 6 weight percent to about 18 weight percent of a pharmaceutically acceptable hydrophilic polymer, from about 0.2 weight percent to about 9.5 weight percent of a lubricant, and from about 3 weight percent to about 15 weight percent of a filler; all weight percentages based upon the total weight of the tablet dosage form. Other aspects of the invention relate to the use of this formulation in the treatment of epilepsy and to methods for manufacturing this dosage form.

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CONTROLLED RELEASE COMPOSITIONS OF DIVALPROEX SODIUM.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

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

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

US Patent No. 6,511,678 to Abbott Laboratories claims a controlled release tablet formulation releasing not more than about 30% valproate after 3 hours, 40 to about 70% after 9 hours, 55 to about 95% after 12 hours and not less than 85% after 18 hours, when measured in a type 2 dissolution apparatus, at 100 rpm, at a temperature of $37\pm0.5^{\circ}$ C., in 500 ml of 0.1N HCl for 45 minutes, followed by 900 ml of 0.05M phosphate buffer containing 75 mM sodium lauryl sulfate, pH 5.5, for the remainder of the testing period.

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

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

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

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to a controlled release tablet composition for once daily administration of a valproate salt. The composition comprises of divalproex sodium (10 – 90% w/w) as the active valproate salt, and a hydrophilic matrix-forming polymer system (less than 20% w/w) comprising preferably one or more cellulose polymers or alginate polymers. In addition it comprises, either a gum preferably xanthan gum, a lubricant like glyceryl behenate (Compritol 888 ATO^{R}) or a water insoluble diluent like heavy calcium carbonate (2 – 20% w/w) or a combination of these. The said composition delivers the dose of divalproex sodium in a controlled manner such that when evaluated for "*in-vitro*" dissolution with an identical strength of a reference tablet formulation Depakote ER tablets, the test product shows a comparable dissolution profile.

Controlled release tablets of divalproex sodium for once daily administration requires significant control of drug release so that the therapeutic benefit is extended satisfactorily throughout the period of 24 hours. Typical controlled formulations of Divalproex exhibit the variation between peak and trough plasma levels of valproate over a 24-hour dosing

period. The US 6,528,090 patent uses a hydrophilic polymer matrix of a cellulose derivative namely hydroxy propyl methyl cellulose at a concentration of more than 20% w/w of the tablet, more preferably around 30% w/w. As a formulator, it is desirable that other excipients for controlling release of the active ingredient be used at a minimum so that the patient is exposed to ingredients other than the active at a minimum concentration. In addition use of high polymer concentrations like HPMC have significant limitations including deficient flow properties making direct tabletting difficult and the dependence of the release of medicinal substance on the salt content and pH of the release medium. This is discussed in more detail in US Patent 6,579,953 awarded to BASF. In contrast, the present inventors have unexpectedly found that by employing a hydrophilic polymer at a concentration of less than 20%w/w, preferably less than 16%w/w in combination with either a gum or a lubricant or a water insoluble diluent, or a combination of these, they could obtain a similar and comparable control in drug release, to that achieved by the reference product, which uses 30%w/w of polymer. Comparative dissolution profiles showed a good level of similarity in drug release between identical strengths of the products under said invention and Depakote ER tablets that is the reference product.

The granules may be prepared either by dry or wet granulation process using a uniform admixture of the drug with hydrophilic polymers, a gum, a lubricant and a water insoluble diluent or a combination of these. The resulting granules are blended with required quantity of one or more other lubricants and compressed into tablets. The inventive composition of the present invention is capable of being compressed into tablets at normal environmental conditions. There is no requirement for controlled atmospheric conditions as discussed in PCT Application No. WO 03/103635, which requires presence of controlled atmospheric conditions of 27 to 35 ^{0}C and a relative humidity of less than 40%, preferably less than 20%. In accordance with the present invention, a new oral polymeric controlled release formulation suitable for once-a-day administration of valproate compounds, such as divalproex sodium, has been achieved. This formulation exhibits significant advantages over the sustained release valproate formulations of the prior art. This formulation minimizes the variation between peak and trough plasma levels of valproate over a 24-hour dosing period. This formulation follows a zero-order release pattern thus producing essentially flat plasma levels of valproate,

once steady-state levels have been achieved. This results in a significantly lower incidence of side effects for patients consuming such a formulation.

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

Water-insoluble polymers were selected from methacrylates, acrylic acid copolymers, acrylamides, polyethylenes, polyvinyl alcohol and celluloses like cellulose mono-, di- and tri-acylate, cellulose mono-, di-, and tri-acetate, ethyl cellulose, or cellulose acrylate.

The composition under discussion also includes pharmaceutically acceptable inert excipients, like, fillers, binders, lubricants, glidants, and colorants, among others.

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

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

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

Glidants were selected from calcium silicate, magnesium silicate, silicon dioxide and talc.

The examples below provide a summary of the experimental work that forms the basis of the pharmaceutical composition of the present invention.

Controlled release tablets were prepared using the following materials in the stated quantities and are given in examples 1 to 8:

Example 1

S.No	Ingredients	Qty(mg)/Tab	% on tab wt
1	Divalproex sodium	539.77	53.97
2	Methocel K 100 M	140	14
3	Avicel PH102	122.86	21.89
4	Compritol	56	5.6
5	Xanthan Gum	5	0.5
6	Avicel PH102	95	9.5
7	Syloid 244 FP	24	2.4
8	Talc	18	1.8
9	Purified water	q.s	q.s
	Total	1000	100%
Coating	Opadry II (grey) 85G57680	24 mg	2.5 - 3.0%

Manufacturing procedure: Sift divalproex sodium, Methocel K 100 M, Avicel pH 102 and Compritol through 40 mesh sieve. Mix them in a mixer for 5 minutes. Prepare binding agent by dissolving Xanthan gum in required quantity of water and granulate the above contents using granulator. Dry the wet granules in a drier and pass the granules

through 20# of sifter by milling and sifting. Sift ingredients Avicel pH 102, Syloid and talc through 40 mesh sieve of sifter and mix with the dried granules in a blender. Compress the blend into tablets. Coat with Opadry II in aqueous suspension to a weight gain of 2.5 to 3.0%. Dissolution was performed in 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm and the dissolution profile is given in Figure 1.

