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(54) **Title:** SOFT-CHEW TABLET PHARMACEUTICAL FORMULATIONS

(57) **Abstract:** A product and process of manufacturing an edible soft-chewable dosage form for the delivery of pharmaceutically active ingredients or nutritional agents to an animal or human subject, by forming a granulated soft-chew mass by appropriate mixing and sifting steps, and forming tablets with a compression press. Such soft-chew dosage forms have hardness of less than about 2 kilopond and friability of less than about 1% at 300 rotations (per USP). The process for manufacturing such compressed soft-chew tablets employs compression (tablet) pressing equipment to produce soft-chew tablets of consistent weight and texture.

## **SOFT-CHEW TABLET PHARMACEUTICAL FORMULATIONS**

### **CROSS REFERENCE TO RELATED APPLICATION**

[0001] This application claims priority to United States Patent Application 62/269,951, filed December 19, 2015, the entire contents of which are incorporated by reference.

### **FIELD OF INVENTION**

[0002] This invention relates products and processes for the manufacture of soft-chewable tablet pharmaceutical or nutritional dosage forms, for the oral administration of active pharmaceutical ingredients or nutritional agents.

### **BACKGROUND**

[0003] Chewable pharmaceutical dosage units, such as chewable tablets and soft-chewable tablets, are known and have been commercialized for pediatric, geriatric and involuntary (where subject by instinct will not accept the medication meant to be swallowed e.g. animals) patient populations. Chewable tablets are also of value to competent patients as an alternative to tablets or capsules that must be swallowed whole. The formulation of a drug into a chewable dosage form can increase patient acceptance of a medication in patients that resist or are unable to swallow conventional tablets or capsules.

[0004] The texture of a chewable dosage unit form is an important factor in the acceptance of oral dosage forms by patients in need of medication. Conventional dosage forms, such as chewable compressed tablets, using conventional ingredients, can make the tablet gritty or otherwise unappealing to many patients. Soft-chewable tablet dosage units, having a soft texture, pleasant mouth feel, and palatable taste with adequate flavoring agents, provide a solution to such problems. In addition, these features can address the problem of the disagreeable taste of many active pharmaceutical ingredients. Appropriate chewable dosage form can also address texture problems caused by dry dusty, granular, and pulverant properties of many pharmaceutical ingredients.

**[0005]** A soft-chewable pharmaceutical dosage unit is a solid pharmaceutical dosage unit at room temperature that has low hardness and higher moisture content than a conventional tablet or hard chewable tablet. The dosage unit may be designed to be chewed and swallowed by a human or an animal. Such a dosage unit exhibits a plastic rheological behavior and can be formed by many manufacturing processes described in prior art into many different shapes. A soft-chewable pharmaceutical dosage unit after forming should be dimensionally stable. The ingredients of such a soft-chewable pharmaceutical dosage unit may be of pharmaceutical grade.

**[0006]** A semi plastic oral dosage form unit has a soft texture and hardness such that the unit is intended to be chewed and swallowed. The texture of the unit is such that it does not appreciably dissolve in the mouth. A semi plastic oral dosage form unit is formed by compression on rotary tablet press and exhibits hardness of less than 2 kilopond, preferably less than 1 kilopond, and more preferably has no measurable hardness when measured with a tablet hardness tester, which has excellent flexibility, is breakage and chip resistant and yet may be easily chewed and swallowed by human or animal.

**[0007]** Several soft-chewable pharmaceutical dosage units are described in the prior art. For example, U.S. Pat. No. 4,327,076 describes a soft-chew antacid tablet formed by blending three - premixes and compression, but without a granulation and sifting step. The tablets have a hardness of 3 kp (col. 9, top).

**[0008]** For example, U.S. Pat. No. 6,387,381 discloses an extrudate formed of a matrix having starch, sugar, fat, polyhydric alcohol and water.

**[0009]** A process for manufacturing soft-chewable dosage form for drug delivery is described in prior art U.S. Pat. No. 6,387,381. It discloses a soft-chewable medication vehicle for drug delivery of an active ingredient to animal or human subjects, not containing ingredients of animal origin, without use of heat and without addition of water. The formed mixture was formed into individual chunks using a Formax F6™ molding machine with dies for production of chunk-like shapes, and packaged for storage.

[0010] US 2014/0141055 discloses a process using a rotary molding machine for the manufacture of semi-plastic pharmaceutical unit doses that have lower hardness and higher moisture than conventional hard chewable tablets. The disclosed rotary molding process works by displacing dough between a rotary mold roller and removal from the mold without a punch mechanism.

[0011] WO 2004/014143 discloses compositions and processes for the delivery of an additive to an organism in a form suitable for consumption, including in the form of a soft-chew composition.

[0012] US 2009/0280159 and US 2011/0223234 relate to palatable edible soft-chewable medication vehicles. The processes described in these publications relate to the problem that heat generated during the extrusion process causes deterioration in the stability of the active ingredient in the mixture.

[0013] Machines for the production of molded food patties have been described to be useful for the manufacturing of soft-chews for administration to non-human animals. Such machines are molding machines that have been originally developed for use in producing molded food products, for example the Formax F6™ molding machine made by the Formax Corporation or the molding machines disclosed in U.S. Pat. Nos. 3,486,186; 3,887,964; 3,952,478; 4,054,967; 4,097,961; 4,182,003; 4,334,339; 4,338,702; 4,343,068; 4,356,595; 4,372,008; 4,535,505; 4,597,135; 4,608,731; 4,622,717; 4,697,308; 4,768,941; 4,780,931; 4,818,446; 4,821,376; 4,872,241; 4,975,039; 4,996,743; 5,021,025; 5,022,888; 5,655,436; and 5,980,228.

[0014] The use of extruders, forming machines and rotary molding machines exhibit problems associated with the weight and physical forms of a final dosage form. Moreover, the use of such technologies may require conditioning of the final dosage form (e.g. drying or curing final formed structure) for consolidation of shape and structure of formed structure.

[0015] Use of such technologies, equipment and processes is complex, cumbersome, and something that is not traditionally used in typical pharmaceutical oral solid dosage form manufacturing set-up.

[0016] A tablet press is a mechanical device that compresses powder into tablets of uniform size and weight. A press can be used to manufacture tablets/pellets of a wide variety of materials, including pharmaceuticals, cleaning products, and cosmetics. There are two types of press machines, eccentric-type and rotary-type. The rotary-type is generally more widely used, because it facilitates high production performance with narrow weight variation along with ease of use.

[0017] Accordingly, alternate processes for manufacturing soft-chew tablet formulations on a large scale using commonly installed pharmaceutical manufacturing equipment using such as a rotary (tablet) compression press would be desirable.

### **SUMMARY OF THE INVENTION**

[0018] The present invention overcomes the disadvantages and shortcomings of known chewable dosage forms by providing a simplified manufacturing process for soft-chewable dosage unit formulation comprising a highly palatable composition to patients, which is formed by conventional compression techniques using conventional pharmaceutical equipment, such as a rotary tablet press. Typically, conventional tablets manufactured on a rotary tablet press are formulated and processed so the tablets have a hardness of more than **10** kiloponds (kp) and any lower hardness in the art is discouraged to keep the tablet friability acceptable. But, the present inventors have found that many conventional soft-chew tablet formulations, made in the prior art using molding or extrusion techniques, can be manufactured more efficiently, reliably, and reproducibly, using a tablet press. The compressed soft-chew dosage forms of the current invention have hardness of less than **2** kp, or may have hardness of less than **1** kp, or may have no measurable hardness when tested with a conventional tablet hardness tester. Despite the low hardness, such compressed soft tablets have friability of less than **1.0%**, or less than **0.5** %, or less than **0.1%** for **100** rotations (per USP); **200** rotations or **300** rotations.

[0019] The soft-chewable formulations are prepared according to methods conventional in the art, such as wet or dry granulation processes.

[0020] In one embodiment, the invention is directed to a palatable, soft-chewable pharmaceutical composition for oral administration to an involuntary subject population, for example, very young children, senile patients, or animals (i.e., for veterinary use), comprising a therapeutically

effective amount of a pharmaceutically active ingredient in an immediate or controlled release form, and a palatability improving agent in an amount sufficient make the pharmaceutical composition palatable to the subject population. By the term "involuntary subject population," it is meant patients who cannot be conventionally instructed to chew and/or swallow a tablet or capsule.

**[0021]** An active pharmaceutical ingredient for use in the process or product according to the current invention (or active ingredient, or pharmaceutically active agent or pharmaceutically acceptable active ingredient) is a substance used in a pharmaceutical dosage form, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in a patient population (humans or animals).

**[0022]** Any pharmaceutically active ingredient or nutritional agent may be provided in the process of the invention and in the product according to the invention. Those of ordinary skill in the pharmaceutical arts will be entirely familiar with the identity of such active ingredients which may include antibiotics, analgesics, antiviral, antifungal, anti-parasitic, hormones, anti-inflammatory (including nonsteroidal anti-inflammatory), steroids, behavior modifiers, vaccines, antacids, laxatives, anticonvulsants, sedatives, tranquilizers, antitussives, antihistamines, decongestants, expectorants, appetite stimulants and suppressants, cardiovascular drugs, minerals and vitamins along with other supplement and nutraceutical agents.

