

[00389] The ganaxolone particles generated by the methods described herein can be utilized in solid or aqueous liquid dosage formulations, such as controlled release formulations, solid dose fast melt formulations, lyophilized formulations, tablets, capsules, aqueous dispersions, or aerosol formulations.

XIII. Other Formulations Utilizing Small Particles of Ganaxolone

[00390] In certain embodiments, the present invention is directed to a pharmaceutical composition comprising particles comprising (i) ganaxolone thereof, (ii) a cellulosic polymer and (iii) sodium lauryl sulfate; wherein 90% of the particles by weight have an effective particle size of less than about 500 nm. Another embodiment comprises (i), (ii), (iii) and (iv) a complexing agent. In other embodiments, the particles comprising (i), (ii) and (iii) above, and (i), (ii), (iii) and (iv) can have any effective particle size, range, or any other characteristic (e.g., pharmacokinetic profile) as disclosed herein. Additionally an ionic dispersion modulator and a water soluble spacer can be added. These formulations can also contain a polymer selected from the group consisting of polyvinylpyrrolidone, polysaccharides, copolymers of vinyl acetate and vinyl pyrrolidone, polyvinyl alcohol, copolymers of vinyl acetate and vinyl alcohol, carboxymethylcellulose and mixtures thereof.

[00391] In certain embodiments, the cellulosic polymer of (ii) is hydroxypropylmethylcellulose (Pharmacoat 603).

[00392] In certain embodiments, the present invention is directed to a pharmaceutical composition comprising particles comprising (i) ganaxolone thereof, (ii) a polymer selected from the group consisting of polyvinylpyrrolidone, polysaccharides, copolymers of vinyl acetate and vinyl pyrrolidone, polyvinyl alcohol, copolymers of vinyl acetate and vinyl alcohol, carboxyalkylcelluloses, and mixtures thereof, and (iii) a material selected from the group consisting of sodium lauryl sulfate and dioctyl sodium sulfosuccinate, wherein 90% of the particles by weight have an effective particle size of less than about 500 nm. In other embodiments, the particles comprising (i), (ii) and (iii) above, can have any effective particle size, range, or any other characteristic (e.g., pharmacokinetic profile) as disclosed herein. These formulations can also contain a cellulosic polymer.

[00393] In certain embodiments, the polymer of (ii) is a copolymer of vinyl acetate and vinyl pyrrolidone.

[00394] In certain embodiments, the ionic dispersion modulator is an organic or inorganic salt which does not contain a sulfonic acid or sulfonic acid/inorganic salt counterion group at the end of an alkyl chain containing more than one saturated carbon atom bonded to the carbon atom bearing the sulfonic acid moiety.

[00395] In certain embodiments, the water soluble spacer is a saccharide or inorganic salt which do not contain a sulfonic acid or sulfonic acid/inorganic salt counterion group at the end of an alkyl chain containing more than one saturated carbon atom bonded to the carbon atom bearing the sulfonic acid moiety.

[00396] The formulations of the present invention can also include a complexing agent including but are not limited to parabens, organic acids, organic acid salts, aromatic acids and aromatic esters inorganic acids, inorganic salts, and combinations thereof. Complexing agents do not contain a sulfonic acid or sulfonic acid/inorganic salt counterion group at the end of an alkyl chain containing more than one saturated carbon atom bonded to the carbon atom bearing the sulfonic acid moiety.

[00397]. The formulations of the present invention can also include preservatives including but are not limited to parabens, organic acids, organic acid salts, aromatic acids, aromatic esters, inorganic acids, inorganic salts, pharmaceutically acceptable salts and combinations thereof.

[00398] Wetting agents such as sodium lauryl sulfate also do not appear to affect the post milling particle size under storage conditions at ambient temperature. However, addition of wetting agents during the milling process does improve the processing properties such as reduction of back pressure and more efficient grinding by reducing the overall viscosity of the milling slurry.

[00399] An anti-foaming agent can also be added to improve the milling process. For example, presence of simethicone (e.g., at 0.01% level) during the milling process Did not alter characterization of the formulation and greatly improved the efficiency and reliability of the milling process. The addition of simethicone also produces a final aqueous formulation that will foam less and provide more accurate dosing for the patient. In certain embodiments, the ranges of ganaxolone, HPMC, PVA, SLS, parabens, benzoic acid/sodium benzoate and simethicone in the milling and the final suspension formulations are given in TABLE 1 as a weight percent (wt%) based on the total weight of the respective compositions.

TABLE 1		
Component	Milling Compositional Range, wt% to total weight	Formulation Compositional Range, wt% to total weight
GNX	10 to 30	3 to 20
	Or 15 to 27	Or 4 to 10
	Or 10 to 25	Or 4 to 6
HPMC	2 to 10	2 to 10
	Or 2 to 6	Or 2 to 6
PVA	0 to 5	0 to 5
	Or 0.5 to 2.5	0.5 to 2.5
SLS	0 to 1	0 to 1
	Or 0.1 to 0.5	0.1 to 0.5
Simethicone, 100% or 3x levels if 30% emulsion used	0 to 1	0 to 1
	Or 0 to 0.04	Or 0 to 0.04
Methylparaben	0 to 0.25	0 to 0.25
	Or 0 to 0.1	Or 0 to 0.1%
Propylparaben	0 to 0.25	0 to 0.25
	Or 0 to 0.04	Or 0 to 0.04
Sodium Benzoate/ Benzoic acid	0 to 0.2	0 to 0.2

[00400] The particles disclosed above can be prepared according to any of the methods disclosed herein or by the methods described in U.S. Patent Nos. 6,375,986; 6,428,814; 6,432,381; 6,592,903; 6,908,626; or 6,969,529; the disclosures of which are hereby incorporated by reference.

[00401] In certain embodiments, the invention is directed to a pharmaceutical composition comprising particles comprising (i) ganaxolone thereof, (ii) a polymer selected from the group consisting of polyvinylpyrrolidone, polysaccharides, copolymers of vinyl acetate and vinyl pyrrolidone, polyvinyl alcohol, copolymers of

vinyl acetate and vinyl alcohol, carboxyalkylcelluloses, cellulosic polymers and mixtures thereof, and (iii) a material selected from the group consisting of sodium lauryl sulfate and dioctyl sodium sulfosuccinate (DOSS) and (iv) an ionic dispersion modulator and (v) a water soluble spacer, wherein 90% of the particles by weight have an effective particle size of less than about 500 nm (or any effective particle size, range, or any other characteristic as disclosed herein), wherein the composition comprises (a) an immediate release component comprising a first portion of the particles and providing an immediate release of the ganaxolone or pharmaceutically acceptable salt thereof; and (b) a controlled release component comprising a second portion of the particles and providing a controlled release of the ganaxolone or pharmaceutically acceptable salt thereof.

[00402] In certain embodiments, the controlled release component provides a release selected from the group consisting of sustained release or delayed release.

[00403] In certain embodiments, the controlled release component comprises a coating comprising a hydrophobic material, coated on the second portion of particles.

[00404] In certain embodiments, the controlled release component comprises a matrix comprising the second portion of particles dispersed in a hydrophobic material.

[00405] In certain embodiments, the immediate release component and the controlled release component are independently selected from the group consisting of a tablet, a pill, multiparticulates, a powder, a capsule, a solid dispersion, a solid solution, a pellet, or a granule.

[00406] In certain embodiments, the hydrophobic material is selected from the group consisting of an acrylic polymer, a cellulosic polymer, shellac, zein, fatty alcohols, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, waxes, stearic acid, stearyl alcohol, and mixtures thereof.

[00407] In certain embodiments, the hydrophobic material is an enteric polymer.

[00408] In certain embodiments, the enteric polymer is selected from the group consisting of shellac, acrylic polymers, cellulose derivatives, polyvinyl acetate phthalate and mixtures thereof.

[00409] In certain embodiments, the delayed release component provides a dose of the ganaxolone or pharmaceutically acceptable salt thereof delayed by from about 2 hours to about 12 hours after administration.

[00410] In certain embodiments, the delayed release component provides a dose of the ganaxolone or pharmaceutically acceptable salt thereof delayed by from about 2 hours to about 8 hours after administration.

[00411] In certain embodiments, the delayed component provides a dose of the ganaxolone or pharmaceutically acceptable salt thereof delayed by from about 3 hours to about 7 hours after administration.

[00412] In certain embodiments, the controlled release component provides a sustained release of the ganaxolone or pharmaceutically acceptable salt thereof for about 2 hours to about 6 hours after administration.

[00413] In certain embodiments, the controlled release component provides a sustained release of the ganaxolone or pharmaceutically acceptable salt thereof for about 3 hours to about 10 hours after administration.

[00414] In certain embodiments, the coating further comprises a plasticizer, a colorant, a detackifier, a surfactant, an anti-foaming agent, a lubricant or a mixture thereof.

[00415] In certain embodiments, the immediate release component and the controlled release component independently comprise one or more pharmaceutically acceptable additives from the group consisting of carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, or one or more combinations thereof.

[00416] The pharmaceutical dosage forms disclosed herein having an immediate release component and a controlled release component in this section (XIII) can provide any pharmacokinetic profile as disclosed herein.

[00417] The dosage forms can be prepared according to any of the methods disclosed herein or by the methods described in U.S. Patent Nos. 5,209,746; 5,213,808; 5,221,278; 5,260,068; 5,260,069; 5,308,348; 5,312,390; 5,318,588; 5,340,590; 5,391,381; 5,456,679; 5,472,708; 5,508,040; 5,840,329; 5,980,508; 6,214,379; 6,228,398; 6,248,363; 6,514,518; 6,569,463; 6,607,751; 6,627,223; 6,730,325; 6,793,936; 6,902,742 and 6,923,988, the disclosures of which are hereby incorporated by reference.

XII. Methods of Use of Ganaxolone Formulations

[00418] The ganaxolone formulations described herein can be administered in therapeutically effective amounts for the treatment of a subject that has had or is anticipating a convulsive state including, but not limited to, status epilepticus, epileptic seizures or spasms. Specific types of epileptic seizures include, but are not limited to, tonic-clonic (Grand Mal), partial (Focal) seizures, catamenial seizures, acute repetitive seizure, psychomotor (complex partial) seizures, absence (Petit Mal) seizure, and myoclonic seizures.

[00419] The ganaxolone formulations described herein can also be used for the treatment of Infantile Spasms (IS). Infantile Spasm is a specific type of seizure seen in an epilepsy syndrome of infancy and early childhood known as West Syndrome. The onset is predominantly in the first year of life, typically between 3-6 months. The typical pattern of IS is a sudden bending forward and stiffening of the body, arms, and legs; although there can also be arching of the torso. Spasms tend to begin soon after arousal from sleep. Individual spasms typically last for 1 to 5 seconds and occur in clusters, ranging from 2 to 100 spasms at a time. Infants may have dozens of clusters and several hundred spasms per day. Infantile spasms usually stop by age 5, but are often replaced by other seizure types. West Syndrome is characterized by infantile spasms, abnormal and chaotic brain wave patterns, and mental retardation.

[00420] Additional conditions where the ganaxolone small particle formulations described herein can be used to treat include, but are not limited to, anxiety, stress, panic, depression and depression related disorders (e.g., post-partum depression), insomnia, premenstrual syndrome, Post Traumatic Stress Disorder (PTSD), substance abuse withdrawal (e.g. alcohol, benzodiazepine, barbiturate and cocaine), and hypertension. The ganaxolone formulations described herein can also be used in the treatment of pain, migraine headaches and headaches (including migraine) associated with the pre and peri-menstrual period.

[00421] Other conditions diseases which the ganaxolone formulations described herein can be used to treat include sphingolipid storage diseases, such as Neimann Pick Type-C (NPC) and Mucopolipidosis Type IV (ML-IV) lipid accumulation.

[00422] Additionally, the ganaxolone formulations described herein can be used for the treatment of neurodegenerative diseases including, but not limited to, AIDS-associated dementia, Alzheimer's disease, Huntington's disease, and Parkinson's disease diseases.

[00423] Actual dosage levels of the ganaxolone formulations described herein may be varied to obtain an amount of active ingredient that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, on the route of administration, on the desired duration of treatment, and other factors. However, one aspect of the formulations and compositions described herein is to provide ganaxolone formulations that comprise therapeutically effective amounts of ganaxolone such that the ganaxolone blood plasma levels being maintained at steady state are from about 10 ng/ml to about 100 ng/ml (C_{min}) upon administration. In one embodiment, the ganaxolone formulations described herein can be used for the treatment of Infantile Spasms or an epilepsy related disorder wherein the formulation provides a therapeutically effective amount of ganaxolone (C_{min}) of about 25 to 50 ng/ml of ganaxolone in the blood plasma at steady state. In another embodiment, the ganaxolone formulations described herein can be used for the treatment of a non-epilepsy related disorder wherein the formulation provides a therapeutically effective amount of ganaxolone (C_{min}) of about 15 to 30 ng/ml of ganaxolone in the blood plasma at steady state.

XIII. Pharmacokinetic Analysis

[00424] Any standard pharmacokinetic protocol can be used to determine blood plasma concentration profile in humans following administration of a ganaxolone formulation described herein, and thereby establish whether that formulation meets the pharmacokinetic criteria set out herein. For example, a randomized single dose crossover study can be performed using a group of healthy adult human subjects. The number of subjects should be sufficient to provide adequate control of variation in a statistical analysis, and is typically about 10 or greater, although for certain purposes a smaller group can suffice. Each subject receives administration at time zero a single dose (e.g., 300 mg) of a test formulation of ganaxolone, normally at around 8 am following an overnight fast. The subjects continue to fast and remain in an upright position for about 4 hours after administration of the ganaxolone formulation. Blood samples are collected from each subject prior to administration (e.g., 15 minutes) and at several intervals after administration. For the present purpose it is preferred to take several samples within the first hour and to sample less frequently thereafter. Illustratively, blood samples could be collected at 15, 30, 60 and 120 minutes after

administration, and then every hour from 2 to 10 hours after administration. Additional blood samples may also be taken later, for example at 12 and 24 hours after administration. If the same subjects are to be used for study of a second test formulation, a period of at least 7 days should elapse before administration of the second formulation. Plasma is separated from the blood samples by centrifugation and the separated plasma is analyzed for ganaxolone by a validated high performance liquid chromatography/tandem weight spectrometry (LC/APCI-MS/MS) procedure such as, for example, Ramu et al., Journal of Chromatography B, 751 (2001) 49–59.

[00425] Plasma concentrations of ganaxolone referenced herein are intended to mean total ganaxolone concentrations including both free and bound ganaxolone.

Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions and solid dose forms of the ganaxolone formulation described herein. Aqueous dispersions of ganaxolone are stable at temperatures from 4°C up to 40°C for at least 3 months.

EXAMPLES

[00426] This invention is further illustrated by the following examples that should not be construed as limiting. Those of skill in the art of pharmaceutical formulation will readily appreciate that certain modifications to the examples described herein may be needed, particularly for changes in formulation batch size. Any methods, materials, or excipients which are not particularly described will be generally known and available those skilled in the drug design and assay and pharmacokinetic analysis. The particle size data, for examples in which a ganaxolone particle size is reported, were obtained using a Horiba LA-910 Laser Light Scattering Particle Size analyzer (Horiba Instruments, Irvine, California) and reported as volume weighted median (D50). Studies of ganaxolone particles in liquids, beads, powders and immediate release dosage forms in SGF and SIF are performed by dispersing an appropriate amount of the ganaxolone formulation into 20 mL of SGF or SIF in a vial to obtain a measuring concentration of ganaxolone of about 0.5 mg/mL. For example, in one embodiment, 200 mg of a ganaxolone suspension formulation containing 5 wt% of ganaxolone and appropriate levels of HPMC, PVA, SLS, and preservatives was dispersed into 20 mL of SGF or SIF in a vial for measurement. The vial is immersed

in an oil bath kept at 36 to 38°C for 3h. The sample is assessed visually for signs of flocculation and particle size is measured on a Horiba LA-910 to obtain D50 values.

Abbreviations

The following abbreviations are used in the examples below. Other abbreviations used in the examples will be understood by those of skill in the art of pharmaceutical formulations.

GNX	Ganaxolone
HDPE	High Density Polyethylene
HPMC	Hydroxypropylmethylcellulose
PVA	Polyvinyl alcohol
SLS	Sodium Lauryl Sulfate
DOSS	Sodium docusate
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
WT	Weight

Example 1

[00427] The purpose of this example is to describe the preparation of an aqueous dispersion of ganaxolone comprising particles having an effective particle size of less than 500 nm.

[00428] Crystalline ganaxolone is premixed with polyvinylpyrrolidinone/vinyl acetate (S-630), and sodium lauryl sulfate at concentrations of 30%, 10%, and 0.1% (weight/weight of milling slurry) in deionized water, respectively, and milled under high energy milling conditions (Dyno[®]-Mill (Willy Bachofen AG)) water jacketed with a grinding media consisting of ZrO₂ having a size ranging 0.4 to 0.6 mm. The crystalline ganaxolone is milled with the grinding media for a total of 1 hour. The milling temperature is not allowed to exceed 50°C. The milling concentration is about 30% ganaxolone by weight vs. the milling media. The milling media contains about 10% weight/volume of the PVP/VA(S-630) and 0.1% SLS. The resulting blended ganaxolone dispersion is separated from the grinding media by filtration through a 5 micron filter to yield a ganaxolone dispersion which can then be evaluated for performance in animal pharmacokinetics. Liquid aqueous dispersions are

formulated by diluting the milled dispersion with deionized water to a final concentration of 50 mg/ml after the addition of sucrose, methyl and propylparaben and artificial strawberry flavoring (0.005% volume/volume).

Example 2

[00429] The purpose of this example is to describe the preparation of an aqueous dispersion of ganaxolone comprising particles having an effective particle size of about 150 nm.

[00430] Crystalline ganaxolone is premixed with polyvinylpyrrolidone/vinyl acetate (S-630), and dioctyl sodium sulfosuccinate at concentrations of 30%, 2.5%, and 0.05% (weight/weight) in deionized water, respectively, and milled under high energy milling conditions (Dyno[®]-Mill (Willy Bachofen AG)) water jacketed with a grinding media consisting of zirconium oxide beads having a size ranging 0.1 to 0.2 mm. The crystalline ganaxolone is milled with the grinding media for a total of 1 hour. The milling temperature is not allowed to exceed 50°C. The milling concentration is about 30% ganaxolone by weight vs. the milling media. The milling media contains about 10% weight/weight of the PVP/VA(S-630) and 0.05% DOSS (weight/weight) and deionized water. The resulting blended ganaxolone dispersion is separated from the grinding media by filtration through a 5 micron to yield a ganaxolone dispersion which can then be evaluated for performance in animal pharmacokinetics. Liquid aqueous dispersions are formulated by diluting the milled dispersion with deionized water to a final concentration of 50 mg/ml after the addition of sucrose, methyl and propylparaben and artificial strawberry flavoring (0.01% volume/volume).

Example 3

[00431] The purpose of this example is to describe the preparation of an aqueous dispersion of ganaxolone comprising particles having an effective particle size of about 150 nm.

[00432] Crystalline ganaxolone is premixed with hydroxypropylmethylcellulose, and DOSS at concentrations of 25%, 10%, and 0.3% (weight/weight) in deionized water, respectively (in alternative methods, the HPMC can be in a range from about 0.5% to 5% or 1.5% to 3%), and milled under high energy milling conditions (Dyno[®]-Mill (Willy Bachofen AG)) water jacketed with a grinding media consisting of zirconium oxide beads having a size ranging 0.1 to 0.2 mm. The crystalline ganaxolone is

milled with the grinding media for a total of 1 hour. The milling temperature is not allowed to exceed 50°C. The milling concentration is about 25% ganaxolone by weight vs. the grinding media. The grinding media consists of 0.1 to 0.2 mm ZrO₂ beads filling 85% of the grinding vessel volume (volume/volume). The resulting blended ganaxolone dispersion is separated from the grinding media by filtration through a 5 micron filter to yield a ganaxolone dispersion which can then be evaluated for performance in animal pharmacokinetics. Liquid aqueous dispersions are formulated by diluting the milled dispersion with deionized water containing 2% HPMC and 0.1% SLS (Weight/Weight) to a final concentration of 20 mg/ml for animal testing. A suitable dispersion for human use would require the addition of sucrose, methyl and propylparaben and artificial strawberry flavoring (0.005% volume/volume).

Example 4

[00433] The purpose of this example is to describe the preparation of an aqueous dispersion of ganaxolone comprising particles having an effective particle size of about 100 nm.

[00434] Crystalline ganaxolone is premixed with hydroxypropylmethylcellulose, and sodium lauryl sulfate at concentrations of 25%, 2%, and 0.1% (weight/weight) in deionized water, respectively (in alternative methods, the HPMC can be in a range from about 0.5% to 10% or 1.5% to 3%), and milled under high energy milling conditions (Dyno[®]-Mill (Willy Bachofen AG)) water jacketed with a grinding media consisting of zirconium oxide beads having a size ranging 0.1 to 0.2 mm. The crystalline ganaxolone is milled with the grinding media for a total of 2 hours at 15 meters/sec ejection velocity. The milling temperature is not allowed to exceed 50°C. The milling concentration is about 25% ganaxolone by weight vs. the milling media. The milling media contains about 2% weight/weight of the HPMC and 0.1% SLS (w/w) in deionized water. The resulting blended ganaxolone dispersion is separated from the grinding media by filtration through a 5 micron filter to yield a ganaxolone dispersion which can then be evaluated for performance in animal pharmacokinetics by diluting with distilled water containing 2% HPMC and 2.5% sucrose (w/w) to a final concentration of 20 mg/ml).

