ABSTRACT

Pharmaceutical compositions comprising particles of metaxalone or its derivatives, wherein from about 10-100%, by weight, of the metaxalone particles have particle sizes greater than about 250 μm. Processes for preparing the pharmaceutical compositions, are also disclosed.

CLAIMS:

1. A pharmaceutical formulation prepared using particles of metaxalone or its derivatives, wherein a particle size distribution of the metaxalone has a D_{90} in the range of about 100 µm to about 250 µm.

2. A pharmaceutical formulation prepared using particles of metaxalone or its derivatives, wherein from about 10-100%, by weight, of the metaxalone particles have particle sizes greater than about 250 µm.

3. A pharmaceutical formulation prepared using particles of metaxalone or its derivatives, wherein from about 30-80%, by weight, of the metaxalone particles have particle sizes greater than about 250 µm.

4. A pharmaceutical formulation prepared using metaxalone particles having particle sizes greater than about 250 µm present in the range from about 30-80%, by weight, wherein dissolution of metaxalone from the compositions is not less than about 80% within 120 minutes after immersion in 900 ml of 0.5% sodium lauryl sulphate in water with 100 rpm stirring, using USP Type II apparatus.

5. A pharmaceutical formulation of any of claims 1-4 wherein moisture content of the formulation is not more than about 5% by weight.

6. A pharmaceutical formulation of any of claims 1-5 containing ethyl urethane impurity at not more than about 1% by weight of the metaxalone content.

7. A pharmaceutical formulation of any of claims 1-6 containing total metaxalone-derived impurities at not more than about 2% by weight of the metaxalone content.

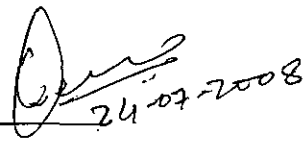
8. A pharmaceutical formulation of any of claims 1-7 containing 800 mg of metaxalone and producing metaxalone C_{max} values of about 2800 ng/mL to about 4600 ng/mL, and AUC_{0-t} values of about 24000 ng·hour/mL to about 38000 ng·hour/mL, in plasma after oral administration of a single dose to healthy humans.

9. A pharmaceutical formulation for oral administration, comprising:

Metaxalone	800 mg
Alginic acid	45 mg
Ammonium calcium alginate	30 mg
Starch	50 mg
Magnesium stearate	10 mg

prepared using metaxalone particles wherein from about 10-100%, by weight, of the metaxalone particles have particle sizes greater than about 250 µm.

Dated: 24th day of July 2008.

Signed  24-07-2008

S.V.N Raju

Associate Director,

IntellectualProperty Management,

Integrated Product Development,

Dr. Reddy's Laboratories Limited,

Bachupally, RR District – 500072.

ORIGINAL 25 JUL 2008

FORM 2
THE PATENT ACT 1970
(39 of 1970)
&
The Patents Rules, 2003
~~PROVISIONAL~~/COMPLETE SPECIFICATION
(See section 10 and rule 13)

1. TITLE OF THE INVENTION: PHARMACEUTICAL COMPOSITIONS COMPRISING METAXALONE
2. APPLICANT **(a) Name:** Dr Reddys Laboratories Limited **(b) Nationality:** Indian **(c) Address:** Harshal P Bhagwatwar Ph.D. Intellectual Property Management Integrated Product Development Dr Reddys Laboratories Limited Survey Nos. 42, 45 & 46, Bachupalli, **Qutubullapur, RR District – 500 072, AP, India**
3. PREAMBLE TO THE DESCRIPTION

~~PROVISIONAL~~	COMPLETE
The following ~~specification particularly describes the invention and the manner in which it is to be performed.~~	The following specification particularly describes the invention and the manner in which it is to be performed

4. DESCRIPTION (Description shall start from next page.) Enclosed in separate sheet
5. CLAIMS (not applicable for provisional specification. Claims should start with the preamble "I/We claim" on separate page)
6. DATE AND SIGNATURE (to be given at the end of last page of specification)
7. ABSTRACT OF THE INVENTION (to be given along with complete specification on separate page)

Note:-
**Repeat boxes in case of more than one entry.*
**To be signed by the applicants(s) or by authorized registered patent agent.*
**Name of the applicant should be given in full, family mane in the beginning.*
**Complete address of the applicant should be given stating the postal index no./code, state and country.*
**Strike out the column which is/are not applicable.*