#### DETAILED DESCRIPTION

**[0023]** The current inventors have found that by appropriate granulation of pharmaceutical or nutritional formulations, a soft-chew composition is formed that can be pressed into soft-chew tablets using conventional tablet press equipment. This is distinguished from prior art methods for the manufacture of soft-chew tablets that require expensive and complex molding or extrusion equipment. Accordingly, this invention provides unit dosage forms for the administration of pharmaceutically active agents (drugs) or nutritional agents to humans or animals orally, wherein the dosage forms are soft-chew tablets formed by compression in a tablet press.

**[0024]** In an embodiment of this invention, a soft-chew mass is formed by blending appropriate active ingredients and excipients. The soft-chew mass is compressed in tablet press to provide tablets with minimal hardness, of less than or equal to about 2 kp. In an embodiment, the tablets have hardness of less than or equal to about 1 kp. In an embodiment, the tablets have no measurable hardness in a tablet hardness testing apparatus and a friability of less than about 1% at up to 300 rotations in a friability apparatus. The tablets so obtained are "soft chew" tablets.

**[0025]** The soft-chew mass may or may not be flowable at room temperature. In an embodiment, the soft-chew mass may not be flowable at room temperature of about 20°C (or below). In an embodiment, the soft-chew mass may be flowable at temperatures greater than room temperature. In an embodiment, soft chew mass may be treated with heat in an equipment where, heat is applied directly to a static solid bed, directly to a moving solid bed, or directly to a fluidized solid bed to affect soft chew mass flowability.

**[0026]** In an embodiment, a process is provided for the manufacture of a compressed soft-chew tablet unit dosage form for the oral administration of an active pharmaceutical ingredient or a nutritional agent, in which a soft-chew tablet or semi-plastic tablet is formed by compressing a soft-chew mass on a compression press, and wherein the soft-chew tablets have a hardness of less than about 2 kp and a friability of less than about 1% at 300 rotations.

**[0027]** In an embodiment, a process is provided for the manufacture of a compressed soft-chew tablet unit dosage form for the oral administration of an active pharmaceutical ingredient or a nutritional agent, in which a soft-chew mass mixture is provided including an active pharmaceutical ingredient or a nutritional agent, wherein the soft-chew mass is a granulate formed with a granulation and sifting step, and wherein the soft-chew mass granulate is pressed into tablets using a tablet press, and wherein the soft-chew tablets have a hardness of less than about 2 kp and a friability of less than about 1% at 300 rotations.

**[0028]** In an embodiment, this invention provides a process for the manufacture of an edible compressed soft-chew tablet or semi plastic oral unit dosage form employing the steps of (a) mixing at least one active ingredient with at least one dry or liquid component to form a liquid premix; (b) blending dry ingredients having at least one of each of a bulking agent, a lipid, a

flavoring agent, a disintegrating agent, a binding agent, a surfactant, a preservative, a lubricating agent, and an anti-sticking to form a uniform dry ingredient mixture; (c) blending the premix and the uniform dry ingredient mixture to form a granulated compacted soft-chew mass; (d) sifting the granulated compacted soft-chew mass through at least one sifting screen to form uniform granules of the soft-chew mass; and (d) adding a lubricant or anti sticking agent to the uniform granules of the soft-chew mass and compressing the resulting mixture in a tablet press to form soft-chew tablets.

**[0029]** By the term "active ingredient" or "active agent," it is meant an active pharmaceutical ingredient or nutritional agent. By the term "fluid," it is meant a material that is flowable or malleable. A fluid material may be a viscous liquid, with a viscosity comparable, for example, to water, vegetable oil, honey, or peanut butter.

**[0030]** In an embodiment, two or more mixtures are prepared in the inventive process. A first mixture is a premix containing the active ingredient, and a second mixture is a blend of dry ingredients. The premix and dry ingredient blend may be blended together to form a soft-chew mass.

**[0031]** In an embodiment, the active ingredient is mixed with a vegetable oil to form a premix. The vegetable oil may be, for example, soybean oil, olive oil, flaxseed oil, canola oil, or corn oil.

**[0032]** In an embodiment, this invention provides a unit dosage form for the oral administration of a pharmaceutical agent or nutritional agent to a human or animal, comprising a tablet manufactured according to the processes as disclosed herein, wherein the tablet is chewed and swallowed.

**[0033]** In one embodiment, the nutritional agent or pharmaceutically active ingredient is added to the composition by dry blending.

**[0034]** In an embodiment, the bulking agent is microcrystalline cellulose.

[0035] In one embodiment, the nutritional ingredient or pharmaceutically active ingredient may be dissolved, emulsified, or suspended in a non-aqueous solvent before addition. The nutritional or pharmaceutically active ingredient may be soluble, partially soluble, or insoluble in water.

[0036] A nutritional agent may include vitamins, minerals, glycosaminoglycan or its active members, amino acids or combination thereof that are useful in human or animal nutrition.

[0037] An active pharmaceutical ingredient may include any approved or experimental drug. By "approved," it is meant that the drug is approved for human or veterinary use by a regulatory agency in any country that makes such drug approvals. For example, the pharmaceutically active ingredient may be selected from an anesthetic agent, anthelmintic agent, analgesic agent, steroid, corticosteroid agent, NSAID agent, antiemetic agent, anti-thyroidal agent, parasitocidal agent, appetite stimulant, antihistamine agent, antifungal agent, antiprotozoal agent, or anti-depressant.

[0038] In an embodiment, the nutritional ingredient or active pharmaceutical ingredient may be in granular form, and is coated, or further coated, with a suitable coating. For example, the coating could be a coating polymer that coats and protects the nutritional ingredient or pharmaceutically active agent, or masks an offensive taste and/or offensive odor. In an embodiment, the coating could be a functional coating, e.g. an extended-release coating, delayed-release coating, controlled-release coating, barrier coating, or a combination thereof.

[0039] In an embodiment, the nutritional ingredient or pharmaceutically active ingredient could be conjugated with other ingredients, such as cyclodextrins, surfactants, solubility or bioavailability enhancers, etc., to inhibit interactions with other excipients or with the environment, or to promote the chemical stability, improve solubility, enhance bioavailability, or improve the palatability of the nutritional ingredient or pharmaceutically active agent. Similarly, the pharmaceutically active ingredient may be incorporated into a novel drug delivery system, such as microspheres, microcapsules, liposomes, niosomes, nanoparticles, microemulsions, or nanoemulsions to protect the drug or permit organ targeting.

[0040] The rate of release of the nutritional or pharmaceutically active ingredient from the chewable formulation may be modulated or controlled by, for example, the use of controlled or

sustained release agents (e.g. polymers) or by using excipients (e.g. disintegrants) that promote in rapid release, as appropriate.

**[0041]** In some embodiments a single excipient has more than one function in the formulation of the present invention. For example, propylene glycol and glycerol may be present and have a simultaneous role as a plasticizer, humectants, antimicrobial agents, or any combination of any two or more thereof, in this formulation. Oils, lipids or fats may have a role as a lubricant, plasticizer, binders, or any combination of any two or more thereof. Any suitable excipient may be used.

**[0042]** In an embodiment, the composition of the soft-chewable dosage form includes a lipid that may be a liquid vegetable oil, or a solid hydrogenated vegetable oil. The vegetable oil may be, for example, soybean oil, olive oil, flaxseed oil, canola oil, or corn oil.

**[0043]** In one embodiment, the composition of the soft-chewable dosage unit as defined above, is provided wherein a texturing agent, selected from the group comprising of modified corn starches, polyols, poly(ethylene) oxide, microcrystalline cellulose co-processed with guar gum and the like, is added.

**[0044]** A polyol may include propylene glycol, glycerin, polyethylene glycol and mixtures thereof.

**[0045]** In one embodiment, the chewable formulation includes one or more fillers. A filler may be used to increase the total mass of the chewable formulation to a manageable size or to enhance the flow properties of final powder or granules to be compressed in a rotary tablet press.

**[0046]** In one embodiment, the composition of the soft-chewable dosage form, is provided with a binding agent. The binding agent may be polyethylene glycol. The polyethylene glycol may be admixed to dry ingredients for mixing. The polyethylene glycol may be melted and added to at least one other dry ingredient and mixed to form the uniform dry ingredient mixture.

[0047] In an embodiment, the soft-chew tablet of this invention may have at least one active ingredient, and includes a vegetable oil and microcrystalline cellulose in a ratio of about 2:1 to about 1:2.5, w/w, and wherein the tablet is manufactured by compression on a tablet press.

[0048] For example, one or more diluents may be used in combination with silicified microcrystalline cellulose. Examples of diluents include starches and their derivatives (e.g. hydrogenated starch hydrolysate), celluloses and their derivatives (e.g. cellulose acetate), protein matrices (soy protein, dextrates, wheat gluten, whey, corn cob, corn gluten), carbohydrates (e.g. maltodextrin, polydextrose), sugars and sugar alcohols (glucose, lactose, fructose, maltose, dextrose, sucrose, maltitol, xylitol, isomalt, mannitol), silicates, calcium phosphates, calcium sulfate, dextrates, kaolin, magnesium carbonate, polymethacrylates, talc, salts (e.g. sodium chloride) or any combination of any two or more thereof.

[0049] In an embodiment, the composition includes a starch, or a modified starch, or a mixture of starch and a modified starch.

[0050] Diluents may also serve a role in fat or oil absorption, disintegration, and binding, providing nutrition, lubrication or any combination of any two or more thereof. The diluents may also be used for taste masking or modifying texture, for example microcrystalline cellulose co-processed with guar gum and/or modified corn starches.