Example 5

[00435] In Example 5, ganaxolone particles with an effective particles size under 500 nm were obtained utilizing the parameters of Example 1 utilizing 30% ganaxolone, 10% polyvinylpyrrolidinone/vinyl acetate, 0.3% DOSS, 0.1 to 0.2 mm ZrO₂ beads at 85% volume with a milling residence time of about 30 minutes.

Example 6

[00436] In Example 6, ganaxolone particles with an effective particles size under 500 nm were obtained utilizing the parameters of Example 1 utilizing 30% ganaxolone, 10% HPMC, 0.3% DOSS, 0.1 to 0.2 mm ZrO₂ beads at 85% volume with a milling residence time of about 30 minutes.

Example 7

In Example 7, ganaxolone particles with an effective particles size under 200 nm were obtained utilizing the parameters of Example 1 utilizing 30% ganaxolone, 2% HPMC, 0.1% SLS, 0.1 to 0.2 mm ZrO₂ beads at 80% volume with a milling residence time of about 2 hours.

Example 8

[00437] In Example 8, ganaxolone particles with an effective particles size under 250 nm were obtained utilizing the parameters of Example 1 utilizing 30% ganaxolone, 10% polyvinylpyrrolidinone/vinyl acetate, 0.1% SLS, 0.4 to 0.6 mm glass beads at 85% volume with a milling residence time of about 1 hour.

Example 9

[00438] The dispersion from a previous example, before addition of flavoring/sweeteners/preservatives is sprayed in a fluidized bed granulator (e.g. Wurster column) maintaining a bed temperature of 80°C onto sucrose spherical beads of about 50 um diameter. The ganaxolone composition is sprayed at a level of about 30-40% weight to bead weight and is dried. These ganaxolone microparticulate beads can be filled into gelatin capsules for an immediate release formulation or some of the beads may be re-introduced into the granulator and an Eudragit L30 D 55 dispersion is applied with spray guns facing downward to a 0.5% coating level (weight/weight). These coated beads can now be used with the uncoated beads in a automatic capsule

filler at a 40%/60% ratio (uncoated/coated) to provide a 300 mg Ganaxolone dose in a total weight of about 800 mg.

Example 10

Dissolution Testing for Ganaxolone Formulations:

Generally, all experiments are conducted at 36°C to 38°C. The dissolution medium preferably is SGF or SIF containing 10% of sodium lauryl sulfate (SLS). The volume of the medium is 900 mL. The operating speeds are 75 rpm for Apparatus 1 (basket) and 50 rpm for Apparatus 2 (paddle) for solid-oral dosage forms and 25 rpm for suspensions. A 40-mesh screen is used in almost all baskets, but other mesh sizes may be used when the need is documented by supporting data.

[00439] Apparatus 2 is generally preferred for tablets. Apparatus 1 is generally preferred for capsules and for dosage forms that tend to float or that disintegrate slowly. A sinker, such as a few turns of platinum wire, may be used to prevent a capsule from floating.

[00440] The test time is generally 30 to 60 minutes, with a single time point specification for pharmacopeia purposes. To allow for typical disintegration times, test times of less than 30 minutes are to be based on demonstrated need. Dissolution test times and specifications usually are established on the basis of an evaluation of dissolution profile data. Typical specifications for the amount of active ingredient dissolved, expressed as a percentage of the labeled content (Q), are in the range of 70% to 80% Q dissolved. A Q value in excess of 80% is not generally used, as allowance needs to be made for assay and content uniformity ranges.

[00441] For an oral dispersion, add 20 ml or a volume equivalent to 1000 mg ganaxolone to each Type II vessel at 75 RPM paddle speed containing 500 mL SGF containing 10% SLS at 36 to 38°C and at 45 minutes obtain a 5 ml sample via syringe. Filter 3 ml from each container through a syringe fitted filter disk (.05 micron) into an eppendorf type centrifuge tube and centrifuge at 10000 RPM for 30 minutes. Carefully pipette 2 ml of supernatant from the tube into a 10 ml volumetric flask. Dilute to 10 ml with methanol and stopper and invert at least 5 times.

[00442] Analyze a sample from each volumetric in duplicate with a validated HPLC assay as follows:

Column: Waters, SunFire, 250 x 4.6 mm, 5 μ m

Mobile phase: ACN / MeOH / water = 65 / 5 / 30 (v/v)

Flow rate: 1.0 ml/min

Detection: RI

Sample conc.: 0.1 to 0.4mg/ml mg/ml in MeOH

Run time: 45 min

Injection volume: 50 μ l

Ganaxolone: RT~20 min

Make a standard solution of ganaxolone at 1mg/ml in methanol and dilute to 0.5, 0.25 and 0.125 mg/ml in methanol and inject 50 μ l of each concentration before and after each duplicate run. Plot the results against the standard curve to determine the % ganaxolone dissolved. For a pulsatile or delayed release solid dosage form, the general method is similar except that 10% SLS in SGF is used initially (first hour) and then the media is replaced with SIF containing 10%SLS and another dissolution period is evaluated (3 hours). Using USP intestinal fluid adjusted to pH 6.8, approximately 70% of the weight of the enteric coated Ganaxolone particles will be released within 3 hours at 75 RPM paddle speed.

For drug release profiles for Ganaxolone formulations, see Example 29.

Example 11

[00443] Purpose-bred Beagle dogs are obtained and housed in a USDA-approved facility in accordance with AAALAC guidelines. Expected dog weights are from 8 to 12.0 kg at the beginning of the evaluation, and are weighed prior to each period of the study. Animals are block randomized into groups of 3 per treatment. Each study will test ganaxolone formulations (as described in Examples 1-3) along with a reference group which is administered a conventional ganaxolone- β -cyclodextrin formulation (reference formulation). Fasted animals are fasted overnight without water prior to each study day. Designated fed dogs are fed a can (about 400 gm) of Alpo "Chunky with Beef for Dogs," which has 55% of total calories from fat, approximately 45 minutes prior to dosing. When administering aqueous dispersions, test ganaxolone aqueous dispersion formulations and ganaxolone reference formulations are diluted

with deionized water within 2 hours of dosing to deliver about 10 mg/kg ganaxolone in a volume of 2.0 ml/kg. If the liquid suspension is to be administered without dilution, a dose of 5 to 10 mg/kg is given via oral gavage followed by a 7.5 to 10 ml/kg water flush. When administering ganaxolone capsules, both test capsule and reference capsules are given in a dose of about 10 mg/kg. Capsules are administered orally as is typical. Standard laboratory chow and water are offered ad libitum 4 h after dosing. To eliminate the variability of drug absorption among the dogs, all studies should be conducted in a randomized crossover design. Approximately 2 milliliters of blood sample are withdrawn with a 21G needle and via direct venipuncture sampling at predose, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 24 h and 48 h. Blood is immediately transferred to a potassium EDTA blood collection tube (VACUTAINER, Becton Dickinson, Franklin Lakes, NJ, USA) and is stored on ice until the samples are centrifuged at 2500-4000 rpm for 15 min. The plasma is transferred to polypropylene tubes, and samples are stored at -70°C until analyzed by liquid chromatography/tandem mass spectrometry (LC/MS/MS).

[00444] A validated method using liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (LC/APCI-MS/MS) for the determination of ganaxolone in dog plasma is used for the analysis of the all samples. This method is conducted in accordance with the validated method previously published (Ramu *et al* Journal of Chromatography B, 751 (2001) 49-59).

Example 12. PK Data Processing

[00445] WinNonlin v. 3.1 (Scientific Consulting, Inc., Apex, NC) is used for non-compartmental analysis of the data. Area under the plasma concentration-time curve ($AUC_{0-72\text{ h}}$) is calculated from observed plasma concentrations from 0 to 72 h. Any plasma concentrations below the limit of quantitation are set equal to zero. Geometric and arithmetic mean and geometric standard error of the mean (S.E.M.) of AUC, observed maximum plasma concentration ($C_{\max}$), and time of $C_{\max}$ ($T_{\max}$) can be calculated with Microsoft Excel. Treatment and animal effects on the AUC values and observed $C_{\max}$ are determined with the statistical programs of SAS (SAS Institute, Inc., Cary, NC, USA). Also, an interaction model with dog, formulation, and fed/fasted state is examined to confirm the interaction of food with formulation. The AUC and $C_{\max}$ values are log-transformed to normalize the distributions. The

Wilcoxon matched-pairs signed ranks test is used to evaluate differences in $T_{\max}$ values between groups. Differences are only considered significant at $p \leq 0.05$.

Example 13. Ganaxolone Sub-Micron Particle Suspensions

[00446] Ganaxolone submicron particle suspension formulations comprising HPMC, SLS and PVA as stabilizers show useful stability profiles under storage conditions. Submicron particle formulations containing 5 wt% ganaxolone based on the total weight of the formulation and varying amounts of HPMC, SLS and PVA were stored at ambient temperature for 7 months. Visual assessments were made with regard to appearance of these formulations. The results are shown in Table 2.

TABLE 2. Non-preserved ganaxolone particle formulations containing HPMC, SLS and PVA				
Entry	HPMC (wt%)	SLS (wt%)	PVA (wt%)	Visual Assessment after 7 Months
1	2	0.2	1	white suspension, trace amount of solid on bottom
2	2	0.2	1.5	white suspension, small amount solid at bottom
3	2	0.2	2	white suspension, small amount of solid at bottom
4	2	0.2	2.5	white suspension, some solid at bottom
5	2	0.2	3	settled, partially clear liquid on top
6	2	0.2	3.5	settled, near clear liquid on top
7	2	0.2	4	settled, clear liquid on top
8	5	0.3	1	white suspension, no apparent settling
9	5	0.3	1.5	white suspension, small amount of solid at bottom
10	5	0.3	2	white suspension, some solid at bottom
11	5	0.3	2.5	white suspension, some solid at bottom
12	5	0.3	3	two layers, partially clear layer on top
13	5	0.3	3.5	settled, clear liquid on top
14	5	0.3	4	settled, clear liquid on top
15	5	0.2	1	white suspension, no apparent settling

TABLE 2. Non-preserved ganaxolone particle formulations containing HPMC, SLS and PVA				
Entry	HPMC (wt%)	SLS (wt%)	PVA (wt%)	Visual Assessment after 7 Months
16	2.5	0.2	1.25	white suspension, no apparent settling

Example 14. Physical Stability in Gastric and Intestinal Fluids

[00447] Physical stability of ganaxolone particle suspension formulations in simulated gastric and intestinal fluids were tested at 36-38°C unstirred unless otherwise specified.

[00448] Ganaxolone suspension formulations containing HPMC and a surfactant such as SLS or sodium docusate or DOSS, prepared as described in Example 39 underwent flocculation in SGF and SIF.. Test results for two formulations, Ex-39F (15% GNX, 7.5% HPMC and 0.3% SLS) and Ex-39E (15% GNX, 2.5% HPMC and 0.1% DOSS) are shown in Table 3. The particle size growth occurred primarily in the first 1 to 1.5 h after the SGF or SIF treatment, as the D50 values reached micron levels after 90 min (entries 2 and 3, Table 3). It is interesting to note that these formulations are quite stable in deionized water (entries 1 and 5).

TABLE 3. Stability of ganaxolone particle formulations containing only HPMC and SLS or DOSS in various fluids (initial D50: 106 nm) at 36°C to 38°C			
Entry	Formulation	Testing Conditions	D50
1	Ex-39F	Water, 90min	148 nm
2	Ex-39F	SIF, 90 min	1.341 um
3	Ex-39F	SGF, 90 min	1.722 um
4	Ex-39F	Water, 3h	124 nm
5	Ex-39F	SIF, 3h	2.581 um
6	Ex-39F	SGF, 3h	1.787 um
7	Ex-39E	SGF, 100 min	1.382 um
8	Ex-39F	0.2 N NaCl solution, 90 min	1.349 um

Example 15. Ganaxolone Suspension Formulations Containing Polyvinyl**Alcohol (PVA)**

[00449] The stabilization effect of PVA is demonstrated by formulation Ex-40A. This formulation was prepared by diluting the final milling slurry as described in Example 40 (Ex-40) with a diluent containing appropriate amounts of HPMC, PVA and SLS (Table 4, entries 1 and 2) in deionized water. After 3h, the D50 values grew only about 19 nm from an initial of 142 nm. As a comparison, the milling slurry Ex-40 which does not contain PVA underwent flocculation under the same conditions with the D50 value increasing to 360 nm in SIF and 699 nm in SGF from the same initial value of 142 nm (entries 4-5). Further, formulation Ex-49A, having nearly identical composition to those of formulation Ex-40A except containing no PVA, showed a D50 value of 300 nm after 3h in simulated gastric fluid, an increase of 176 nm from the initial D50 of 124 nm (entry 4).

TABLE 4 ¹ . Effect of PVA on Ganaxolone Suspension Stability in SGF and SIF							
Entry	Formulation	GNX%	HPMC%	SLS%	PVA%	D50 (nm)	Test Conditions
1	Ex-40A	5	5	0.3	1	161	SGF, 3h
2	Ex-40A	5	5	0.3	1	157	SIF, 3h
3	Ex-49A	5	5	0.1	0	300	SGF, 3h
4	Ex-40	25	2	0.1	0	699	SGF, 3h
5	EX-40	25	2	0.1	0	360	SIF, 3h

1 Percentages based on w%/total formulation wt and condition include storage at 36°C to 38°C without stirring

Example 16. Effect of Ganaxolone /HPMC Ratio on Ganaxolone Suspension**Formulation Stability In SGF and SIF**

[00450] Ganaxolone to HPMC ratio is important to ganaxolone suspension formulation stability in SGF and SIF. Ganaxolone suspension formulations containing 15 wt% ganaxolone, 3 wt% HPMC, 1 wt% PVA, 0.1 wt% methylparaben, 0.02 wt% propylparaben, and 0.05-0.2 wt% SLS in deionized water showed increase in D50 value of 155 to 261 nm in SGF (entries 2-3, Table 5) after 2h. The increase in D50 does not correlate with the concentrations of SLS. Diluting these formulations with additional HPMC to 5 wt% ganaxolone and 5 wt% HPMC while keeping other components constant resulted in particle size growth of only <28 nm in 70 min

(entries 5-11 and 13, Table 5). As shown in Table 2, the particle size growth primarily occurred during the first 1 to 1.5h of treatment. Thus these formulations were significantly more stable in SGF than those having larger ganaxolone to HPMC ratios. Increasing HPMC level to 8.5% provided little additional stabilization benefit. The data also showed that the exact level of SLS in these formulations had little impact on gastrointestinal stability.

[00451] Formulations in entries 14-16 of Table 5 had 0.2% methylparaben and had similar stability performance in SGF and SIF.

Table 5. Gastric and Intestinal Stabilities of Ganaxolone Particles								
Entry	GNX wt%	HPMC wt%	SLS wt%	Methyl Paraben wt%	Propyl Paraben wt%	PVA wt%	D50 (nm)	Test Conditions ¹
1	5	3	0.05	0.1	0.02	1	171	Initial
2	15	3	0.05	0.1	0.02	1	331	SGF, 2h
3	15	3	0.1	0.1	0.02	1	326	SGF, 2h
4	15	3	0.2	0.1	0.02	1	432	SGF, 2h
5	5	5	0.2	0.1	0.02	1	180	initial
6	5	5	0.2	0.1	0.02	1	182	SGF, 70 min
7	5	5	0.2	0.1	0.02	1	190	SIF, 70 min
8	5	5	0.1	0.1	0.02	1	209	SGF, 70 min
9	5	5	0.05	0.1	0.02	1	204	SGF, 70 min
10	5	5	0.025	0.1	0.02	1	207	SGF, 70 min
11	5	5	0.017	0.1	0.02	1	203	SGF, 70 min
12	5	8.5	0.017	0.1	0.02	1	201	SGF, 70 min
13	5	5	0.025	0.1	0.02	2	202	SGF, 70 min
14	5	5	0.017	0.2	0.02	1	185	Initial
15	5	5	0.017	0.2	0.02	1	209	SGF, 3h
16	5	5	0.017	0.2	0.02	1	213	SIF, 3h

¹ Test temperature is the same as that described in Example 14.

Example 17. Formulations Containing Sodium Benzoate as Preservatives

[00452] Ganaxolone suspension formulations containing sodium benzoate as preservatives with citric acid/sodium citrate (pH 4.0) as buffering agents were also evaluated. With 0.17 wt% sodium benzoate, 0.13 wt% citric acid and 0.01 wt% sodium citrate added, two formulations containing of 5 wt% ganaxolone, 5 wt% HPMC, 1 wt% PVA, and 0.1 wt% SLS in deionized water with initial D50 values of 196 and 321 nm respectively showed good stability against flocculation in both SGF and SIF (Table 6).

TABLE 6. SGF and SIF stabilities of ganaxolone suspension formulations containing sodium benzoate as preservatives					
Entry	citric acid, wt%	Sodium benzoate, wt%	Sodium Citrate, wt%	D50 (nm) no sonication/1 min sonication	Testing Conditions ¹
1	0.13	0.17	0.01	196/176	Initial
2	0.13	0.17	0.01	222/191	SGF, 3h
3	0.13	0.17	0.01	248/201	SIF, 3h
4	0.13	0.17	0.01	321/314	Initial
5	0.13	0.17	0.01	327/320	SGF, 3h
6	0.13	0.17	0.01	328/321	SIF, 3h

¹ Test temperature is the same as that described in Example 14.

Example 18. Effect of PVA on C_{max}

[00453] The addition of PVA to ganaxolone suspension formulations reduces the C_{max} levels. C_{max} levels were determined for ganaxolone suspension formulations containing 1:1 GNX/HPMC (wt%), SLS (0.2-0.4% SLS/GNX), and with and without PVA (20% PVA/GNX). Particles of 110 nm, 140 nm, and 320 nm were orally administered into beagle dogs at a dose of 5 mg/kg under fed and fasted conditions. The pharmacokinetics results are shown in Table 7. The formulation with no PVA (Ex-18A) achieved higher exposure than those with PVA (Ex-18B and Ex-18C). However, addition of PVA reduced variability between the fed and fasted states especially for the AUC values. The ratio of C_{max} to AUC was also lower with PVA added. Formulation Ex-18C is identical to Ex-18B except for added preservatives (0.1 wt% MP, 0.02 wt% PP and 0.09 wt% sodium benzoate at pH 4) and particle size

is larger due to the presence of the preservative. It is surprisingly found that the Ex-18C formulation had higher exposure than Ex-18B formulation despite that the particle size (D50) of Ex-18C is more than double those of Ex-18B (320 nm vs. 140 nm). The Ex-18C formulation shows even less variability as well as enhanced total exposure as compared to the smaller particle size formulation (Ex-18A). The food effect is slightly greater in the optimized suspension due to prolonged drug absorption due to larger particle size.

TABLE 7. Comparative PK results in beagle dogs for ganaxolone suspension formulations with and without PVA at comparable dose levels (5 mg/kg)

Formulation Reference	Particle Size (D50)	PVA/ Preservative	C _{max} (ng/mL)	AUC _{0-72 hr} (ng*h/mL)	Food Intake
Ex-18A	110nm	None/None	448 ±96	2422±1059	Fasted
Ex-18A	110nm	None/None	1194 ±104	4637 ±2600	Fed
Ex-18B	140nm	Yes/None	268 ±36	1643 ±295	Fasted
Ex-18B	140nm	Yes/None	640 ±92	3525±1190	Fed
Ex-18C	320nm	Yes/Yes	243 ±40	1855 ± 321	Fasted
Ex-18C	320nm	Yes/Yes	642 ± 40	5512 ± 681	Fed

[00454] Data provided in Table 8 further demonstrates the reduced variability between fed and fasted state for ganaxolone formulations containing PVA. The Ex-18D formulation has a particle size of 120 nm, which is very similar to that of Ex-18A above. This formulation was identical to Ex-18A except PVA was added. In this study, a fed/fasted effect of 1.6-1.7X AUC₀₋₇₂(fed): AUC₀₋₇₂(fasted) was obtained.

TABLE 8.		AUC ₍₀₋₇₂₎ (ng*h/mL)		AUC _{inf} (ng*h/mL)		C _{max} (ng/mL)	
	Group #	MEAN	SD	MEAN	SD	MEAN	S D
Formulation Ex-18D in Fasted Males	1	1440	460	1616	474	273	45
Formulation Ex-18D in Fed Males	2	2403	422	2624	430	563	92

[00455] Data provided in Table 8 further demonstrates the reduced variability between fed and fasted state for ganaxolone formulations containing PVA. The Ex-18D formulation has a particle size of 120 nm, which is very similar to that of Ex-18A

above. This formulation was identical to EX-18A except PVA was added. In this study, a fed/fasted effect of 1.6-1.7X $AUC_{0-72}(\text{fed}) : AUC_{0-72}(\text{fasted})$ was obtained.