Example 2

S.No	Ingredients	Qty(mg)/Tab	% on tab wt
1	Divalproex sodium	539.77	54.09
2	Avicel PH102	156	15.63
3	Xanthan Gum	130	14.59
4	Lactose monohydrate	50	5
5	Xanthan Gum	4	0.4
6	Avicel PH102	70	7
7	Compritol 888 ATO	6	0.6
8	Syloid 244 FP	24	2.4
9	Talc	18	1.8
10	Purified water	q.s	q.s
	Total	997.77 mg	100%
Coating	Opadry II (grey) 85G57680	24 mg	2.5 - 3.0%

Manufacturing procedure:

Sift divalproex sodium, Avicel pH 102, Xanthan gum and lactose monohydrate through 40 mesh sieve. Mix them in a mixer for 5 minutes. Prepare binding agent by dissolving Xanthan gum in required quantity of water and granulate the above contents using granulator. Dry the wet granules in a drier and pass the granules through 20 mesh of sifter by milling and sifting. Sift ingredients Avicel pH 102, Compritol, Syloid and talc through 40 mesh of sifter and mix with the dried granules in a blender. Compress the blend into tablets. Coat with Opadry II in aqueous suspension to a weight gain of 2.5 to 3.0%. Dissolution was performed in 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm and the dissolution profile is given in Figure 2.

Example 3

S.No	Ingredients	Qty(mg)/Tab	% on tab wt
1	Divalproex sodium	539.77	54.31
2	Avicel PH102	141	14.18
3	Xanthan Gum	130	13
4	Lactose monohydrate	80	8
5	Avicel PH102	55	5.5
6	Compritol 888 ATO	6	0.6
7	Syloid 244 FP	24	2.4
8	Talc	18	1.8
9	Purified water	q.s	q.s
Coating	Opadry II (grey) 85G57680	24 mg	2.5 - 3.0%

Manufacturing procedure:

Sift divalproex sodium, Avicel pH 102, Xanthan gum and lactose monohydrate through 40 mesh sieve. Mix them in a mixer for 5 minutes. Granulate the above mixed materials with purified water. Dry the wet granules in a drier and pass the granules through 20# of sifter by milling and sifting. Sift ingredients Avicel pH 102, Compritol, Syloid and talc through 40 mesh of sifter and mix with the dried granules in a blender. Compress the blend into tablets. Coat with Opadry II in aqueous suspension to a weight gain of 2.5 to 3.0%. Dissolution was performed in 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm and the dissolution profile is given in Figure 3.

Example 4

S.No	Ingredients	Qty(mg)/Tab	% on tab wt
1	Divalproex sodium	539.77	53.92
2	Avicel PH102	102	10.18
3	Sodium Alginate (Keltone HVCR)	145	14.48
4	Calcium carbonate (heavy)	97	9.7
5	Avicel PH102	70	7
6	Compritol 888 ATO	6	0.6
7	Syloid 244 FP	24	2.4
8	Talc	18	1.8
9	Purified water	q.s	q.s
	Total	1001 mg	100%
Coating	Opadry II (grey) 85G57680	24 mg	2.5 - 3.0%

Manufacturing procedure:

Sift ingredients divalproex sodium, Avicel pH 102, sodium alginate and heavy calcium carbonate through 40 mesh. Mix them in a mixer for 5 minutes. Granulate the above mixed materials with purified water. Dry the wet granules in a drier and pass the granules through 20 mesh of sifter by milling and sifting. Sift ingredients Avicel pH 102, Compritol, Syloid and talc through 40 mesh of sifter and mix with the dried granules in a blender. Compress the blend into tablets. Coat with Opadry II in aqueous suspension to a weight gain of 2.5 to 3.0%. Dissolution was performed in 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm and the dissolution profile is given in Figure 4.

Example 5

S.No	Ingredients	Qty(mg)/Tab	% on tab wt
1	Divalproex sodium	539.77	53.97
2	Avicel PH102	110.23	11
3	Xanthan Gum	90	9
4	Sodium Alginate (Keltone HVCR)	55	5.5
5	Calcium carbonate (heavy)	37	3.7
6	Lactose monohydrate	50	5
7	Compritol 888 ATO	6	0.6
8	Avicel PH102	70	7
9	Syloid 244 FP	24	2.4
10	Talc	18	1.8
11	Purified water	q.s	q.s
Coating	Opadry II (grey) 85G57680	24 mg	2.5 - 3.0%

Manufacturing procedure:

Sift ingredients divalproex sodium, Avicel pH 102, xanthan gum, sodium alginate, heavy calcium carbonate and lactose monohydrate through 40 mesh. Mix them in a mixer for 5 minutes. Granulate the above mixed materials with purified water. Dry the wet granules in a drier and pass the granules through 20 mesh of sifter by milling and sifting. Sift ingredients Avicel pH 102, Compritol, Syloid and talc through 40# of sifter and mix with the dried granules in a blender. Compress the blend into tablets. Coat with Opadry II in aqueous suspension to a weight gain of 2.5 to 3.0%. Dissolution was performed in 500 ml

0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm and the dissolution profile is given in Figure 5.