[0051] In one embodiment, the chewable formulation includes one or more binders. Binders improve the binding properties of the compacted mass, to assist the formation of compact dosage units. Any suitable binder known in the art may be used. In one embodiment, the binder is selected from gums such as xanthan gum or guar gum, alginates, celluloses and their derivatives such as methylcellulose or microcrystalline cellulose, fats or lipids, starches and their derivatives, dextrans, celluloses and their derivatives, povidones, silicates, mineral oils, vegetable oils, polymethacrylates, polyethylene oxides, gums, waxes, chitosan, polycarbophil, agar, or carbomers, or any combination of any two or more thereof. In some embodiments, the binder is a dry binder such as povidone.

[0052] In an embodiment, the formulation of this invention may include one or more palatability enhancers. Palatability enhancers improve the taste of material that is chewed. Advantageously, palatability enhancers may improve the palatability of soft-chewable formulations comprising bitter, acrid, obnoxious, unpleasant, or otherwise unpalatable nutritional or pharmaceutically active agents.

[0053] In one embodiment, the palatability enhancer is a taste masking agent, a flavoring agent, an aroma modifier, or a taste modifier, or any combination of any two or more thereof.

[0054] Flavoring agents may be used to improve the palatability of the chewable tablets. Any type of flavoring agent can be used provided it improves the palatability of the product, typically by improving either its taste and/ or smell. The use of a flavoring agent may also assist with dose compliance. Flavors can be natural (derived from animal or plant sources), semisynthetic, or artificial. In one embodiment, the flavoring agent is an artificial flavoring agent, semi-synthetic flavoring agent, a natural flavoring agent, or nature identical flavoring agent.

[0055] In an embodiment, the formulation of this invention may include liquid components that are absorbed on the surface of a lipid absorbing pharmaceutical ingredient selected from one or more of microcrystalline cellulose, silicified microcrystalline cellulose, and a combination of microcrystalline cellulose and guar gum. The liquid components absorbed on the surface of the lipid absorbing pharmaceutical ingredient may be mixed with the uniform dry ingredient mixture and then sifted again through at least one finer sifting screen to form further finer granules of the soft-chew composition mixture. In an embodiment, a nutritional agent or a pharmaceutically active ingredient is admixed with the liquid components prior to mixing with the lipid absorbing pharmaceutical ingredient.

[0056] Plasticizers may be used to the formulation to improve plasticity and malleability of dosage units of the present invention. In one embodiment, a plasticizer may be selected from alcohols, glycols (such as propylene glycol), lanolin, wool fat, liquid paraffin, mineral oil, petrolatum, benzyl phenylformate, chlorobutanol, diethyl phthalate, glycerol, polyethylene glycol, propylene glycol, sorbitol, triacetin, benzyl phenyl formate, dibutyl sebacate, tributyl

citrate, triethyl citrate, or any combination of any two or more thereof. Other plasticizers known in the art may also be used.

**[0057]** In one embodiment, the dosage units of this invention may include a non-active ingredient including of one or more of a starch, a polysaccharide, a humectant, a polyol, water-soluble poly(ethylene oxide) resin

**[0058]** In one embodiment, the dosage units of this invention may include a humectant. A humectant is used to retain moisture in the dosage unit. A humectant of value in this invention may be selected from sodium and potassium chloride, benzalkonium chloride, aluminium silicate, sodium propionates, sodium and potassium phosphates, sugars, sulfites, hydrogenated starch hydrolysate, etc. Liquid humectants include, but are not limited to, glycols, polyols, sugar alcohols, vegetable oils and mineral oil, hydrogenated vegetable oils, hydrocarbons, triacetin, liquid paraffin, or any combination of any two or more thereof. Other humectants known in the art may also be used.

**[0059]** In one embodiment, the dosage units of this invention may include an antioxidant. An antioxidant inhibits oxidation and may be of benefit as a preservative, or to maintain the chemical stability of an active or inactive ingredient. An antioxidant may be selected from propyl gallate, ascorbic acid and its derivatives, sodium formaldehyde sulfoxylate, malic acid, fumaric acid, editic acid, thiols, polyphenols, sodium EDTA, sodium ascorbate, sodium metabisulfite, butylated hydroxytoluene, butylated hydroxyanisole, butylated hydroxyanisole & butylated hydroxytoluene co-processed with zeamays oil or natural substances such as flavanoids, tocopherols, carotenes, cysteine, or any combination of any two or more thereof. Other antioxidants known in the art may also be used. The antioxidants are generally added to the formulation in amounts of from about **0.01** to about **2.0%**, based upon total Weight of the formulation, with about **0.1** to about **1.0%** being especially preferred.

**[0060]** In an embodiment, the formulation of this invention may include a preservative selected from the group including parabens (methylparaben and/or propylparaben), benzalkonium chloride, benzethonium chloride, benzoic acid, citric acid, fumaric acid, benzyl alcohol, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben,

imidurea, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thimerosal and quaternary ammonium compounds. Other preservatives known in the art may also be used.

**[0061]** In one embodiment, the chewable formulation of this invention may include a non-aqueous solvent, for example glycerin. A non-aqueous solvent may disperse, solubilize or enhance solubilization of the nutritional or pharmaceutically active agent. The non-aqueous solvent may also enhance the binding of the formulation and the consistency and texture of the soft-chewable dosage form.

**[0062]** In one embodiment, the chewable formulation of this invention may include a disintegrating agent. A disintegrating agent may be used to enable the inventive chewable tablets to break down on contact with water, saliva, or gastric fluid in the stomach to quickly release the active ingredient. A disintegrating agent may be selected from povidones, croscarmellose sodium, sodium starch glycollate, celluloses and their derivatives, starches and their derivatives, gelatin, silicon dioxide, or any combination of any two or more thereof. Other disintegrating agents known in the art may also be used. Disintegration may be tested and measured using USP Disintegration Test <701> for uncoated tablets, using water as medium.

**[0063]** In an embodiment, a granulated compacted soft-chew mass is formed, and the mass is dried by equipment using direct or indirect conduction heat applied to a static solid bed, a moving solid bed, or a fluidized solid bed. The granulated mass may be dried at room temperature, for example about  $25^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . Alternatively, the granulated mass may be dried at a controlled temperature of about  $50^{\circ}\text{C}$  or less.

**[0064]** In an embodiment, the process of this invention may include sifting, or milling, of dry components or a granulated mass, or a mixture of both through sifting screens with mesh sizes commonly known in the art. Mesh sizes for sifting screens may include Mesh # 4 or 5 or 6 or 7 or 8 or 10 or 12 or 14 or 16 or 18 or 20 or 25 or 30 or 35 or 40 or 45 or 50 or 60 or other mesh sizes commonly known in the art. Components may be sifted through at two or more screens with different mesh sizes one after other in gradual or random order of mesh sizes.

**[0065]** In an embodiment, the uniform dry ingredient mixture or the granulated compacted soft-chew mass are sifted through sifting equipment using impaction, attrition, compression or cutting.

**[0066]** In an embodiment, the uniform dry ingredient mixture or the granulated compacted soft-chew mass are uniformly mixed using equipment using diffusion mixing, convection mixing or pneumatic mixing.

**[0067]** In an embodiment, the process of this invention may employ pre-compression force applied to the granulated compacted soft-chew mass before application of main compression force for compression of soft-chews.

**[0068]** In an embodiment, the granulated compacted soft-chew mass is fed into a compression die by gravity feed, power assisted feed, by centrifugal force, or by compression coating.

**[0069]** In an embodiment, the soft-chew tablets of this invention may incorporate an abuse-deterrent technology, which can include one or more of high-melting-point excipients that resist heating and injecting; taste modifiers that resist covert administration, snorting (ingestion of a powdered material through the nose) and dose dumping (extraction of API from tablets); water insoluble excipients that resist extraction and drink adulteration; waxy excipients that resist snorting; viscosity modifiers that resist dissolution, injection and dose dumping; low-density excipients that resist drink adulteration; and dyes, that resist adulteration.

**[0070]** The breaking force of tablets is commonly called hardness in the pharmaceutical literature. The term crushing strength is also frequently used to describe the resistance of tablets to the application of a compressive load.

**[0071]** The measure of the mechanical integrity of tablets is their breaking force or hardness, which is the force required to cause them to fail (i.e., break) in a specific plane. Various equipment is used for hardness measurements, for example a Monsanto Hardness Tester, Stokes Hardness tester, Pfizer Hardness Tester, Strong-Cobb Hardness Tester, or Schleuniger Hardness tester. Tablet hardness can be expressed using various units depending on the

equipment used for hardness measurement. The units for tablet hardness measurement are newtons, pounds, Strong-Cobb units, and kiloponds.

[0072] For the hardness measurements for exemplarily examples in this invention, a Schleuniger Hardness tester was used, and hardness was measured in kiloponds or newtons. This apparatus has two parallel platens between which a tablet is placed. A load is applied and the value of the hardness is measured. The platen faces are polished smooth and precision-ground perpendicularly to the direction of movement. Perpendicularity is preserved during platen movement, and the mechanism is free of any bending or torsion displacements as the load is applied. The contact faces are larger than the area of contact with the tablet.

[0073] In one embodiment, the chewable formulation of this invention includes dosage units which have hardness of less than 2 kilopond, preferably less than 1 kilopond, and more preferably has no measurable hardness when measured with a tablet hardness tester.

[0074] In an embodiment, the chewable formulation of this invention includes dosage units with hardness less than 3.0 Strong Cobb units, preferably less than 1.5 Strong Cobb units, or more preferably no measurable hardness when measured with a tablet hardness tester.

[0075] In an embodiment, the chewable formulation of this invention includes dosage units with hardness less than 5.0 pound, preferably less than 2.5 pound, or more preferably no measurable hardness when measured with a tablet hardness tester.