TABLE 8.		$AUC_{0-72} \text{ hr}$ (ng*h/mL)		AUC_{inf} (ng*h/mL)		C_{max} (ng/mL)	
	Group #	MEAN	SD	MEAN	SD	MEAN	SD
Formulation Ex-18D in Fasted Males	1	1440	460	1616	474	273	45
Formulation Ex-18D in Fed Males	2	2403	422	2624	430	563	192

Example 19. Use of Simethicone in the Milling Process

[00456] Presence of simethicone (e.g., at 0.1 wt% level) during the milling process results in more stable ganaxolone suspensions (i.e. the particles experienced less post-milling particle size growth compared to those produced without simethicone during the milling). The experimental results for two nearly identical milling runs except simethicone levels are shown in Table 9.

TABLE 9.						
Millin g Run	Size (g)	Ingredients (Concentrations) During Milling, wt%	Simethicon e during milling, wt%	Residence Time (min)	D50 (end of milling)	D50 (fullycu red)
Ex-42	1200	ganaxolone(25%), HPMC(5%), SLS (0.1%), PVA (1%), methylparaben (0.1%), propylparaben (0.02%)	0.1 %	27.5	180	327
Ex-44	1200	ganaxolone (25%), HPMC(3%), SLS (0.1%), PVA (1%), methylparaben (0.1%), propylparaben (0.02%)	0	25.4	162	380

Example 20. Control of Particle Size by Adjusting the Residence Time of Milling

[00457] Milling runs in deionized water are conducted with 1 wt% PVA and appropriate amounts of preservatives in addition to HPMC (3 to 5 wt%) and SLS (0.05 to 0.1 wt%) utilizing 0.1-0.2 mm zirconium oxide beads (entries 1-4, Table 3). Each wt% is based on the total weight of the milling mixture (without zirconium oxide beads). For entries 1, 3, and 4, the preservatives were 0.1 wt% methylparaben and 0.02 wt% propylparaben and for entry 5, the preservative was 0.1 wt% sodium benzoate buffered with 0.12 wt% citric acid and 0.0093 wt% sodium citrate. After the effective particle size (D50 reached between 150-170 nm, runs 2 and 3 were stopped, while run 1 was allowed to continue. Data suggests that continued milling did not reduce the particle size any further. However, it did produce more stable particles compared to the runs with shorter residence time. Further, after run 3 was re-milled two days later (D50 303 nm) under the same conditions for additional 69 min of residence time (entry 5), the particles became even more stable.

[00458] Milling runs were also conducted with only HPMC and SLS. PVA and preservatives were added post-milling (entries 5-9, Table 10). As in the case of run 1, longer residence time resulted in more stable particles.

Milling Run	D50 at end of milling (nm) ^e	Residence Time (min)	Increase in D50 4 weeks after milling (nm)
1 ^a	153	75	39
2 ^b	160	25	201
3 ^c	162	25.4	209
4 ^d	167	69	23
5 ^f	143	33	177
6 ^f	139	35	156
7 ^f	155	34	160
8 ^f	163	24	217
9 ^f	142	68	52

a. Ganaxolone concentration (15%), PVA (1%), methylparaben (0.1%) and propylparaben (0.02%) were present during milling; b. Ganaxolone concentration (25%), PVA (1%), sodium benzoate (0.1%), citric acid (0.12%), sodium citrate (0.0093%) and simethicone (0.025%) were present during milling; c. Ganaxolone concentration (25%), PVA (1%), methylparaben (0.1%), propylparaben (0.02%) were

present during milling; d. Milling slurry of entry 3 (2x diluted) was re-milled after 2 days; e. Particle size was measured on a Horiba LA-910 particle size analyzer; f. PVA (1%), methylparaben (0.1%), propylparaben (0.02%) were added post-milling.

Example 21. Preparation of Pharmaceutically Useful Ganaxolone Suspension

Formulations (50 mg/mL) from the Milling Slurry

[00459] Method A (one-step dilution): A milling slurry of known ganaxolone concentration prepared as described in Examples 37-52 is diluted with appropriate amount of diluent containing appropriate levels of excipients and other necessary components such as preservatives, flavoring, sweetener and antifoaming agent to achieve 50 mg/mL drug concentration.

[00460] Method B (two-step dilution): A milling slurry prepared as described in Examples 37-52 is first diluted to an intermediate drug concentration (ca. 80 mg/mL) with appropriate amount of diluent containing appropriate levels of excipients and all necessary components such as preservatives, flavoring and sweetener, antifoaming agent. For example, for a milling slurry with an initial ganaxolone concentration of 25 wt% is diluted by mixing one part of the milling slurry with two parts of the diluent will give the intermediate concentration of 8 wt% which is roughly equivalent to 80 mg/mL (assuming the density of the slurry is about 1 g/mL). The appropriate concentrations of excipients and other components are chosen for the diluent so that all components are present at the desired levels after the intermediate dilution. The precise ganaxolone concentration is then determined by appropriate assay (e. g. HPLC). The final dilution is performed with appropriate amount of diluent containing the correct levels of all excipients and other components.

Example 22. Effect of HPMC, SLS, and PVA Levels on Paraben-Containing Ganaxolone Suspension Formulations

[00461] The effect HPMC, SLS, and PVA levels on the stability of paraben-containing ganaxolone particle formulations was studied. Each of the aqueous suspension formulations contains 5 wt% ganaxolone, 0.1 wt% methylparaben, 0.02 wt% propylparaben, each based on the total weight of the formulation, and varying amounts of HPMC, SLS and PVA in deionized water. Visual Assessments were conducted after 7 months of storage at ambient temperature to assess the formulation stability. The compositions and the stability results are shown in Table 11.

TABLE 11. Paraben-containing ganaxolone suspension formulations containing HPMC, SLS and PVA				
Entry	HPMC(wt%)	SLS(wt%)	PVA(wt%)	Visual Assessment after 7 Months
1	2	0.1	3.5	settled, partially clear liquid on top
2	5	0.3	1	white suspension, small amount of solid at bottom
3	5	0.3	1.5	white suspension, some solid at bottom
4	5	0.3	2	white suspension, some solid at bottom
5	5	0.3	2.5	white suspension, some solid at bottom
6	5	0.3	3	white suspension, small partially clear layer on top
7	5	0.3	3.5	settled, clear liquid on top
8	5	0.3	4	settled, clear liquid on top
9	3	0.2	1	white suspension, some solid on bottom
10	3	0.2	1.5	white suspension, substantial solid on bottom
11	3	0.2	2	white suspension, substantial solid on bottom
12	3	0.2	2.5	settled, partially clear liquid on top
13	3	0.2	3	settled, partially clear liquid on top
14	3	0.2	3.5	settled, near clear liquid on top
15	3	0.2	4	settled, clear liquid on top

[00462] The data of Table 11 shows that 5 wt % HPMC 0.3 wt% SLS at 0.3 wt% ganaxolone formulations showed good stability with the amount 1 wt% to 3 wt% PVA range (entries 2-6). When PVA levels are further increased to 3.5 to 4 wt% while the other components are held constant, some settlement of particles at the bottom and clear liquid on the top of the formulations was observed (entries 7 & 8).

[00463] Formulations listed in entries 9-11 showed good stability with the amount of PVA ranging from 1 wt% to 2 wt% while the amounts of HPMC (3 wt%) and SLS (0.2

wt%) were held constant. When the PVA level increased to 2.5 to 4 wt% while the other components were held constant some settlement of particles at the bottom and clear liquid on the top of the formulations (entries 12-15) was observed.

[00464] There appears to be an optimal compositional range for obtaining good formulation stability. Less than or equal to 3.5 wt% of PVA (or 0.5 to 2.5 wt%) is desirable in obtaining good stability of paraben containing ganaxolone formulations, especially at 5 wt % (or 3 wt%) or lower HPMC concentrations.

Example 23. Effect of Preservative on Ganaxolone Suspension Formulation Stability in SGF and SIF

[00465] The effect of a preservative on ganaxolone suspension formulation stability in SGF and SIF were studied. Formulations listed in entries 1-6, Table 12A contained 8-9.5 wt% of GNX, 4-4.8 wt% of HPMC, 0.24-0.29 wt% SLS, 6-7 wt% of sucrose, based on the total weight of the formulation. Various amounts of parabens as shown in Table 12A were added immediately prior to dispersion and storage in SGF and SIF at 36-38 °C.

[00466] It can be seen from Table 12A that parabens have a stabilizing effect on the ganaxolone particle formulations in SGF and SIF when added immediately prior to dispersion into these media. The median particle size (D50) grew to around 200-270 nm from the initial value of 106 nm. These results compared favorably to those of the base formulations (without paraben) whose D50 exceeded 1 micron after 90 minutes in SGF or SIF as shown in Table 2. Furthermore, one minute of sonication of the formulations after one-hour of storage reduces the particle sizes to around 141 to 147 nm.

[00467] Significantly, when parabens or sodium benzoate were added as complexing agents after milling and the ganaxolone particles were allowed to cure to reach the end pint where the particles become stable, dispersion and storage in SGF and SIF at 36-38 °C for 3h caused virtually no increase in particle size (D50). The results are shown in Table 12B.

TABLE 12A. Effect of methylparaben and propylparaben on physical stability of ganaxolone suspension formulations (Initial D50 106 nm)				
Entry	Methylparaben wt%	Propylparaben wt%	D50 no sonication, nm (1 min sonication)	Test Conditions 36 to 38°C

TABLE 12A. Effect of methylparaben and propylparaben on physical stability of ganaxolone suspension formulations (Initial D50 106 nm)				
Entry	Methylparaben wt%	Propylparaben wt%	D50 no sonication, nm (1 min sonication)	Test Conditions 36 to 38°C
1	0.07	0	251 (144)	SGF, 1h
2	0.07	0	187 (141)	SIF, 1h
3	0	0.014	269 (144)	SGF, 1h
4	0	0.014	191 (141)	SIF, 1h
5	0.1	0.02	218 (147)	SGF, 1h
6	0.1	0.02	208 (142)	SIF, 1h

Table 12B. Test results in SGF and SIF for cured ganaxolone particles complexed with a complexing agent ^a				
Entry	Complexing agent/amount (%) w/w)	Initial D50 unsonicated (1min sonication)	D50 no sonication, nm, after storage in SGF, 3h (1 min sonication)	D50 no sonication, nm, after storage in SIF, 3h (1 min sonication)
1	Methylparaben/0.1% Propylparaben/0.02%	314 nm (311 nm)	326 nm (313 nm)	344 nm (330 nm)
2	Sodium benzoate/0.09% Citric acid/0.12% Sodium citrate/0.093%	321 nm (314 nm)	322 nm (312 nm)	329 nm (313 nm)

^a The composition of the test formulation are: 5% ganaxolone, 5% HPMC, 0.1% SLS (all based on total weight of the formulation).

Example 24. The Synergistic Effect of Preservative and PVA in Combination on Physical Stability Of Ganaxolone Suspension Formulations

[00468] The synergistic effect of a preservative and PVA combination on ganaxolone suspension formulation physical stability was studied. All formulations contained 4.5-8 wt% GNX, 2.2-4 wt% HPMC, 0.09-0.24 wt% SLS, 4.5-9 wt% sucrose, based on the total weight of the formulation, and varying amounts of paraben and PVA as shown in Table 13.

TABLE 13. Synergistic effects of parabens and PVA on stabilizing ganaxolone suspension formulation in SGF and SIF (initial D50 120 nm)					
Entry	Methylparaben, wt%	Propylparaben wt%	PVA, wt%	D50, nm (1 min)	Test Conditions ¹

				sonication)	
1	0.1	0.02	0	218 (147)	SGF, 1h
2	0.1	0.02	0	208 (142)	SIF, 1h
3	0.07	0.015	1.3	149 (139)	SGF, 1h
4	0.08	0.016	1.1	150 (138)	SIF, 1h

¹ Test temperature is the same as that described in Example 14.

[00469] Results in Table 13 indicate that ganaxolone suspension formulations containing both parabens and PVA showed additional physical stability in both simulated gastric (SGF) and intestinal (SIF) fluids. While the ganaxolone particle size in formulations containing only parabens grew more than 80 nm in 1h in both gastric and intestinal fluid (Table 13, entries 1-2), those in formulations containing ca. 1% PVA in addition to the parabens grew only slightly (less than 30 nm) (entries 3-4). These results suggest synergies between parabens and PVA in stabilizing the ganaxolone particles in gastric and intestinal fluids. Furthermore, one minute of sonication of the formulations containing both parabens and PVA after one-hour of storage reduces the particle sizes to around 138 to 139 nm.

Example 25. Effects of multiple preservatives on pharmacokinetics (PK)

[00470] In the following examples, the effect of the combination of parabens and sodium benzoate and/or benzoic acid on pharmacokinetics was studied, versus the effect of sodium benzoate and/or benzoic acid without parabens. The particle sizes for both formulations were similar (320 nm for Ex-18C and 360 nm for Ex-25A). Studies were conducted using both fasted and fed beagle dogs and the PK results are summarized in Table 14.

[00471] Results in Table 14 indicate that paraben/sodium benzoate/benzoic acid combined preserved ganaxolone suspension formulations provide a lower food effect (about 3 times) than sodium benzoate alone formulations (about 4 times) at 5 mg/kg. Moreover, the paraben/sodium benzoate/benzoic acid combined preserved formulation showed significant improvement in exposure variability as compared to the sodium benzoate only formulation.

Table 14. Comparative PK results in beagle dogs (5 mg/kg, fed/fasted) for ganaxolone particle formulations preserved with sodium benzoate only and sodium benzoate/parabens combination.				
Formulation	Preservatives	C _{max} (ng/mL)	AUC ₀₋₇₂ hours (ng*h/mL)	Food Intake
Ex-25A	Sodium benzoate/benzoic acid	267 ± 93	1551 ± 264	Fasted
Ex-25A	Sodium benzoate/benzoic acid	802 ± 157	6352 ± 2469	Fed
Ex-18C	Parabens + sodium benzoate/benzoic acid	243 ± 40	1855 ± 321	Fasted
Ex-18C	Parabens + sodium benzoate/benzoic acid	642 ± 40	5512 ± 681	Fed

[00472] For liquid formulations amounts of formulation components are given as weight percent of the total formulation weight (w%/ w) unless otherwise indicated. For solid dosage forms formulation components are given as a percent of ganaxolone (w%/GNX). For example, in a solid dosage form, 100% HPMC indicates that the weight of HPMC in the formulation is equal to the weight of ganaxolone in the formulation.

[00473] Particle size measurements for liquid ganaxolone suspensions are made using a Horiba LA 910 Particle Size Analyzer adding liquid ganaxolone suspension via a 5 ml pipette into the Horiba chamber (containing approx. 125 ml distilled water that has been blanked) to achieve a tungsten light transmittance of 75 to 80%. Other settings are a recirculation setting of 4, stirring setting of 1, and relative refractive index of 115-010.

Example 26. Spray Layered Ganaxolone Formulation

[00474] 100 g of a sphere (20-35 mesh) are added to a Glatt GPCG-3 fluidized bed with Wurster column insert (4 inch), inlet temperature of 50 to 60 °C and air temp of 30 to 50 °C (total air volume approx. 150-200 cubic cm/hr). A 17.6% total solids content slurry containing ganaxolone (197nm, 71% of solids content),

hydroxymethylpropylcellulose (Pharmacoat 603, 14.9% of solids), SLS (0.1% of solids), sucrose (13.4% of solids), and 30% simethicone emulsion (DC7-9245, 0.1% of solids) with total weight of sprayed suspension being 697 g (574 ml water), is sprayed (bottom spray) through 1.2 mm nozzles at 10 ml/min and 1.5 bar of pressure until a layering of 123% is achieved as compared to initial bead weight.

[00475] Dispersion in water (1 g in 300 ml) at 36-38 °C spinning at 75 RPM demonstrated complete disintegration within 10 minutes. Dissolution of ganaxolone coated sugar beads into SGF or SIF at 0.5 mg/ml at 36-38 °C for 1 hour showed agglomeration (settling in container) and effective particle size of > 5 μ m.

Example 27. Preparation of Dried Solid Ganaxolone Particle Formulations

[00476] Ganaxolone particle suspension (1.0 g), prepared as described above in Examples 37-52 is placed in a 25 ml glass scintillation vial fitted onto a Buchi rotary evaporator. The vial is spun at approx. 150 rpm and the water bath temperature is set between 70-90 °C. Vacuum is gradually applied for the initial 2 minutes to minimize bumping. After bumping is no longer a problem, full vacuum is applied (approx. 2-4 mbar) until a powder free of any water or visible condensation is observed (approx. 10 min). The vial is then dried on the evaporator for an additional 10-15 minutes.

[00477] In cases where additional components are required to be added to the ganaxolone particle suspension prior to drying, these components are weighed into the vial first and approx. 0.5 g of deionized water is added to obtain a complete solution. To this solution is then added 1.0 g of the ganaxolone particle suspension. The content in the vial is swirled manually. After the content is thoroughly mixed, the vial is fitted onto a Buchi rotary evaporator to dry the content as described above.

Example 28. Preparation of Simulated Gastric and Intestinal Fluid

Simulated Intestinal Fluid (SIF)

[00478] Monobasic potassium phosphate (6.8 gm) and sodium hydroxide (0.616gm) are added into 250 ml of distilled water in a 1000 ml volumetric flask and swirled until dissolved. 700 ml distilled water is added and the pH checked. The pH is adjusted to pH 6.8 +/- 0.1 by adding either 0.2N sodium hydroxide or 0.2N hydrochloric acid and the volume is brought to 1000 ml.

Simulated Gastric Fluid (SGF)

[00479] Sodium chloride (2 gm), 750 ml distilled water, and 7.0 ml of concentrated hydrochloric acid are added into a 1000 ml volumetric flask. The flask is swirled to mix and the volume brought to 1000 ml with distilled water. The pH should be approx. 1.2.

Example 29. Dispersion Tests of Solid Ganaxolone Particle Formulations in Simulated Gastric and Intestinal Fluid

[00480] The solid ganaxolone particle formulation is dispersed in simulated gastric and intestinal fluid and their dispersibility is monitored by visual assessment for flocculation and particle size measurement using a Horiba-LA-910 particle analyzer. The detailed procedure is described below.

In-Process Immediate Release Blend or Liquid Dispersion

[00481] In a 25 ml translucent HDPE vial (total fill volume) with HDPE cap is placed appropriate amount of ganaxolone formulation (e.g. 9.8 mg dried ganaxolone powder containing 76% ganaxolone and appropriate levels of excipients) to achieve a final ganaxolone concentration of approx 0.5 mg/ml when diluted with 15 ml of simulated gastric or intestinal fluid. After adding the dispersant, the vial is shaken manually until formulation is completely dispersed. The vial is then placed in a heated oil bath at 37 °C unstirred unless specified otherwise until the desired test time. The vial is removed from the bath and inspected visually for signs of flocculation. It is then shaken before particle size measurement using a Horiba-LA-910 particle analyzer. Typically the materials are incubated for 3 hours to approximate the human gastric emptying period.

Particle size measurement

[00482] If measuring coated beads where the bead core contains insoluble materials, calculate the weight of bead core in the SIF or SGF experiment, disperse an equal weight of core beads into the same volume of SIF or SGF and pour the entire amount into 120 gm of distilled water in the Horiba LA-910 chamber. Blank the instrument and drain. Add 120 gm distilled water and pour the entire quantity of incubated formulation (in 15 ml SGF or SIF) into the Horiba chamber. Measure the particle size. This process subtracts any particle size interference from the core beads. In the case of MCC cores, which are insoluble, measure the particle size by the method used for liquid suspension. After the initial particle size measurement of the re-dispersed

ganaxolone formulation, sonicate at the low power setting on the Horiba LA-910 for 1 minute, unless specified otherwise, and re-measure the particle size. As for any suspension or dispersion study the D50 difference as well as overlapping the 2 traces can give a qualitative indication of how much of the formulation forms a loose agglomerate.

-Dispersion of Ganaxolone Suspensions, Tablets and Capsules (Immediate and Delayed Release)

[00483] Place the ganaxolone solid dosage form in a type II dissolution apparatus with basket at 37 °C containing SGF at 0.5 to 1.0 mg/ ml ganaxolone concentration for the immediate release component. Stir at 75 RPM and sample at 1 hour for the particle size. Measure the particle size as described above (15 mL aliquot) using a direct measurement method if all excipients are water soluble or by filtering through a 5 micron filter or by blanking using the same blend quantity minus ganaxolone dispersed under the same conditions as the immediate release ganaxolone coated beads above. If a delayed release or pulsatile release dosage, after the SGF incubation, replace the SGF with SIF (to make 0.5 to 1 mg/ml of ganaxolone in the delayed release component. Utilize the same conditions as for SGF but let stir for 3 hours. Sample and measure the particle size as described above for the SGF portion of the study.

Example 30. Ganaxolone Dispersion Test Results

[00484] Table 15 shows test results for a ganaxolone particle suspension formulation (12.6% ganaxolone, 2.6% HPMC, 0.026% SLS, 0.018% simethicone emulsion (30% simethicone in water) and 2.4% sucrose) and two other dried forms (rotary evaporation dried and spray layered onto sucrose or microcrystalline cellulose beads). The spray layered form was prepared by evaporating the layering slurry onto sugar beads (Paulaur 30/35 mesh) through a fluidized bed coating process yielding approximately 35% ganaxolone loading (%wt GNX/% total bead wt), as assayed by HPLC – refractive index. Although the initial liquid formulation had D50 values of 343 and 361 nm after 3h in both gastric and intestinal fluids at 36-38 °C, the two dried forms had D50 values in the range of 11-25 micrometers in the same test. Further, the action of 1 minute sonication did not return D50 to its original value.