Example 6

S.No	Ingredients	Qty(mg)/Tab	% on tab wt
1	Divalproex sodium	539.77	53.97
2	Methocel K 100 M	140	14
3	Avicel PH102	127.36	12.73
4	Compritol	50	5
5	Syloid 244 FP	24	2.4
6	Avicel PH102	95	9.5
7	Compritol	6	0.6
8	Talc	18	1.8
9	Purified water	q.s	q.s
	Total	1000 mg	100%
Coating	Opadry II (grey) 85G57680	24 mg	2.5 - 3.0%

Manufacturing procedure:

Sift divalproex sodium, Methocel K 100 M, Avicel pH 102 and Compritol through 40 mesh sieve. Mix them in a mixer for 5 minutes. Granulate the above mixed materials with purified water. Dry the wet granules in a drier and pass the granules through 20 mesh of sifter by milling and sifting.

Sift ingredients Avicel pH 102, Syloid, Compritol and talc through 40 mesh sieve of sifter and mix with the dried granules in a blender. Compress the blend into tablets. Coat with Opadry II in aqueous suspension to a weight gain of 2.5 to 3.0%. Dissolution was performed in 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm and the dissolution profile is given in Figure 6.

Example 7

S.No	Ingredients	Qty(mg)/Tab	% on tab wt
1	Divalproex sodium	539.77	53.97
2	Avicel PH102	156	15.6
3	Xanthan Gum	136	13.6
4	Lactose monohydrate	50	5
5	Avicel PH102	70	7

6	Compritol 888 ATO	6	0.6
7	Syloid 244 FP	24	2.4
8	Talc	18	1.8
9	Purified water	q.s	q.s
	Total	1000 mg	100%
Coating	Opadry II (grey) 85G57680	24 mg	2.5 - 3.0%

Manufacturing procedure:

Sift ingredients divalproex sodium, Avicel pH 102, xanthan gum and lactose monohydrate through 40 mesh. Mix them in a mixer for 5 minutes. Granulate the above mixed materials with purified water. Dry the wet granules in a drier and pass the granules through 20 mesh of sifter by milling and sifting. Sift ingredients Avicel pH 102, Syloid, Compritol and talc through 40 mesh of sifter and mix with the dried granules in a blender. Compress the blend into tablets. Coat with Opadry II in aqueous suspension to a weight gain of 2.5 to 3.0%. Dissolution was performed in 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm and the dissolution profile is given in Figure 7.

Example 8

S.No	Ingredients	Qty(mg)/Tab	% on tab wt
1	Divalproex sodium	539.77	53.91
2	Methocel K 100 M	130	12.98
3	Avicel PH102	123.36	12.32
4	Xanthan Gum	15	1.5
5	Compritol	50	5
6	Avicel PH102	95	9.48
7	Compritol	6	0.6
8	Syloid 244 FP	24	2.4
9	Talc	18	1.8
10	Purified water	q.s	q.s
	Total	1000 mg	100%
Coating	Opadry II (grey) 85G57680	24 mg	2.5 - 3.0%

Manufacturing procedure:

Sift ingredients divalproex sodium, Methocel K 100M, Avicel pH 102, xanthan gum, and Compritol through 40 mesh. Mix them in a mixer for 5 minutes. Granulate the above mixed materials with purified water. Dry the wet granules in a drier and pass the granules through 20 mesh of sifter by milling and sifting. Sift ingredients Sift ingredients Avicel

pH 102, Syloid, Compritol and talc through 40 mesh of sifter and mix with the dried granules in a blender. Compress the blend into tablets and coat with Opadry II in aqueous suspension. Dissolution was performed in 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm and the dissolution profile is given in Figure 8.

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

CLAIMS:

We claim:

1. An oral controlled release composition comprising from about 10 – 90% w/w of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium and valpromide, not more than 20% w/w of a pharmaceutically acceptable polymer, about 0.1 to 10% of a lubricant, and 2 – 25% w/w of filler; all weight percentages are based upon the total weight of the tablet dosage form.

2. An oral controlled release composition of claim 1 comprising -

a. from about 30 – 60% w/w of divalproex sodium, in admixture with;

b. about 6 – 18% w/w of a pharmaceutically acceptable polymer,

c. about 0.2 – 9.5% w/w of a lubricant, and

c. from about 3 – 15% w/w of a filler;

all weight percentages are based upon the total weight of the tablet dosage form.

3. An oral controlled release composition of claim 1, wherein said active ingredient is divalproex sodium.

4. An oral controlled release composition of claim 1, wherein the pharmaceutically acceptable polymer is preferably a hydrophilic polymer.

5. An oral controlled release composition of claim 4, wherein said hydrophilic polymer is selected from the group consisting of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, vinyl acetate copolymers, methacrylic acid copolymers polysaccharides, polyethylene oxide and maleic anhydride/methyl vinyl ether copolymers, alginates and their salts, gums or a combination of these.

6. An oral controlled release composition of claim 5, wherein said hydrophilic polymer is hydroxypropyl methylcellulose.

7. An oral controlled release composition of claim 5, wherein said hydrophilic polymer is a gum, preferably xanthan gum.

8. An oral controlled release composition of claim 5, wherein said hydrophilic polymer is sodium alginate.

9. An oral controlled release composition of claim 5, wherein said hydrophilic polymer is a combination of hydroxypropyl methylcellulose and xanthan gum or a combination of an sodium alginate and xanthan gum.

10. An oral controlled release composition of claim 1, wherein said lubricant is glyceryl behenate (Compritol).

11. An oral controlled release composition of claim 10, wherein said lubricant is from about 0.2 to about 9.5 weight percent based upon the total weight of the tablet dosage form.

12. An oral controlled release composition of claim 1, wherein the filler is preferably water insoluble.

13. An oral controlled release composition of claim 12, wherein said filler is selected from microcrystalline cellulose, dibasic calcium phosphate, calcium carbonate, calcium sulfate, and starch or a combination of these.

14. An oral controlled release composition of claim 13, wherein the filler is heavy calcium carbonate.

15. An oral controlled release composition of claim 14, wherein said heavy calcium carbonate is from about 3 to about 15 weight percent based upon total weight of the tablet dosage form.