[0076] In an embodiment, the chewable formulation of this invention includes dosage units with hardness less than 20.0 newtons, preferably less than 10 newtons, or more preferably no measurable hardness when measured with a tablet hardness tester.

[0077] A friability value of about 1 percent or less (when measured as per USP test) is desirable for tablets in order for them to withstand the stress of handling during production, packaging, and transport.

[0078] In one embodiment the formulation comprises of dosage units with friability less than 1%, preferably less than 0.5%, or more preferably less than 0.1% for 100 rotations (per USP), or 200 rotations, or 300 rotations.

[0079] For traditional tablet compression using rotary tablet press, tablet hardness is traditionally kept 3 kilopond or more. As dosage form size increases, compression force is increased to produce tablet with even higher hardness.

[0080] For tablets having hardness 5 kilopond or less, a high order of tablet rejection results because of stress during production, packaging, and transport. For such tablets tablet friability is generally between 0.1 and 1.0 % when performed as per USP test.

[0081] As tablet hardness decreases, tablet friability generally increases. But the instant inventors have unexpectedly found that for exemplarily formulations herein, soft-chewable tablets with hardness less than 2 kilopond or lower, friability remains less than 1%, preferably less than 0.5 %, more preferably less than 0.1% for 100 rotations (per USP); 200 rotations or 300 rotations.

[0082] In one embodiment, the soft-chewable tablet maintains a characteristic selected from chewiness, hardness, compression energy, adhesion, cohesiveness, springiness, and modulus, and any combination of any two or more thereof (when measured by the texture analyzer as per procedure for example 1) sufficient to provide a chewable texture.

[0083] In one embodiment, the dosage unit of this invention (e.g. soft-chew) has a weight between about 0.1 and about 10 g. In one embodiment, the dosage unit has a weight between about 0.5 and about 4.0 g. In one embodiment, the dosage unit has a weight between about 0.1 g and about 3.0 g. In another embodiment, the weight of the dosage unit is between about 0.1 g and about 2.0 g.

[0084] In an embodiment, weight of the dosage unit can be between about 0.1 and about 1.0 g; or between about 1.1 g and about 2.0 g; or between about 2.1 g and about 3.0 g; or between about 3.1g and about 4.0 g; or between about 4.1 g and about 5.0 g.

[0085] In an embodiment, the dosage unit (e.g. soft-chew) of this invention can have an imprint on at least one surface of the dosage unit. In a specific embodiment this imprint can be on the top surface of the dosage unit. Such imprint can be e.g. letters, numbers, logos or symbols etc. An imprint can also be on the bottom surface.

[0086] In one embodiment, the dosage unit has a score or groove on one of the surfaces. This cross score has the effect that it facilitates the dividing of the dosage unit and allows more exact dosing of the active pharmaceutical ingredient according to the body weight, and/ or age of the patient.

[0087] Such dosage units can have different weights, dimensions and shapes that can be adapted to the weight and need of the target patient population to allow accurate dosing. Dosage forms can be to different weights, dimensions and shapes known in the art. For example, the soft-chew tablets of this invention can be round, capsule-shaped, or have a modified shape.

[0088] The soft-chewable tablets of this invention can be packaged as bulk primary packaging, or as singular unit primary packaging.

## EXAMPLES

### Example 1

Table 1

Ingredients	
Active	% w/w
Placebo Active	3.0
Granulation Aid	
Soybean Oil	15.0
Zea Mays Oil & BHA & BHT	0.1
Glycerin	19.0
Intragranular Addition	
Microcrystalline Cellulose	21.0
Pregelatinized Corn Starch	5.0
Extragranular Addition	
Pregelatinized Corn Starch	3.0
Beef Flavor	19.0
Sodium Lauryl Sulfate	0.2

Poly(ethylene) Oxide	1.0
Maltodextrin	3.0
Modified Corn Starch	3.0
Crosscarmellose Sodium	3.7
Color	0.01
Polyethylene Glycol 3350	2.0
Flow Aid	
Magnesium Stearate	1.0
Colloidal Silicon Dioxide	1.0
Total	100.0

### [0089] Procedure

1. Two methods were employed using the formulation summarized in Table 1. In the first method, a placebo active was added as part of granulation aid components, and in the second method placebo active was added as part of extra-granular addition, remaining procedure was same for both methods.
2. The intragranular ingredients and the active were passed through a sifting screen followed by uniform mixing.
3. The extragranular ingredients were passed through a sifting screen followed by uniform mixing.
4. Granulation aid components were added to the intragranular blend and mixed thoroughly until uniformly mixed, followed by melting polyethylene glycol 3350 and quickly adding this to granulated mass, followed by uniform mixing.
5. The granulated mass from step 4 was passed through a sifting screen to form uniform granules.
6. The extragranular blend from step 3 was added to screened granules from step 5, followed by uniform mixing.
7. Blended granules from step 6 were passed through a sifting screen.
8. Magnesium stearate and colloidal silicon dioxide mixed with small amount of granules from step 6 and passed sifting screen.

9. The milled (sifted) components from step 8 were added to granules from step 6 followed by uniform mixing followed by compressing on a rotary tablet press using 18mm x 18 mm rounded square punch.

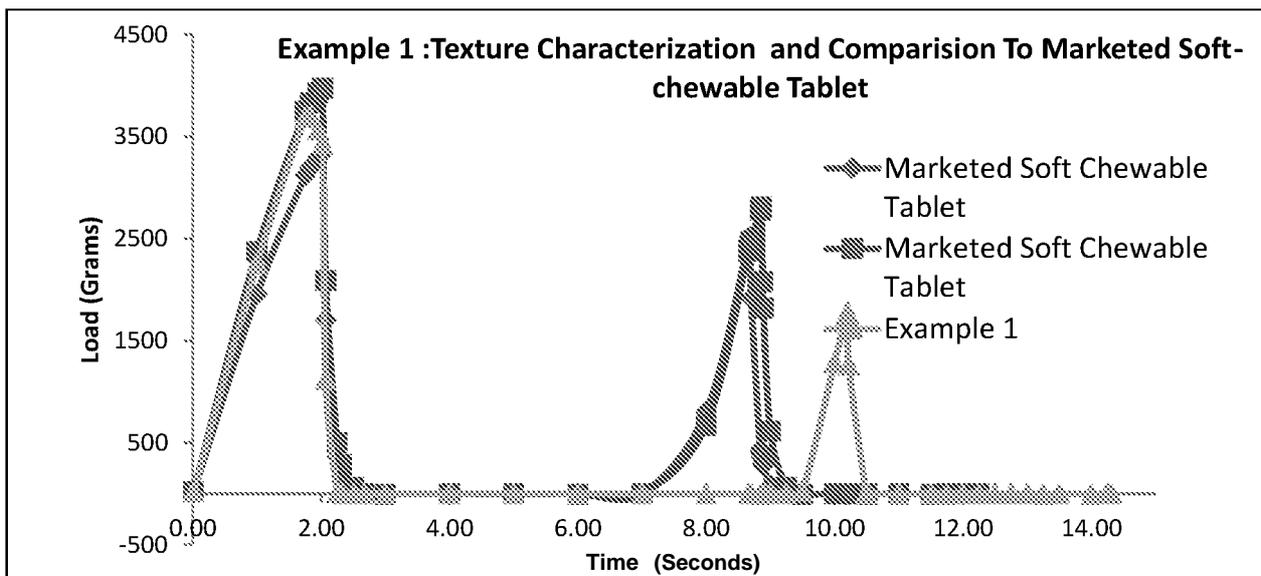
[0090] Texture Analysis was performed using CT3 Texture Analyzer using TA3/100 probe and 25,000g load cell and 5g trigger load, over 4mm using 2mm/s test speed and using data rate of 100 points/second.

Table 2: Example 1: Tablet Characterization and Comparison to Marketed Soft-chewable Tablet Compared to Example 1

Test Parameters	Marketed Soft-chewable Tablet	Example 1
Formulation Approach	Unconventional Molding Method	Conventional Tablet Press Compression Method
Physical Characterization		
Weight(g)	3.600 -3.750	3000
Shape	Trapezoidal	Square
Color	Multiple Strengths with different colors	Yellowish Brown
Top[W(mm),L(mm)]	16.10, 17.40	18 x 18
Bottom [W(mm),L(mm)]	17.80, 18.60	18 x 18
Thickness (mm)	9.20 -9.60	8.00 - 9.00
Disintegration Time (min)	20- 26	10 -15
Tablet Hardness (kp)	0	0
Tablet Friability (%)	0	0
Soft-chew Characterization <sup>1</sup>		
Hardness	3000 -3900 g	3698.00 g - 3866.00 g
Deformation at Hardness	3.95 -4.00 mm	1.78 mm - 3.58 mm
Adhesiveness	0.00- 0.20 mJ	0.00 mJ - 0.10mJ
Cohesiveness	0.30 - 0.34	0.00 -0.15
Gumminess	1100.00 g - 1450.00 g	4.00g - 546.00 g
Chewiness	24.40 mJ - 93.70 mJ	0.00 -42.70 mJ

<sup>1</sup> Using CT3 Texture Analyzer

Chart 1: Example 1: Texture Characterization and Comparison to Marketed Soft-chewable Tablet



## Example 2 (Conventional Hard Chewable Tablet)

Table 3

Ingredients	%
<b>Step 1 Ingredients</b>	
Carprofen	5.00
Artificial Beef Flavor	20.0
Silicified Microcrystalline Cellulose	17.95
Polycarbophil	2.50
Polyethylene Glycol 3350	6.00
Microcrystalline Cellulose & Guar Gum	3.00
Pregelatinized Corn Starch	24.0
Lactose Monohydrate	15.0
Crosscarmellose Sodium	2.50
<b>Step 2 Ingredients</b>	
Color 1	0.03
Color 2	0.02
Talc	2.00
Magnesium Stearate	2.00
<b>Total</b>	<b>100</b>

**[0091]** Procedure

1. All step 1 ingredients were individually weighed and passed through a sifting screen and uniformly mixed.
2. The step 2 ingredients were mixed along with small quantity of pre-mix from step 1.
3. The ingredients from step 2 were added to the remaining pre-mixed ingredients from step 1 and mixed for uniform mixing for 2-3 minutes and further subjected to compression on rotary tablet press for 500 mg fill weight.