TABLE 15. Dispersion Results of Ganaxolone suspension containing HPMC, SLS, Sucrose and Simethicone (no complexing agent added) or after the removal of water via Rotary Vacuum Evaporation (Rotovap) or Spray Layered onto Sugar Beads				
Entry	Dosage Form	D50 (μ m) / D50 after 1 min sonication	Visual Observation	Dispersion conditions ¹
1	layering slurry	0.211/0.202	Uniform suspension	Initial
2	layering slurry	0.343/0.291	Flocculated	SGF, 3h
3	layering slurry	0.361/0.247	Flocculated	SIF, 3h
4	Rotvap Dried	0.325/0.305	Uniform suspension	Distilled water, ambient, 5 min
5	Rotvap Dried	11.1/2.2	flocculation	SGF, 100 min
6	Rotvap Dried	11.3/3.1	flocculation	SIF, 100 min
7	Layered on sugar beads	19.5/8.8	flocculation	SGF, 3h
8	Layered on sugar beads	25.5/7.6	flocculation	SIF, 3h

¹ Temperature for SGF and SIF tests is the same as that described in Example 14.

Example 31. Effects of sucrose, HPMC, SLS and PVA on ganaxolone particle formulations without a complexing agent (Table 16)

[00485] As the data in Table 16 shows, higher level of SLS resulted in less particle growth upon dispersion in simulated gastric and intestinal fluids (entries 1-2) for non-Complexed ganaxolone particle formulations. Doubling the sucrose level from 46.6 to 98.3%, while keeping the SLS level constant showed positive, but smaller effects on dispersion (entry 3). Addition of ca. 10% PVA showed similar effect to that of doubling sucrose level at the same SLS level (entry 4).

TABLE 16. Dispersion Test Results of Dried Non-Complexed Ganaxolone Particle Formulations ((initial D50: 147 nm, from Milling run Ex-21) in Both Simulated Gastric and Intestinal Fluids

Entry	Sucrose % (w/GNX)	HPMC% (w/GNX)	SLS % (w/GNX)	PVA % (w/GNX)	D50 (μm) /1min sonication	Dispersion Conditions ¹
1	46.6	22.1	0.93	0	24.7/1.2	SGF
					14.9/1.6	SIF
2	46.6	22.1	2.79	0	0.984/0.2 6	SGF
					1.21/0.28	SIF
3	98.3	22.1	0.98	0	13.9/0.30	SGF
					12.2/0.28	SIF
4	48.8	22.1	0.98	9.75	12.3/3.19	SGF
					11.2/4.22	SIF

¹ Conditions are the same as Example 14

Example 32. Dispersion of Solid Ganaxolone Particle Formulations with a Paraben Complexing Agent

Example 32a. Solid particles prepared from 6-month old suspension formulation containing a complexing agent

[00486] Solid ganaxolone particles prepared from a 6-month old stable suspension formulation as described in Example 45 (Ex-45) containing 52% HPMC, 10.4% PVA, 1.25% parabens, and 1.0% SLS re-dispersed well in both simulated gastric and intestinal fluids at 36-38 °C (entry 5, Table 17). Addition of 54.8% of sucrose further improved the re-dispersibility especially in simulated gastric fluid (entry 3). Adding additional 2.3% SLS to this formulation further reduced particle growth upon dispersion, particularly in simulated gastric fluid (entry 4). Doubling the sucrose level also provided positive stabilization effect (entry 2).

TABLE 17. Dispersion Test Results of Dried Stable Ganaxolone Formulations containing a complexing agent ((Ex-45) in Simulated Gastric and Intestinal Fluids (D50: 205 nm)						
Entry	Sucrose % (w/GNX)	HPMC %(w/GNX)	SLS % (w/GNX)	Parabens ^a % (w/GNX)	D50 (μm) /1min sonication	disperse conditions ^b

TABLE 17. Dispersion Test Results of Dried Stable Ganaxolone Formulations containing a complexing agent ((Ex-45) in Simulated Gastric and Intestinal Fluids (D50: 205 nm)						
Entry	Sucrose % (w/GNX)	HPMC %(w/GNX)	SLS % (w/GNX)	Parabens ^a % (w/GNX)	D50 (μm) /1min sonication	disperse conditions ^b
1	104.2	52.1	1.0	1.25	0.203	DI water, ambient
2	104.2	52.1	1.0	1.25	0.329/0.215	SGF, 2h
					0.333/0.217	SIF, 2h
3	54.8	52.1	1.0	1.25	0.363/0.213	SGF, 3h
					0.333/0.216	SIF, 3h
4	54.8	52.1	3.3	1.25	0.314/0.211	SGF, 3h
					0.328/0.219	SIF, 3h
5	0	52.1	1.0	1.25	0.408/0.285	SGF, 3h
					0.367/0.283	SIF, 3h

^a1.04% methylparaben and 0.21% propylparaben; ^b Temperature for SGF and SIF tests is the same as that described in Example 14.

Example 32b. Solid particles prepared from a 1 week old ganaxolone suspension formulation containing methylparaben as the complexing agent

[00487] Solid ganaxolone particles prepared from a 1-week old methylparaben suspension formulation containing 0.98% methylparaben in addition to 24.4% HPMC, 0.15% simethicone (30% emulsion in water), 1.46% SLS were tested for dispersion in both simulated gastric and intestinal fluids at 36-38 °C (Table 18). Consistent with previous observations, higher level of SLS resulted in less particle size growth upon dispersion (entry 2) in both gastric and intestinal fluid. Addition of 25% sucrose to the above formulation further reduced particle size growth upon dispersion (entry 3). Addition of 9.76% PVA provided less obvious benefit.

TABLE 18. Dispersion Test Results of Dried Ganaxolone (GNX) Particle Formulations Prepared from Milling Slurry Containing Methylparaben in Gastric and Intestinal Fluids (initial:310 nm nm): Effects of Sucrose, SLS, PVA and Simethicone (all % expressed as wt%/GNXwt)

Entry	Sucrose %	HPMC %	30% SE	SLS %	Methyl-paraben %	PVA %	D50 (μm) / D50 (μm) after 1 min sonication	Dispersion Conditions ¹
1	0	24.4	0.15	1.46	0.98	0	30.0/ 0.333	A
							19.5/0.312	B
2	0	24.4	0.15	2.93	0.98	0	5.6/0.303	A
							8.2/0.302	B
3	25	24.4	0.15	2.93	0.98	0	0.517/0.291	A
							0.807/0.288	B
4	24.4	24.4	0.15	2.93	0.98	9.76	2.29/0.309	A
							2.13/0.328	B
5	0	24.4	0.49	2.93	0.98	0	9.02/0.304	A
							11.23/0.314	B
6	0	24.4	0.98	2.93	0.98	0	7.66/0.315	A
							9.44/0.311	B

¹ Re-disperse conditions: A, simulated gastric fluid, 36-38 °C, 3h; B. Simulated intestinal fluid, 36-38 °C, 3h. SE = Simethicone

Example 33. Head to head comparison of re-dispersibility in simulated gastric and intestinal fluids of solid ganaxolone particles: With and without a complexing agent (Methylparaben) added

[00488] Two liquid ganaxolone particles formulations were prepared as described in Examples 51 and 52 respectively: one contained 0.98% methylparaben in addition to 24.3% HPMC and 1.46% SLS (Ex-51) and the other one contained only comparable levels of HPMC and SLS (Ex-52). When these two liquid formulations tested side by side in simulated gastric and intestinal fluid at 37 °C, the complexing agent containing formulation Ex-51 (entry 1, Table 19) showed significantly less particle size growth compared to the formulation Ex-52 without the complexing agent (entry 2, Table 19). With additional amounts of HPMC and SLS added (entries 3-4, table 19), similar results were obtained. These results are consistent with those discussed earlier. Solid ganaxolone particles prepared from the suspensions listed in entries 3-4, Table 19

were re-dispersed in simulated gastric and intestinal fluid, the paraben-containing formulation showed less particle size growth than its no-paraben counterpart (entries 3-4, Table 20).

Table 19. Gastric and intestinal stability study of formulations prepared from Ex-51 and Ex-52: Effect of Methyl paraben as the complexing agent (formulations tested as suspension)					
Entry	HPMC (w/GNX)	SLS % (w/GNX)	Methylparaben % (w/GNX)	D50 (μm) No Sonication/1 min sonication	Test conditions ¹
1	24.4	1.46	0.98	0.382/0.324	A
				0.394/0.326	B
2	23.5	1.41	0	0.897/0.290	A
				7.36/0.283	B
3	47.1	2.82	0	0.828/0.258	A
				0.933/0.267	B
4	48.8	2.93	0.98	0.350/0.314	A
				0.353/0.313	B

¹ dispersion conditions: A, simulated gastric fluid, 36-38 °C, 3h; B. Simulated intestinal fluid, 36-38 °C, 3h.

[00489] Additional comparative dispersion studies of solid ganaxolone particles with and without parabens were carried out in simulated gastric and intestinal fluids. Ganaxolone particles with 0.98% methylparaben as the complexing agent (allowed to cure for 1 week) showed significant less particle growth upon dispersion at 37 °C than that containing no complexing agent (entries 2-3, Table 20). Presence of 9.4-9.8% PVA did not significantly alter the dispersion behaviors of solid ganaxolone particles with and without the complexing agent (entries 1&4, 2&3, table 20). For formulation listed in entry 4, Table 19, addition of ca 52% of sucrose significantly reduced particle size growth upon dispersion (entry 8, table 6.6). However, doubling the sucrose level did not show any significant additional benefit (entry 9, Table 20). Similar trends were observed for solid ganaxolone formulations containing no complexing agent (entries 6&7, 10&11, Table 20). Compared with formulation listed in entry 8, Table 20, lowering the levels of sucrose, HPMC and SLS resulted in larger particle size upon dispersion, especially in simulated intestinal fluid (entry 5, Table 20).

TABLE 20. Comparative Dispersion Results of Dried Ganaxolone Particle Formulations Prepared from a ganaxolone suspension with Methylparaben (Ex-51, 24.4% HPMC, 0.98% methylparaben, initial D50:148 nm, complexed D50: 310 nm cured for 7 days at 20 °C) and without Methylparaben (Ex-52, D50: 147 nm) in Gastric and Intestinal Fluids: Effects of Sucrose, SLS, PVA

Entry	Sucrose % (w/GNX)	HPMC (w/GNX)	SLS % (w/GNX)	PVA %(w/GNX)	Methyl- paraben % (w/GNX)	D50 (µm) No sonication/1 min sonication	disperse conditions ¹
1	0	48.3	2.90	9.8	0.98	0.69/0.332	SGF, 3h
						1.14/0.336	SIF, 3h
2	0	46.6	2.80	9.4	0	4.04/0.768	SGF, 3h
						3.57/0.677	SIF, 3h
3	0	47.1	2.82	0	0	4.02/1.12	SGF, 3h
						4.13/1.24	SIF, 3h
4	0	48.8	2.93	0	0.98	0.636/0.314	SGF, 3h
						1.28/0.322	SIF, 3h
5	15.4	32.9	1.9	0	1.3	0.754/0.317	SGF, 3h
						2.64/0.322	SIF, 3h
6	47.0	23.5	2.8	0	0	2.89/0.303	SGF, 3h
						15.87/0.296	SIF, 3h
7	94.1	23.5	2.8	0	0	6.89/0.280	SGF, 3h
						13.98/0.288	SIF, 3h
8	51.8	49.3	3.0	0	0.98	0.366/0.283	SGF, 3h
						0.413/0.304	SIF, 3h
9	103.8	46.7	2.8	0	0.98	0.383/0.292	SGF, 3h
						0.588/0.304	SIF, 3h
10	52.1	52.1	3.1	0	0	2.09/0.301	SGF, 3h
						3.94/0.316	SIF, 3h
11	104.4	47.1	3.1	0	0	2.72/0.293	SGF, 3h

TABLE 20. Comparative Dispersion Results of Dried Ganaxolone Particle Formulations Prepared from a ganaxolone suspension with Methylparaben (Ex-51, 24.4% HPMC, 0.98% methylparaben, initial D50:148 nm, complexed D50: 310 nm cured for 7 days at 20 °C) and without Methylparaben (Ex-52, D50: 147 nm) in Gastric and Intestinal Fluids: Effects of Sucrose, SLS, PVA

Entry	Sucrose % (w/GNX)	HPMC (w/GNX)	SLS % (w/GNX)	PVA %(w/GNX)	Methyl- paraben % (w/GNX)	D50 (µm) No sonication/1 min sonication	disperse conditions ¹
						5.46/0.301	SIF, 3h

¹ Temperature for SGF and SIF tests is the same as that described in Example 14.

Example 34. Effect of salts on dispersion of dried ganaxolone particle formulations with and without a complexing agent added

[00490] Sodium chloride is very effective in improving dispersion of a dried ganaxolone particle formulation (described in Example 51) cured with a complexing agent in both simulated gastric and intestinal fluid. The results are shown in Table 21. At 1.5 w%/ GNX level, sodium chloride reduced D50 from 13.2 µm to 3.17 µm upon dispersion in simulated gastric fluid at room temperature (entries 1-2). Raising the sodium chloride level to 2.0 % relative to ganaxolone, under the same conditions, decreased D50 to 0.548 µm in gastric fluid. Above 3.0%, sodium chloride essentially prevented particle size growth upon dispersion in gastric and intestinal fluid (entries 6-9, 11, Table 21). At low sodium chloride level, additional stabilization effect can be obtained by adding a water soluble spacer which has more plasticity than salts. The water soluble spacer used to illustrate this point is sucrose. As shown in entry 4, at 1.5% sodium chloride level, addition of 2.5% of sucrose (relative to ganaxolone) reduced D50 to the same level as 3.0% sodium chloride. Increasing the sucrose level to 5% provided little additional benefit (entry 3). For the stabilized solid ganaxolone particle formulation containing methylparaben as a complexing agent and cured for > 7 days, the increase in D50 values is primarily caused by loose aggregation upon dispersion. A 1 min sonication at the low power setting readily reverses these loose aggregates back to individual smaller particles, as shown in Table 21.

[00491] For the regular ganaxolone particle formulation that has not been stabilized by a complexing agent, addition of sodium chloride at a level as high as 23.5% relative to

ganaxolone resulted in D50 of 22.7 μm upon dispersion in simulated gastric fluid at room temperature. This significant increase in D50 upon dispersion can only be partially reversed after 1 min low power sonication (entry 12, table 21). The actual particle distribution traces (after 1 min low power sonication) for entries 9 (with methylparaben) and 12 (without methylparaben) are shown in Figure 5.

Table 21. Effect of sodium chloride on dispersion of dried ganaxolone particles (with and without complexing agent) and in simulated gastric and intestinal fluid (SGF and SIF)								
Entry	HPMC %w/ GNX	SLS %w/GNX	Simethicone 30% emulsion %w/GNX	Methylparaben w/GNX	NaCl %w/GNX	Sucrose %w/GNX	D50(μm) sonication / D50(μm) after 1 min sonication	Dispersion conditions
1	24.4	1.46	0.15	0.98	0	0	13.2/0.332	SGF, 5 min, rt
2	24.4	1.46	0.15	0.98	1.5	0	3.17/0.337	SGF, 5 min, rt
							4.45/0.353	SIF, 5 min, rt
3	24.4	1.46	0.15	0.98	1.5	5	0.364/0.316	SGF, 5 min, rt
							0.396/0.322	SIF, 5 min, rt
							0.490/0.331	SGF, 3h, 36-38 °C, stirred
							0.561/0.329	SIF, 3h, 36-38 °C, stirred
4	24.4	1.46	0.15	0.98	1.5	2.5	0.395/0.323	SGF, 5 min, rt
							0.370/0.312	SIF, 5 min, rt
							0.416/0.326	SGF, 3h, 36-38 °C, stirred
							0.533/0.331	SIF, 3h, 36-38 °C, stirred
5	24.4	1.46	0.15	0.98	2.0	0	0.548/0.334	SGF, 5 min, rt
							0.506/0.326	SIF, 5 min, rt
6	24.4	1.46	0.15	0.98	3.0	0	0.355/0.319	SGF, 5 min, rt
							0.367/0.315	SIF, 5 min, rt
							0.485/0.329	SGF, 3h, 36-38 °C, stirred
							0.609/0.334	SIF, 3h, 36-38 °C, stirred
7	24.4	1.46	0.15	0.98	6.1	0	0.338/0.314	SGF, 5 min, rt
							0.429/0.337	SIF, 5 min, rt
8	24.4	1.46	0.15	0.98	12.2	0	0.353/0.317	SGF, 5 min, rt

Table 21. Effect of sodium chloride on dispersion of dried ganaxolone particles (with and without complexing agent) and in simulated gastric and intestinal fluid (SGF and SIF)								
Entry	HPMC % w/ GNX	SLS % w/GNX	Simethicone 30% emulsion %w/GNX	Methylparaben w/GNX	NaCl %w/GNX	Sucrose %w/GNX	D50(μ m) no sonication / D50(μ m) after 1 min sonication	Dispersion conditions
							0.367/0.318	SIF, 5 min, rt
9	24.4	1.46	0.15	0.98	24.4	0	0.344/0.319	SGF, 5 min, rt
10	24.4	1.46	0.15	0.98	24.4	0	0.440/0.322	SGF, 70 min, 36-38 °C
							0.459/0.324	SIF, 70 min, 36-38 °C
11	24.4	1.46	0.15	0.98	36.6	0	0.346/0.315	SGF, 5 min, rt
							0.372/0.317	SIF, 5 min, rt
12	23.5	1.41	0.14	0	23.5	0	22.7/8.9	SGF, 5 min, rt

[00492] Other salts are also effective in improving re-dispersibility of solid ganaxolone particles in simulated gastric and intestinal fluid. Shown in table 22 are test results of sodium citrate.

Table 22. Effect of sodium citrate on dispersion of dried ganaxolone particles (complexing agent added) in simulated gastric and intestinal fluid (SGF and SIF)							
Entry	HPMC % w/ GNX	SLS %w/GNX	Simethicone 30% emulsion %w/GNX	Methylparaben % w/GNX	Na Citrate %w/GNX	D50(μ m) No sonication/ 1 min sonication	Disperse conditions
1	24.4	1.46	0.15	0.98	24.4	0.454 /0.333	SGF, 5 min, rt
2	24.4	1.46	0.15	0.98	24.4	0.820 /0.337	SGF, 70 min, 36-38 °C

Table 22. Effect of sodium citrate on dispersion of dried ganaxolone particles (complexing agent added) in simulated gastric and intestinal fluid (SGF and SIF)							
Entry	HPMC % w/ GNX	SLS %w/GNX	Simethicone 30% emulsion %w/GNX	Methylparaben % w/GNX	Na Citrate %w/GNX	D50(μm) No sonication/ 1 min sonication	Disperse conditions
3	24.4	1.46	0.15	0.98	24.4	0.982 /0.342	SiF, 70 min, 36- 38 °C

Example 35. Preparation of solid ganaxolone particles containing sucrose, sodium chloride in addition to the milling excipients

[00493] The following was placed in a 25 ml glass scintillation vial: 5.13 mg of sucrose crystals and 12.5 mg of 25% wt sodium chloride solution. Deionized water (0.5 g) was then added to dissolve the sucrose crystals and to achieve a homogeneous solution.

[00494] Aqueous ganaxolone suspensions (1 g) containing 20.5% ganaxolone, 5.0% HPMC, 0.3% sodium lauryl sulfate, 0.2% methylparaben 0.03% simethicone (30% emulsion in water) (all %w/w) was then added to the vial and the mixture was swirled to mix well. The contents in the vial were then evaporated under reduced pressure (rotary vacuum evaporator at 2-4 mbar) at 70-85 °C until a dry powder was obtained.

[00495] The examples listed in Table 23 were prepared in the same fashion with appropriate amounts of each component.

Table 23				
Example	Milling Slurry (g)	NaCl solution (25% wt)	Sucrose (g)	Deionized water (g)
1	1.0	0.3	0	0.5
2	1.0	0.2	0	0.5
3	1.0	0.1	0	0.5
4	1.0	0.05	0	0.5
5	1.0	0.025	0	0.5

6	1.0	0.0125	0.01025	0.5
7	1.0	0.0164	0	0.5

Example 36. Effect of Boiling on Ganaxolone Formulations With and Without a Complexing Agent

[00496] Approx. 2g of the milling slurry of Ex-51 and Ex-52 prepared as described in Examples 51 and 52 respectively was placed in a 25 ml glass vial and the vial was closed tightly. The vials were heated in 100 °C oil bath. The particle size of Ex-51 which contained methylparaben as complex agent did not change after heating. In contrast, Ex-52 which did not contain a complexing agent increased its D50 and the increase appeared to be time dependent. Also, both formulations became more viscous with Ex-51 becoming a semi-solid (it was diluted with water for particle size measurement).

TABLE 24			
Formulation	Initial D50 (nm) before/after 1 min sonication	D50 (nm) after 20 min at 100° C	D50 (nm) after 4h at 100 °C
Ex-51	320/298	326/311	320/310
Ex-52	149/140	246/207	317/302

Example 37. Dispersion test results of solid ganaxolone particle formulations with sodium benzoate as curing agent in simulated gastric and intestinal fluid

[00497] Solid ganaxolone particle formulations containing sodium benzoate/benzoic acid as a complexing agent were prepared according to the milling method for formulations with parabens as complexing agent (see method described in Example 52) except using ganaxolone particle suspension containing 21.25% ganaxolone, 5% HPMC, 0.3% Sodium lauryl sulfate, 0.03% simethicone emulsion (30%) with 0.09% sodium benzoate, 0.12% citric acid and 0.0093% sodium citrate added post-milling (all %w/w) (Ex-52) and cured for 12 days at the time of use.