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

17. An oral controlled release composition of claim 16, wherein wet granulation is carried out using a binder selected from polyvinylpyrrolidone, carboxyvinyl polymer, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, dextrin, maltodextrin, gums like xanthan gum, starch, acacia, and tragacanth

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

a) dry blending a mixture of from about 30 to about 60% w/w of divalproex sodium, from about 6 to about 18% w/w of hydroxypropyl methylcellulose, 0.2 – 9.5% w/w of a lubricant, and from about 3 – 15% w/w of a filler; to form a uniform mixture of the dry ingredients;

b) wet granulating the dry uniform mixture from step by aqueous solution of xanthan gum or water

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

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

e) compressing the blend of step (d)

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

a) dry blending a mixture of from about 30 to about 55% w/w of divalproex sodium, from about 10 to about15% w/w of hydroxypropyl methylcellulose and from about 20to about 45% w/w of dibasic calcium phosphate to form a mixture of the dry ingredients;

b) obtaining slugs on compression machine.

c) sizing the slugs from step b) to get granules having an average size below about 0.84 mm; and

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

e) compressing the blend of step (d).

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

21. A method of treating epilepsy comprising administering once daily, to a patient in need of such treatment, a controlled release tablet dosage form prepared according to claims 18-19.

22. An oral controlled release composition of claim 1, wherein the formulation is film coated to a weight gain of 2.5 to 3.0% based upon total weight of the tablet dosage form.