25 JUL 2008

ORIGINAL

FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

&

THE PATENTS RULES, 2003

COMPLETE SPECIFICATION

(See section 10 and rule 13)

PHARMACEUTICAL COMPOSITIONS COMPRISING METAXALONE

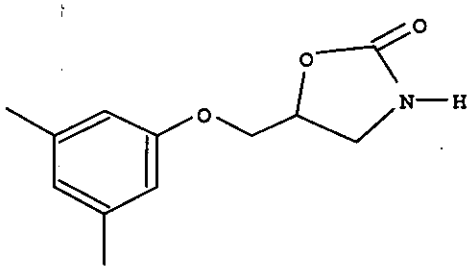
Dr. Reddy's Laboratories Limited
An Indian company having its registered office at
7-1-27, Ameerpet
Hyderabad-500 016,
A.P. India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

PHARMACEUTICAL COMPOSITIONS COMPRISING METAXALONE

INTRODUCTION TO THE INVENTION

The present invention relates to pharmaceutical compositions comprising metaxalone or its pharmaceutically acceptable derivatives or mixtures thereof. The invention further relates to processes for preparing the compositions and their methods of use. Metaxalone has a chemical name 5-[(3, 5-dimethyphenoxy) methyl]-2-oxazolidinone and is represented by structural Formula I.



Formula I

Metaxalone is skeletal muscle relaxant used to relieve the pain of muscle injuries, spasms, sprains, and strains. Metaxalone is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. It is marketed under the brand SKELAXIN®, and is available in tablets having a strength of 800 mg. The general dosage for adults and children over 12 years of age is one 800 mg tablet, taken three to four times daily.

Metaxalone is a white to almost white, odorless crystalline powder freely soluble in chloroform, soluble in methanol and in 96% ethanol, but practically insoluble ether or water.

U.S. Patents 6,407,128 and 6,683,102 disclose methods of increasing the oral bioavailability of metaxalone by administration of an oral dosage form with food. The administration with food results in an increase in the maximum plasma drug concentration (C_{max}) and extent of absorption (AUC_{0-t}) of metaxalone, as compared to administration without food. U.S. Patent No. 4,722,938 discloses a method of use of metaxalone. International Application Publication Nos. WO 2004/019937, WO 2004/066981, WO 2005/048996 and WO 2005/087204, and U.S. Patent Application

Publication No. 2005/0063913 disclose various pharmaceutical compositions of metaxalone.

Painful musculoskeletal conditions require prompt relief; therefore, compositions exhibiting a quick onset of action are desirable. In the above publications and from other literature it is disclosed that when poorly soluble, hydrophobic drug substances are administered in solid dosage forms, such as tablets or capsules, then the particle size can be reduced by methods such as *micronization to achieve a desired dissolution profile.*

It has been surprisingly found that in the context of the present invention that metaxalone having rather coarse average particle sizes still can produce the same profile as that of a commercially available product. This shows that metaxalone solubility and dissolution are not affected by particle size.

The present invention thus provides pharmaceutical compositions wherein metaxalone is not in a micronized form, thus providing cost effective processes to prepare a solid dosage form containing a relatively higher proportion of drug when compared to the total weight of a composition.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising metaxalone, including its pharmaceutically acceptable derivatives.

The present invention relates to pharmaceutical compositions comprising metaxalone with defined particle size of metaxalone or its derivatives.

In one embodiment, the present invention includes pharmaceutical compositions comprising metaxalone or its derivatives wherein metaxalone particles having particle sizes greater than about 250 µm are present in the range from about 10-100%, or from about 30-80 %, by weight.

In an embodiment, the present invention includes pharmaceutical compositions of metaxalone or its derivatives wherein a particle size distribution D_{90} value is in the range of about 100 µm to about 250 µm.

In embodiments of the invention, pharmaceutical compositions comprising metaxalone or its derivatives have bulk densities of metaxalone in the range of about 0.3-0.8 g/ml.

In embodiments of the invention, pharmaceutical compositions comprising metaxalone or its derivatives have tapped densities of metaxalone in the range of about 0.5-1 g/ml.

In embodiments of the invention, pharmaceutical compositions comprising metaxalone or its derivatives have bulk densities of final blends in the range of about 0.3-0.8 g/ml.

In embodiments of the invention, pharmaceutical compositions comprising metaxalone or its derivatives have tapped densities of final blends in the range of about 0.4-0.8 g/ml.