[00498] As shown in Table 25, solid ganaxolone particles prepared from milling slurry Ex-52 containing 23.5% HPMC, 1.41% SLS and 0.14% simethicone emulsion (30%) showed poor re-dispersibility. Post-milling addition of sodium benzoate (0.42%), citric acid (0.56%) and sodium citrate (0.043%) to this suspension improved its re-dispersibility in gastric and intestinal fluid (entry 3). As in the case of paraben-

containing solid formulations, addition of sodium chloride (23.5%) further reduced its D50 upon dispersion in simulated gastric and intestinal fluid (entry 4).

Table 25

Entry	HPMC % w/GNX	SLS %w/ GNX	Simethicone 30% emulsion %w/GNX	Sodium benzoate/citric acid/sodium citrate% w/GNX	NaCl %w/ GNX	D50(μ m) no sonication/D50 (μ m) 1 min sonication	Dispersion conditions
1	23.5	1.41	0.14	0	0	37.2/4.9	SGF, 5 min rt
2	23.5	1.41	0.14	0	23.5	22.7/8.9	SGF, 5 min, rt
3	23.5	1.41	0.14	0.42/0.56/0.04 3	0	16.5/0.747	SGF, 5 min, rt
						14.3/0.525	SIF, 5 min, rt
4	23.5	1.41	0.14	0.42/0.56/0.04 3	23.5	9.0/0.347	SGF, 5 min, rt
						7.5/0.343	SIF, 5 min, rt

Example 38. Filterability of Ganaxolone particle suspensions with and without a complexing agent (methylparaben)

[00499] Ganaxolone particle suspension (247 mg, Ex-51) containing 20.5% ganaxolone, 5% HPMC, 0.3% sodium lauryl sulfate, 0.2% methylparaben and 0.03% simethicone emulsion (30%) was diluted with deionized water (100 ml) and thoroughly mixed to obtain 0.5 mg/ml ganaxolone concentration.

[00500] Ganaxolone particle suspension (235 mg, Ex-52) containing 21.25% ganaxolone, 5% HPMC, 0.3% sodium lauryl sulfate, 0.03% simethicone emulsion was diluted with deionized water (100 mL) and thoroughly mixed to obtain 0.5% mg/ml ganaxolone concentration.

[00501] The filterability of the diluted suspensions was evaluated by transmittance (lamp) and particle size change before and after filtration. To obtain about 75% transmittance (lamp) before filtration, for dilute suspension of Ex-51, 10 g was mixed with 120 mL of deionized water in the Horiba LA-910 sample chamber and the particle size was measured. The chamber was drained and rinsed with water. In the chamber was then mixed 10 g of the dilute suspension filtered through a 1 micron glass fiber syringe filter and 120 ml deionized water the particle size was measured.

[00502] For the dilute suspension of Ex-52, 25 g of the suspension and 80 ml of deionized water was used. The transmittance (%T lamp) and D50 were compared before and after filtration to determine the amount of ganaxolone particles retained on the filter. Higher transmittance indicates lower particle concentration in the measuring chamber. Further, decreasing D50 after filtration indicates the removal of particles with altered physical properties (aggregates or adhesion onto the membrane) during filtration. As data in Table 26 shows, a significant amount of the ganaxolone particles complexed by methylparaben were retained by the filter as depicted by the loss of lamp transmittance value which indicates how many particles are in the sample chamber (entry 1). This statement is also consistent with significant back pressure encountered during filtration. In contrast, the ganaxolone particles not associated with a complexing agent were not retained by the filter (entry 2). In this case, virtually no back pressure was encountered.

TABLE 26. Filterability of ganaxolone particles with and without a complexing agent								
entry	HPMC% (w/GNX)	SLS% (w/GNX)	Simethicone emulsion 30% (w/GNX)	Methylparaben % (w/GNX)	Before filtration		After filtration	
					D50 (μm)	%T (lamp)	D50 (μm)	%T (lamp)
1	24.4	1.46	0.15	0.98	0.324	77.5	0.191	94.4
2	23.5	1.41	0.14	0	0.152	77.1	0.146	79.1

Example 37. Milling of Ganaxolone Particles In Aqueous Medium Containing HPMC and Sodium Lauryl Sulfate (Batch Mode)

[00503] Ganaxolone particles in deionized water (180 g) containing a 30 wt% ganaxolone (Marinus Pharmaceuticals Inc., Connecticut, USA), 3 wt% HPMC, and 0.1% (w/w) sodium lauryl sulfate was milled in a DYNO Mill KDL (Willy A. Bachofen A. G., Maschinenfabrik, Basel, Switzerland) with a 300 mL glass batch chamber and utilizing 0.1-0.2 mm zirconium oxide beads (85% of the chamber volume). The milling was conducted for 120 min at a tip speed of 22.5 m/s. The particle size (D50) after milling was 106 nm.

Example 38. Milling of Aqueous Ganaxolone Dispersion Containing HPMC (Continuous Mode)

[00504] Powdered ganaxolone aqueous dispersion (1200 g) comprising a mixture of 20 wt% ganaxolone and 3 wt% HPMC was milled in a DYNO Mill KDL with a 600 mL SiC lined continuous chamber and 0.4 mm yttrium stabilized zirconium oxide beads (88% volume loading). The milling slurry was re-circulated via a peristaltic pump (250 mL/min) through a jacketed stainless steel holding tank chilled between 0-12 °C. The tip speed was 10 m/s. The product temperature at the outlet was kept below 45 °C. The progress of the milling run was followed by particle size measurement (D50) at various time points. After 2 hours of milling, the slurry with a D50 of 330 nm was filtered through a 10 µm cartridge and stored refrigerated.

Example 39. Milling of Aqueous Ganaxolone Dispersion Containing HPMC (Continuous Mode)

[00505] Powdered ganaxolone aqueous dispersion (1000 g) comprising a mixture of 15 wt% ganaxolone and 2.5 wt% HPMC was milled in a DYNO Mill KDL as described for Example 38. After 70 min residence time, D50 was 125 nm. The slurry was split into 6 portions (Ex-39A-F) and different excipients were added to each portion. The final amounts of the excipients of each formulation are listed in the Table 27.

TABLE 27						
Formulation	A	B	C	D	E	F
HPMC% (w/w)	2.5	2.5	2.5	5.0	2.5	7.5
SLS% (w/w)	0	0	0.3	0.1	0	0.3
DOSS% (w/w)	0	0	0	0	0.1	0

Example 40. Milling of Ganaxolone Particles In Aqueous Medium Containing HPMC and Sodium Lauryl Sulfate (Continuous Mode)

[00506] Ganaxolone particles in deionized water (1200 g) containing 15 wt% ganaxolone, 3 wt% HPMC, and 0.05 wt% Sodium lauryl sulfate was milled in a DYNO Mill KDL with a 600 mL SiC lined continuous chamber and 0.4 mm yttrium

stabilized zirconium oxide beads (90% volume loading). The milling slurry was re-circulated via a peristaltic pump (250 mL/min) through a jacketed stainless steel holding tank chilled between 0-12 °C. The tip speed was 10 m/s. The product temperature at the outlet was kept below 45 °C. About 15 min into the milling, additional 0.05% SLS was added as a concentrated solution. The progress of the milling run was followed by particle size measurement (D50) at various residence time points (plot shown in FIGURE 4). After milling, the slurry was filtered through a 10 µm cartridge and stored refrigerated. Residence times of approximately 30 minutes or more produced sub-micron ganaxolone particles having D50 of 100 nm to 150 nm.

Example 41. Milling of Ganaxolone Particles In Aqueous Medium Containing HPMC, Sodium Lauryl Sulfate, Polyvinyl Alcohol, Methylparaben and Propylparaben (Continuous Mode)

[00507] Ganaxolone particles in deionized water (1000 g) containing 15 wt% ganaxolone, 3 wt% HPMC, 1 wt% polyvinyl alcohol, 0.1 wt% methylparaben, 0.02 wt%, and propylparaben was milled in a DYNO Mill KDL with a 600 mL SiC lined continuous chamber and 0.4 mm yttrium stabilized zirconium oxide beads (90% volume bead loading). The milling was conducted according to the method described in Example 38. During the milling, two portions of 0.025% (w/w) of sodium lauryl sulfate were added as a concentrate solution. After 72.9 min of residence time, the D50 was 153 nm. The milling slurry was split into three containers, additional sodium lauryl sulfate was added to two of the containers so that the total SLS levels reached 0.1 and 0.2% w/w respectively. The slurries were stored at ambient temperature and particle size became fully sable after 6 days (D50 values: 205, 188 and 193 respectively).

Example 42. Milling of Ganaxolone Particles In Aqueous Medium Containing HPMC, Sodium Lauryl Sulfate, Polyvinyl Alcohol, Methylparaben, Propylparaben and Simethicone (Continuous Mode)

[00508] Ganaxolone particles in deionized water (1200 g) containing 25 wt% ganaxolone, 5 wt% HPMC, 1 wt% polyvinyl alcohol, 0.1 wt% sodium lauryl sulfate, 0.1 wt% methylparaben, 0.02 wt% propylparaben, and 0.1 wt% simethicone in

deionized water was milled in a DYNO Mill KDL with a 600 mL SiC lined continuous chamber and 0.4 mm yttrium stabilized zirconium oxide beads (90% volume bead loading). The milling was conducted according to the method described in Example 38. After 27.5 min of residence time, the D50 was 180 nm. The milling slurry was filtered through a 10 μ m cartridge and diluted (2x) with diluent 5% (w/w) HPMC, 1% (w/w) polyvinyl alcohol, 0.1% (w/w) sodium lauryl sulfate, 0.1% (w/w) methylparaben and 0.02% (w/w) propylparaben and 0.1% (w/w) simethicone and stored at ambient temperature for particle size to stabilize. The D50 became 327 nm after the particles were fully cured.

Example 43. Milling of Ganaxolone Particles In Aqueous Medium Containing HPMC, Sodium Lauryl Sulfate, Polyvinyl Alcohol, Sodium Benzoate, Citric Acid and Sodium Citrate (Continuous Mode)

[00509] Ganaxolone particles in deionized water (1200 g) containing 25 wt% ganaxolone, 5 wt% HPMC, 1 wt% polyvinyl alcohol, 0.1 wt% sodium benzoate, 0.12 wt% citric acid, 0.1 wt% sodium lauryl sulfate, 0.0093 wt% sodium citrate, and 0.025 wt% simethicone was milled in a DYNO Mill KDL with a 600 mL SiC lined continuous chamber and 0.4 mm yttrium stabilized zirconium oxide beads (90% volume bead loading). The milling was conducted in the same fashion as described in Example 38. After 25.0 min of residence time, the D50 was 160 nm. The milling slurry was filtered through a 10 μ m cartridge and stored at ambient temperature. Its particle size (D50) became 361 nm after 4 weeks.

Example 44. Milling of Ganaxolone Particles In Aqueous Medium Containing HPMC, Sodium Lauryl Sulfate, Polyvinyl Alcohol, Methylparaben and Propylparaben (Continuous Mode)

[00510] Ganaxolone particles in deionized water (1200 g) containing 25 wt% ganaxolone, 3 wt% HPMC, 1 wt% polyvinyl alcohol, 0.1 wt% sodium lauryl sulfate, 0.1 wt% methylparaben and 0.02 wt% propylparaben was milled in a DYNO Mill KDL with a 600 mL SiC lined continuous chamber and 0.4 mm yttrium stabilized zirconium oxide beads (90% volume bead loading). The milling was conducted according to the method described in Example 43. After 25.4 min of residence time, the D50 was 162 nm. The milling slurry was filtered through a 10 μ m cartridge and diluted (2x) with diluent containing 7.5% (w/w) HPMC, 1% (w/w) polyvinyl alcohol,

0.1% 9w/w) sodium lauryl sulfate, 0.1% (w/w) methylparaben and 0.02% (w/w) propylparaben in water to obtain a liquid dispersion. The dispersion was stored at ambient temperature for particle size to stabilize. The D50 was 306 nm after 2 days and 380 nm in 4 weeks. Additional additives, for example flavoring agent and a sweetener, can be added to the liquid dispersion either before or after curing to obtain the final ganaxolone particle formulation.

Example 45. Re-milling of Aqueous Ganaxolone Slurry Containing HPMC, Sodium Lauryl Sulfate, Polyvinyl Alcohol, Methylparaben, and Propylparaben (Continuous Mode)

[00511] The final milling slurry obtained in Example 44 was re-milled two days later according to the method described in Example 44 for 69 min of residence time. The D50 was 164 nm. It became 200 nm in 7 to 10 days and remained the same when tested 6 months later.

Example 46. Milling of Aqueous Ganaxolone Dispersion Containing HPMC (Continuous Mode)

[00512] Powdered ganaxolone aqueous dispersion (1200 g) comprising a mixture of 15 wt% ganaxolone and 3 wt% HPMC was milled in a DYNO Mill KDL as described for Example 38. During milling, 2 portions of 0.05% w/w sodium lauryl sulfate were added to keep the milling slurry fluid. After 50.8 minutes of residence time, D50 was 116 nm.

Example 47. Milling of Aqueous Ganaxolone Dispersion Containing HPMC, sodium lauryl sulfate and simethicone (Continuous Mode)

[00513] Powdered ganaxolone aqueous dispersion (1200 g) comprising a mixture of 30 wt% ganaxolone and 5 wt% HPMC, 0.2 wt% sodium lauryl sulfate and 100 ppm simethicone was milled in a DYNO Mill KDL as described for Example 38. After 24.0 minutes of residence time, D50 was 163 nm.

Example 48. Milling of Aqueous Ganaxolone Dispersion Containing HPMC, sodium lauryl sulfate and simethicone (Continuous Mode)

[00514] Powdered ganaxolone aqueous dispersion (1200 g) comprising a mixture of 25 wt% ganaxolone and 5 wt% HPMC, 0.3 wt% sodium lauryl sulfate and 100 ppm simethicone was milled in a DYNO Mill KDL as described for Example 38. After 67.7 minutes of residence time, D50 was 145 nm.

Example 49. Milling of Aqueous Ganaxolone Dispersion Containing HPMC, sodium lauryl sulfate and simethicone (Continuous Mode)

[00515] Powdered ganaxolone aqueous dispersion (1500 g) comprising a mixture of 25 wt% ganaxolone and 5 wt% HPMC, 0.1 wt% sodium lauryl sulfate and 0.028% simethicone 30% emulsion was milled in a DYNO Mill KDL as described for Example 38, except the tip speed was 15 m/s. After 39 minutes of residence time, D50 was 113 nm.

Example 50. Milling of Aqueous Ganaxolone Dispersion Containing HPMC, sodium lauryl sulfate and simethicone (Continuous Mode)

[00516] Three additional milling runs were performed in the same fashion as described for Example 46 except on larger scales. The residence time was 33, 35, and 34 minutes respectively and at the end of milling, the D50 was 143, 139, and 155 nm (after 1 minute sonication) respectively. The milled slurries from these runs were diluted in a two-step fashion as described in Example 21 to 50 mg/mL ganaxolone formulations with appropriate levels of excipients such as HPMC, PVA and SLS and other desirable components such as preservatives, sweetener and artificial flavors. The D50 values of the 50 mg/mL formulations were 320, 295, and 315 nm respectively.

Example 51. Milling of Aqueous Ganaxolone Dispersion with Complexing Agent for Solid Dosage Form

[00517] Ganaxolone was wet milled in a 600 ml chamber using a DYNO-Mill KDL equipped with four 64 mm polyurethane agitator discs. The mill was operated at 3000 RPM or a tip speed of 10 m/sec. The mill was loaded with 88 vol% of 0.4 mm yttrium stabilized zirconium oxide beads. The milling slurry (1200 gm) contained 25 wt% ganaxolone, 5 wt% hydroxypropyl methylcellulose (Pharmacoat 603), 0.0333wt%

30% simethicone emulsion, 0.3 wt% sodium lauryl sulfate and 0.2 wt% methylparaben. This slurry was circulated through the mill via a peristaltic pump and returned to a cooled reservoir where it was re-circulated through the mill. The mill was operated in this recirculation mode, keeping the slurry temperature at 35 – 40 °C, for a total of 410 minutes. Using a free or void volume of 262 ml in the mill, a residence time of 90 minutes was calculated. The product slurry was filtered through a 20 micron polypropylene cartridge filter to give 1185 g of milled ganaxolone slurry. The particle size (D50) measured on a Horiba LA 910 was 164 nm without sonication /153 nm with 1 min. sonication at low power. After 7 days the particle size increased to 320 nm /309 nm sonicated. The D50 did not change after this curing period for the duration of all other studies conducted with this formulation.

Example 52. Milling of Aqueous Ganaxolone Dispersion without Complexing Agent for Solid Dosage Form

[00518] Ganaxolone was wet milled in a 600 ml chamber using a DYNO-Mill KDL equipped with four 64 mm polyurethane agitator discs. The mill was operated at 4000 RPM or a tip speed of 15 m/sec. The mill was loaded with 88 vol% of 0.4 mm yttrium stabilized zirconium oxide beads. The milling slurry (1200 gm) contained 25 wt% ganaxolone, 5 wt% hydroxypropylmethyl cellulose (Pharmacoat 603), 0.3% sodium lauryl sulfate and 0.033 wt% simethicone emulsion (30% in water, Dow Corning Q7-2587). This slurry was circulated through the mill via a peristaltic pump and returned to a cooled reservoir where it was re-circulated through the mill. The mill was operated in this recirculation mode, keeping the slurry temperature at 40 to 50 °C, for a total of 340 minutes. Using a free or void volume of 262 ml in the mill, a residence time of 75 min. is calculated. The product slurry was filtered through a 20 micron polypropylene cartridge filter to give 1271 gm of milled ganaxolone slurry. The particle size (D50) measured on a Horiba LA 910 was 103 nm / 102 nm sonicated. After 7 days the particle size increased slightly to 136nm / 112 nm sonicated.

Example 53. Immediate Release Ganaxolone 300 mg Capsules With and Without Complexing Agent

[00519] Suspensions (1200 grams) in water containing 25 wt% ganaxolone, 5.0% wt% hydroxypropyl methylcellulose (Pharmacoat 603), 0.0333 wt% of 30% simethicone emulsion, and 0.2 wt% sodium lauryl sulfate, either with 0.05 wt% methylparaben

(capsule Ex. 1) or with no methylparaben (capsule Ex. 2, 5.2 wt% of HPMC instead of 5 wt%) are prepared. Each wt% is based on the total weight of the suspension.

[00520] The ganaxolone particles are milled using conditions as described in Example 51. For formulations with complexing agent (Capsule Form 1), ganaxolone nanoparticles having a particle size (D50) of about 120 nm as measured by Horiba LA 910 particle size analyzer are obtained immediately after milling. This volume-weighted-median particle size grows to about 220 nm after 7 days of curing at ambient temperature, indicating that ganaxolone complex is formed. The D50 does not change after this curing period for the duration of the study. For Capsule Form 2 (without complexing agent), ganaxolone nanoparticles having the same particle size (D50) (about 120 nm) are obtained immediately after milling.

[00521] Sucrose (48.5 g) and NaCl (6.5 g) (together about 13 wt% of solids) and water (800 ml) is added to each of the ganaxolone suspensions for Capsule Form 1 and 2 and the resulting mixtures are homogenized for 20 minutes for spray drying. The compositions of the mixtures to be spray dried are given in Table 28.

TABLE 28. Composition of spray mixture prior to spray layering				
	Capsule Example 1		Capsule Example 2	
	Ganaxolone Complex		Ganaxolone (No Paraben)	
Component	Weight, gram	Wt% /total solid wt, %	Weight, gram	Wt% based on total solid weight, %
Ganaxolone	300	71.7	300	71.4
HPMC	60	14.3	62.4	14.9
Simethicone	0.12	0.03	0.12	0.03
SLS	2.4	0.57	2.4	0.57
Methylparaben	0.60	0.14	0	0
Sucrose	48.5	11.6	48.5	11.5
Sodium chloride	6.5	1.6	6.5	1.5
Total	418.12	100	419.92	100

(1)

[00522] For each of Capsule Form 1 and 2, 100 grams of microcrystalline cellulose (MCC) beads (e.g. Celsphere, 30/35 mesh) are added to a Glatt GPCG-3 fluidized bed with Wurster column insert (4 inch), inlet temperature of about 55°C and air temp of about 40°C (total air volume approx. 175 cubic cm/hr). About 2000 grams of each spray mixture are sprayed (bottom spray) through 1.2 mm nozzles at 11 mls/min and 1.5 bar of pressure until a layering of about 400 wt% is achieved as compared to initial beads weight. The theoretical compositions of the spray layered ganaxolone complex particles (Capsule Form 1) and ganaxolone particles (Capsule Form 2) are shown in Table B. Actual Spray layering yields have been > 90% theoretical for both form 1 and 2.