Figure 1

Dissolution Media: 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm

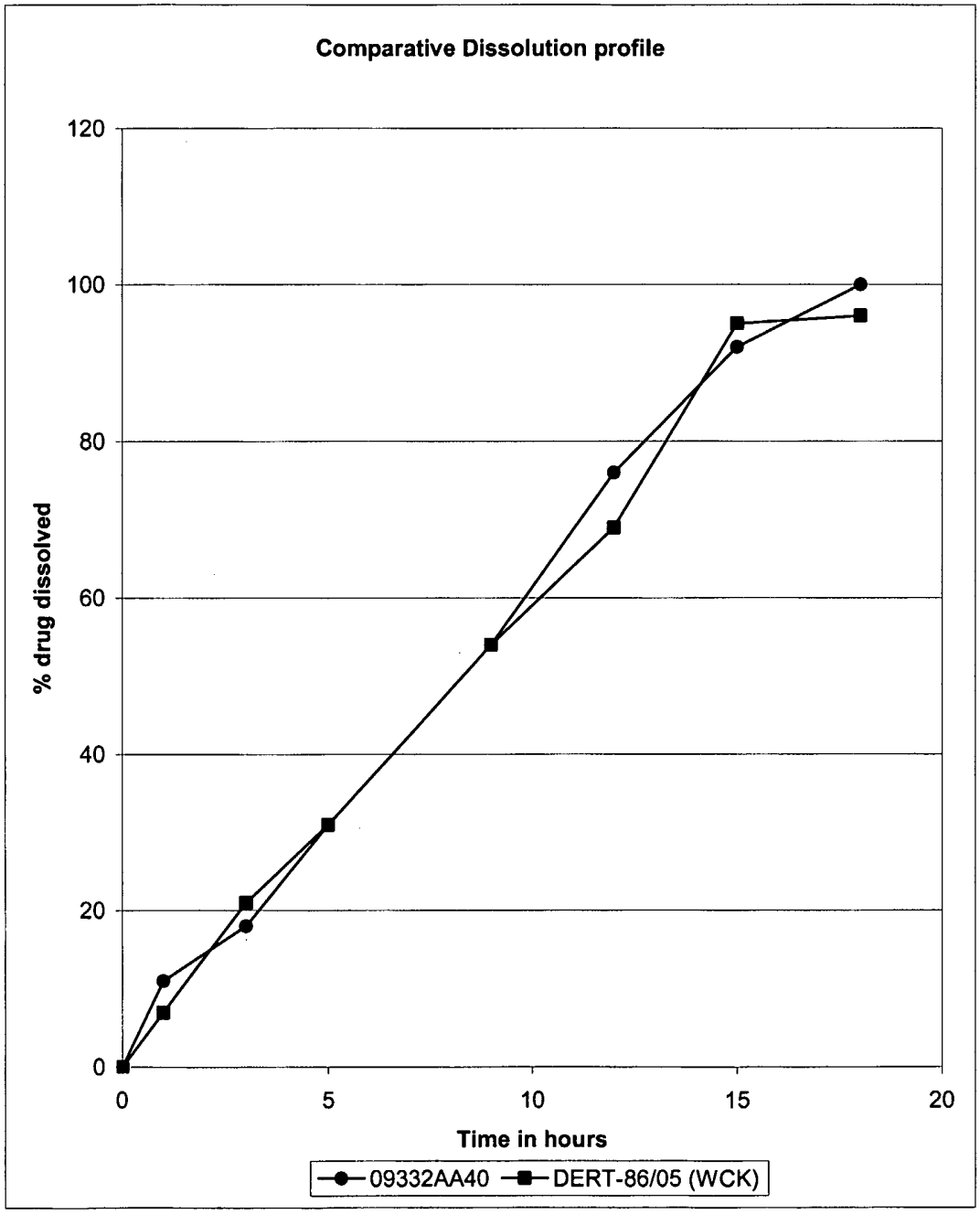

Figure 2

Dissolution Media: 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm

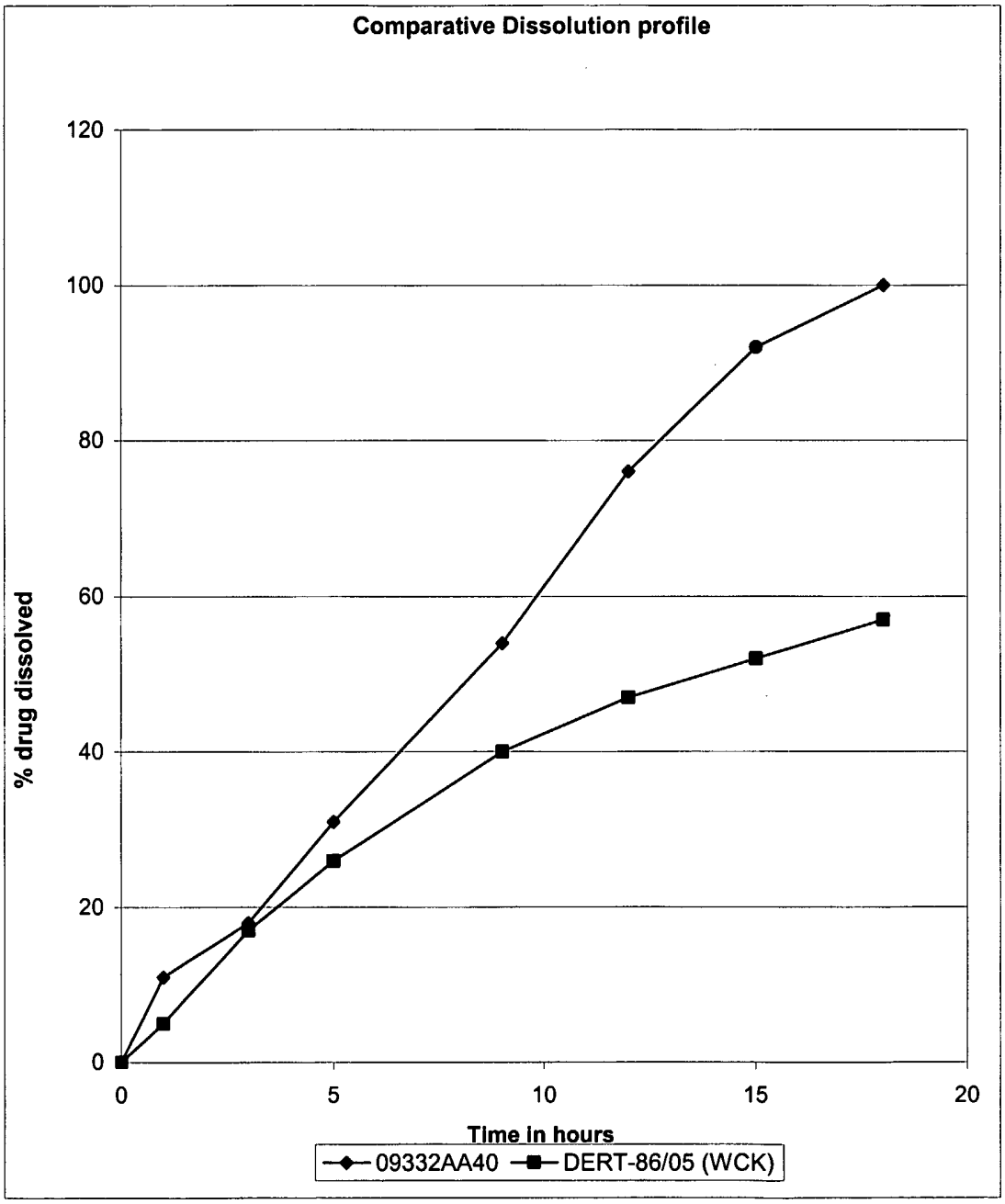

Figure 3