In an embodiment, the present invention relates to pharmaceutical compositions of metaxalone wherein dissolution of metaxalone from the compositions is not less than about 80% within 120 minutes after immersion into 900 ml of 0.5% sodium lauryl sulphate in water at 100 rpm, using USP Type II apparatus.

In embodiments, the invention relates to processes for preparation of pharmaceutical compositions comprising metaxalone.

In embodiments, the invention relates to methods of using pharmaceutical compositions of the present invention in the treatment of discomforts associated with acute, painful musculosketal conditions.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising metaxalone, including its pharmaceutically acceptable derivatives.

The invention also relates to processes for preparing the compositions and their methods of use.

Metaxalone is a skeletal muscle relaxant used to relieve the pain of muscle injuries, spasms, sprains, and strains. The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate, or the nerve fiber. The drug does not directly relax tense skeletal muscles in man.

Pharmaceutically acceptable derivatives of metaxalone include, but are not limited to, its salts, polymorphs, solvates, esters, hydrates, enantiomers, racemates, and mixtures thereof.

Being an insoluble compound, according to the literature it is expected that particle size reduction would improve the solubiltiy of metaxalone. Some of the known compositions involve a reduced particle size of metaxalone to improve the dissolution profile. It has now been found that particle size does not significantly affect the solubility and dissolution profile of metaxalone.

In one of the embodiments, the present invention includes a defined range of particle sizes of metaxalone.

In an embodiment, the invention includes pharmaceutical compositions comprising metaxalone of defined particle sizes.

The percentages of particles with different sizes that exist in a total powder is the particle size distribution. It is represented in certain ways. Particle size is the maximum dimension of a particle, normally expressed im micrometers. Particle size distributions can be expressed in terms of, D_{10}, D_{50}, D_{90} and $D_{[4,3]}$. The D_{10}, D_{50} and D_{90} represent the 10th, median or 50th, and 90th percentiles of the particle size distribution, respectively, as measured by volume. That is, the D_{10}, D_{50}, D_{90} are values of the distribution such that 10%, 50%, 90% of the particles have a volume of this value or less, or are the percentages of particles smaller than that size. D_{50} also is known as the median diameter of particles. It is one of the important parameters representing characteristics of powders. For example, if D_{50}=5 μm, it means 50% of the particles are smaller than 5 μm. Similarly, if D_{10}=5 μm, 10% particles are less than or equal to 5 μm, and if D_{90}=5 μm, 90% of particles are less than or equal to 5 μm. $D_{[4,3]}$ is the volume moment mean of the particles, or the volume weighted particle size.

In an embodiment, the present invention includes metaxalone or its derivatives, wherein the percentage of particles of metaxalone or its derivatives with particle sizes greater than about 250 μm is in the range of about 30% to about 100%, or about 30% to about 80%, or about 50% to about 80%, by weight.

In an embodiment, the present invention includes pharmaceutical compositions comprising metaxalone or its derivatives, wherein the percentage of particles of metaxalone or its derivatives with particle sizes greater than about 250 μm is in the range of about 30 to about 100%, or from about 40 to about 90%, or from about 50 to about 80%, by weight.

In embodiments, the invention includes processes for preparing metaxalone of defined particle sizes, which may be directly obtained from processes for

preparing metaxalone or alternatively may be obtained by techniques such as roll compacting and milling through a desired mesh screen.

In an embodiment, the invention includes pharmaceutical compositions comprising metaxolone with defined particle sizes and at least one pharmaceutically acceptable excipient.

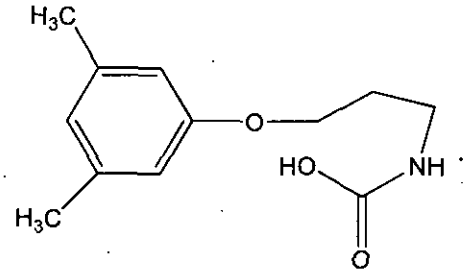
The pharmaceutical formulations of the present invention include solid dosage forms such as tablets, capsules, granules, pellets, pills, etc.

For solid dosage forms there are various important physical parameters of metaxalone as well as that of final blends containing metaxalone and excipients (impacting the properties of dosage forms), such as moisture content (determined by techniques such as Karl Fischer ("KF") apparatus or an infrared moisture balance), bulk density and tapped density, compressibility index, Hausner ratio such as determined by USP density apparatus), flow property (such as determined by a Flowdex apparatus), etc. These physical parameters would affect the processes for preparation of the compositions.