## Examples 3 and 4

Table 4 Examples 3 and 4

	Example 3	Example 4
Ingredients	% w/w	% w/w
<b>Active</b>		
Carprofen	0.84	3.34
<b>Granulation Aid</b>		
Soybean Oil	16.00	9.00
Zea Mays Oil & BHA & BHT	0.10	0.10
Glycerin	20.00	13.00
Polyethylene Glycol 600	-	9.00
Povidone K 30	2.00	2.00
<b>Intragranular Addition</b>		
Polycarbophil	0.30	-
Silicified Microcrystalline Cellulose	16.06	18.66
Pregelatinized Corn Starch	7.00	7.00
Calcium Sulfate Dihydrate	1.30	2.50
Artificial Beef Flavor	8.00	15.00
Crosscarmellose Sodium	2.50	2.50
Polyethylene Glycol 600	-	-
Polyethylene Glycol 3350	2.00	-
<b>Extragranular Addition</b>		
Pregelatinized Corn Starch	4.00	5.00
Artificial Beef Flavor	10.00	3.00
Sodium Lauryl Sulfate	0.20	0.20
Poly(ethylene) Oxide	1.00	1.00
Modified Corn Starch	3.00	-
Crosscarmellose Sodium	2.50	2.50
Calcium Sulfate Dihydrate	1.70	1.70
Lactose Monohydrate	1.50	4.50
<b>Total</b>	<b>100.00</b>	<b>100.00</b>

## [0092] Procedure: Example 3

1. The active, soybean oil and Zea Mays Oil & BHA & BHT are weighed accurately and uniformly mixed to form a dispersion.

2. Simultaneously, a dispersion was prepared by adding povidone to glycerin and properly mixing.
3. Intra granular dry ingredients were passed through a sifting screen followed by uniform mixing.
4. Dispersions from step 1 and step 2 were used as granulation aid, adding them one after another to pre-mixed ingredients from step 3.
5. The formed doughy mass was passed through a sifting screen to get wet granules.
6. Extragranular ingredients were passed through a sifting screen followed by uniform mixing.
7. Approximately half the quantity of the extragranular blend from step 6 was added to the wet granules formed in step 5 and uniformly mixed.
8. The formed slightly dry granular mass was further passed through sifting screen to obtain granules.
9. The formed granules are uniformly mixed with remaining quantity of extra granular blend from step 6 and further subjected to compression on rotary tablet press using 18mm x 18 mm rounded square punch for 3.0 gram target fill weight.

**[0093]** Procedure: Example 4

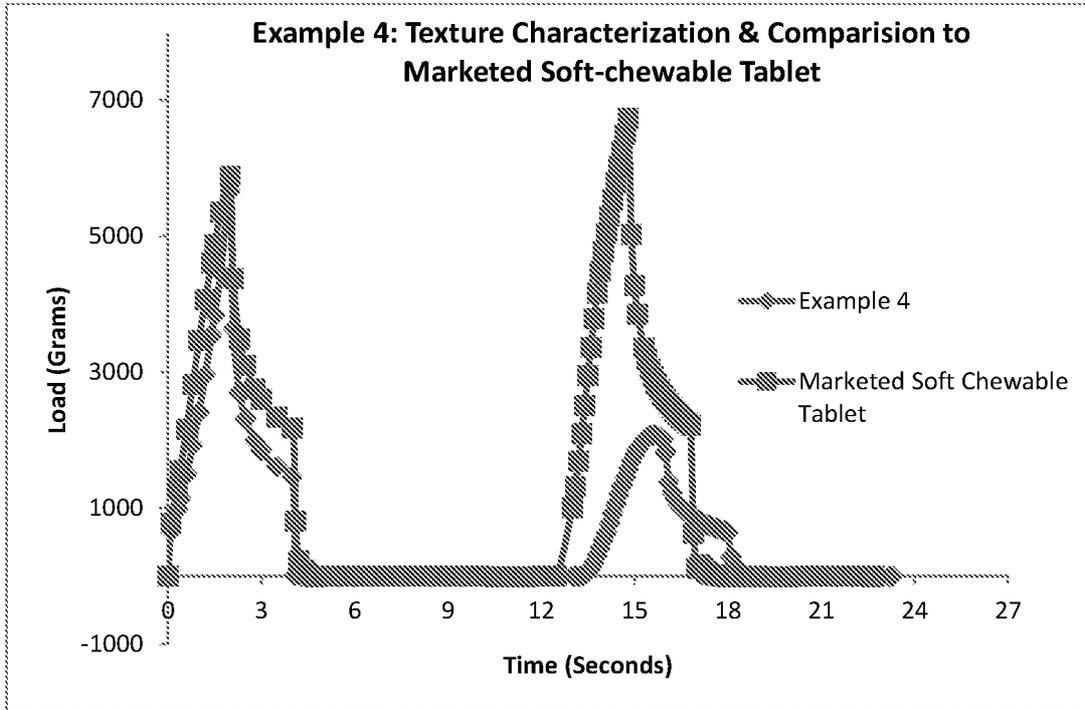
1. Active, soybean oil and Zea Mays Oil & BHA & BHT are weighed accurately and uniformly mixed to form a dispersion.
2. Simultaneously, a dispersion was prepared by adding Povidone and Polyethylene Glycol 600 to Glycerin and properly mixing.
3. The Intragranular dry ingredients were mixed together and passed through a sifting screen.
4. The extragranular dry ingredients were mixed together and passed through a sifting screen.
5. The pre-mix from step 3 was added to a Rapid Mixer Granulator (RMG) bowl of appropriate size and mixed for 2 minutes with 60 rpm impeller speed.
6. The Dispersion from step 1 was added slowly in about 1 minute and mixed further for 4 minutes with 60 rpm impeller speed and 150 rpm chopper speed.

7. The dispersion from step 2 was added slowly in about 2 minute with 50 rpm impeller speed and 150 rpm chopper speed.
8. The formed doughy mass was passed through a sifting screen to get wet granules.
9. Approximately half the quantity of the extragranular blend from step 4 was added to the wet granules formed in step 8 and uniformly blended.
10. The formed slightly dry granular mass was further passed through a sifting screen to get granules.
11. The formed granules had a Loss on Drying (LOD) value of 7.76 %w/w @ 105° C in 9:35 minutes.
12. The formed granules are uniformly mixed with the remaining quantity of the extragranular blend from step 4 and further subjected to compression on rotary tablet press using 18mm x 18 mm rounded square punch for 3.0 gram target fill weight.
13. The compressed tablets exhibited tablets hardness of 0 newton or kilopond when measured using conventional hardness tester and had tablet friability of 0.02 %w/w.
14. Texture Analysis was performed using CT3 Texture Analyzer using TA/RT/KIT probe and 25,000g load cell and 510 g trigger load, over 4mm using 2mm/s test speed and using data rate of 10 points/ second.

**[0094]** Table 5: Example 2, 3 & 4 Tablet Characterization:

Test Parameters	Example 2	Example 3	Example 4
Weight(g)	0.500	3.0	3.0
Shape	Square	Square	Square
Color	Light Brown	Yellow-Brown	Yellow-Brown
Dimension (mm)	-	18 x 18	18 x 18
Thickness (mm)	4 - 5	7 - 8	8.00 - 9.00
Disintegration Time (min)		10 -15	20-21
Tablet Hardness (Kp)	16-18	0	0
Tablet Hardness (N)	170 N	-	0
Tablet Friability (% w/w)	-	0	0.02
LOD @ 105 0C	6 -7	-	7 - 8

Chart 2: Example 4: Texture Characterization and Comparison to Marketed Soft-chewable Tablet

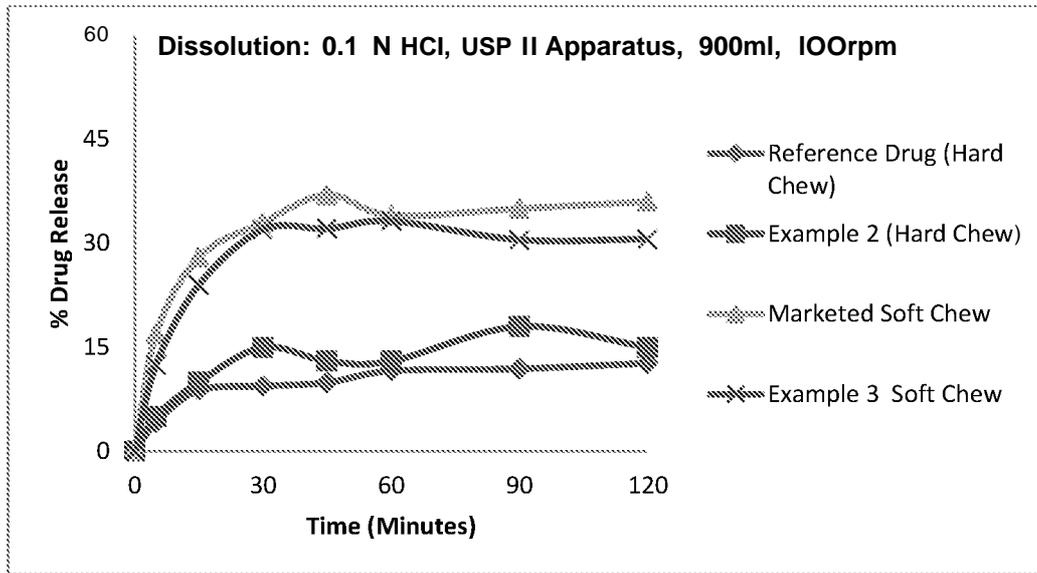


IN VITRO ANALYSIS (MULTIMEDIA DISSOLUTION TESTING)