Dissolution Media: 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm

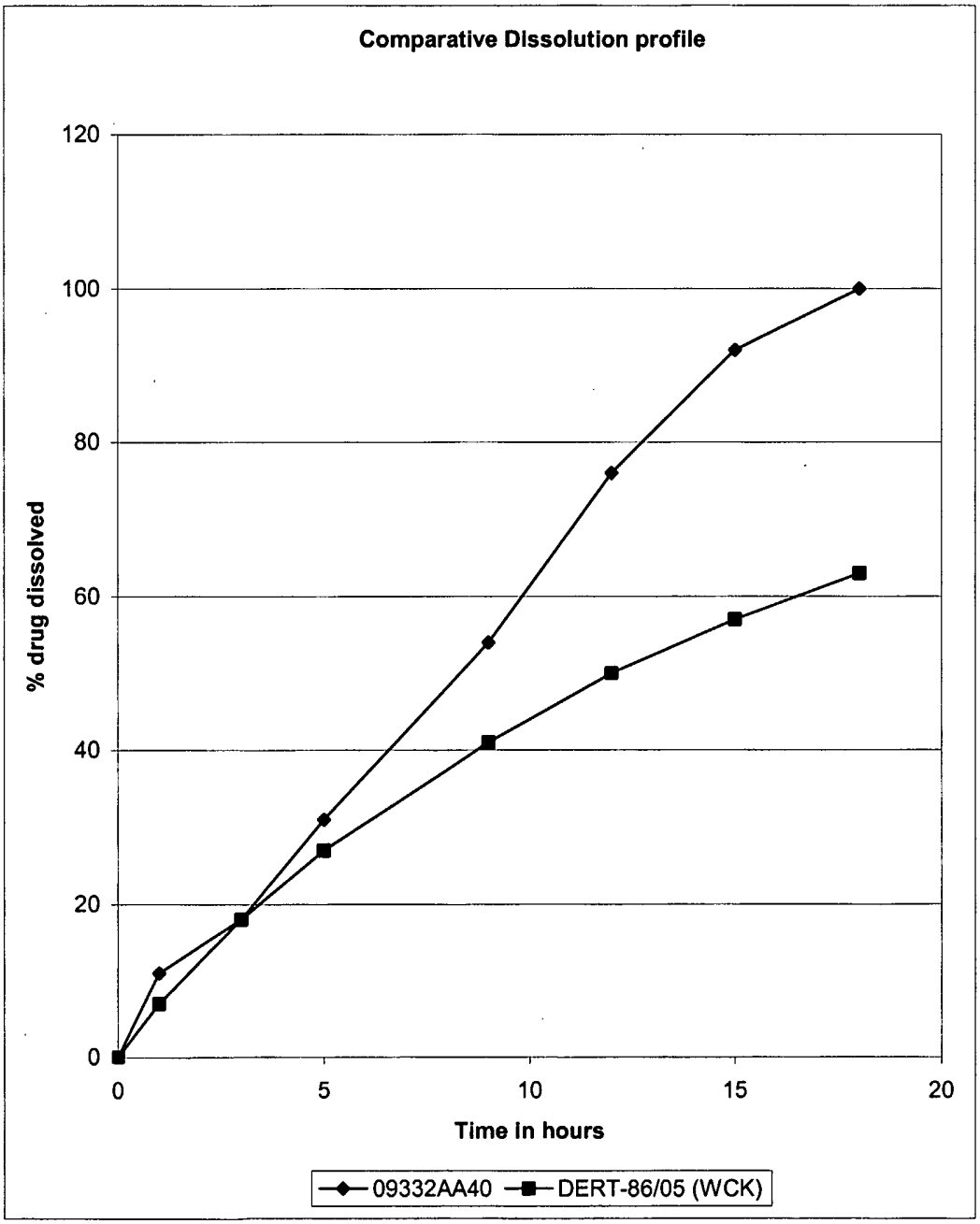

Figure 4

Dissolution Media: 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm

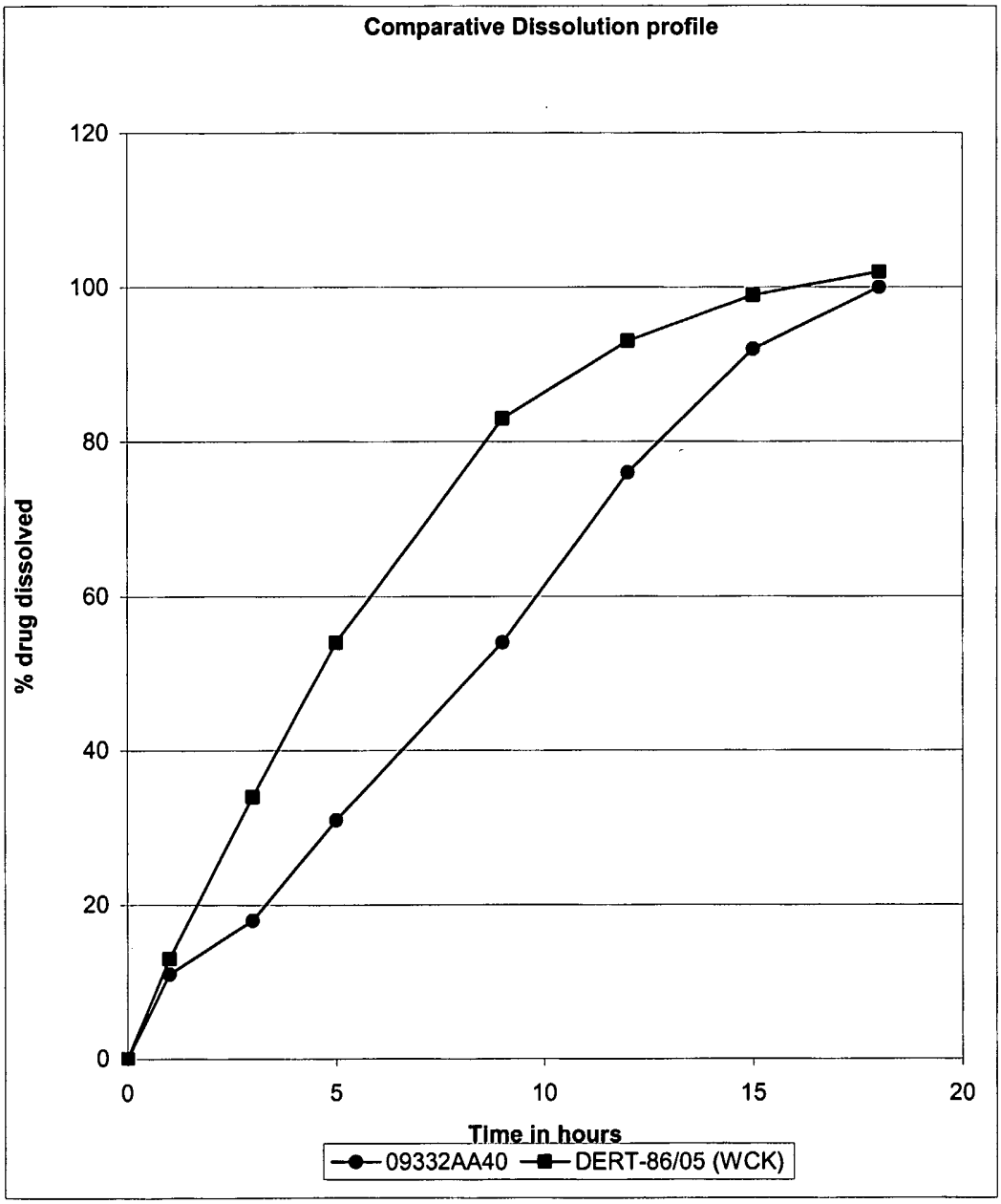

Figure 5

