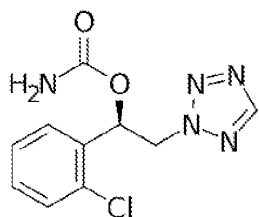


TECHNICAL FIELD OF THE INVENTION

The present invention relates, in general, to a pharmaceutical field, and more precisely it relates to oral liquid dosage forms of Cenobamate or a pharmaceutically acceptable salt, solvate or hydrate thereof. In particular, the present invention relates to ready to use, liquid dosage forms and a dry powder for reconstitution, processes for the preparation thereof and a method of using the same.

BACKGROUND OF THE INVENTION

The carbamate compounds are known to be effective anticonvulsants for the treatment of central nervous system diseases. Cenobamate is a protuberant anti-epileptic drug indicated for the treatment of partial-onset seizures in adult patients. Cenobamate, chemically known as [(1R)-1-(2-Chlorophenyl)-2-(tetrazol-2-yl) ethyl] carbamate having a molecular formula of $C_{10}H_{10}ClN_5O_2$ and a molecular weight of 267.67 g/mol and has the following structural formula:



It is marketed in the form of tablets under the trade name of XCOPRI® in USA. Cenobamate is presently available as tablet form in various strengths of 12.5mg, 25mg, 50mg, 100mg, 150mg and 200mg.

The solid oral dosage formulations such as capsules or tablets are usually intended for adults who can easily swallow large tablets. However, many patients, particularly the elderly and paediatric patients, experience difficulty in swallowing or chewing tablet dosage forms. This has resulted in the widespread practice of crushing tablets to form powder and powder being combined with Ora-sweet and/or Ora-Plus to produce suspension prior to administration. Such extemporaneous preparations have raised concerns over this practice, as they are prone to inaccurate dosing, inconsistent dosing, contamination and harm to the patient. Thus, oral liquid compositions are the best option for dealing with this scenario. As such, there is a need to develop a Cenobamate formulation that can be easily administered to paediatric patients and adults with difficulty in swallowing and using in GI tube, etc.

Palatability is another main element of patient acceptability of an oral paediatric medicine. It is more challenging to administer formulation which does not have a favourable shape, taste, flavour, etc to children and they generally reject to take those medicines. When a child is unable to take medicine orally, it is intravenously administered, and he and his caregivers then may experience stress. Design of the formulation of an oral paediatric medicine should be considered together with its palatability. It will therefore be desirable to have Cenobamate containing dosages in liquid forms which also contain sweeteners and flavours which makes such dosage forms having palatability and more patient compliance.

The oral, liquid dosage forms provide assurance of dosage uniformity upon administration to patients and eliminates difficulty of administration. Liquid

dosage forms can also provide physicians more flexibility in designing dosage regimens for patients. Such liquid dosage forms are advantageous to paediatric patients, geriatric patients and those patients who are unable to take oral therapy.

Among various liquid dosage forms available including solutions, syrups, suspensions, elixirs, and concentrates, pharmaceutical suspension offers unique advantages to many patients. Pharmaceutical suspensions are very useful commercially for infants, children, and older patients who have difficulty in swallowing. Such products are marketed either as suspensions or often as powders for reconstitution.

The main reason for the development of pharmaceutical suspensions of Cenobamate in the present invention is because of drug poor water solubility. Additionally, suspensions also aim to prevent the bitter taste of the Cenobamate, and increase the oral absorption and bioavailability, as well as the Cenobamate's stability.

Liquid dosage forms present more challenge because of solubility and stability in presence of various excipients and solvents in case of solution and for physical stability in case of oral suspensions. There are also a number of "challenges" surrounding the suspension formulation and development of these forms. Creating an attractive, stable-in-time, safe, and effective oral liquid suspension composition is a technically challenging endeavour when compared to aqueous solutions, tablets, and capsules.

Liquid dosage forms of Cenobamate or pharmaceutically acceptable salt thereof are not much explored by the formulation scientists. The prior arts mentioned in the forthcoming paragraphs are incorporated herein by references for all the purposes.

WO 2022250499A1 (hereinafter referred as '499 publication) discloses the aqueous formulation of Cenobamate which is in the form of a suspension formulation. The specification of '449 publication teaches oral aqueous formulation which essentially comprises poloxamer particularly Poloxamer 188 as a wetting agent, thickener, dispersants and viscosity regulating agent that is used to stabilize the active ingredient (i.e. Cenobamate) or increase the viscosity of the oral aqueous formulation. Preferred suspending agent according to the specification of '449 publication is smectite clay. Such preferred wetting agent and suspending agent has not been used in the oral liquid formulations of the present invention being the first major difference between the present invention and the invention disclosed in the specification of '449 publication. Thus, the stability achieved by the present invention and results provided in the present specification are without using (i) poloxamer and ii) suspending agent particularly smectite clay preferred in the specification of '449 publication. The whole experimental section described in '449 publication is the formulation comprising Poloxamer (Poloxamer 188) and Smectite clay (Veegum HV) and they showed the success of the product due to the presence of this two essential component. Therefore, it is difficult for a skilled person to envisage stability and solubility of the oral solution disclosed in the specification of '449 publication without using these two main

elements of Poloxamer (Poloxamer 188) and Smectite clay (Veegum HV). Whereas the present invention showed superior physical and chemical stability of the product without using these two main elements disclosed in '449 publication. Thus, the present invention having novelty and inventive step over the cited '449 prior art.

The present disclosure further relates to systems and methods of a dry powder Cenobamate formulation for reconstitution into a liquid suspension for delivery to a patient.

OBJECT OF THE INVENTION

The principal object of the present invention is to provide liquid dosage forms of Cenobamate or pharmaceutically acceptable salt thereof.