TABLE 29. Composition of spray layered particles after spray drying				
	Capsule Form 1		Capsule Form 2	
	Ganaxolone Complex		Ganaxolone (No Methyl Paraben)	
Component	Weight, gram	Wt% /total solid wt, %	Weight, gram	Wt% based on total solid weight, %
Ganaxolone	300	57.9	300	57.7
HPMC	60	11.6	62.4	12.0
Simethicone	0.12	0.02	0.12	0.02
SLS	2.4	0.46	2.4	0.46
Methylparaben	0.60	0.12	0	0
Sucrose	48.5	9.4	48.5	9.3
NaCl	6.5	1.25	6.5	1.25
MCC beads	100	19.3	100	19.2
Total	518.12	100	519.92	100

[00523] The spray layered ganaxolone complex particles (Capsule Form 1) or ganaxolone particles (Capsule Form 2) are then filled into gelatin capsules with a fill weight of 518-520 mg coated beads to achieve a 300 mg dose.

Examples 54. Delayed Release Ganaxolone 300 mg Capsules (With and Without Complexing agent)

[00524] Ganaxolone containing immediate release beads (500 g, Capsule Form 1) or ganaxolone multiparticulates (500 g, Capsule Form 2) prepared as described in Example 53 and as shown in Table 30 are loaded directly into a rotary granulator/coater (Freund CF-360 granulator) for enteric coating. The rotating particle bed is sprayed with a coating solution containing 50 wt% Eudragit® L 30-D55, 2.5 wt% talc, 1.5 wt% dibutyl sebacate, 20 wt% ethanol, 23.5 wt% isopropyl alcohol, and 2.5 wt% water. A coating level of about 8 wt% is achieved. The ganaxolone content in each coated bead is about 53.4 wt% based on the total weight of the coated beads.

[00525] About 295 mg of uncoated capsule Form 1 or 2 and 240 mg coated beads from capsule Form 1 or 2 thus obtained are hand-filled into gelatin capsule shells, respectively, to form modified release ganaxolone complex 300 mg capsules (Capsule Form 3) or ganaxolone 300 mg modified release capsules without methylparaben (Capsule Form 4). These particulates are substantially insoluble in the stomach due to the enteric coating but substantially soluble in the intestine. The total capsule fill weight is 565 mg.

Example 55. Pulsatile Release Ganaxolone 300 mg Capsules (With and Without Complexing Agent)

[00526] For Capsule Form 5, uncoated ganaxolone beads obtained for Capsule Form 1 and as described in Table 29 are mixed with coated ganaxolone obtained for Capsule Form 3 (Example 54) at a 60 wt% to 40 wt% ratio to obtain a mixture. About 540 mg of the blended mixture is hand-filled in a hard gelatin capsule to obtain a pulsatile ganaxolone complex 300 mg capsule.

[00527] Similarly, for Capsule Form 6, uncoated ganaxolone multiparticulates obtained for Capsule Form 2 and as described in Table 29 are mixed with coated ganaxolone multiparticulates obtained for Capsule Form 4 at a 40 wt% to 60 wt% ratio to obtain a mixture. The ganaxolone content in the mixture is about 55.5 wt%. About 540 mg of the blended mixture is filled in a gelatin capsule to obtain a pulsatile ganaxolone 300 mg capsule (without complexing agent).

Examples 56. Ganaxolone 300 mg Capsules in Swelling Plug Devices (With and Without Complexing Agent)

[00528] About 520 mg of the beads obtained above in Example 53, Capsule Forms 1 and 2, are hand-filled into a swelling plug device as described previously. The half-capsule shell is made from a poly(methylmethacrylate) material which does not dissolve in the stomach. The open end of the capsule shell is plugged with a cylindrical plug formed from a co-poly(alkylene oxide) crosslinked by reaction with unsaturated cyclic ether group. The plugged capsule half is finally sealed with a water-soluble gelatin to obtain ganaxolone complex 300 mg capsule (Capsule Form 7) and ganaxolone 300 mg capsule (without methyl paraben) (Capsule Form 8).

Example 57. Delayed Release Ganaxolone 300 mg Capsules in Swelling Plug Devices (With and Without Complexing Agent)

[00529] The sealed devices obtained in Example 56, with and without complexing agent, are further coated with an enteric coating to obtain delayed release ganaxolone complex 300 mg device (Capsule Form 9) and ganaxolone 300 mg device (without methylparaben) (Capsule Form 10). For example, the sealed devices are coated in a Hi-Coater (Vector Corp., Marion, Iowa, USA) with a coating solution containing 50 wt% Eudragit® L 30-D55, 2.5 wt% talc, 1.5 wt% dibutyl sebecate, 20 wt% ethanol, 23.5 wt% isopropyl alcohol, and 2.5 wt% water. A coating level of about 10 wt% is achieved. The coated devices are substantially insoluble in the stomach but substantially release all ganaxolone in the intestine

Example 58. Pulsatile Release Ganaxolone Tablets Containing a Modified Release Inner Core and an Immediate Release Coating

[00530] The following is the process for preparing pulsatile release ganaxolone tablets in accordance with the invention. In this formulation the relative amounts of water-soluble film-forming substance (polyvinylpyrrolidone) and water-insoluble film-forming substance (ethylcellulose) in the second coat of the encapsulated pellets are in the ratio of 1:20.

[00531] Ganaxolone particle suspension formulation (12.6% ganaxolone, 2.6% HPMC, 0.026% SLS, 0.018% simethicone emulsion (30% simethicone in water), 0.3% sodium chloride and 2.4% sucrose is dried by rotary evaporation and spray

layered onto sucrose beads. The spray layered form is prepared by evaporating the layering slurry onto sugar beads (Paulaur 30/35 mesh) through a fluidized bed coating process yielding approximately 60% ganaxolone loading (%wt GNX/% total bead wt).

[00532] The resulting spray layered beads are dried (40° C., 5-10 hr.) and screened, first through a 12-mesh screen to remove aggregates and then over a 20-mesh screen to remove fines.

[00533] The ganaxolone containing beads (25 kg) are tumbled in a coating pan and simultaneously dusted with talc (USP, 1.28 kg.) containing blue dye (FD & C Blue No. 1 Lake Dye, 0.0129 kg.) and sprayed with a solution of polyvinylpyrrolidone (0.0570 kg.) and ethylcellulose (50 c.p.s., 1.14 kg.) in ethanol (alcohol, 95%, 27.3 kg). The second coat as thus constituted consists of 2% water-soluble film-forming substance, 46% water-insoluble film forming substance and 52% dusting powder. The resulting encapsulated beads are dried (40° C.) to a moisture content between 0.6% and 1.0% and screened successively through 12-mesh and 20-mesh screens. The encapsulated beads as thus constituted of sugar beads, ganaxolone particles as first coat and PVP, ethylcellulose second coat.

[00534] A mixture of anhydrous lactose (4 kg.), microcrystalline cellulose (5.14 kg.), ethylcellulose (50 c.p.s., 2.8 kg.) and hydrogenated vegetable oil (1.19 kg.) is milled, and blended with 25 kg of encapsulated ganaxolone beads. The resulting blend is compressed into tablets, each weighing 700 mg and each containing 300 mg of ganaxolone. The tableting mixture as thus constituted consists of 17.5% diluent, 22.7% diluent-binder, 12% binder and 5.22% hydrophobic lubricant and 42.5% ganaxolone. The tablets as thus constituted consist of encapsulated beads and tableting mixture.

Example 59. Enterically Coated Ganaxolone Tablets

[00535] Ganaxolone particle suspension formulation Ex-52 after curing for 7 days with the addition of 0.05% methylparaben is prepared as a spray granulate containing sucrose (3%) and sodium chloride (1.5%). The resulting granulate is dried (40° C., 5-10 hr.) and screened, first through a 12-mesh screen to remove aggregates and then over a 20-mesh screen to remove fines.

[00536] Prosolv 90, Ganaxolone spray granulate, and Dipotassium Phosphate Powder, are added sequentially into a Bohle Bin Blender (BL07C, Warminster, Pennsylvania,

USA) and blended for 10 ± 0.1 minutes at 11 ± 1 rpm. Additional Prosolv 90 and Sodium Starch Glycolate are added and blended for 10 ± 0.1 minutes at 11 ± 1 rpm. The material is then milled and then passed through a 0.5 mm screen (35 Mesh).

Blend Component	Weight	% w/w
Silicified Microcrystalline Cellulose, NF (Prosolv 90)	4.255 kg	37.0
Sodium Starch Glycolate, NF, EP	0.230 kg	2.00
Sodium Chloride	0.287 kg	2.5
Magnesium Stearate	0.0575 kg	0.5
Dipotassium Phosphate Powder, USP, PE	0.230 kg	2.00
Ganaxolone spray granulate	6.44 kg	56.0
Totals	11.5 kg	100.0

[00537] The Ganaxolone Blend is loaded into a tablet compressing machine, such as a Fette 1200 B Tool Tablet Press (TP06) or equivalent, and tablets are formed using oval upper and lower punches. Tablets are obtained having an average core tablet weight of 750.0 mg (containing approx. 300 mg ganaxolone) with average acceptable upper and lower tablet weight limits of $\pm 5.0\%$.

[00538] Friability is determined by Current USP <1216> at the beginning and end of each compression run and is NMT 0.5%. Disintegration times are determined using Current USP <701> at the beginning and end of each compression batch.

Disintegration time is NMT 5 minutes.

[00539] An enteric coat is applied to the tablet cores as follows: The enteric coating comprising Opadry® Enteric from Colorcon® and the over coat comprising Opadry® clear applied sequentially as aqueous coating suspensions using a coating pan. The tablet cores are preheated to 46°C (Exhaust air temperature). The pan speed is adjusted to provide adequate tablet flow and the coating suspensions are sprayed onto the tablets at an atomizing air pressure of 18 – 30 psi; an inlet air temperature of 60 – 70°C for over coat, and of 42 – 50°C for the enteric coat; an exhaust air temperature of 40 to 50°C for the over coat and 30 to 35°C for the enteric coat; a spray rate of 15 to 50 ml/ min.; and an inlet air flow of 175 to 300 CFM. One of skill in the art will understand that the processing parameters for coating are dependent in part upon the size of the batch to be coated and can be adjusted accordingly. The enteric coating should be applied so that a tablet core weight gain of 8 – 15% w%/ tablet core weight

is achieved. Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, a methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, or a combination comprising one or more of the foregoing enteric polymers may be used in place of the Opadry Enteric coating.

Example 60. Ganaxolone Immediate Release Tablet

[00540] Ganaxolone tablet core are prepared as described above in Example 59. Over coat comprising Opadry® clear is applied as an aqueous coating suspensions using a coating pan. The tablet cores are preheated to 46°C (Exhaust air temperature). The pan speed is adjusted to provide adequate tablet flow and the coating suspensions are sprayed onto the tablets at an atomizing air pressure of 18 – 30 psi; an inlet air temperature of 60 – 70°C, an exhaust air temperature of 40 to 50°C, a spray rate of 15 to 50 ml/ min.; and an inlet air flow of 175 to 300 CFM. A color coating such as Colorcon Opaspray or Opalux may be applied prior to the final application of Opadry clear to provide a colored tablet.

Example 62. Enterically Coated Ganaxolone Tablets Containing Sugar Beads

[00541] Ganaxolone particle suspension formulation with or without complexing agent is prepared as a described in Examples 52 (Ex-52A, containing 0.05% methylparaben and cured for 7 days) and 52 (Ex-52, no complexing agent). To each of these compositions is added sucrose (3%) and sodium chloride (1.5%). Sufficient water is added as in Example 53 to make a dispersion containing about 18% solid content.

[00542] For each of the particle suspensions 100 grams of sugar beads (e.g. Paulaur 30/35 mesh) are added to a Glatt GPCG-3 fluidized bed with Wurster column insert (4 inch), inlet temperature of about 55°C and air temp of about 40°C (total air volume approx. 175 cubic cm/hr). About 2000 grams of each spray mixture are sprayed (bottom spray) through 1.2 mm nozzles at 10 mls/min and 1.5 bar of pressure until a layering of about 400 wt% is achieved as compared to initial sugar beads weight. The compositions of the spray layered ganaxolone particles on a sugar bead containing 60% Ganaxolone or ganaxolone complex particles by total bead weight is achieved. Lactose monohydrate, ganaxolone beads, and dipotassium phosphate powder, are added sequentially into a Bohle Bin Blender (BL07C, Warminster, Pennsylvania,

USA) and blended for 10 ± 0.1 minutes at 11 ± 1 rpm. Additional Prosolv 90 and sodium starch glycolate are added and blended for 10 ± 0.1 minutes at 11 ± 1 rpm. The material is then milled and then passed through a 0.5 mm screen (35 Mesh).

Blend Component	Weight	% w/w
Lactose monohydrate	3.128 kg	27.2
Sodium Starch Glycolate, NF, EP	0.230 kg	2.00
Sodium Chloride	0.287 kg	2.5
Magnesium Stearate	0.0575 kg	0.5
Dipotassium Phosphate Powder, USP, PE	0.230 kg	2.00
Ganaxolone spray layered beads	7.567 kg	65.8
Totals	11.5 kg	100.0

[00543] The Ganaxolone Blend is loaded into a tablet compressing machine, such as a Fette 1200 B Tool Tablet Press (TP06) or equivalent, and tablets are formed using oval upper and lower punches. Tablets are obtained having an average core tablet weight of 790 mg (containing 300 mg ganaxolone) with average acceptable upper and lower tablet weight limits of $\pm 5.0\%$.

[00544] Friability and disintegration times are as described in Example 59.

[00545] An enteric coat is applied to the tablet cores as follows: The enteric coating comprising Opadry[®] Enteric from Colorcon[®] and the over coat comprising Opadry[®] clear applied sequentially as aqueous coating suspensions using a coating pan. The tablet cores are preheated to 46°C (Exhaust air temperature). The pan speed is adjusted to provide adequate tablet flow and the coating suspensions are sprayed onto the tablets at an atomizing air pressure of 18 – 30 psi; an inlet air temperature of 60 – 70 °C for over coat, and of 42 – 50°C for the enteric coat; an exhaust air temperature of 40 to 50°C for the over coat and 30 to 35°C for the enteric coat; a spray rate of 15 to 50 ml/ min.; and an inlet air flow of 175 to 300 CFM. One of skill in the art will understand that the processing parameters for coating are dependent in part upon the size of the batch to be coated and can be adjusted accordingly. The enteric coating should be applied so that a tablet core weight gain of 8 – 15% w%/ tablet core weight is achieved. Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, a methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, or a

combination comprising one or more of the foregoing enteric polymers may be used in place of the Opadry Enteric coating.

EXAMPLE 63: Pharmacokinetic Analysis Of 200 Mg Of Ganaxolone Complex Suspension (50mg/ml) Containing Pva Administered In 6 Healthy Volunteers In The Fasted State.

[00546] Following an overnight fast of at least 10 hours, 6 healthy subjects were administered ganaxolone (4 ml of a 50 mg/ml suspension manufactured as in example 50 as the ganaxolone complexed composition) with 240 mL (8 fluid ounces) of water. No food allowed for at least 4 hours post-dose. Water was allowed as desired except for one hour before and after drug administration. Other oral fluids (juices, coffee, carbonated beverages etc.) were not permitted from 4 hours pre-dose to 4 hours post-dose. Grapefruits or grapefruit juice intake was prohibited during the entire study. A standardized meal was provided at 4 hours post-dose.

[00547] Blood samples (4 ml) for PK analysis were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours following dosing using dipotassium EDTA as the anti-coagulant. Plasma was generated by centrifugation at around 4-8k RPM for 15 minutes at 0 °C, frozen below -20°C for storage and shipping and analyzed using a validated HPLC/MS/MS/MS method with an LOQ of 1 ng/ml. Results yielded a mean C_{max} of 37 ± 25 ng/ml and an AUC₍₀₋₂₄₎ of 184 ± 104 ng*h/ml.

EXAMPLE 64: Effect Of Freeze/Thaw Cycles On The Stability Of Ganaxolone Formulations With And Without A Complexing Agent

[00548] Ganaxolone formulations Ex-51 and Ex-52 (with and without complexing agent as described in Examples 51 and 52 respectively), were tested for freeze thaw stability as follows:

[00549] 10 gm of each formulation was placed into a 25 ml HDPE scintillation vial with HDPE cap. These were placed into a 500 ml glass beaker containing approx. 1 inch of Styrofoam packing (to slow freezing process) and placed into an insulated carton containing crushed dry ice. The vials were stored overnight and then thawed at room temperature for 1 hour. This process was repeated for the same vials 2x comprising 3 freeze/thaw cycles. The particle size for each formulation was measured by the method already described and compared to control material stored at room temperature in the same container closure system.

Table 30. Particle size (D50) before and after freezing/thaw cycles for ganaxolone particles with and without a complexing agent (methylparaben)		
Formulation	Initial D50 (nm) Before/after 1 min sonication	D50 (nm) after 3 freeze/thaw cycles Before/after 1min sonication
Ex-51	320/298	319/310
Ex-52	149/140	822/341

We Claim:

1. A composition comprising particles comprising ganaxolone, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.
2. A composition comprising particles comprising ganaxolone; and a complexing agent, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.
3. A composition comprising particles comprising ganaxolone; and an ionic dispersion modulator, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.
4. A composition comprising particles comprising ganaxolone; and a vinyl polymer, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.
5. A composition comprising particles comprising ganaxolone; and an effective amount of a complexing agent to stabilize the particle growth after an initial particle growth and endpoint is reached, wherein the volume weighted median diameter (D50) of the particles before the initial growth is from about 50 to about 200 nm and the D50 after the endpoint is reached is from about 100 nm to about 350 nm.
6. A composition comprising particles comprising ganaxolone; and an effective amount of an ionic dispersion modulator to reduce agglomeration of the particles, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 350 nm.
7. A composition comprising particles comprising ganaxolone; and a complexing agent in an amount of from about 0.1% to about 5%, w/w, based on the weight of the composition, wherein the volume weighted median (D50) of the particles is from about 50 nm to about 350 nm.

8. A composition comprising particles comprising ganaxolone; and an ionic dispersion modulator in an amount of from about 1% to about 50%, w/w, based on the weight of the composition, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 350 nm.
9. A composition comprising particles comprising ganaxolone; and a hydrophilic polymer, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.
10. A composition comprising particles comprising ganaxolone; a hydrophilic polymer; and a wetting agent, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.
11. A composition comprising particles comprising ganaxolone; a hydrophilic polymer; a wetting agent; and a complexing agent, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.
12. A composition comprising particles comprising ganaxolone; a hydrophilic polymer; a wetting agent; a complexing agent; and an ionic dispersion modulator.
13. A composition comprising:
 - particles comprising ganaxolone in an amount from about 10% to about 80%, w/w, based on the total weight of the composition;
 - a hydrophilic polymer in an amount from about 3% to about 50%, w/w, based on the weight of the composition;
 - a wetting agent in an amount from about 0.05% to about 2%, w/w, based on the weight of the composition;
 - a complexing agent in an amount from about 0.1% to about 5%, w/w, based on the weight of the composition; and
 - an ionic dispersion modulator in an amount from about 1% to about 50%, w/w, based on the weight of the composition.
14. The composition of claim 13, wherein the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, polyvinyl alcohol and a mixture

thereof; the wetting agent is sodium lauryl sulphate; the complexing agent is selected from the group consisting of a paraben, benzoic acid and a mixture thereof; and the ionic dispersion modulator is sodium chloride.

15. The composition of claim 1, further comprising an excipient selected from the group consisting of a hydrophilic polymer, a wetting agent, a complexing agent, an ionic dispersion modulator, a water soluble spacer, and a mixture thereof.
16. A solid formulation comprising stable ganaxolone particles and at least one pharmaceutically acceptable excipient, the stable ganaxolone particles exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 200% when the formulation is dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg ganaxolone/mL and placed in a heated bath at 36° to 38° C for 1 hour, as compared to the D50 of the ganaxolone particles when the formulation is dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the ganaxolone particles dispersed in distilled water is from about 50 nm to about 1000 nm.
17. The solid formulation of claim 16, in the form of a tablet or capsule containing the stable ganaxolone particles and at least one excipient, the stable ganaxolone particles exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 200% when the tablets or capsules are dispersed in SGF or SIF at a concentration of 0.5 to 1 mg ganaxolone/mL at 36° to 38° C using a Type II dissolution apparatus and a stirring rate of 75 RPM for 1 hour, as compared to the D50 of the ganaxolone particles when the tablets or capsules are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the ganaxolone particles when the tablets or capsules are dispersed in distilled water is from about 50 nm to about 1000 nm.
18. A solid formulation comprising stable ganaxolone particles and at least one pharmaceutically acceptable excipient, the stable ganaxolone particles exhibiting a volume weighted median diameter (D50) of less than about 750 nm when the formulation is dispersed in simulated gastric fluid (SGF) for one hour followed by

simulated intestinal fluid (SIF) for three additional hours, at a concentration of 0.5 to 1 mg ganaxolone/mL at a temperature of 36° to 38° C.