Bulk density is defined as a property of particulate materials. It is the mass of many particles of the material divided by the volume they occupy. The volume includes the space between particles as well as the space inside the pores of individual particles. The bulk density of powders is usually reported both as "freely settled" and "tapped" densities (where the tapped density refers to the bulk density of the powder after a specified compaction process, usually involving vibration of the container). In embodiments the present invention relates to pharmaceutical compositions of metaxalone or it derivatives wherein the bulk density of metaxalone or its derivatives is in the range of about 0.3 to about 0.8 g/ml.

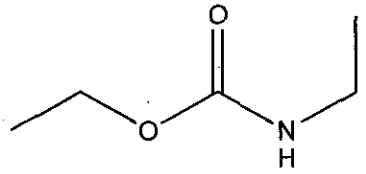
In another embodiment the present invention relates to the pharmaceutical compositions of metaxalone or it derivatives where in, the tapped density of metaxalone is in the range of about 0.5 to about 1 g/ml.

It has been observed that metaxalone is unstable in alkaline environments leading to formation of a malone stage II impurity (Formula II).



Formula II

Also, in acidic environments metaxalone forms an ethyl urethane impurity (Formula III).



Formula III

"Total impurities" in a composition include all of the impurities derived from metaxalone that are generated in preparing the composition and/or during storage of the composition.

In an embodiment the invention includes stable pharmaceutical compositions comprising metaxalone.

In an embodiment the invention includes pharmaceutical compositions of metaxalone wherein an ethyl urethane impurity is present at not more than about 1% by weight of the metaxalone content.

In an embodiment the invention includes pharmaceutical compositions of metaxalone wherein the total impurities derived from metaxalone are not more than about 2% by weight of the metaxalone content.

Sometimes moisture contents of pharmaceutical compositions may affect the stability of metaxalone. In an embodiment the invention includes pharmaceutical compositions comprising metaxalone wherein the moisture content of the compositions is not more than about 5% w/w.

In certain embodiments, the pharmaceutical compositions of the present invention may be processed using the techniques of direct compression, dry granulation, or wet granulation.

In an embodiment, the present invention relates to processes of preparation of metaxalone compositions where inactive excipient ingredients include but are not limited to one or more of diluents, binders, disintegrants, glidants, lubricants, sweeteners, flavoring agents, coloring agents, solvents, and film forming agents. Desirably, the agents are chemically and physically compatible with the metaxalone.

Various excipients that can be used in the present invention of metaxalone compositions include the following:

Diluents:

Various useful fillers or diluents include but are not limited to starches, lactose, mannitol (Pearlitol™ SD200), cellulose derivatives, confectioners sugar and the like. Different grades of lactose include but are not limited to lactose monohydrate, lactose DT (direct tableting), lactose anhydrous, Flowlac™ (available from Meggle Products), Pharmatose™ (available from DMV) and others. Different grades of starches include but are not limited to maize starch, potato starch, rice starch, wheat starch, pregelatinized starch (commercially available as PCS PC10 from Signet Chemical Corporation) and Starch 1500, Starch 1500 LM grade (low moisture content grade) from Colorcon, fully pregelatinized starch (commercially available as National 78-1551 from Essex Grain Products) and others. Different cellulose compounds that can be used include crystalline cellulose and powdered cellulose. Examples of crystalline cellulose products include but are not limited to CEOLUS™ KG801, Avicel™ PH 101, PH102, PH301, PH302 and PH-F20, and PH-112, microcrystalline cellulose 114, and microcrystalline cellulose 112. Other useful diluents include but are not limited to carmellose, sugar alcohols such as mannitol (Pearlitol™ SD200), sorbitol, xylitol, calcium carbonate, magnesium carbonate, dibasic calcium phosphate, and tribasic calcium phosphate.

Binders:

Various useful binders include but are not limited to hydroxypropylcelluloses (Klucel™ LF), hydroxypropylcelluloses (Klucel EXF) hydroxypropyl methylcelluloses or hypromelloses (Methocel™), polyvinylpyrrolidones or povidones (PVP-K25, PVP-K29, PVP-K30, PVP-K90), Plasdone™ S 630 (copovidone), powdered acacia, gelatin, guar gum, carbomers (e.g. Carbopol™), methylcelluloses, polymethacrylates, and starches.