Liquid dosage forms are designed as ready to use liquids and as powder for reconstitution into liquid orals include liquids, liquid dispersions, suspensions, solutions, emulsions, sprays, spot-on, syrups, elixirs, drops, gels, solution-gels, concentrates and the like.

Yet another objective of the present invention is to provide liquid dosage forms of Cenobamate for the treatment of partial-onset seizures in adult patients.

A yet another object of the present invention is to provide process for the preparation of liquid dosage forms of Cenobamate or pharmaceutically acceptable salt thereof.

A yet another object of the present invention is to provide method for the treatment of a disease or disorder that can be treated as a positive allosteric modulator of the γ -aminobutyric acid (GABAA) ion channel comprising administering to a patient, such as human, an effective dosage amount of a liquid dosage form comprising Cenobamate or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients or additives as disclosed and described herein.

The liquid dosage forms of the present invention are useful for administering a liquid dosage form to paediatric, geriatric and other patients who are unable to take solid oral therapy while also compensating for a good organoleptic property and remaining suitably stable.

Yet another objective of the present invention is to provide an alternative dosage form to solid tablet formulation.

The main object of the present invention is to provide ready to use suspension or dry powder for reconstitution for oral administration comprising Cenobamate comprise sweetener(s) and flavouring agent(s), which achieves to mask the bitter taste of the Cenobamate and provides pleasant taste, acceptable palatability and improved stability.

Another object of present invention is to provide oral suspension having dose flexibility for patients who need special doses of the drug and have difficulties in swallowing oral solid dosage forms.

Still another object of the present invention is to provide a convenient process for preparation of oral pharmaceutical suspension of Cenobamate.

It is another object of the present invention to provide an oral liquid pharmaceutical composition in the form of a suspension comprising Cenobamate or its pharmaceutically acceptable esters, salts, solvates, polymorphs, enantiomers or mixtures thereof with one or more pharmaceutically acceptable excipients and/or surface modifier wherein the pharmaceutically acceptable excipient is selected from the group comprising of suspending agent, antioxidant, anticaking agent, antifoaming agent, pH adjusting agent, coloring agent, sweetening agent, , buffer, diluent, preservative and mixtures thereof.

A yet another object of the present invention is to provide liquid dosage forms of Cenobamate or pharmaceutically acceptable salt thereof having palatability, prolonged stability and improved and/or comparable pharmacokinetic profile or bioavailability when compared to the known or marketed Cenobamate formulations.

A yet another object of the present invention is to use the liquid dosage forms of the present invention for the treatment of central nervous system diseases such as anxiety, depression, convulsion, epilepsy, migraine, bipolar disorder, drug abuse, smoking, attention deficit hyperactivity disorder (ADHD), obesity, sleep disorders, neuropathic pain, stroke, cognitive disorders, neurodegeneration, and/or muscle spasm.

The present disclosure provides a ready to use liquid suspension or dry powder for reconstitution formulation comprising Cenobamate or a pharmaceutically acceptable salt, solvate or hydrate thereof, and the said composition is essentially free from poloxamer and smectite day.

In particular embodiments, Polyoxyl Castor Oil, Polysorbate 80 and Sodium Lauryl Sulphate is included with the active compound in a suspension formulation for wide pH range even in low concentrations. In some embodiments, hydroxy ethyl cellulose, carbomer and Colloidal Silicon Dioxide shows a synergistic effect on redispersibility/suspendability of a suspension formulation with a cellulosic viscosity modifier or Copovidone.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention will now be more specifically illustrated as hereunder.

This document discloses a ready to use liquid suspension and powder formulation suitable for reconstitution with a pharmaceutically acceptable carrier to form a suspension oral dosage form of Cenobamate. Advantages of the present invention include dose titration accuracy, better compliance and prolonged stability in comparison with conventional immediate release non-suspension dosage forms.

In the present invention, unless indicated otherwise, all ingredient concentrations are presented in units of % weight/volume (% w/v).

The term "about" can indicate a difference of 10 percent of the value specified. The term "about" as and were used in this specification means $\pm 10\%$ of the mentioned value. However, when the term "about" is used in connection with pH, it should be considered as ± 2 unit of the pH value. Numerical ranges as used herein are meant to include every number and subset of numbers enclosed within that range, whether particularly disclosed or not. Further, these numerical ranges should be construed as providing support for a claim directed to any number or subset of numbers in that range.

The dosage amount of Cenobamate for the prevention, alleviation or treatment of the above diseases may typically vary depending on the severity of the disease, the body weight and the metabolic status of the subject. A "therapeutically effective amount" for an individual patient refers to an amount of the active ingredient sufficient to achieve a therapeutic effect.

The term "Cenobamate" as used in the present invention includes, but is not limited to, Terbutaline per se, pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof, and also its various crystalline and amorphous forms.

Examples of the pharmaceutically acceptable salts of Cenobamate include independently, acetate, benzenesulfonate, benzoate, bitartrate, calcium acetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate,

gluceptate, gluconate, glutamate, glycoloyl arsanilate, hexylresorcinate, hydravamine, hydrobromide, hydrochloride, hydrogencarbonate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate or hemisuccinate, sulfate or hemi-sulfate, tannate, tartrate, oxalate or hemi-tartrate, teoclate, procaine, aluminum, ammonium, tetramethylammonium, calcium, lithium, magnesium, potassium, sodium and zinc.

Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide.