19. The solid formulation of claim 18 in the form of a tablet or capsule containing the stable ganaxolone particles and at least one excipient, the stable ganaxolone particles exhibiting a volume weighted median diameter (D50) of less than about 750 nm when the tablets or capsules are dispersed in simulated gastric fluid (SGF) for one hour followed by simulated intestinal fluid (SIF) for three additional hours, at a concentration of 0.5 to 1 mg ganaxolone/mL at a temperature of 36° to 38° C using a Type II dissolution apparatus and a stirring rate of 75 RPM.
20. The solid formulation of claims 16 or 18 in the form of a powder.
21. The solid formulation of claim 17, wherein the tablet or capsule provides an immediate release of the ganaxolone particles.
22. The solid formulation of claim 19, wherein the tablet or capsule provides a sustained or delayed release of the ganaxolone particles.
23. The solid formulation of claim 16, wherein the stable ganaxolone particles exhibit an increase in volume weighted median diameter (D50) of from 0% to not more than about 200% when the formulation is dispersed in 15 mL of SGF or SIF.
24. The solid formulation of claim 16, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles dispersed in distilled water is from about 100 nm to about 500 nm.
25. The solid formulation of claim 25, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles dispersed in distilled water is from about 100 nm to about 350 nm.
26. The solid formulation of claim 16 or 18, wherein the ganaxolone is in an amount from about 10% to about 80%, w/w, based on the weight of the solid formulation.

27. The solid formulation of claim 16 or 18, wherein the excipient comprises a complexing agent.
28. The solid formulation of claim 27, wherein the complexing agent is in an amount from about 0.05% to about 5%, w/w, based on the weight of the solid formulation.
29. The solid formulation of claim 27, wherein the complexing agent is a substance containing a phenol moiety, an aromatic ester moiety or an aromatic acid moiety.
30. The solid formulation of claim 27, wherein the complexing agent is selected from the group consisting of parabens, organic acids, carboxylic acids, aromatic acids, aromatic esters, acid salts of amino acids, methyl anthranilate, sodium metabisulphite, ascorbic acid and its derivatives, malic acid, isoascorbic acid, citric acid, tartaric acid, sodium sulphite, sodium bisulphate, tocopherol, water- and fat-soluble derivatives of tocopherol, sulphites, bisulphites and hydrogen sulphites, para-aminobenzoic acid and esters, 2,6-di-t-butyl-alpha-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amylhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), pyrocatechol, pyrogallol, propyl/gallate, nordihydroguaiaretic acid, phosphoric acids, sorbic and benzoic acids, esters, ascorbyl palmitate, derivatives and isomeric compounds thereof, pharmaceutically acceptable salts thereof, and mixtures thereof.
31. The solid formulation of claim 27, wherein the complexing agent is selected from the group consisting of parabens, pharmaceutically acceptable salts thereof and mixtures thereof.
32. The solid formulation of claim 27, wherein the complexing agent is selected from the group consisting of benzoic acid, pharmaceutically acceptable salts thereof and mixtures thereof.
33. The solid formulation of claim 31, wherein the paraben is selected from the group consisting of methylparaben, ethylparaben, propylparaben, pharmaceutically acceptable salts thereof and mixtures thereof.

34. The solid formulation of claim 33, wherein the complexing agent is methylparaben in an amount from about 0.05% to about 5%, w/w, based on the weight of the solid formulation.
35. The solid formulation of claim 16 or 18, wherein the excipient comprising a hydrophilic polymer.
36. The solid formulation of claim 35, wherein the hydrophilic polymer is in an amount from about 3% to about 50%, w/w, based on the weight of the solid formulation.
37. The solid formulation of claim 35, wherein the hydrophilic polymer is selected from the group consisting of a cellulosic polymer, a vinyl polymer and mixtures thereof.
38. The solid formulation of claim 37, wherein the cellulosic polymer is a cellulose ether.
39. The solid formulation of claim 38, wherein the cellulose ether is in an amount from about 3% to about 50%, w/w, based on the weight of the solid formulation .
40. The solid formulation of claim 38, wherein the cellulose ether is hydroxypropylmethylcellulose.
41. The solid formulation of claim 37, wherein the vinyl polymer is polyvinyl alcohol.
42. The solid formulation of claim 41, wherein the polyvinyl alcohol is in an amount from about 0.1% to about 5%, w/w, based on the weight of the solid formulation.
43. The solid formulation of claim 16 or 18, wherein the excipient comprises a wetting agent.
44. The solid formulation of claim 43, wherein the wetting agent is in an amount from about 0.01% to about 10%, w/w, based on the weight of the solid formulation.

45. The solid formulation of claim 43, wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, a pharmaceutically acceptable salt of docusate, and mixtures thereof.
46. The solid formulation of claim 16 or 18, wherein the excipient comprises an ionic dispersion modulator.
47. The solid formulation of claim 46, wherein the ionic dispersion modulator is in an amount from about 1% to about 50%, w/w, based on the weight of the solid formulation.
48. The solid formulation of claim 46, wherein the ionic dispersion modulator is a salt.
49. The solid formulation of claim 48, wherein the salt is an inorganic salt.
50. The solid formulation of claim 49, wherein the inorganic salt is selected from the group consisting of a magnesium salt, a calcium salt, a lithium salt, a potassium salt, a sodium salt and mixtures thereof.
51. The solid formulation of claim 50, wherein the inorganic salt is sodium chloride.
52. The solid formulation of claim 48 wherein the salt is an organic salt.
53. The solid formulation of claim 52, wherein the organic salt is selected from the group consisting of a citrate salt, a succinate salt, a fumarate salt, a malate salt, maleate salt, a tartrate salt, a glutarate salt, a lactate salt and mixtures thereof.
54. The solid formulation of claim 16 or 18, wherein the excipient comprises a water soluble spacer.
55. The solid formulation of claim 54, wherein the water soluble spacer is in an amount from about 2% to about 60%, w/w, based on the weight of the solid formulation.

56. The solid formulation of claim 54, wherein the water soluble spacer is a saccharide or an ammonium salt.
57. The solid formulation of claim 56, wherein the saccharide is selected from the group consisting of fructose, sucrose, glucose, lactose, mannitol and mixtures thereof.
58. The solid formulation of claim 16 or 18, wherein the excipient comprises a hydrophilic polymer and a wetting agent.
59. The solid formulation of claim 16 or 18, wherein the excipient comprises a hydrophilic polymer, a wetting agent and a complexing agent.
60. The solid formulation of claim 16 or 18, wherein the excipient comprises a hydrophilic polymer, a wetting agent and an ionic dispersion modulator.
61. The solid formulation of claim 16 or 18, wherein the excipient comprises a hydrophilic polymer, a wetting agent, an ionic dispersion modulator and a complexing agent.
62. The solid formulation of claim 16 or 18, wherein the excipient comprises hydroxypropylmethylcellulose, sodium lauryl sulfate, methylparaben and simethicone.
63. The solid formulation of claim 16 or 18, wherein the excipient comprises hydroxypropylmethylcellulose, sodium lauryl sulfate, methylparaben, sodium chloride and simethicone.
64. The solid formulation of claims 16 or 18, wherein the excipient comprises hydroxypropylmethylcellulose, sodium lauryl sulfate, methylparaben, sodium chloride, polyvinyl alcohol and simethicone.
65. The solid formulation of claims 16 or 18, wherein the excipient comprises hydroxypropylmethylcellulose, polyvinyl alcohol, sodium lauryl sulfate, sodium chloride and methylparaben.

66. The solid formulation of claim 58, further comprising an ionic dispersion modulator.
67. The solid formulation of claim 16 or 18, which is prepared by contacting ganaxolone particles with the excipient such that the size of the particles exhibits an increase in volume weighted median diameter of from about 20% to about 300% and an endpoint is reached such that the particles are stable.
68. The solid formulation of claim 67, wherein the endpoint is from about 1 to about 20 days.
69. The solid formulation of claim 16, exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 150%, not more than about 100%, or not more than about 50%, after being dispersed in 15 ml of simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) in a concentration of 0.5 mg ganaxolone/ml and placed in a heated bath at 36° to 38° C for 1 hour without stirring, as compared to the D50 of the particles dispersed in distilled water at the same concentration, wherein the volume weighted median diameter (D50) of the particles dispersed in distilled water is from about 50 nm to about 1000 nm.
70. The solid formulation of claim 17, exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 150%, not more than about 100%, or not more than about 50%, when the tablets or capsules are dispersed in SGF or SIF at a concentration of 0.5 to 1 mg ganaxolone/mL at 36° to 38° C using a Type II dissolution apparatus and a stirring rate of 75 RPM for 1 hour, as compared to the D50 of the ganaxolone particles when the tablets or capsules are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the ganaxolone particles when the tablets or capsules are dispersed in distilled water is from about 50 nm to about 1000 nm.
71. The solid formulation of claim 18, wherein the stable particles exhibit a volume weighted median diameter (D50) of less than about 750 nm, less than about 600 nm, or less than about 500 nm, when the formulation is dispersed in simulated gastric fluid (SGF) for one hour followed by simulated intestinal fluid (SIF) for three additional

hours, at a concentration of 0.5 to 1 mg ganaxolone/mL at a temperature of 36° to 38° C with or without stirring.

72. The solid formulation of claim 19, wherein the stable particles exhibit a volume weighted median diameter (D50) of less than about 750 nm, less than about 600 nm, or less than about 500 nm, when the tablets or capsules are dispersed in simulated gastric fluid (SGF) for one hour followed by simulated intestinal fluid (SIF) for three additional hours, at a concentration of 0.5 to 1 mg ganaxolone/mL at a temperature of 36° to 38° C using a Type II dissolution apparatus and a stirring rate of 75 RPM.
73. The solid formulation of claim 16 or 18, wherein the excipient is selected from the group consisting of a hydrophilic polymer, a wetting agent, a complexing agent, an ionic dispersion modulator, a water soluble spacer, and mixtures thereof.
74. An oral solid dosage form comprising (i) a controlled release component comprising a first portion of particles comprising ganaxolone; and a controlled release material, and (ii) an immediate release component comprising a second portion of particles comprising ganaxolone, the first and second portion of ganaxolone particles having a volume weighted median diameter (D50) of from about 50 nm to about 1000 nm.
75. The oral dosage form of claim 74, wherein the ratio of ganaxolone in controlled release to immediate release is from about 4:1 to about 1:4.
76. The oral dosage form of claim 74, wherein the ratio of ganaxolone in controlled release to immediate release is from about 3:2 to about 2:3.
77. The oral dosage form of claim 74, wherein the ratio of ganaxolone in controlled release to immediate release is about 1:1.
78. The oral dosage form of claim 74, wherein the volume weighted median diameter (D50) of the particles is from about 100 nm to about 450 nm.
79. The oral dosage form of claim 74, wherein the volume weighted median diameter (D50) of the particles is from about 100 nm to about 350 nm.

80. The oral dosage form of claim 74, further comprising a complexing agent.
81. The pharmaceutical dosage form of claim 74, further comprising a hydrophilic polymer.
82. The oral dosage form of claim 74, further comprising a wetting agent.
83. The oral dosage form of claim 74, further comprising an ionic dispersion modulator.
84. The oral dosage form of claim 74, wherein the controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of ganaxolone particles and overcoated with the controlled release material.
85. The oral dosage form of claim 74, wherein the controlled release component comprises a plurality of matrices comprising the first portion of ganaxolone particles dispersed in the controlled release material.
86. The oral dosage form of claim 74, wherein the controlled release component comprises a tablet comprising the first portion of ganaxolone particles dispersed in the controlled release material.
87. The oral dosage form of claim 74, wherein the controlled release component comprises a granulation comprising the first portion of ganaxolone particles and the controlled release material.
88. The oral dosage form of claim 74, wherein the immediate release component comprises a plurality of pharmaceutically acceptable beads coated with the second portion of ganaxolone particles.
89. The oral dosage form of claim 74, wherein the immediate release component comprises a plurality of matrices comprising the first portion of ganaxolone particles dispersed in an excipient.

90. The oral dosage form of claim 74, wherein the immediate release component comprises a tablet comprising the second portion of ganaxolone particles dispersed in an excipient.
91. The oral dosage form of claim 74, wherein the immediate release component comprises a granulation comprising the second portion of ganaxolone particles and an excipient.
92. The oral dosage form of claim 74, wherein the immediate release component comprises the second portion of ganaxolone particles in powder form.
93. The oral dosage form of claim 74, wherein the controlled release component and the immediate release component are contained in a capsule.
94. The oral dosage form of claim 74, wherein the controlled release component is a tablet and the immediate release component is coated onto the tablet.
95. The oral dosage form of claim 74, wherein the controlled release component and the immediate release component are in a bi-layer tablet.
96. The oral dosage form of claim 74, wherein the controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of ganaxolone particles and overcoated with the controlled release material and the immediate release component comprises a plurality of pharmaceutically acceptable beads coated with the second portion of ganaxolone particles, the controlled release component and immediate release component contained in a capsule.
97. The oral dosage form of claim 74, wherein the controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of ganaxolone particles and overcoated with the controlled release material and the immediate release component comprises a tablet comprising the second portion of ganaxolone particles dispersed in an excipient, the controlled release component and immediate release component contained in a capsule.

98. The oral dosage form of claim 74, wherein the controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of ganaxolone particles and overcoated with the controlled release material and the immediate release component comprises a granulation comprising the second portion of ganaxolone particles and an excipient, the controlled release component and immediate release component contained in a capsule.
99. The oral dosage form of claim 74, wherein the controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of ganaxolone particles and overcoated with the controlled release material, and the immediate release component comprises a granulation comprising the second portion of ganaxolone particles and an excipient, the controlled release component dispersed in the immediate release component in the form of a compressed tablet.
100. The oral dosage form of claim 74, wherein the controlled release component comprises a compressed tablet and the immediate release component is compression coated over the controlled release tablet.
101. The oral dosage form of claim 74, wherein the controlled release material is a hydrophobic material selected from the group consisting of an acrylic polymer, a cellulosic polymer, shellac, zein, fatty alcohols, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, waxes, stearic acid, stearyl alcohol, and mixtures thereof.
102. The oral dosage form of claim 101, wherein the hydrophobic material is pH dependent.
103. The oral dosage form of claim 102, wherein the hydrophobic material dissolves in a pH of about 5.5 to about 6.5.
104. The oral dosage form of claim 102, wherein the pH dependent material is selected from the group consisting of shellac, acrylic polymers, cellulose derivatives, polyvinyl acetate phthalate and mixtures thereof.

105. The oral dosage form of claim 84, wherein the controlled release material is coated onto the drug layered bead in an amount of about 3% to about 25% based on the total weight of the component.
106. The oral dosage form of claim 105, wherein the controlled release material is coated onto the drug layered bead in an amount of about 8% to about 12% based on the total weight of the component.
107. The oral dosage form of claim 74, providing a pulsatile release of two or more doses of ganaxolone.
108. The oral dosage form of claim 107, providing an immediate release dose after administration and at least one additional dose at a time after administration selected from the group consisting of 3-8 hours, 6-10 hours, 10-14 hours, 14-18 hours, 16-20 hours and 22-24 hours.
109. An oral solid dosage form comprising ganaxolone particles and a controlled release material, the ganaxolone particles having a volume weighted median diameter (D50) of from about 50 nm to about 1000 nm, the dosage form providing a controlled release of the ganaxolone to provide a therapeutic effect for about 8 to about 24 hours after administration.
110. The oral dosage form of claim 109, wherein the ganaxolone particles are dispersed in the controlled release material.
111. The oral dosage form of claim 109, further comprising a hydrophilic polymer, a complexing agent, a wetting agent and an ionic dispersion modulator.
112. An oral solid dosage form comprising particles comprising ganaxolone; and a pH dependent polymer, the ganaxolone particles having a volume weighted median diameter (D50) from about 50 nm to about 1000 nm, the dosage form providing a delayed release of the ganaxolone for a time period from about 2 to about 12 hours after administration.

113. A stable solid dose formulation comprising a plurality of substrates coated with particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume weighted median diameter (D50) from about 50 nm to about 1000 nm, the coated substrates exhibiting an increase in volume weighted median diameter (D50) of 0 to less than 200% after being dispersed in SGF or SIF in a concentration of 0.5-1 mg ganaxolone/ml and placed in a heated bath at 36° to 38° C without stirring for 1 hour as compared to the D50 under the same conditions after being dispersed in distilled water.
114. The stabilized pharmaceutical formulation of claim 113, wherein the volume weighted median diameter (D50) of the coated beads prior to dispersion is from about 0.1 mm to about 5.0 mm.
115. The stabilized pharmaceutical formulation of claim 113, wherein the volume weighted median diameter (D50) of the ganaxolone particles is from about 100 nm to about 450 nm.
116. The stabilized pharmaceutical formulation of claim 113, wherein the volume weighted median diameter (D50) of the ganaxolone particles is from about 100 nm to about 350 nm.
117. The stabilized pharmaceutical formulation of claim 113, wherein the excipient comprises an ionic dispersion modulator.
118. The stabilized pharmaceutical formulation of claim 117, wherein the ionic dispersion modulator is sodium chloride.
119. The stabilized pharmaceutical formulation of claim 113, wherein the ganaxolone particles are dispersed in a liquid to form a suspension and the suspension is spray coated onto the plurality of substrates.

120. The stabilized pharmaceutical formulation of claim 113, wherein the ganaxolone particles are dispersed in a liquid to form a suspension and the suspension is spray granulated with the plurality of substrates.
121. The stabilized pharmaceutical formulation of claim 112, wherein the ganaxolone particles are dispersed in a liquid to form a suspension and the suspension is spray dried to form a powder which is coated onto the plurality of substrates.
122. The stabilized pharmaceutical formulation of any of claims 119-121, wherein the suspension is about 5% to about 35% total solids.
123. The stabilized pharmaceutical formulation of any of claims 119-121, wherein the suspension is about 15% to about 25% total solids.
124. The stabilized pharmaceutical formulation of claim 113, wherein the substrates are inert beads.
125. The stabilized pharmaceutical formulation of claim 113, wherein the substrates are a powder selected from the group consisting of lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrans, dextrans, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol and mixtures thereof.
126. The stabilized pharmaceutical formulation of claim 125, wherein the substrate is mannitol.
127. The stabilized pharmaceutical formulation of claim 125, wherein the substrate is microcrystalline cellulose.
128. The stabilized pharmaceutical formulation of any of claims 119-121, wherein the ganaxolone concentration in the solids is about 50% to about 75%.

129. An immediate release oral solid dosage form comprising ganaxolone particles; and at least one pharmaceutically acceptable excipient, the ganaxolone particles having a volume weighted median diameter (D50) of from about 50 nm to about 1000 nm.
130. The oral dosage form of claim 109, comprising a granulation comprising the ganaxolone particles and the hydrophobic polymer, the granulation compressed into a tablet or filled into a capsule.
131. The oral dosage form of claim 112, comprising a granulation comprising the ganaxolone particles and the pH dependent polymer, the granulation compressed into a tablet or filled into a capsule.
132. The oral dosage form of claim 109, comprising a plurality of pharmaceutically acceptable beads coated with the ganaxolone particles and overcoated with the controlled release material, the overcoated beads compressed into a tablet or filled into a capsule.
133. The oral dosage form of claim 112, comprising a plurality of pharmaceutically acceptable beads coated with the ganaxolone particles and overcoated with the pH dependent polymer, the overcoated beads compressed into a tablet or filled into a capsule.
134. The oral dosage form of any of claims 1, 109, 112 or 129, the ganaxolone particles having a volume weighted median diameter (D50) of from about 50 nm to about 1000 nm prior to incorporation into the dosage form.
135. The oral dosage form of any of claims 1, 109, 112 or 129, further comprising an excipient selected from the group consisting of a hydrophilic polymer, a wetting agent, a complexing agent, an ionic dispersion modulator, a water soluble spacer, and a mixture thereof.
136. A pharmaceutical dosage form comprising particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume

weighted median diameter (D50) from about 50 nm to about 1000 nm, the dosage form providing a ratio of mean blood plasma fed $AUC_{(0-\tau)}$ to fasted $AUC_{(0-\tau)}$ from about 1:1 to about 4:1.

137. A pharmaceutical dosage form comprising particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume weighted median diameter (D50) from about 50 nm to about 1000 nm, the dosage form providing a ratio of mean blood plasma fed C_{max} to fasted C_{max} from about 1.5:1 to about 7:1.
138. The pharmaceutical dosage form of claims 136 or 137, wherein the excipient comprises a complexing agent.
139. The pharmaceutical dosage form of claims 136 or 137, wherein the excipient comprises a hydrophilic polymer.
140. The pharmaceutical dosage form of claims 136 or 137, wherein the excipient comprises a wetting agent.
141. The pharmaceutical dosage form of claims 136 or 137, wherein the excipient comprises an ionic dispersion modulator.
142. The pharmaceutical dosage form of claim 138, providing a ratio of fed $AUC_{(0-\tau)}$ to fasted $AUC_{(0-\tau)}$ from about 1.3:1 to about 4:1.
143. The pharmaceutical dosage form of claim 138, providing a ratio of mean blood plasma fed C_{max} to fasted C_{max} from about 2.5:1 to about 7:1.
144. The pharmaceutical dosage form of claim 139, providing a ratio of mean blood plasma fed $AUC_{(0-\tau)}$ to fasted $AUC_{(0-\tau)}$ from about 1:1 to about 3:1.
145. The pharmaceutical dosage form of claim 139, providing a ratio of mean blood plasma fed C_{max} to fasted C_{max} from about 1.5:1 to about 4:1.