Disintegrants:

Various useful disintegrants include but are not limited to carmellose calcium (Gotoku Yakuhin Co., Ltd.), carboxymethylstarch sodium (Matsutani Kagaku Co., Ltd., Kimura Sangyo Co., Ltd., etc.), croscarmellose sodium (Ac-di-sol™, FMC-Asahi Chemical Industry Co., Ltd.), crospovidones, examples of commercially available crospovidone products including but not limited to crosslinked povidone, Kollidon™ CL [manufactured by BASF (Germany)], Polyplasdone™ XL, XI-10, and INF-10 [manufactured by ISP Inc. (USA)], and low-substituted hydroxypropylcellulose. Examples of low-substituted hydroxypropylcelluloses include but are not limited to low-substituted hydroxypropylcellulose LH11, LH21, LH31, LH22, LH32, LH20, LH30, LH32 and LH33 (all manufactured by Shin-Etsu Chemical Co., Ltd.). Other useful disintegrants include sodium starch glycolate, alginic acid, ammonium calcium alginate, ammonium alginate, calcium alginate, colloidal silicon dioxide, and starch.

Glidants:

One or more glidant materials, which improve the flow of the powder blends and minimize the dosage form weight variation, can be used. Useful glidants include but are not limited to silicone dioxide, talc and combinations thereof.

Lubricants:

An effective amount of any generally accepted pharmaceutical tableting lubricant can be added before compressing the tablets. Useful tablet lubricants include but are not limited to magnesium stearate, glyceryl monostearates, palmitic acid, talc, carnauba wax, calcium stearate sodium, sodium or magnesium lauryl sulfate, calcium soaps, zinc stearate, polyoxyethylene monostearates, calcium silicate, silicon dioxide, hydrogenated vegetable oils and fats, stearic acid and combinations thereof.

Coloring Agents:

Coloring agents can be used to color code the composition, for example, to indicate the type and dosage of the therapeutic agent therein. Suitable coloring agents include, without limitation, natural and/or artificial compounds such as FD&C coloring agents, natural juice concentrates, pigments such as titanium oxide, silicon dioxide, iron oxides, and zinc oxide, combinations thereof, and the like.

Solvents:

Various solvents useful in the processes of preparation of pharmaceutical compositions of the present invention include but are not limited to water, methanol,

ethanol, acidified ethanol, acetone, diacetone, polyols, polyethers, oils, esters, alkyl ketones, methylene chloride, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulphoxide, dimethylformamide, tetrahydrofuran, and mixtures thereof.

Sweeteners:

Compositions of the present invention may include a sweetener. Useful sweeteners include, but are not limited to, sugars, acid saccharin and its various salts such as the sodium or calcium salt; aspartame and alitame, natural sweeteners, sugar alcohols such as sorbitol, sorbitol syrup, mannitol, xylitol and the like, synthetic sweeteners such as acesulfame-K and sodium and calcium salts thereof, hydrogenated starch hydrolysate (lycasin), protein based sweetening agents such as talin (thaumaoccous danielli), and/or any other pharmacologically acceptable sweetener, and mixtures thereof.

Flavoring Agents:

Flavoring agents can also be used to improve the palatability of the compositions. Examples of suitable flavoring agents include, without limitation, natural and/or synthetic (i.e., artificial) compounds such as peppermint, spearmint, wintergreen, cinnamon, menthol, cherry, strawberry, watermelon, grape, banana, peach, pineapple, apricot, pear, raspberry, lemon, grapefruit, orange, plum, apple, fruit punch, passion fruit, chocolate (e.g. white, milk, dark), vanilla, caramel, coffee, hazelnut, combinations thereof, and the like.

Film-forming Agents:

Various useful film-forming agents include but are not limited to cellulose derivatives such as soluble alkyl- or hydroalkyl-cellulose derivatives such as methyl celluloses, hydroxymethyl celluloses, hydroxyethyl celluloses, hydroxypropyl celluloses, hydroxymethyethyl celluloses, hydroxypropyl methylcelluloses, sodium carboxymethyl celluloses, etc., acidic cellulose derivatives such as cellulose acetate phthalate, cellulose acetate trimellitate and methylhydroxypropylcellulose phthalate, polyvinyl acetate phthalate, etc.; insoluble cellulose derivative such as ethylcelluloses and the like, dextrins, starches and starch derivatives, polymers based on carbohydrates and derivatives thereof, natural gums such as gum Arabic, xanthans, alginates, polyacrylic acid, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, polymethacrylates such as derivatives thereof (Eudragit™),

chitosan and derivatives thereof, shellac and derivatives thereof, and waxes and fat substances.