The term “stable” as used herein is intended to mean that a composition of a pharmaceutical product or a method of the present invention does not substantially decompose to form one or more degradation products when stored as per the ICH guideline for stability. For example, there is not more than 0.2% of Hydroxy impurity comes at RRT 1.23, more preferably less than 0.2% of Hydroxy impurity (comes at RRT 1.23) and more preferably less than 0.2 %

Hydroxy impurity (comes at RRT 1.23) identified when the composition of the present invention is stored as per the ICH guideline for stability.

The content of the Cenobamate in the oral aqueous suspension formulation may vary depending on the application of the preparation. In one embodiment, the oral liquid formulation contains the Cenobamate in a concentration of about 1 mg/ml to about 100 mg/ml. In one embodiment, the oral liquid formulation contains the Cenobamate in a concentration of about 1 mg/ml to about 50 mg/ml. In one embodiment, the oral liquid formulation contains the Cenobamate in a concentration of about 5 mg/ml to about 20 mg/ml. In one embodiment, the oral liquid formulation contains the Cenobamate in a concentration of about 5 mg/ml to about 12 mg/ml. In one embodiment, the oral liquid formulation contains Cenobamate in a concentration of about 8 mg/ml to about 12 mg/ml. In one embodiment, the oral liquid formulation contains the Cenobamate in a concentration of about 9 mg/ml to about 11 mg/ml.

In embodiments, a stable oral liquid composition of the present invention comprises Cenobamate in an amount of 0.5 % to 10 %, more preferably 3.8% by weight of the total volume of the composition.

In embodiments, dry powder for reconstitution of the present invention comprises Cenobamate in an amount of 0.5 % to 10 %, more preferably 3.8% by weight of the total volume of the composition.

The term "oral liquid composition" as used in the present invention means a pharmaceutical composition which are homogeneous liquid preparations, usually consisting of a solution, an emulsion, or a suspension, of one or more active ingredients in a suitable liquid base. They are prepared for oral administration either as such or after dilution.

"Dry powder", as used herein, includes any composition which is dry and flowable such as, for example, granules, flakes, spheroids and other forms which can be readily prepared and when added to an ingestible liquid and mixed, give the desired liquid suspension.

It should be understood that herein "suspension" and "dispersion" are used interchangeably to mean a system in which solid particles are dispersed in a liquid.

Suspensions are a class of dispersed system in which a finely divided solid is dispersed uniformly in a liquid dispersion medium. Formulation of a pharmaceutical suspension requires a knowledge of the properties of both the dispersed phase and the dispersion medium. The material for the formulation of suspensions should be carefully selected keeping in mind the route of administration, intended application, and possible adverse effects. The following are the most important factors to be considered during the formulation of pharmaceutical suspensions includes the nature of suspended material, size of suspended particle and viscosity of the dispersion medium.

While developing the oral liquid composition, there are two major challenges in front of formulator viz. thermodynamically unstable system (which affects the content uniformity and sedimentation) and taste. Specifications to manufacture suspensions include assay, microbial limits, particle size distribution of the suspended drug, viscosity, pH, and dissolution.

Particle size distribution is a critical attribute and should be monitored as quality control parameters. Any change in particle size distribution during the shelf life of suspension can have a negative impact on the dissolution kinetics. Particle size would be a critical parameter for micro and nano suspensions.

In one embodiment, the particle sizes of the Cenobamate which could be used to prepare the oral liquid formulation and dry powder for reconstitution are as following: D90 is 200 to 225 μm .

In the laser diffraction method, “D10”, “D50”, “D90” (horizontal axis) and “volume percentage (Volume (%))” (vertical axis) indicate the following values.

D10: The portion of particles with diameters smaller than this value is 10%.

D50: The portions of particles with diameters smaller and larger than this value are 50%. Also known as the median diameter.

D90: The portion of particles with diameters below this value is 90%.

Volume percentage: The highest volume percentage of the particle size distribution displayed.

The pharmaceutical composition of the present invention wherein the Cenobamate is present in the form of solid particles having a particle size distribution wherein D90 is in the range of 5 to 600 microns more preferably 30 to 300 microns.

In one embodiment, the particle size of the Cenobamate can be controlled by a milling process or other available processes. In one embodiment, the aqueous formulation comprises Cenobamate having the above ranges of particle size distribution to give the uniformity to the oral aqueous suspension formulation.

Further as one embodiment the liquid formulation of present invention, vehicle or solvent is selected from glycerine, alcohols, propylene glycol, polyethylene glycol, water, ethanol, isopropyl alcohol or their mixtures thereof. Preferably purified water is used as a solvent. In one embodiment, the liquid pharmaceutical composition of present invention comprises at least 50% to 80% the vehicle or purified water, preferably at least 90%, more preferably at least 95% and most preferably at least 99% of total composition.

The aqueous carrier is selected from the group comprising water, and a mixture of water and a water-miscible organic solvent. In one embodiment, said organic solvents are selected from the group consisting of ethanol, ethylene bromide, butanol, acetone, chloroform, 2-ethylhexanol, methyl ethyl ketone, ethylene chloride, isobutanol, glycerol, methyl isobutyl ketone, dichloromethane, isopropanol, methyl isopropyl ketone, tetrachloroethylene, ethanol, mesityl oxide, carbon tetrachloride, propanol, trichloroethylene, propylene glycol, 1,4- dioxane, butyl ether, dimethylformamide, ethyl ether, diisopropyl ether, dimethyl sulfoxide,

tetrahydrofuran, tert-butyl methyl ether, pyridine, acetonitrile, ethyl acetate, cyclohexane, toluene, hexane, xylene, other suitable solvents, and combinations thereof.