A) Table 6: In 0.1 N HCl

Dissolution Medium	0.1 N HCl, USP II Apparatus, 900ml, 100rpm			
Time Points (Minutes)	Reference Drug (Hard Chew)	Example 2 (Hard Chew)	Marketed Soft-chew	Example 3 Prototype Soft-chew
5	4.2	5	17	12.5
15	8.8	10	28	24.0
30	9.4	15	33	32.0
45	9.9	13	37	32.1
60	11.6	13	34	33.2
90	11.9	18	35	30.5
120	12.7	15	36	30.6

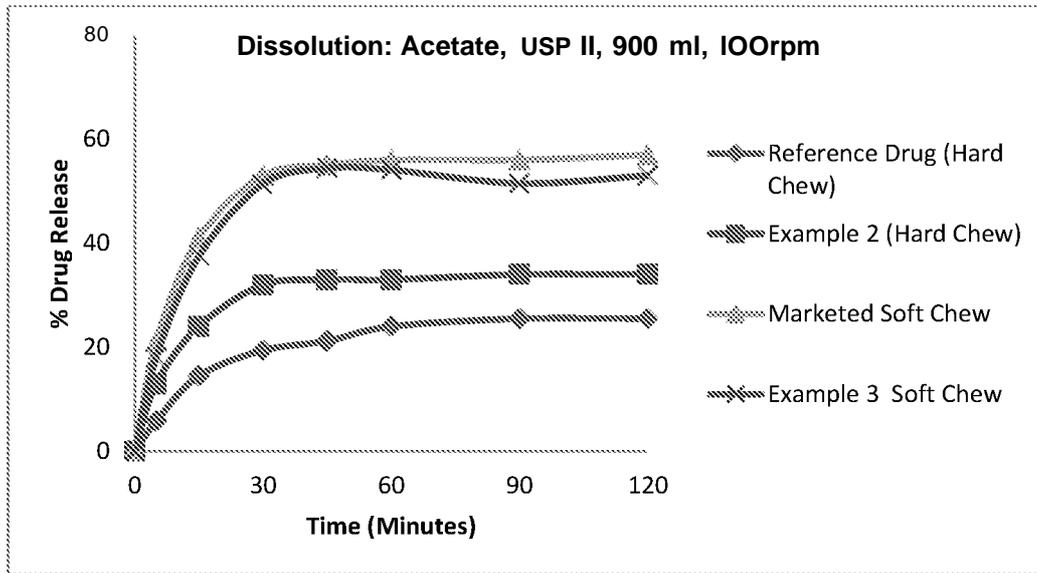
Chart 3: Graph of %Drug Release v/s Time in 0.1 N HCl, USP II Apparatus, 900ml, 100rpm



B] Table 7: In Acetate Buffer pH 4.5

Dissolution Medium	Acetate Buffer pH 4.5, USP II Apparatus, 900ml, 100 rpm			
Time Points (Minutes)	Reference Drug (Hard Chew)	Example 2 (Hard Chew)	Marketed Soft-chew	Example 3 Prototype Soft-chew
5	5.8	13	21	18.0
15	14.5	24	41	37.5
30	19.4	32	53	51.4
45	21.2	33	55	54.4
60	24.0	33	56	54.1
90	25.5	34	56	51.5
120	25.5	34	57	53.0

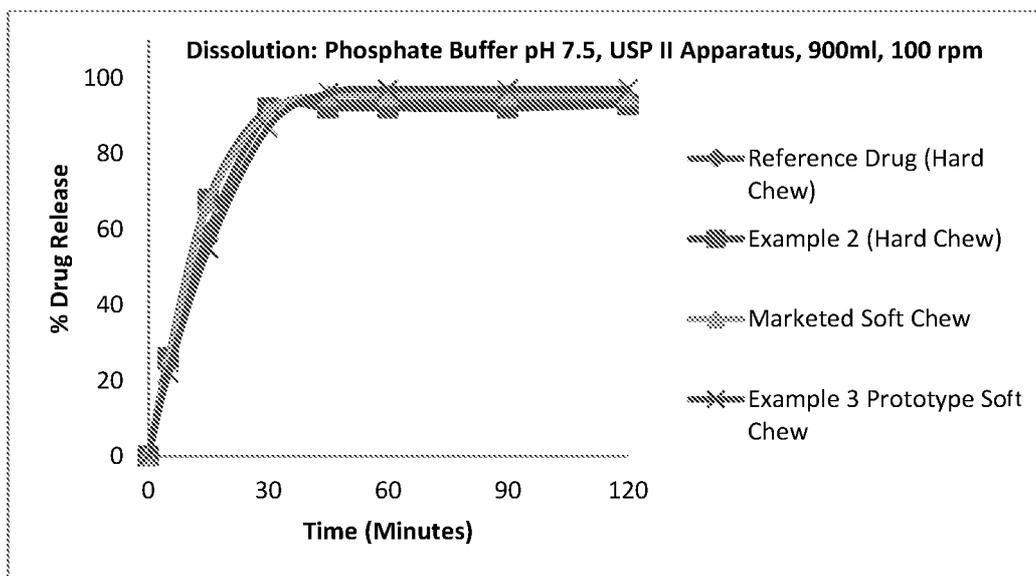
Chart 4: Graph of %Drug Release vs. Time in Acetate, USP II, 900 ml, 100rpm



C] Table 8: In Phosphate Buffer pH 7.5

Dissolution Medium	Phosphate Buffer pH 7.5, USP II Apparatus, 900ml, 100 rpm			
Time Points (Minutes)	Reference Drug (Hard Chew)	Example 2 (Hard Chew)	Marketed Soft-chew	Example 3 Prototype Soft-chew
5	23.8	26.00	25.0	22.0
15	59.2	68.00	66.9	55.0
30	90.8	92.00	91.1	87.0
45	93.2	92.00	95.3	96.0
60	93.6	92.00	95.3	97.0
90	93.7	92.00	95.3	97.0
120	94.1	93.00	95.3	97.0

Chart 5: Graph of %Drug Release vs. Time in pH 7.5, USP II Apparatus, 900ml, 100 rpm



Examples 5-8

Table 9: Examples 5-8

Formulation	Example 5	Example 6	Example 7	Example 8
Ingredients	% w/w	% w/w	% w/w	% w/w
<b>Active</b>				
Cefpodoxime Proxetil	13.50	-	-	-
Enrofloxacin	-	4.54	-	-
Pimobendan	-	-	0.08	-
Deracoxib	-	-	-	3.34
<b>Granulation Aid</b>				
Soybean Oil	7.00	9.00	10.00	15.00
Zea Mays Oil & BHA & BHT	0.10	0.10	0.10	0.10
Glycerin	20.00	13.00	12.00	19.50
Polyethylene Glycol 600	3.00	9.00	10.20	-
Povidone K 30	2.00	2.00	2.00	2.00
Color	-	-	0.01	0.02
<b>Intragranular Addition</b>				
Polycarbophil	-	-	-	0.25
Lactose Monohydrate	-	-	-	-
Sodium Carboxymethylcellulose	20.00	-	-	-
Silicified Microcrystalline Cellulose	3.85	18.15	18.71	15.59
Sodium Lauryl Sulfate	1.50	-	-	-
Pregelatinized Corn Starch	2.00	7.00	7.00	8.00
Calcium Sulfate Dihydrate	-	2.50	2.50	2.50

Artificial Beef Flavor	15.00	15.00	15.00	15.00
Crosscarmellose Sodium	2.00	3.50	-	1.50
Polyethylene Glycol 600	-	-	2.50	1.00
Color	-	-	-	-
Polyethylene Glycol 3350	-	-	-	-
Extragranular Addition				
Pregelatinized Corn Starch	-	4.00	5.00	5.00
Artificial Beef Flavor	3.00	3.00	3.00	3.00
Citric Acid	-	-	-	-
Sodium Carboxymethylcellulose	5.00	-	-	-
Sodium Lauryl Sulfate	-	0.20	0.30	0.20
Poly(ethylene) Oxide	-	1.00	1.00	1.00
Color	0.05	-	-	-
Modified Corn Starch	-	-	-	-
Crosscarmellose Sodium	2.00	1.50	2.50	5.00
Calcium Sulfate Dihydrate	-	2.01	1.70	1.00
Lactose Monohydrate	-	4.50	6.50	1.00
Total	100.00	100.00	100.00	100.00