If desired, the films may contain additional adjuvants for a coating process such as plasticizers, polishing agents, colorants, pigments, antifoam agents, opacifiers, antisticking agents, and the like.

In addition to above coating ingredients, sometimes ready mixed coating materials such as Opadry™ (supplied by Colorcon) are used. These products require only dispersing in a liquid before use.

The present invention further relates to processes for preparing pharmaceutcal compositons, wherein the compositions may be presented as one or more layers and may be coated or uncoated or may be encapsulated.

An aspect of the present invention includes processes for preparation of the pharmaceutical compositions, wherein a specific process embodiment comprises:

1) Sifting the active ingredient and intragranular and extragranular excipients through a sieve.

2) Geometrically mixing the active ingredient with intragranular excipients;

3) Optionally, step 2 materials are blended with glidants and lubricants and compressed. Or optionally the active ingredient and excipients except glidants and lubricants are subjected to roll compaction, and then the compacted material is milled through a sieve.

4) Placing step 2 materials into a granulator and mixing.

5) Dissolving or dispersing a binder in a suitable solvent.

6) Granulating the step 4 dry mix material using the binder from step 5.

7) Drying the wet granules.

8) Sizing the dried granules through a sieve.

9) Blending the dried granules from step 8) or milled granules from step 3) with sifted extragranular excipients.

10) Lubricating the step 9 blend with lubricant by blending.

11) Compressing the final blend of step 10 into tablets with a compression machine.

12) Optionally coating the tablets using a coating solution or dispersion.

13) Alternatively, filling the final blend of step 10 into empty hard gelatin capsules.

In an embodiment the invention utilizes packaging materials for pharmaceutical compositions such as containers and lids of high-density polyethylene (HDPE), low-density polyethylene (LDPE) and or polypropylene and/or glass, and blisters or strips composed of aluminium or high-density polypropylene, polyvinyl chloride, polyvinylidine dichloride, or aluminum/aluminum blisters with a laminated desiccant system. The packages may also comprise various desiccants such as pouches containing silica gel, molecular sieves, etc.

The tablets or capsules prepared as above can be subjected to *in vitro* dissolution evaluation according to Test 711 "Dissolution," in *United States Pharmacopoeia 29*, United States Pharmacopeial Convention, Inc, Rockville, Maryland, 2005 ("USP"), to determine the rate at which the active substance is released from the dosage forms, and the content of the active substance can be determined in solutions using methods such as high performance liquid chromatography (HPLC).

Pharmaceutical formulations of the invention are intended to be administered orally to subjects in need of treatment. In embodiments, oral administration of a single dose of the pharmaceutical formulations containing 800 mg of metaxalone to healthy humans produces metaxalone C_{max} values of about 2800 ng/mL to about 4600 ng/mL, and AUC_{0-t} values of about 24000 ng·hour/mL to about 38000 ng·hour/mL.

Certain specific aspects and embodiments of the invention are described in further detail by the examples below, which examples are provided only for purposes of illustration and should not be construed as limiting the scope of the invention in any manner.

EXAMPLES

Comparative Example: Pharmaceutical compositions for metaxalone 800 mg tablets.

Ingredient	mg/Tablet
Metaxalone	800
Alginic acid	30
Ammonium calcium alginate	45
Maize starch	20
Maize starch	25

Water*	416.7
Maize starch	5
Magnesium stearate	5

* Evaporates during processing.

Particle size distribution parameters of micronized metaxalone used in this comparative example:

D_{90} = 20.59 µm.

D_{50} = 6.82 µm.

D_{10} = 1.74 µm.

Manufacturing process:

1) Metaxalone, maize starch (first quantity), ammonium calcium alginate, and alginic acid were sifted through an ASTM #40 mesh sieve.

2) The above-sifted materials were placed into a rapid mixer granulator and dry mixed for about 10 minutes.

3) Starch slurry was made by dispersing maize starch (second quantity) in a small amount of the water and the slurry was slowly added to previously heated remaining water under continuous stirring to get a translucent paste.