In another embodiment, the aqueous carrier includes water, water buffered to a specific pH with phosphate or carbonate ions, and combinations of aqueous and one or more organic solvents. In a particular embodiment, the aqueous carrier is water. In some embodiments, the aqueous formulation comprises an aqueous carrier in an amount of from 40% to 99%, from 70% to 98%, or from 90% to 95%, by weight of the formulation.

The surface modifier may be one or more of polymers, natural products, dispersing agents, wetting agents and surface-active agents. The polymers may be one or more polyvinyl pyrrolidone, hydroxypropyl methylcellulose, carboxymethyl cellulose sodium, carboxymethyl cellulose calcium, hydroxy propyl cellulose and polyvinyl alcohol. The natural products may be one or more of dextran, xanthan, chitosan, pectin, dextrin, maltodextrin, starch, alginates and pullulan. The surface-active agents may be Kolliphor RH 40 (Polyoxyl Castor Oil), Polysorbate 80, Sodium lauryl sulphate, polyethylene glycols, benzalkonium chloride, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, poloxamines, polyethylene glycol, vitamin E and polyethylene glycol-phospholipid.

Suitable wetting agents for use in the liquid oral suspensions according to the present invention may be one or more of Kolliphor RH 40 (Polyoxyl Castor Oil), Polysorbate 80, Sodium lauryl sulphate, sorbitan esters of fatty acids, sorbitan monolaurate, sorbitan monooleate, sorbitan trioleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, ethylene oxide-propylene oxide block copolymers, lecithins, oleic acid and oleic acid salts, propylene glycol monostearate and monolaurate, glycerol monostearate and monooleate, fatty alcohol- polyethylene glycol ethers, fatty acid-polyethylene glycol esters, sodium dodecyl sulphate, dioctyl sodium sulphosuccinate, ethoxylated mono- and diglycerides, sucrose fatty acid esters, fatty acid salts, ethoxylated triglycerides, polyoxyethylated hydrogenated castor oil, and sterols.

A dispersant or a dispersing agent is a substance, typically a surfactant, which is added to a suspension of solid or liquid particles in a liquid to improve the separation of the particles and to prevent their settling or clumping.

Dispersing agent for present invention is selected from the group consisting of Polyoxyl Castor Oil, polysorbate 80 and Sodium Lauryl sulphate.

The surface modifiers may be present at a concentration range of from about 0.05% to about 10% w/w of the dosage form.

In one embodiment, the Polyoxyl Castor Oil is nonionic solubilizer and emulsifying agent obtained by reacting 1 mole of hydrogenated castor oil with 40 moles of ethylene oxide. The main constituent of Polyoxyl Castor Oil is glycerol polyethylene glycol hydroxystearate, which, together with fatty acid glycerol

polyglycol esters, forms the hydrophobic part of the product. The hydrophilic part consists of polyethylene glycols and glycerol ethoxylate. Polyoxyl Castor Oil which consists of about 20% Glycerol - Mono-(PEG - 12 - Hydroxystearate) units, 12% Glycerol - Di-(PEG - 12 -Hydroxystearate), 6% Glycerol -Tri-(PEG - 12- Hydroxystearate), 7% PEG - 12 -Hydroxystearate, 18% PEG and 35% Glycerol- PEG.

In one embodiment, the aqueous formulation contains Polyoxyl Castor Oil in a concentration of about 0.05 % to about 10% w/v is added to provide sufficient spacing of the settled particles of the active ingredient and to permit the active ingredient to re-disperse.

In one embodiment, the liquid formulation further comprises Polysorbate 80 in a concentration of about 0.5 % to about 10%. can be added as a wetting agent to improve its drug dispersion.

In one embodiment, the liquid formulation further comprises Sodium Lauryl Sulphate in a concentration of about 0.5 % to about 10%. can be added as a wetting agent to improve its drug dispersion.

Suspending agent excipients help active pharmaceutical ingredients stay suspended in the formulation and prevent caking at the bottom of the container. One of the properties of a well-formulated suspension is that it can be easily re-suspended by the use of moderate agitation or shaking.

Suspending agents suitable for use in the liquid oral suspensions of the present invention include Carbomer, Copovidone, cellulose derivatives such as Hydroxy Ethyl Cellulose, methylcellulose, sodium carboxymethylcellulose and hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, alginate, guar gum, xanthan gum, acacia gum, chitosan, dextran, gelatin.

In one embodiment, the liquid formulation further comprises Carbomer & Hydroxy Ethyl Cellulose in a concentration of about 0.5 % to about 10%. can be added as a suspending agent to prevent settling and improve its redispersion property.

It should be understood that herein "suspending agents" and "viscosity modifying agents" are used interchangeably to mean an excipient which keep the Cenobamate solid particles in a dispersed state in a suspension dosage form. Upon storage, the dispersed particles either settle slowly or, and preferably, remain suspended. When the product is sheared, for instance, when shaken by the consumer, the high apparent viscosity of the formulation should fall sufficiently for product to be dispensed easily.

The pH of suspension formulation affects the effectiveness of preservative systems and may even alter the drug in solution.

The pH of the suspension is measured on a regular basis to examine how it impacts the formulations' properties and stability. The suspension flocculation and deflocculation system are changed with the change in pH and presence of ions and

thus the particle charge and interparticle interaction which impact on the change in the Zeta potential (surface charge of particle). The settling rate of particle effects on the stability of suspension due to change in pH.

To keep liquid pharmaceutical composition of present invention stable for longer period of time, the pH may be maintained such that the composition is acidic or neutral. As per one embodiment, pH of the composition should be in the range from about 5 to 7, preferably in the range from about 5 to 6.

The novel formulation has a pH of between about 5.0 to about 6.5, more preferably of between about 5.5 to about 6.5, most preferably 5.5 to 6.0.