Dissolution Media: 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm

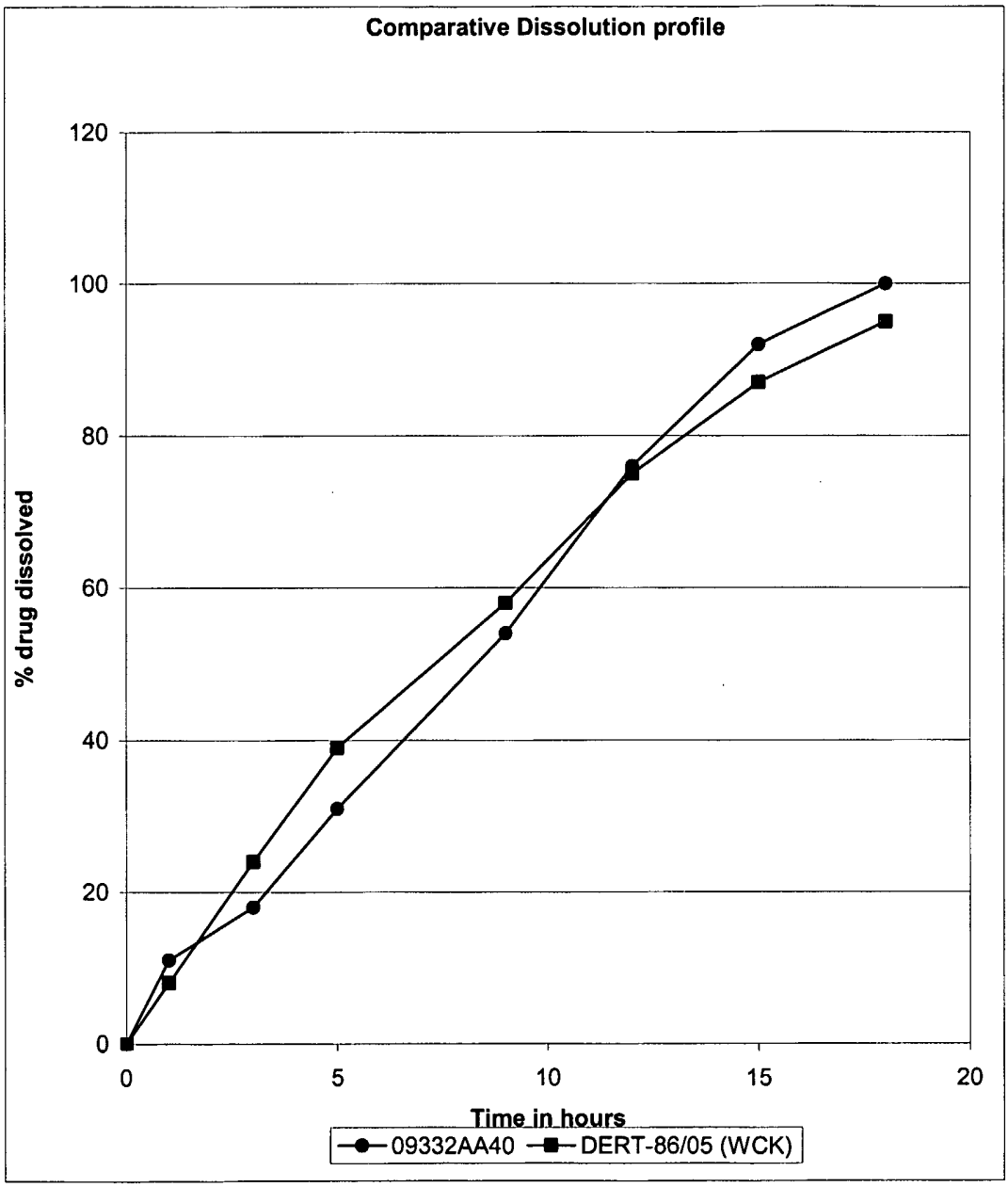

Figure 6

Dissolution Media: 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm

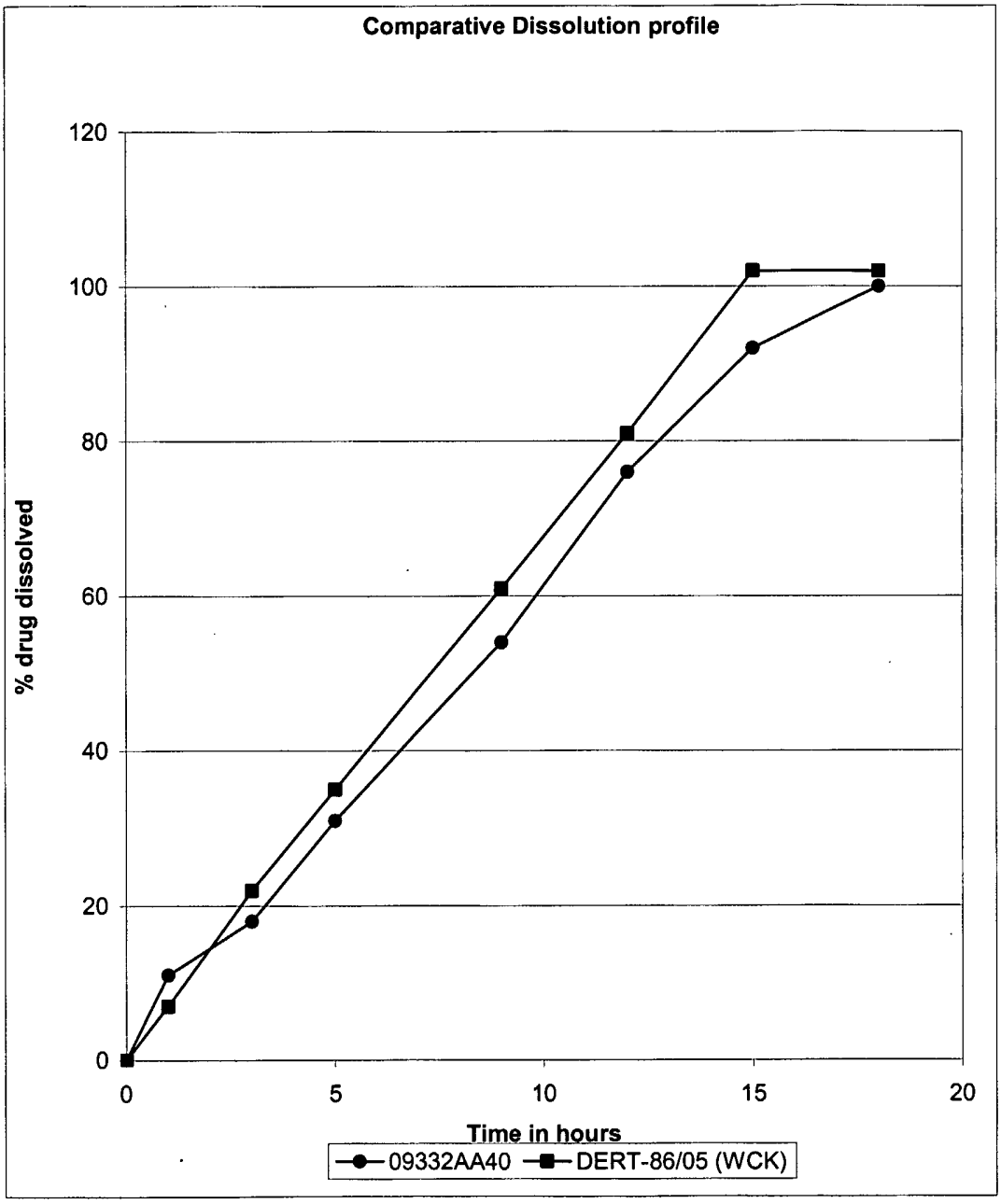

Figure 7