4) The dry mix of step 2 was granulated using starch paste of step 3.

5) The granules were dried in a rapid drier at 60°C for about 45 minutes.

6) Dried granules were passed through an ASTM #20 mesh sieve and retained particles were milled through a 1.5 mm screen and again passed through an ASTM #20 mesh sieve.

7) Maize starch (third quantity) and magnesium stearate were sifted through ASTM #40 mesh and ASTM 80# mesh sieves, respectively.

8) Dried granules of step 6 along with sifted maize starch of step 7 were placed into an octagonal blender and blended for about 5 minutes.

9) The blend of step 8 was further blended with magnesium stearate for about 3 minutes.

10) Final blend of step 9 was compressed into tablets using 19×8 mm punches with a compression machine.

EXAMPLE 1: Pharmaceutical compositions for metaxalone 800 mg tablets.

Ingredient	**mg/Tablet**

Metaxalone	800
Alginic acid	45
Ammonium calcium alginate	30
Maize starch	20
Maize starch	25
Water*	416.7
Maize starch	5
Magnesium stearate	10

* Evaporates during processing.

Particle size distribution of metaxalone used in Example 1: 68.9% by weight of metaxalone particles have particle sizes greater than 250 µm.

Manufacturing process:

1) Metaxalone was sifted through an ASTM #30 mesh sieve.

2) Maize starch (first quantity), ammonium calcium alginate, and alginic acid were sifted through an ASTM #40 mesh sieve.

3) The above-sifted materials were placed into a rapid mixer granulator and dry mixed for about 10 minutes.

4) Starch slurry was made by dispersing maize starch (second quantity) in a small amount of the water and the slurry was slowly added to previously heated remaining water under continuous stirring to get a translucent paste.

5) The dry mix of step 3 was granulated using starch paste of step 4.

6) The granules were dried in a rapid drier at 60°C for about 45 minutes.

7) Dried granules were passed through an ASTM #20 mesh sieve and retained particles were milled through a 1.5 mm screen and again passed through an ASTM #20 mesh sieve.

8) Maize starch (third quantity) and magnesium stearate were sifted through ASTM #40 mesh and ASTM #80 mesh sieves, respectively.

9) Dried granules of step 7 along with sifted maize starch of step 8 were placed into an octagonal blender and blended for about 5 minutes.

10) The blend of step 9 was blended with magnesium stearate for about 3 minutes.

11) The final blend of step 10 was compressed into 3500 tablets with 19×8 mm punches using a compression machine.

EXAMPLE 2: Pharmaceutical compositions for metaxalone 800 mg tablets.

Ingredient	mg/Tablet
Metaxalone	800
Alginic acid	45
Ammonium calcium alginate	30
Maize starch	21
Maize starch	25
Water*	416.7
Maize starch	4
Magnesium stearate	10

* Evaporates during processing.

Particle size distribution of metaxalone used in Example 2:

D_{10}=1.347 µm.

D_{50}= 4.299 µm.

D_{90}=164.998 µm.

Manufacturing process: same as that of Example 1.

Tablets prepared in Example 2, packed in aluminum blister packages, and commercial available reference tablets (SKELAXIN®) in closed HDPE bottles, were stored under conditions of 40°C and 75% RH and metaxalone impurity concentrations were measured by HPLC. Moisture content; ethyl urethane impurity and total impurities, and drug dissolution results are tabulated in Table 1, wherein impurity contents are expressed as percentages of the contained metaxalone.

Table 1

	SKELAXIN®			Example 2		
Storage Time	Initial	1 M	2 M	Initial	1 M	2 M
Moisture (% w/w)	1.43	1.47	1.24	1.71	1.37	0.95
Ethyl urethane (%)	0.01	ND	0.01	0.11	0.1	0.1
Total impurities (%)	0.18	0.25	0.22	0.11	0.1	0.1
Drug dissolution* in 120 minutes (%)	99	96	96	97	96	100

* Tablets were immersed in 900 ml of 0.5 % sodium lauryl sulphate in water, 100 rpm stirring and USP type II apparatus.

NA: Not available.

ND: not detected.

Pharmacokinetic parameters of formulations prepared according to Example 2 were determined in a randomized single dose crossover bioequivalence study involving administration of the test product and the commercial product Skelaxin® to 16 fasting healthy adult males, and plasma metaxalone concentrations were determined at intervals after dosing.