One more embodiment of the present invention is to provide a liquid pharmaceutical composition suitable for oral administration comprising Cenobamate or pharmaceutically acceptable salts thereof, at least one buffer, wherein buffer strength is in the range from 5 to 25 millimolar, at least one preservative present in the range from 0.02% w/v to about 2.0% w/v and wherein the composition is having pH in the range from 4-7.

In one embodiment, suitable buffer for present invention is selected from Citric Acid, Sodium Citrate, Sodium Dihydrogen Phosphate, Disodium Phosphate, Trometamol (Tris), Hydrochloric Acid, Ascorbic Acid, Sodium Ascorbate and anhydrous, monohydrate or dehydrate forms thereof. Further the buffer can be single or any combination of above listed buffer. In a preferred embodiment, combination of Sodium Dihydrogen Phosphate and Disodium Phosphate is to be

used. Buffer used for present invention is having buffer strength in range from 5 to 150 millimolar. Further as per preferred embodiment the buffer strength is in the range from 5 to 25 millimolar.

The resulting oral suspension may be tested with suitable analytical methods to ensure physical and chemical stability. Examples of the analytical methodologies include, but is not limited to, appearance, pH, viscosity, density, assay and related substances, chiral purity assay, homogeneity, re-dispersibility, dissolution and particles size.

The selection of excipients for preparation of suspension formulation depends on the physico-chemical attributes of an active ingredient. The quality and quantity of excipients for formulation need to be optimized considering the solubility and stability of active ingredient in liquid dosage form. Like other dosage forms, for suspension dosage form, certain parameters decided the success of the product ie. the dispersibility, pourability, palatability stability of active ingredient in liquid suspension dosage form is essential.

The selection of surface modifiers and suspending agent is based on the results such as agglomeration, wettability, dispersibility of the active ingredient, sedimentation rate and volume, particle size distribution, caking, re-dispersibility, flocculation, and physico- chemical stability of active ingredient.

The volume of the sedimentation layer is an indicator to the amount of spacing between the particles in the sediment layer. Adequate spacing between the

particles is essential because these particles have to move in order to disperse evenly.

Viscosity can be important from a processing aspect to minimize segregation. In few cases, viscosity has been shown to have an impact on bio-equivalency.

As per another embodiment the liquid pharmaceutical composition may further comprises sweetener.

In one embodiment, suitable sweetener for present invention is selected from acesulfame potassium, sodium cyclamate, aspartame, dextrose, fructose, galactose, inulin, maltitol, maltose, mannitol, sucralose, cyclamate, saccharin, sorbitol, sucrose, trehalose, xylitol, saccharin sodium and aspartame or mixtures thereof. In a preferred embodiment, sucralose is to be used.

The liquid pharmaceutical composition of the present invention can be prepared in absence of sweetener. However, to make it more palatable and easily acceptable by patient especially children, very small amount of sweetener can be added. In one embodiment, the Sweetener for the present invention can be used in the range from about 0.3% w/v to 20% w/v. In another embodiment, the sweetening agent can be used in amount from 5% to 20-% by weight of the total volume of the composition. In the present invention, preferably Sucralose, Sorbitol is used as sweetening agent.

Examples of flavouring agents are grape flavor, cherry, raspberry, black currant, strawberry flavour, caramel chocolate flavour, mint cool flavour, fantasy flavour, meat flavours and the like.

A preferred intense flavouring agent is grape flavor. The flavouring agent is present in an amount ranging from 0.1% w/v to 3.0% w/v, preferably from 0.3% w/v to 2.0% w/v.

In one embodiment, suitable preservative for present invention can be selected from methyl parahydroxybenzoate (methyl paraben), ethyl parahydroxybenzoate (ethyl paraben), propyl parahydroxybenzoate (propyl paraben), butyl parahydroxybenzoate (butyl paraben), isobutyl parahydroxybenzoate (isobutyl paraben), isopropyl parahydroxybenzoate (isopropyl paraben), benzyl parahydroxybenzoate (benzyl paraben), Sodium Benzoate, Benzoic acid, Potassium Sorbate and combinations thereof. In one embodiment the preservative is present in the range from about 0.02% w/v to about 2.0% w/v. In another embodiment, the preservative can be used in amount from 0.1 % to 2.0% by weight of the total volume of the composition.

Preservative includes but are not limited to, cresol, glycerin, hexetidine, imidurea, monothioglycerol, phenol, phenoxyethanol, phenylmercuric acetate, potassium benzoate, propionic acid, propylene glycol, methyl paraben, propyl paraben, ethyl paraben, sodium ethyl paraben, sodium propyl paraben and benzalkonium chloride. In the present invention, preferably sodium benzoate, Methyl Paraben Sodium is used as preservative.

Thus as per one embodiment, the liquid pharmaceutical composition of present inventions remain stable at different temperature conditions even in presence of at least 80% of purified water in to the composition.

According to an embodiment of the present invention, said liquid pharmaceutical composition suitable for oral administration comprises;

- a) 0.5 to 10.0% w/v of Cenobamate,
- b) 0.05 to 10.0% w/v of surface modifying agents
- c) 0.2 to 10.0% w/v of anticaking agent

and pharmaceutically acceptable excipients.