146. The pharmaceutical dosage form of claims 136 or 137, which is a liquid dosage form.
147. The pharmaceutical dosage form of claims 136 or 137, which is an oral solid dosage form.
148. A pharmaceutical dosage form comprising particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume weighted median diameter (D50) from about 50 nm to about 1000 nm, the dosage form providing a mean blood plasma AUC 0-24 hours from about 100 to about 375 ng*h/ml when a dose of 200 mg to 500 mg of the ganaxolone is orally administered to adult subjects in the fasted state.
149. A pharmaceutical dosage form comprising particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume weighted median diameter (D50) from about 50 nm to about 1000 nm, the dosage form providing a mean blood plasma Cmax from about 25 to about 70 ng/ml when a dose of 200 mg to 500 mg of the ganaxolone is orally administered to adult subjects in the fasted state.
150. A pharmaceutical dosage form comprising particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume weighted median diameter (D50) from about 50 nm to about 1000 nm, the dosage form providing a mean blood plasma AUC (0-48) hours from about 400 to about 1200 ng*h/ml when a dose of 200 mg to 500 mg of the ganaxolone is orally administered to adult subjects in the fed state.
151. A pharmaceutical dosage form comprising particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume weighted median diameter (D50) from about 50 nm to about 1000 nm, the dosage form providing a mean blood plasma Cmax from about 60 to about 250 ng/ml when a dose of 200 mg to 500 mg of the ganaxolone is orally administered to adult subjects in the fed state.

152. The pharmaceutical dosage form of any of claims 148-151, wherein the excipient comprises a complexing agent.
153. The pharmaceutical dosage form of any of claims 148-151, wherein the excipient comprises a hydrophilic polymer.
154. The pharmaceutical dosage form of any of claims 148-151, wherein the excipient comprises a wetting agent.
155. The pharmaceutical dosage form of any of claims 148-151, wherein the excipient comprises an ionic dispersion modulator.
156. The pharmaceutical dosage form of any of claims 148-151, in the form of a liquid dosage form.
157. The pharmaceutical dosage form of claims 136 or 137, in the form of an oral solid dosage form.
158. A pharmaceutical dosage form comprising particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume weighted median of from about 50 nm to about 1000 nm, the dosage form providing a mean blood plasma C_{max}/C_{min} ratio of not greater than about 4 to 1 at steady state with a dose of 200 to 500 mg ganaxolone to adult subjects in the fed or fasted state.
159. A liquid pharmaceutical dosage form comprising particles comprising ganaxolone; and at least one pharmaceutically acceptable excipient, the particles having a volume weighted median of from about 50 nm to about 1000 nm, the dosage form providing a mean blood plasma C_{min} value of about 10-40 ng/ml in infants (greater than 4 months old but less than 2 years old) at a ganaxolone dose of about 10 mg/kg at steady state.
160. A liquid pharmaceutical oral suspension comprising ganaxolone, the suspension providing a mean blood plasma C_{max} of about 30 to 45 ng/mL and a

mean blood plasma AUC (0-24) of about 160 to about 210 ng*h/mL, based on a dose of 200 mg ganaxolone to subjects in the fasted state.

161. The liquid pharmaceutical oral suspension of claim 160, comprising ganaxolone, polyvinyl alcohol, sodium lauryl sulphate, methylparaben, propylparaben, sodium benzoate, citric acid, sodium citrate, simethicone, sucralose and flavoring.
162. The liquid pharmaceutical oral suspension of claim 160, comprising about 5% ganaxolone, about 1% polyvinyl alcohol, about 0.1% sodium lauryl sulphate, about 0.1% methylparaben, about 0.02% propylparaben, about 0.9% sodium benzoate, about 0.12% citric acid, about 0.06% sodium citrate, about 0.01% simethicone, about 0.02% sucralose, and flavoring.
163. The liquid pharmaceutical oral suspension of claim 160, providing a mean blood plasma C_{max} of about 37 ng/mL and a mean blood plasma AUC (0-24) of about 185 ng*h/mL, based on a dose of 200 mg ganaxolone to subjects in the fasted state.
164. The pharmaceutical dosage form of any of claims 135, 136 or 148-151, wherein the excipient is selected from the group consisting of a hydrophilic polymer, a wetting agent, a complexing agent, an ionic dispersion modulator, a water soluble spacer, and a mixture thereof.
165. An oral liquid dosage form comprising stable ganaxolone particles and at least one pharmaceutically acceptable excipient, the particles suspended in a pharmaceutically acceptable liquid vehicle, wherein the volume weighted median diameter (D₅₀) of the stable ganaxolone particles does not change by more than about 15% after 10 days storage at room temperature.
166. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D₅₀) of the stable ganaxolone particles does not change by more than about 12% after 10 days storage at room temperature.

167. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 10% after 10 days storage at room temperature.
168. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 8% after 10 days storage at room temperature.
169. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 15% after 20 days of storage at room temperature.
170. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 15% after 40 days of storage at room temperature.
171. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 15% after 60 days of storage at room temperature.
172. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 15% after 80 days of storage at room temperature.
173. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles prior to storage is from about 100 nm to about 450 nm.
174. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles prior to storage is from about 100 nm to about 350 nm.
175. The oral liquid dosage form of claim 165, wherein the excipient comprises a complexing agent.

176. The oral liquid dosage form of claim 174, wherein the complexing agent is a substance containing a phenol moiety, an aromatic ester moiety, an aromatic acid moiety or a mixture thereof.
177. The oral liquid dosage form of claim 176, wherein the complexing agent is selected from the group consisting of parabens, organic acids, carboxylic acids, acid salts of amino acids, methyl anthranilate, sodium metabisulphite, ascorbic acid and its derivatives, malic acid, isoascorbic acid, citric acid, tartaric acid, sodium sulphite, sodium bisulphate, tocopherol, water- and fat-soluble derivatives of tocopherol, sulphites, bisulphites and hydrogen sulphites, para-aminobenzoic acid and esters, 2,6-di-t-butyl-alpha-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amyhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), pyrocatechol, pyrogallol, propyl/gallate, nordihydroguaiaretic acid, phosphoric acids, sorbic and benzoic acids, esters, ascorbyl palmitate, derivatives and isomeric compounds thereof, pharmaceutically acceptable salts thereof, and mixtures thereof.
178. The oral liquid dosage form of claim 177, wherein the complexing agent is selected from the group consisting of a paraben, benzoic acid, a benzoic acid salt and a combination thereof.
179. The oral liquid dosage form of claim 165, wherein the excipient comprises a hydrophilic polymer.
180. The oral liquid dosage form of claim 179, wherein the hydrophilic polymer is selected from the group consisting of a cellulosic polymer, a vinyl polymer and mixtures thereof.
181. The oral liquid dosage form of claim 180, wherein the cellulosic polymer is a cellulose ether.
182. The oral liquid dosage form of claim 181, wherein the cellulose ether is hydroxypropylmethylcellulose.

183. The oral liquid dosage form of claim 180, wherein the vinyl polymer is a vinyl alcohol.
184. The oral liquid dosage form of claim 183, wherein the vinyl alcohol is polyvinyl alcohol.
185. The oral liquid dosage form of claim 165, wherein the excipient comprises a wetting agent.
186. The oral liquid dosage form of claim 185, wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, a pharmaceutically acceptable salt of docusate, or mixtures thereof.
187. The oral liquid dosage form of claim 165, wherein the pharmaceutically acceptable liquid vehicle is an aqueous solution.
188. The oral liquid dosage form of claim 165, wherein the excipient comprising a water soluble spacer.
189. The oral liquid dosage form of claim 188, wherein the water soluble spacer is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharide, a sugar, a sugar alcohol and a mixture thereof.
190. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 15% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes.
191. The oral liquid dosage form of claim 190, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more

than about 15% when placed in a glass vial and heated in a 100° C oil bath for 4 hours.

192. The oral liquid dosage form of claim 190, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 10% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes.

193. The oral liquid dosage form of claim 190, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 5% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes.

194. The oral liquid dosage form of claim 190, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 3% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes.

195. An oral liquid dosage form comprising particles comprising stable ganaxolone particles and at least one pharmaceutically acceptable excipient, the particles suspended in a pharmaceutically acceptable liquid vehicle, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 15% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes.

196. The oral liquid dosage form of claim 195, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 10% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes.

197. The oral liquid dosage form of claim 195, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 5% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes.

198. The oral liquid dosage form of claim 195, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 3% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes.
199. The oral liquid dosage form of claim 195, wherein the excipient comprises a complexing agent.
200. The oral liquid dosage form of claim 199, wherein the complexing agent is a substance containing a phenol moiety, an aromatic ester moiety, an aromatic acid moiety or a mixture thereof.
201. The oral liquid dosage form of claim 200, wherein the complexing agent is selected from the group consisting of parabens, organic acids, carboxylic acids, acid salts of amino acids, methyl anthranilate, sodium metabisulphite, ascorbic acid and its derivatives, malic acid, isoascorbic acid, citric acid, tartaric acid, sodium sulphite, sodium bisulphate, tocopherol, water- and fat-soluble derivatives of tocopherol, sulphites, bisulphites and hydrogen sulphites, para-aminobenzoic acid and esters, 2,6-di-t-butyl-alpha-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amylhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), pyrocatechol, pyrogallol, propyl/gallate, nordihydroguaiaretic acid, phosphoric acids, sorbic and benzoic acids, esters, ascorbyl palmitate, derivatives and isomeric compounds thereof, pharmaceutically acceptable salts thereof, and mixtures thereof.
202. The oral liquid dosage form of claim 201, wherein the complexing agent is selected from the group consisting of a paraben, benzoic acid, pharmaceutically acceptable salts thereof and a combination thereof.
203. The oral liquid dosage form of claim 165, containing at least one preservative in an antimicrobial effective amount.
204. The oral liquid dosage form of claim 165, containing a sweetener.

205. The oral liquid dosage form of claim 204, wherein the sweetener is sucralose.

206. The oral liquid dosage form of claim 205, wherein the sucralose is in an amount of from about 0.005% to about 0.04% based on the total weight of the liquid dosage form.

207. The oral liquid dosage form of claim 165, comprising stable ganaxolone particles, hydroxymethylpropylcellulose, sodium lauryl sulfate, simethicone, sucralose, methylparaben, propylparaben, sodium benzoate, citric acid, sodium citrate, and flavoring, the liquid having a pH of from about 3.8 to about 4.2.

208. The oral liquid dosage form of claim 165, comprising from about 2.5% to about 5% stable ganaxolone particles, from about 2% to about 5% hydroxymethylpropylcellulose, from about 0.1% to about 0.03% sodium lauryl sulfate, from about 0.005% to about 0.02% simethicone, from about .01% to about .03% sucralose, from about 0.05% to about 0.1% methylparaben, from about 0.01% to about 0.02% propylparaben, from about 0.05% to about 0.1% sodium benzoate, from about 0.1% to about 0.15% citric acid, from about .05 to about .1% sodium citrate and from about 0.002% to about .004% flavoring, the liquid having a pH of about 3.8 to about 4.2, wherein all percentages are weight percent to the total liquid formulation weight.

209. The oral liquid dosage form of claim 165, comprising stable ganaxolone particles, hydroxymethylpropylcellulose, polyvinyl alcohol, sodium lauryl sulfate, simethicone, sucralose, methylparaben, propylparaben, sodium benzoate, citric acid, sodium citrate and flavoring, the liquid having a pH of about 3.8 to about 4.2, wherein all percentages are weight percent to the total liquid formulation weight.

210. The oral liquid dosage form of claim 165, comprising from about 2.5% to about 5% stable ganaxolone particles, from about 2% to about 5% hydroxymethylpropylcellulose, about 0.5% to about 1.5% polyvinyl alcohol, from about 0.1% to about .03% sodium lauryl sulfate, from about 0.005% to about 0.02% simethicone, from about 0.01% to about 0.03% sucralose, from about 0.05% to about

0.1% methylparaben, from about 0.01% to about 0.02% propylparaben, from about 0.05 to about 0.1% sodium benzoate, from about 0.05% to about 0.15% citric acid, from about 0.05 to about 0.1% sodium citrate and from about 0.002% to about 0.004% flavoring, the liquid having a pH of about 3.8 to about 4.2, wherein all percentages are weight percent to the total liquid formulation weight.

211. The oral liquid form of any of claims 207 to 210, wherein the stable ganaxolone particles have a D50 of from about 100 nm to about 350 nm.
212. The oral liquid dosage form of claim 165, being prepared by contacting ganaxolone particles with the excipient, wherein the size of the particles exhibits an increase in volume weighted median diameter (D50) of from about 20% to about 300% and reaching an endpoint such that the particles are stable.
213. The oral liquid dosage form of claim 165, wherein the volume weighted median diameter (D50) of the stable ganaxolone particles does not change by more than about 25% when placed in a HDPE container and frozen and thawed three or more times with the time frozen for each cycle being at least 12 hours.
214. The oral liquid dosage form of claim 213, where the temperature used for frozen storage is from about -80°C to about -20°C.
215. The oral liquid dosage form of claim 165, wherein the excipient is selected from the group consisting of a hydrophilic polymer, a wetting agent, a complexing agent, an ionic dispersion modulator, a water soluble spacer, and a mixture thereof.
216. The oral liquid dosage form of claim 165, in frozen form.

FIGURES

FIGURE 1. Curing Process of Ganaxalone-Preservative Particles at Ambient Temperature: Particle Size Growth Was Partially Reversed by 1 minute Sonication (Power Setting: Low) in the Early Stage of the Curing Process.

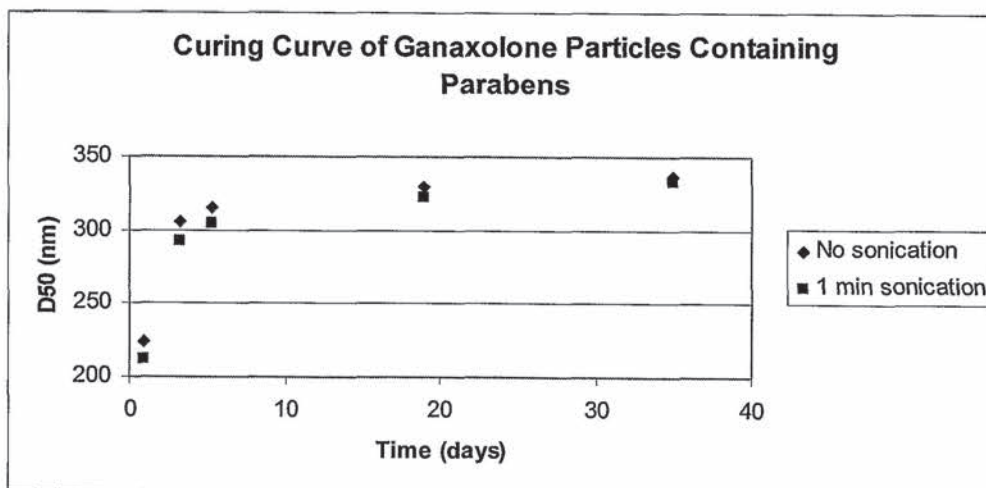
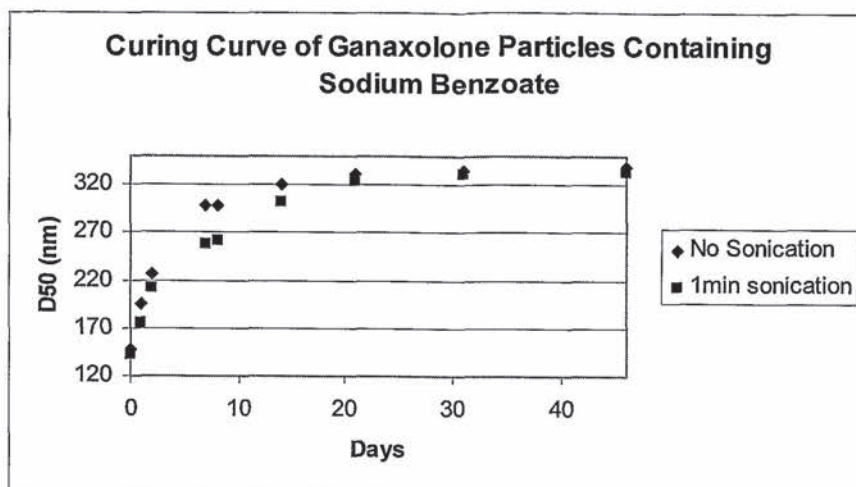


FIGURE 2. Curing of Parabens Preserved and Sodium Benzoate Preserved Ganaxalone Particles at Ambient Temperature: Parabens Preserved Ganaxalone Particles Become Fully Stable in 5-7 Days While the Benzoate Preserved Particles Take About 3 Weeks To Become Fully Stable (D50 Were Unsonicated).

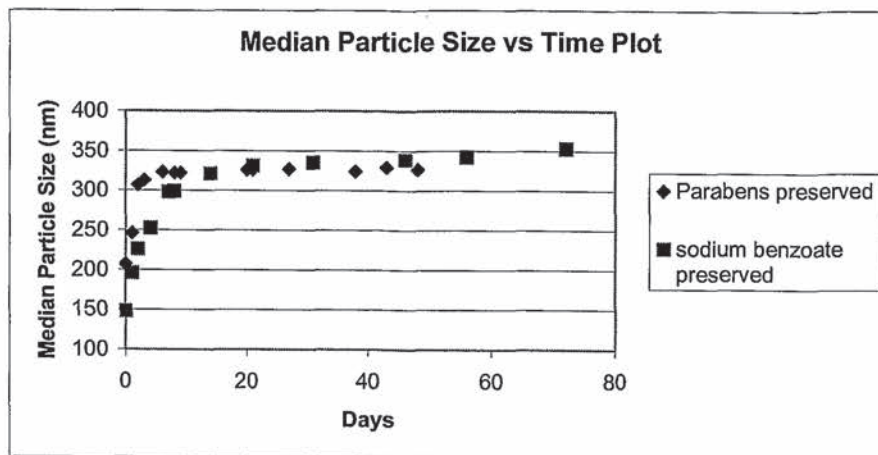


FIGURE 3. Stability plots (D50 vs time) of ganaxalone particles containing no complexing agent: ganaxalone particles without a complexing agent that were milled for less than 2 hours of milling residence time continued to increase gradually in size over a number of months, while the particles milled for more than 2 hours of residence time did not change over six months.

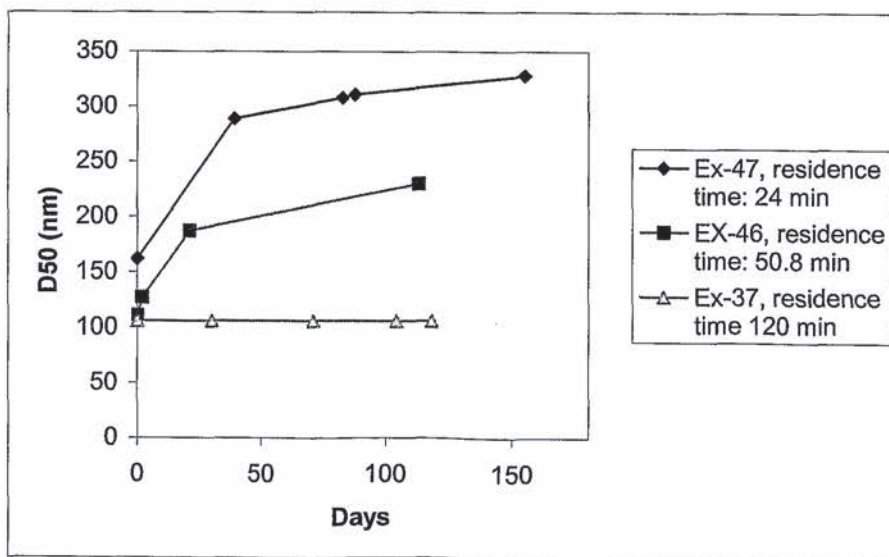


FIGURE 4. Measured D50 values for ganaxolone particles as a function of milling residence time for a typical milling run using a DYNO-Mill KDL equipped with four 64 mm polyurethane agitator discs.

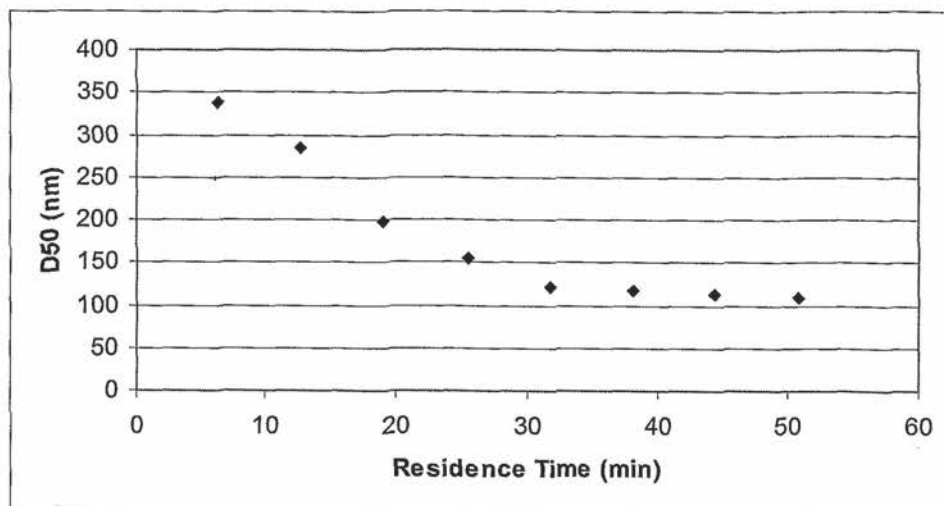


FIGURE 5. Particle Size Distribution (after 1min Low Power Sonication) of Re-suspended Solid Dosage Forms Containing Sodium Chloride in SGF at Room Temperature: With and Without a Complexing Agent (Methylparaben)