The following parameters were calculated:

AUC_{0-t} = the area under plasma concentration versus time curve, from time zero to the last measurable concentration.

$AUC_{0-\infty}$ = area under the plasma concentration versus time curve, from time zero to infinity.

C_{max} = maximum plasma concentration.

T_{max} = Time of the maximum measured plasma concentrations.

The pharmacokinetic parameters from the study were calculated and are summarized in Table 2.

Table 2

Parameter	Example 2 ("T")	SKELAXIN® (R")	Ratio (100×T÷R)
AUC_{0-t} (ng·hour/mL)	30045	30605	98.17
$AUC_{0-\infty}$ (ng·hour/mL)	30728	30969	99.22
C_{max} (ng/mL)	3613	3731	96.81
T_{max} (hours)	3.9	3.3	--

EXAMPLE 3: Comparative dissolution profiles of tablets.

Dissolution parameters:

Medium: 0.5% sodium lauryl sulfate in water.

Stirring speed in rpm: 100.

Volume: 900 ml.

Apparatus: USP Type II apparatus.

Reference: SKELAXIN® 800 mg tablets.

The cumulative percentages of drug dissolved are tabulated in Table 3.

Table 3

Time	SKELAXIN®	Comparative	Example	Example

(Minutes)		Example	1	2
30	43	62	49	47
60	77	91	81	82
90	89	95	91	94
120	98	100	97	98

Tablets prepared in Example 1 and Example 2, packed in aluminum blister packages, and commercial available reference tablets in closed HDPE bottles, were stored under conditions of 40°C and 75% RH for 2 months and data representing total impurities as measured by HPLC have been tabulated in Table 4, where total impurities are expressed as percentages of the contained metaxalone.

Table 4

	SKELAXIN®		Example 1	
Storage Time	1 Month	2 Months	1 Month	2 Months
Total Impurities	0.25	0.22	0.1	0.12

EXAMPLE 4: Pharmaceutical composition for metaxalone 800 mg tablets.

Ingredient	mg/Tablet
Metaxalone	800
Alginic acid	30
Ammonium calcium alginate	45
Maize starch	20
Maize starch	25
Water	416.7
Maize starch	5
Magnesium stearate	10

* Evaporates during processing.

Manufacturing process: same as that of Example 1.

EXAMPLE 5: Pharmaceutical compositions for metaxalone 800 mg tablets.

Ingredient	mg/Tablet
Metaxalone	800

Alginic acid	30
Ammonium calcium alginate	45
Maize starch	50
Magnesium stearate	10

Manufacturing process:

1) Metaxalone, alginic acid, ammonium calcium alginate and maize starch were sifted through an ASTM #40 mesh sieve.

2) Step 1 materials were placed into a blender and blended for about for 10 minutes.

3) Magnesium stearate was sifted through an ASTM #80 mesh sieve.

4) Sifted magnesium stearate was added to the step 2 blend and blended for about 5 minutes.

5) Final blend of step 4 was compressed into tablets using a compression machine.

EXAMPLE 6: Pharmaceutical composition for metaxalone 800 mg tablets.

Ingredient	**mg/Tablet**
Metaxalone	800
Alginic acid	30
Ammonium calcium alginate	45
Maize starch	20
Maize starch	25
Isopropanol*	416.7
Maize starch	5
Magnesium stearate	10

* Evaporates during processing.

Manufacturing process: same as that of Example 1, except that isopropanol is used in place of water.

EXAMPLE 7: Pharmaceutical composition for metaxalone 800 mg tablets.

Ingredient	**mg/Tablet**
Metaxalone	800

Alginic acid	30
Ammonium calcium alginate	45
Maize starch	50
Magnesium stearate	10

Manufacturing process:

1) Metaxalone, alginic acid, ammonium calcium alginate and maize starch were sifted through an ASTM #40 mesh sieve.

2) Step 1 materials were subjected to compaction.

3) The compacts of step 2 were milled through a 1 mm screen and again sifted through an ASTM #20 mesh sieve.

4) Magnesium stearate was sifted through an ASTM #80 mesh sieve.

5) Sifted magnesium stearate was added to materials from step 3 that passed through the sieve.

6) Step 5 materials were placed into a blender and blended for about 5 minutes.

7) The final blend of step 6 was compressed into tablets using a compression machine.