Yet another embodiment of the present invention, said liquid pharmaceutical composition suitable for oral administration comprises;

- a) 0.5 to 10.0% w/v of Cenobamate,
- b) 0.05 to 10.0% w/v of surface modifying agents
- c) 0.2 to 10.0% w/v of anticaking agent
- d) 0.2 to 10.0% w/v of suspending agents
- e) 0.05 to 5.0% w/v of buffering agents
- f) 0.1 to 3% w/v of Flavouring agents
- g) 0.1 to 3% w/v of bitter masker
- h) 0.3 to 20% w/v of sweetener
- i) Purified water

Various test methods are available and these are the check list of **suspension Performance and stability testing** which includes Photo microscopic techniques (Appearance), The Coluter counter (Sedimentation volume and redispersibility),

Graduated cylinders for sedimentation studies (Sedimentation rate), Brookefield Viscometers (Viscosity), Specific gravity measurements (pH, density and specific gravity), Aging tests (Color, Taste and Odor (organoleptic properties)), Zeta potential (Drug content uniformity/Release profile) and Aggregation kinetics.

The invention is further illustrated by the following examples, which are by no means intended to limit the scope of the invention but are given by way of illustration.

Table 1: Composition Details

S. No.	Ingredients	Function	Range % w/w
1	Cenobamate	API	0.50 – 10.00
2	Kolliphor RH 40 (Polyoxyl Castor Oil)	Surfactant/ Wetting agent	0.05 – 10.00
3	Polysorbate 80		0.10 - 10.00
4	Sodium Lauryl Sulphate		0.10 - 10.00
5	Carbomer / Hydroxy Ethyl Cellulose	Suspending agent/ Suspension stabilizer/	0.20 – 10.00
6	Copovidone		0.20 – 10.00
7	Sodium Alginate	Suspending agent/	0.2 – 10.00
8	Colloidal Silicon Dioxide	Anticaking agent/ Suspending agent	0.2 – 10.00
9	Citric Acid Monohydrate	Buffering agent	0.05 – 5.00

10	Sodium Citrate Dihydrate		0.10 – 4.00
11	Sodium Benzoate	Preservative	0.02 – 2.00
12	Methyl Paraben Sodium		0.10 – 2.00
13	Sucralose	Sweetening agent	0.30 – 15.00
14	Sorbitol		5.00 – 20.00
15	Grape Flavor	Flavor	0.10 – 3.00
16	Bitter Masker	Taste masking agent	0.10 – 3.00
17	Purified Water	Solvent	Q.s.

Example 1 - Ready to Use Suspension

S.No.	Components	% W/V of the Total composition
1.	Cenobamate	3.85
2.	Kolliphor RH 40 (Polyoxyl Castor Oil)	0.05
3.	Hydroxy Ethyl Cellulose	0.29
4.	Sodium Alginate	0.58
5.	Citric Acid Monohydrate	0.08
6.	Sodium Citrate Dihydrate	0.28
7.	Sodium Benzoate	0.02
8.	Methyl Paraben Sodium	0.10
9.	Sucralose	0.77
10.	Sorbitol	14.44

11.	Grape Flavor	0.14
13.	Bitter Masker	0.14
14.	Purified Water	79.27

Example 2 - Ready to Use Suspension

S.No.	Components	% W/V of the Total composition
1.	Cenobamate	3.80
3.	Polysorbate 80	0.1
5.	Hydroxy Ethyl Cellulose	0.29
7.	Sodium Alginate	0.57
8.	Colloidal Silicon dioxide	0.48
9.	Citric Acid Monohydrate	0.08
10.	Sodium Citrate Dihydrate	0.28
11.	Sodium Benzoate	0.02
12.	Methyl Paraben Sodium	0.10
13.	Sucralose	0.76
14.	Sorbitol	14.26
15.	Grape Flavor	0.14
17.	Bitter Masker	0.14
18.	Purified Water	79.00

Example 3 - Ready to Use Suspension

S.No.	Components	% W/V of the Total composition
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1.	Cenobamate	3.87
2.	Polysorbate 80	0.1
3.	Carbomer	0.29
4.	Sodium Alginate	0.29
5.	Colloidal Silicon dioxide	0.29
6.	Citric Acid Monohydrate	0.08
7.	Sodium Citrate Dihydrate	0.28
8.	Sodium Benzoate	0.02
9.	Methyl Paraben Sodium	0.10
10.	Sucralose	0.48
11.	Sorbitol	14.52
12.	Grape Flavor	0.15
13.	Bitter Masker	0.15
14.	Purified Water	79.39

Manufacturing Process

1. Dispense API and excipients separately as per manufacturing formula in RLAF
2. Add sodium methyl paraben in purified water under stirring and mixed well until completely dissolved to form a clear solution.
3. Add sodium benzoate to step 2 under stirring and mixed well until completely dissolved to form a clear solution.
4. Add sorbitol to step 3 under stirring and mixed well until it is uniformly mixed to form a clear solution.
5. Add Suspending agents-(Carbomer) step 4 under stirring and mixed well until lump free dispersion is obtained.

6. Add sodium alginate to step 5 under stirring and mixed well until lump free dispersion is obtained.
7. Add Surfactant/wetting agent (Kolliphor RH 40 (Polyoxyl Castor Oil) or Polysorbate 80 or Sodium Lauryl Sulphate under stirring to step 6 and mixed until uniformly mixed to form a lump free dispersion.
8. Add colloidal silicon dioxide under stirring to step 7 and mixed until uniformly mixed to form a lump free dispersion.
9. Add Citric acid monohydrate to step 8 under stirring and mixed well until it is completely dissolved.
10. Add Sodium citrate dihydrate to step 9 under stirring and mixed well until it is completely dissolved.
11. Add Cenobamate to step 10 under stirring and mixed well until it is uniformly dispersed to form a lump free suspension.
12. Add bitter Masker to step 11 under stirring and mixed well until it is completely dissolved to form a lump free suspension.
13. Add sucralose to step 12 under stirring and mixed well until it is completely dissolved to form a lump free suspension.
14. Add Grape flavour to step 13 and mixed well until it is uniformly mixed to form a lump free suspension.
15. Volume make up was done using purified water to attain the desired batch size.
16. Homogenize the above prepared suspension of step 15 for NL T 15 mins to form a uniform lump free suspension.