**[0095]** Procedure: Example 5

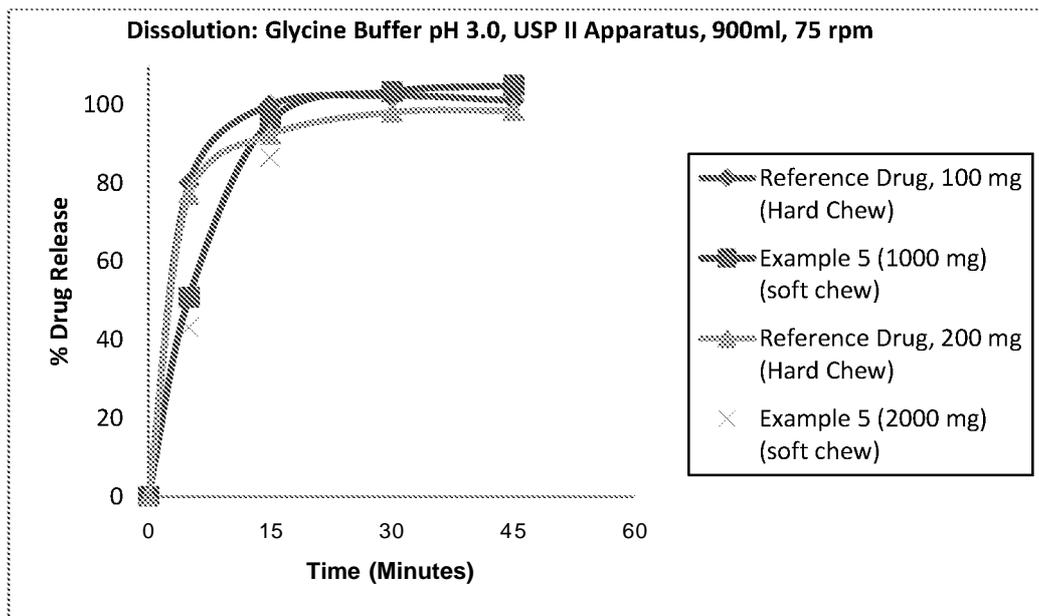
1. Soybean oil and Zea Mays Oil & BHA & BHT are weighed accurately and uniformly mixed to form a dispersion.
2. Simultaneously, a dispersion is prepared by adding Polyethylene Glycol 600 to Glycerin and properly mixing.
3. Cefpodoxime Proxetil (Active) was part of the intragranular addition. All intragranular dry ingredients were mixed uniformly and passed through sifting screen.
4. The dispersions from step 1 and step 2 are used as granulation aid, adding them one after another to the pre-mixed ingredients from step 3.
5. The formed doughy mass was passed through a sifting screen to get wet granules.
6. The extragranular ingredients were mixed uniformly and passed through a sifting screen.
7. Approximately half the quantity of the extragranular blend from step 6 was added to the wet granules formed in step 5 and mixed uniformly.
8. The formed slightly dry granular mass was passed through sifting screen to get granules.
9. The formed granules were mixed uniformly with remaining quantity of extragranular blend and further subjected to compression on rotary tablet press using 15.3mm x 15.3mm

rounded square punch for 2000mg fill weight & 12.3 x 12.3mm rounded square for 1000mg fill weight separately.

Table 10: Comparative Dissolution in Glycine Buffer pH 3.0

Dissolution Medium	Glycine Buffer pH 3.0, USP II Apparatus, 900ml, 75 rpm			
Time Points (Minutes)	Reference Drug, 100 mg (Hard Chew)	Example 5 (1000 mg) (soft-chew)	Reference Drug, 200 mg (Hard Chew)	Example 5 (2000 mg) (soft-chew)
5	79.8	50.8	77.1	43.2
15	99.9	95.8	92.3	86.4
30	102.2	103.3	98.0	99.0
45	101.00	104.8	98.40	103.0

Chart 6: Graph of %Drug Release vs. Time in Glycine Buffer pH 3.0, USP II Apparatus, 900ml, 75 rpm



[0096] Procedure: Examples 6-8.

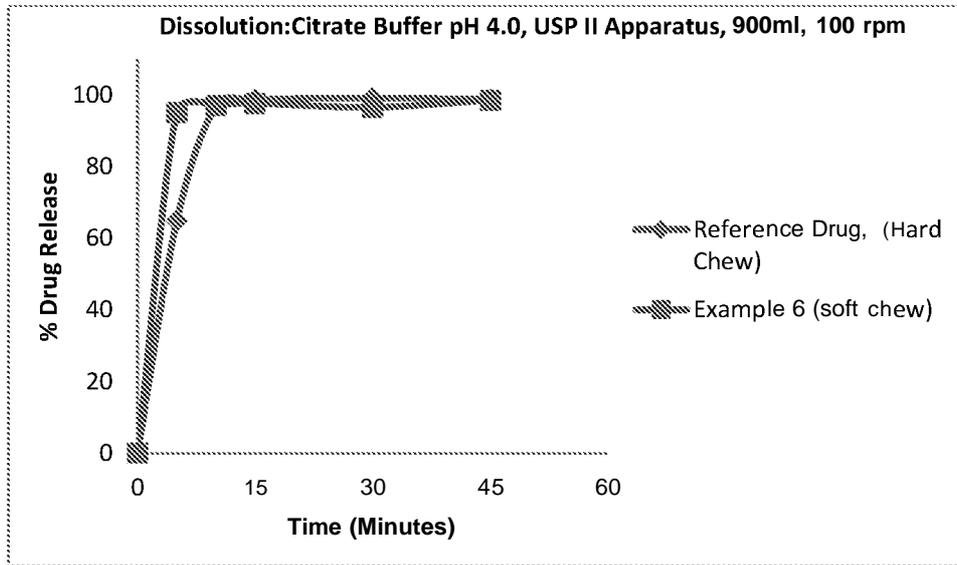
1. The active, soybean oil and Zea Mays Oil & BHA & BHT were uniformly mixed to form a dispersion.
2. Simultaneously, a dispersion was prepared by weighing the remaining granulation aid ingredients followed by properly mixing.
3. Intra granular dry ingredients were uniformly mixed and passed through a sifting screen.

4. The dispersions from step 1 and step 2 were used as a granulation aid, adding them one after another to pre-mixed ingredients from step 3.
5. The formed mass was passed through sifting screens to get wet granules.
6. The extragranular ingredients were mixed uniformly and passed through a sifting screen.
7. Approximately half the quantity of the extragranular blend from step 6 was added to the wet granules formed in step 5 and mixed uniformly.
8. The formed slightly dry granular mass was passed through a sifting screen to obtain granules.
9. The formed granules are uniformly mixed with remaining quantity of extra granular blend and further subjected to compression on rotary tablet press.

Table 11: Comparative Dissolution in Citrate Buffer pH 4.0

Dissolution Medium	Citrate Buffer pH 4.0, USP II Apparatus, 900ml, 100 rpm	
Time Points (Minutes)	Reference Drug, (Hard Chew)	Example 6 (soft-chew)
5	64.9	95.2
10	96.9	97.2
15	98.7	97.7
30	99.2	96.6
45	98.8	98.6

Chart 7: Graph of %Drug Release v/s Time in Citrate Buffer pH 4.0, USP II Apparatus, 900ml, 100 rpm



**CLAIMS**

1. A process for the manufacture of a compressed soft-chew tablet unit dosage form for the oral administration of an active pharmaceutical ingredient or a nutritional agent, comprising a soft-chew tablet or semi-plastic tablet formed by compressing a soft-chew mass on a compression press, and wherein the soft-chew tablets have a hardness of less than about 2 kp and a friability of less than about 1% at 300 rotations.
2. A process for the manufacture of a compressed soft-chew tablet unit dosage form for the oral administration of an active pharmaceutical ingredient or a nutritional agent, comprising a soft-chew mass mixture comprising an active pharmaceutical ingredient or a nutritional agent, wherein the soft-chew mass is a granulate formed with a granulation and sifting step, and wherein the soft-chew mass granulate is pressed into tablets using a tablet press, and wherein the soft-chew tablets have a hardness of less than about 2 kp and a friability of less than about 1% at 300 rotations.
3. A process for the manufacture of a compressed soft-chew tablet unit dosage form for the oral administration of active pharmaceutical agents or nutritional agents comprising the steps of:
  - a. mixing at least one active ingredient with at least one dry or liquid component to form a fluid premix;
  - b. blending dry ingredients comprising a bulking agent, a lipid, a flavoring agent, a disintegrating agent, a binding agent, a surfactant, a preservative, a lubricating agent, and an anti-sticking agent, or a mixture thereof, to form a uniform dry ingredient mixture;
  - c. blending the premix and the uniform dry ingredient mixture to form a granulated compacted soft-chew mass;
  - d. sifting the granulated compacted soft-chew mass through at least one sifting screen to form uniform granules of the soft-chew mass;

- e. adding a lubricant or anti sticking agent to the uniform granules of the soft-chew mass and compressing the resulting mixture in a tablet press to form soft-chew tablets.
4. A process for the manufacture of an edible compressed soft-chew tablet or semi plastic unit oral dosage form comprising the steps of:
  - a. mixing at least one active ingredient with a vegetable oil to form a premix;
  - b. blending dry ingredients comprising a bulking agent, a lipid, a flavoring agent, a disintegrating agent, a binding agent, a surfactant, a preservative, a lubricating agent, and an anti-sticking agent, or a mixture thereof, to form a uniform dry ingredient mixture;
  - c. blending the premix and the uniform dry ingredient mixture to form a granulated compacted soft-chew mass;
  - d. sifting the granulated compacted soft-chew mass through at least one sifting screen to form uniform granules of the soft-chew mass;
  - e. adding a lubricant or anti sticking agent to the uniform granules of the soft-chew mass and compressing the resulting mixture in a tablet press to from soft-chew tablets.
5. A process for the manufacture of an edible compressed soft-chew tablet and/ or semi plastic oral dosage form unit of very low hardness and excellent friability, wherein soft-chew tablet and/or semi plastic oral dosage unit is formed by compressing soft-chew composition mixture on compression (tablet) press.
6. The process of claim 3, wherein the tablet is a semi-plastic oral dosage form unit.
7. The process of claim 3, wherein the active ingredient is selected from an active pharmaceutical ingredient or a nutritional agent.