Dissolution Media: 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm

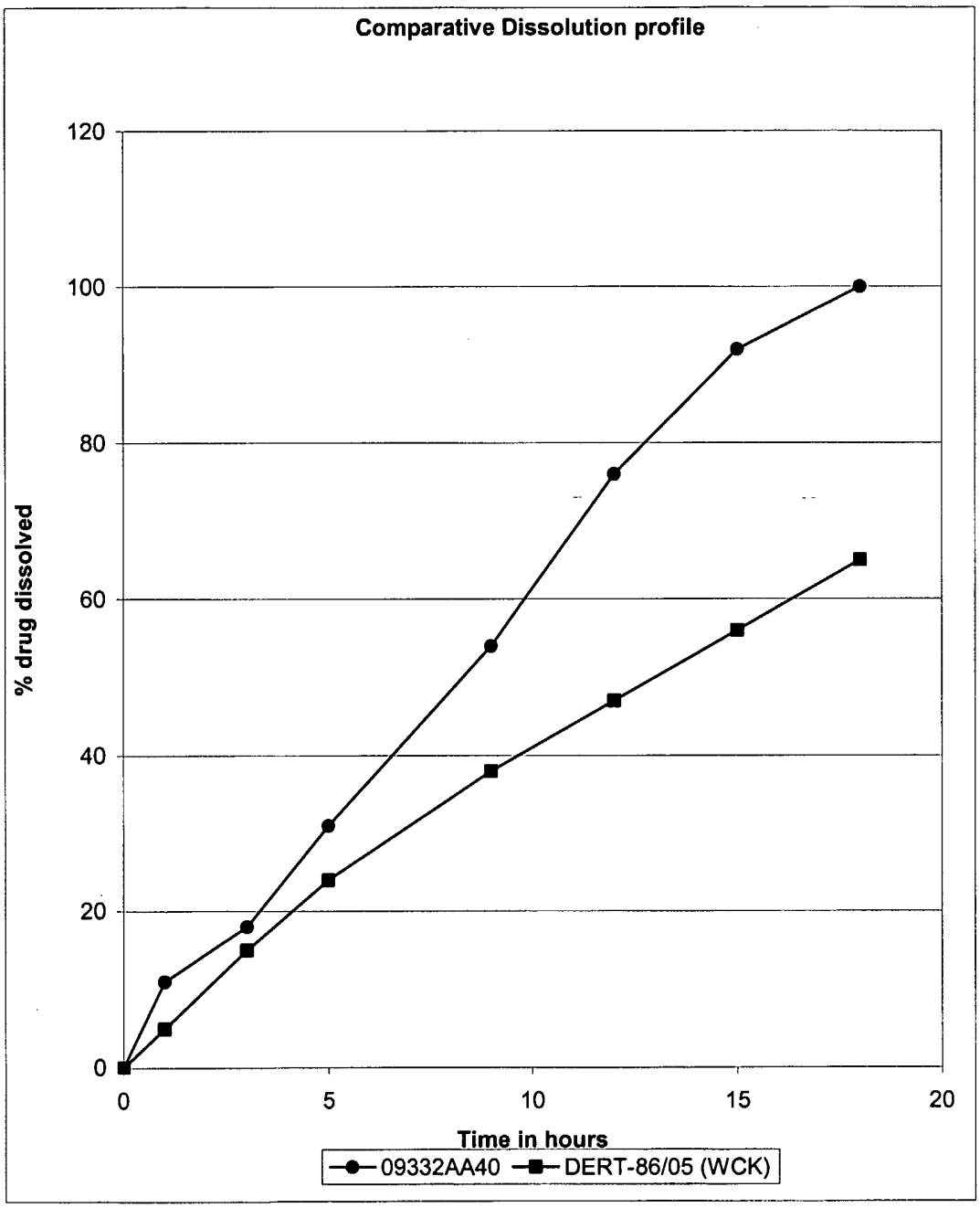

Figure 8
Dissolution Media: 500 ml 0.1 N HCl for 45 min followed by 900 ml 0.05M Phosphate Buffer at pH 5.5 with 75 mM SLS, USP II Apparatus at 100 rpm