Example 4 - Powder for reconstitution

S.No.	Components	% W/V of the Total composition
1.	Cenobamate	3.88
2.	Sodium Lauryl Sulfate	0.1
3.	Hydroxy Ethyl Cellulose	0.29
4.	Sodium Alginate	0.58
5.	Citric Acid Monohydrate	0.08
6.	Sodium Citrate Dihydrate	0.28
7.	Sodium Benzoate	0.02
8.	Methyl Paraben Sodium	0.10
9.	Sucralose	0.78
10.	Sorbitol	14.56
11.	Grape Flavor	0.15
12.	Bitter Masker	0.15

Example 5 - Powder for reconstitution

S.No.	Components	% W/V of the Total composition
1.	Cenobamate	3.81
2.	Kolliphor RH 40 (Polyoxyl Castor Oil)	0.10
3.	Copovidone/crospovidone	0.29
4.	Sodium Alginate	0.57
5.	Colloidal Silicon Dioxide	0.48
6.	Citric Acid Monohydrate	0.08

7.	Sodium Citrate Dihydrate	0.28
8.	Sodium Benzoate	0.02
9.	Methyl Paraben Sodium	0.10
10.	Sucralose	0.76
11.	Sorbitol	14.27
12.	Grape Flavor	0.14
13.	Bitter Masker	0.14

Example 6 – Powder for reconstitution

S.No.	Components	% W/V of the Total composition
1.	Cenobamate	3.85
2.	Polysorbate 80	0.10
3.	Copovidone/crospovidone	0.29
4.	Sodium Alginate	0.58
5.	Colloidal Silicon Dioxide	0.48
6.	Citric Acid Monohydrate	0.08
7.	Sodium Citrate Dihydrate	0.28
8.	Sodium Benzoate	0.02
9.	Methyl Paraben Sodium	0.10
10.	Sucralose	0.77
11.	Sorbitol	14.44
12.	Grape Flavor	0.14
13.	Bitter Masker	0.14

Example 7 – Ready to Use Suspension

S.No.	Components	% W/V of the Total composition
1.	Cenobamate	3.88
2.	Sodium Lauryl Sulfate	0.10
3.	Copovidone/crospovidone	0.29
4.	Sodium Alginate	0.58
5.	Colloidal Silicon Dioxide	0.48
6.	Citric Acid Monohydrate	0.08
7.	Sodium Citrate Dihydrate	0.28
8.	Sodium Benzoate	0.02
9.	Methyl Paraben Sodium	0.10
10.	Sucralose	0.78
11.	Sorbitol	14.55
12.	Grape Flavor	0.15
13.	Bitter Masker	0.15
14.	Purified Water	78.57

Test Methods

Sedimentation Rate

Item	Equipment	Manufacturer/Model	Asset
1.	100ml graduated cylinders, Class A glass	N/A	N/A

Stability study of composition of Example 2, 3 was performed at different temperature and relative humidity conditions for 3 months and results are as described below;

- Shake the suspension well as described.
- 2. Pour 100 mL of the sample into a 100-mL measuring cylinder and start the timer.
- 3. Securely seal the measuring cylinder with parafilm to prevent water loss.
- 4. Measure and record the amount of sediment after 1hour, 2 hours, 3 hours, 4hours, 5 hours and 249 hours.

Rheological Consideration of a Suspension is of Great Importance for the Stability Because Viscosity can modify the Sedimentation Rates. Maintaining the Proper Viscosity of Suspensions is Also Important to Ensure the Accuracy of Dosing and Ease of Application.

Dissolution profile Study

Table 2 given below shows the dissolution profile of Cenobamate suspension of Example 2, and 3 of the present invention carried out in 900 ml of 0.1 N HCl for 1 hour using Apparatus USP Type II (Paddle), at 75 rpm speed. The release profile (cumulative % of drug released) is given in Table 2.

Table 2: Dissolution profile of Cenobamate suspension of Example 2 and 3

S. No.	Times point (Min)	Example 2		Example 3	
		% Release	% RSD	% Release	% RSD
1	5	91	4.4	84	1.1

2	10	96	4.9	91	0.5
3	15	97	5.5	94	0.8
4	30	98	5.4	98	1.3
5	45	98	5.2	101	1.3
6	60	98	4.9	102	1.3

Storage Stability Test

The storage stability of the suspension has been tested over 2 months at 25° C. and 60% RH and 7 days at Stress condition of 60°C. At each time point of the stability program the composition of suspension was analysed by HPLC chromatography and the amount of Cenobamate and its known impurities were determined by a validated HPLC assay. Other tests such as sedimentation rate or redispersibility, during the storage period were performed.

Table 3: Stability Data of Example 2

Parameters	Specification	Initial	7 Days 60°C	2 Months RT (25°C)
Description	Off-white colour suspension	Off-white colour suspension	Off-white colour suspension	Off-white colour suspension
pH	5.0 - 6.5	5.934	5.887	5.962

Assay	90 - 110 %	96.9	92.2	98.6
Density	0.936 - 1.144	1.025	1.028	1.027
5	0.01N HCl, 900mL, Type II (Paddle), 75 rpm	92	79	91
10		97	90	97
15		98	94	100
30		99	97	101
45		99	97	101
60		99	96	101
1 N-Carbamate impurity	NMT 0.15%	0.014	0.014	0.013
1 N-Keto impurity	NMT 0.15%	0.006	0.006	0.006
1 N-Hydroxy impurity	NMT 0.15%	ND	ND	NA
Keto impurity	NMT 0.2%	0.003	0.001	NA
Hydroxy impurity	NMT 0.15%	0.002	0.073	0.003
Single max impurity	NMT 0.2%	0.009	0.009	0.013
Total impurity	NMT 1.2%	0.049	0.116	0.043

Those skilled in the art to which the present invention pertains may make modifications resulting in other embodiments employing principles of the present invention without departing from its spirit or characteristics, particularly upon considering the foregoing teachings. Accordingly, the described embodiments are to be considered in all respects only as illustrative, and not restrictive, and the scope of the present invention is, therefore, indicated by the appended claims rather than by the foregoing description or drawings. Consequently, while the present invention has been described with reference to particular embodiments, modifications of structure, sequence, materials and the like apparent to those skilled in the art still fall within the scope of the invention as claimed by the Applicant.