8. A soft-chew tablet comprising at least one active ingredient, wherein the tablet has a vegetable oil and microcrystalline cellulose in a ratio of about 2:1 to about 1:2.5, w/w, wherein the tablet is manufactured by compression on a tablet press.
9. The process according to claim 3, wherein the uniform granules of the soft-chew mass are sifted a second time through at least one additional sifting screen with a finer mesh to form granules of a smaller size.
10. The process according to claim 3, where the uniform dry ingredient mixture or the granulated compacted soft-chew mass are sifted through sifting equipment using impaction, attrition, compression or cutting.
11. The process according to claim 3, where uniform dry ingredient mixture or the granulated compacted soft-chew mass are uniformly mixed using equipment using diffusion mixing, convection mixing or pneumatic mixing.
12. The process of claim 3, wherein the granulated compacted soft-chew mass is dried at room temperature  $25 \pm 10^\circ \text{C}$ .
13. The process of claim 3, wherein the granulated compacted soft-chew mass is dried at controlled temperature of less than  $50^\circ \text{C}$ .
14. The process of claim 3, wherein the granulated compacted soft-chew mass is dried by equipment where heat is applied directly to a static solid bed, directly to a moving solid bed, or directly to a fluidized solid bed.
15. The process of claim 3, wherein the granulated compacted soft-chew mass is dried by equipment using indirect conduction heat applied to a static solid bed, a moving solid bed, or a fluidized solid bed.
16. The process of claim 3, wherein a non-active ingredient comprises of one or more of a starch, a polysaccharide, a humectant, a polyol, water-soluble poly(ethylene oxide) resin.
17. The process of claim 3, wherein the binding agent is polyethylene glycol.

18. The process of claim 17 wherein the polyethylene glycol is admixed to dry ingredients for mixing.
19. The process of claim 17 wherein the polyethylene glycol is melted and added to at least one other dry ingredient and mixed to form the uniform dry ingredient mixture.
20. The process of claim 3, wherein at least one ingredient has more than one function.
21. The process of claim 3, wherein the soft-chew tablet or semi plastic oral dosage form is an oral pharmaceutical dosage form for human use.
22. The process of claim 3, wherein the soft-chew tablet or semi plastic oral dosage form is an oral pharmaceutical dosage form for veterinary use.
23. The process of claim 3, wherein the lipid is a liquid vegetable oil, or a solid hydrogenated vegetable oil.
24. The process of claim 23 wherein the vegetable oil is soybean oil.
25. The process of claim 16 wherein the starch is a modified starch, or a mixture of starch and a modified starch.
26. The process of claim 3, wherein any liquid components are absorbed on the surface of a lipid absorbing pharmaceutical ingredient selected from one or more of microcrystalline cellulose, silicified microcrystalline cellulose, and a combination of microcrystalline cellulose and guar gum.
27. The process of claim 26 wherein the liquid components absorbed on the surface of the lipid absorbing pharmaceutical ingredient are mixed with the uniform dry ingredient mixture and then sifted again through at least one finer sifting screen to form further finer granules of the soft-chew composition mixture.

28. The process of claim 26 wherein a nutritional agent or a pharmaceutically active ingredient is admixed with the liquid components prior to mixing with the lipid absorbing pharmaceutical ingredient.
29. The process of claim 16, wherein the polyol is selected from the group consisting of propylene glycol, glycerin, polyethylene glycol and mixtures thereof.
30. The process of claim 3, where the active ingredient is coated with a taste masking coating.
31. The process of claim 3, wherein the active ingredient is coated with controlled release coating.
32. The process of claim 3, wherein the active ingredient is conjugated with at least one other ingredient.
33. The process of claim 3, wherein the active ingredient is incorporated into a drug delivery systems selected from microspheres, microcapsules, liposomes, niosomes, nanoparticles, microemulsions, or nanoemulsions.
34. The process of claim 3, wherein pre-compression force is applied to the granulated compacted soft-chew mass before application of main compression force for compression of soft-chews.
35. The process of claim 3, wherein during compression, the granulated compacted soft-chew mass is fed into a compression die by gravity feed, power assisted feed, by centrifugal force, or by compression coating.
36. A soft-chewable tablet unit dosage form for the oral administration of a pharmaceutical agent or nutritional agent to a human or animal, comprising a tablet manufactured according to the process of claim 1, wherein the tablet is chewed and then swallowed.
37. The soft-chewable tablet of claim 36, having a hardness of less than 2 kilopond when measured using a tablet hardness tester.

38. The soft-chewable tablet of claim 36, having a hardness of less than 1 kilopond when measured using a tablet hardness tester.
39. The soft-chewable tablet of claim 36, that does not register any hardness when measured using a tablet hardness tester.
40. The soft-chewable tablet of claim 36, having friability after 300 rotations of about 1% or less; or about 0.5% or less; or about 0.2% or less.
41. The soft-chewable tablet of claim 36, having friability after 200 rotations of about 1% or less; or about 0.5% or less; or about 0.2% or less.
42. The soft-chewable tablet of claim 36, having friability after 100 rotations of about 1% or less; or about 0.5% or less; or about 0.2% or less.
43. The soft-chewable tablet of claim 36, wherein the tablet disintegrates in less than about 15 minutes according to the USP disintegration test <701> using water as the medium.
44. The soft-chewable tablet of claim 36, wherein the tablet disintegrates in less than about 30 minutes according to the USP disintegration test <701> using water as the medium.
45. The soft-chewable tablet of claim 36, wherein the tablet disintegrates in less than about 60 minutes according to the USP disintegration test <701> using water as the medium.
46. The soft-chewable tablet of claim 36, wherein the tablet has abuse-deterrent characteristics.
47. The soft-chewable tablet of claim 36, wherein the tablet provides controlled release of the nutritional agent or pharmaceutically active agent.
48. The soft-chewable tablet of claim 36, wherein the tablet is a round tablet.
49. The soft-chewable tablet of claim 36, wherein the tablet is a capsule shaped tablet.
50. The soft-chewable tablet of claim 36, wherein the tablet is a modified shaped tablet.

51. The soft-chewable tablet of claim 36, wherein the tablet is of any shape and size used in the pharmaceutical, nutraceutical and supplement industry.
52. The soft-chewable tablet of claim 36, wherein the tablet maintains a characteristic selected from chewiness, hardness, compression energy, adhesion, cohesiveness, springiness, adhesive force, resilience, modulus, when measured by a texture analyzer, or a combination of any two or more such characteristics sufficient to provide a chewable texture.
53. The soft-chewable tablet of claim 36, wherein the tablet is coated with coating agent.
54. The soft-chewable tablet of claim 36, wherein the tablet is packaged as bulk primary packaging.
55. The soft-chewable tablet of claim 36, wherein the tablet is packaged as singular unit primary packaging.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/67443

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A61K 9/00, A61K 47/12 (2017.01) CPC - A61K 47/18, A61K 9/5123, A61K 9/5015 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC(8) A61K 9/00, A61K 47/12 (2017.01) CPC A61K 47/18, A61K 9/5123, A61K 9/5015  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched CPC A61K 47/18, A61K 9/5123, A61K 9/5015 (Keyword limited, terms below)  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, Google Patents, Google Scholar (NPL); Keywords: compressed soft-chew tablet unit dosage oral administration nutritional agent semi-plastic tablet hardness		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2010/0010101 A 1 (Cherukuri) 14 January 2010 (14.01.2010) para [0002], [0022]-[0026], [0034]-[0038], [0044], [0050]-[0057], [0077], [0080], [0082], [0115], [0125], [0128], [0132], [0151], [0154], [0156]-[0159], [0206]-[0209], [0212], [0264], [0301]	1-5, 7-31, 34, 36-42, 47-55 ----- 6, 32-33, 35, 43-46
Y	US 2014/0141055 A 1 (Kluger et al.) 22 May 2014 (22.05.2014) para [0002], [0013]	6
Y	US 2015/0307504 A 1 (Singh) 29 October 2015 (29.10.2015) para [0015], [0017], [0049], [0050]	32, 46
Y	US 2005/0158383 A 1 (Boehm et al.) 21 July 2005 (21.07.2005) para [0009], [0010], [0011], [0033], [0037], [0072], [0092], [0093], [0167]	33
Y	US 2006/0141009 A 1 (Huron et al.) 29 June 2006 (29.06.2006) para [0020], [0028], [0057], [0065]	35
Y	US 2013/0252979 A 1 (Meier et al.) 26 September 2013 (26.09.2013) para [0001], [0050], [0064], [0067]	43-45
A	US 2003/0175336 A 1 (Luber et al.) 18 September 2003 (18.09.2003) para [0001], [0032]-[0034], [0038]	1-55
A	US 4327076 A (Puglia et al.) 27 April 1982 (27.04.1982) entire document	1-55
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 20 February 2017		Date of mailing of the international search report 27 MAR 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774