I/We Claim,

1. A pharmaceutical composition suitable for oral administration comprising i) a therapeutically effective amount of Cenobamate or a pharmaceutically acceptable salt, solvate or hydrate thereof, ii) a surface modifier wherein the surface modifier selected from the group which is essentially free of poloxamer and smectite clay, and iii) one or more pharmaceutically acceptable excipients.
2. The pharmaceutical composition as claimed in Claim 1, wherein the surface modifiers selected from the group consisting of Kolliphor RH 40 (Polyoxyl Castor Oil), Sodium lauryl sulphate, Polysorbate 80, polyethylene glycols, benzalkonium chloride, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, poloxamines, polyethylene glycol, vitamin E and polyethylene glycol-phospholipid or a combination thereof
3. The pharmaceutical composition as claimed in Claim 1, wherein the composition comprising the anticaking agent.
4. The pharmaceutical composition as claimed in Claim 3, wherein anticaking agent is colloidal silicon dioxide.
5. The pharmaceutical composition as claimed in claim 1, wherein said composition is a ready-to-use liquid composition or dry powder for reconstitution.
6. The pharmaceutical composition as claimed in claim 5, wherein said ready-to-use liquid composition is a suspension.
7. The pharmaceutical composition as claimed in claim 5, wherein said pharmaceutical composition provided as a dry powder composition adapted for reconstitution with vehicle into a multiple dose suspension which comprises from about 5mg to about 50 mg of Cenobamate per unit amount of composition.

8. The pharmaceutical composition as claimed in Claim 1 wherein the Cenobamate is present in the form of solid particles having a particle size distribution wherein D90 is in the range of 5 to 600 microns more preferably 30 to 300 microns.
9. The pharmaceutical composition as claimed in Claim 1, wherein the pharmaceutically acceptable excipients are selected from the group consisting of vehicles, anticaking agents, buffering agents, stabilizers, suspending agents, preservatives, sweeteners and flavouring agents.
10. The pharmaceutical composition as claimed in Claim 7, wherein the suspending agents selected from the group consisting of Carbomer, Hydroxy Ethyl Cellulose, methylcellulose, copovidone, sodium alginate, colloidal silicon dioxide, sodium carboxymethylcellulose, hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, alginate, guar gum, xanthan gum, acacia gum, chitosan, dextran and gelatin, glycerin, dextrin, , guar gum, hydroxypropyl cellulose, , polyethylene Oxide, polyvinyl Alcohol, povidone and propylene glycol alginate.
11. The pharmaceutical composition as claimed in Claim 9, wherein the sweetening agents selected from the group consisting of acesulfame potassium, sodium cyclamate, aspartame, dextrose, fructose, galactose, inulin, maltitol, maltose, mannitol, sucralose, cyclamate, saccharin, sorbitol, sucrose, trehalose, xylitol, saccharin sodium and aspartame or mixtures thereof.
12. The pharmaceutical composition as claimed in Claim 9, wherein the flavouring agents selected from the group consisting of grape flavour, cherry, raspberry, black currant, strawberry flavour, caramel chocolate flavour, mint cool flavour, fantasy flavour, meat flavours and the like.
13. The pharmaceutical composition as claimed in Claim 9, wherein the buffering agents selected from the group consisting of Citric Acid, Sodium Citrate dihydrate, Sodium

Dihydrogen Phosphate, Disodium Phosphate, Trometamol (Tris), Hydrochloric Acid, Ascorbic Acid, Sodium Ascorbate and anhydrous and monohydrate or dehydrate.

14. The pharmaceutical composition as claimed in Claim 1, comprising,
- a. 0.5% to 10.0% w/v of Cenobamate
 - b. 0.05% to 10.0% w/v of surface modifiers free of poloxamer and smectite clay
 - c. 0.2 % to 10.0% w/v of anticaking agents
 - d. 0.2 % to 10.0% w/v of suspending agents.
 - e. 0.3 % to 20.0 % w/v of sweeteners
 - f. 0.05 % to 5.0 % w/v of buffering agents
 - g. 0.1 % to 3.0 % w/v of flavouring agent
 - h. 0.02 % to 2.0 % w/v of preservatives
 - i. 40.0% to 98% w/v of vehicles
15. The pharmaceutical composition as claimed in claim 1, wherein said composition having a viscosity of 100-1500 millipoises at 25°C.
16. The pharmaceutical composition as claimed in claim 1, wherein the composition having a pH of 5-7.
17. The pharmaceutical composition as claimed in claim 1, which is an immediate release dosage form that exhibits in-vitro dissolution rate more than 90% of drug release within 30 minutes, when said dosage form is placed in a dissolution vessel filled with 900 ml of 0.1N HCL, pH 1.2 maintained at 37±0.5° C. and stirred at a paddle speed of 75 rpm using a USP Type II (paddle) apparatus.