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(54) Title: CONTROLLED RELEASE COMPOSITIONS OF METAXALONE

(57) Abstract: The present invention relates to a controlled release compositions of metaxalone for oral administration and processes for their preparation.

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CONTROLLED RELEASE COMPOSITIONS OF METAXALONE

Technical Field of the Invention

The present invention relates to controlled release compositions of metaxalone for oral administration, and processes for their preparation.

Background of the Invention

Metaxalone, 5-[(3,5-dimethyphenoxy) methyl]-2-oxazolidinone, is a 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 name SKELAXIN®, and is available in two strengths, 400 mg and 800 mg tablets. The general dosage for adults and children over 12 years of age is two 400 mg tablets (800 mg) or one 800 mg tablet, taken three to four times daily.

According to American Hospital Formulary Service (AHFS) Drug Information, following oral administration of a single 800mg dosage of metaxalone, mean peak plasma concentrations are attained in 2 hours. The onset of action is within 1 hour and duration of action is about 4 to 6 hours. It has a plasma half-life of 2-3 hours, thus requiring multiple dosing. Repeated administration of a very high dosage drug effectuates patient inconvenience and is very bothersome for ambulatory patients, leading to poor patient compliance.

Painful, musculoskeletal conditions require prompt relief; therefore, compositions exhibiting a quick onset of action are desirable. When poorly soluble, hydrophobic drug substances, such as metaxalone, are administered in solid dosage forms, such as tablets or capsules, their rate of dissolution is rather slow. As a result, absorption from the gastrointestinal tract into systemic circulation is also slow. However, if such drugs are to be administered in oral dosage forms and would be used for clinical indications, where a rapid onset of therapeutic activity is desirable, the slow rate of dissolution and absorption may put limitations on their therapeutic utility. Therefore, there is a need for oral controlled release pharmaceutical composition that provides desirable plasma levels of metaxalone for twice-a-day or once-a-day therapy.

U.S. Patents Nos. 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 maximal drug concentration (C_{max}) and extent of absorption (AUC_{last}) of metaxalone as compared to administration without food.

U.S. Patent No. 4,722,938 describes methods of using musculoskeletal relaxants such as metaxalone.

International Publication No. (PCT) WO 2004/019937 discloses a pharmaceutical composition that includes metaxalone and pharmaceutically acceptable excipients, characterized in that the pharmaceutical composition has enhanced oral bioavailability. The metaxalone used may be a micronized, a salt form of metaxalone, a high-energy crystalline form of metaxalone or an amorphous metaxalone.

International Publication No. (PCT) WO 2004/108067 discloses a programmed drug delivery system which is useful for targeted drug delivery to a specific site in the gastrointestinal tract, at which site the beneficial agent may be delivered as a pulse, or in a controlled manner.

U.S. patent application Ser. No. 20050063913 A1, describes the composition comprising metaxalone particles having an effective average particle size of less than about 2000nm and at least one surface stabilizer that is preferably adsorbed to or associated with the surface of the drug particles.

Since metaxalone is indicated for acute painful musculoskeletal conditions that require quick relief it would be desirable to have a dosage form that maintains a balance between the amount of the drug released immediately and amount of drug released over an extended period. Further it is also desired to have a dosage form that maintains the plasma level of metaxalone without any troughs and peaks.

There are two major differences between the pharmacokinetic profiles of immediate release with controlled release drug formulations. First, the time to achieve the C_{max} in the plasma is often longer in the controlled release versus the immediate release formulation. In controlled released formulations, a long t_{max} is particularly disadvantageous to patients seeking urgent treatment (especially in acute painful

musculoskeletal conditions) and to maintain minimum effective concentration (MEC) levels. A second difference in the pharmacokinetic profiles of controlled release in comparison to immediate release drug formulations is that the duration of sustained plasma levels is longer in the controlled release formulations. The longer duration of such sustained plasma levels facilitated by controlled release formulations are advantageous to all patients, prolonging the desired biological effect. Therefore, although the controlled release formulation facilitates a substantially longer period of time in maintaining plasma levels of drug or active metabolite(s), it suffers from the drawback of requiring longer periods of time to achieve the C_{max}, when compared to immediate release formulations.

Thus, there remains a long felt need for improved controlled release formulations for metaxalone, including dosage formulations that might have one or more desirable characteristics of both immediate release and controlled release metaxalone formulations.

Summary of the Invention

In one general aspect there is provided a controlled release pharmaceutical composition for metaxalone that provides a therapeutically effective blood concentration level of metaxalone for a sustained period of time of up to at least twelve hours.

In another general aspect there is provided a controlled release pharmaceutical composition for metaxalone which includes a therapeutically effective amount of metaxalone and at least one rate controlling polymer, wherein the composition provides a constant release profile for a sustained period of time of up to at least twelve hours.

The composition of the present invention may be a matrix-type dosage form, multiple unit dosage form or an osmotic dosage form.

In one embodiment, the composition may be a matrix type dosage form, a reservoir type dosage form or combinations of both. Matrix-type dosage forms are those in which the drug is distributed uniformly in the one or more rate controlling material and reservoir type dosage forms utilize polymeric coating over the core of the metaxalone. A combination of the reservoir and matrix type includes extended or sustained release coatings on extended release matrices.

Embodiments of the matrix type dosage form include one or more of the following features. For example, the matrix may be formulated into tablets of a single monolithic matrix, bilayered matrix or a multi-layered matrix.

The monolithic matrix may have a uniform mixture of the core containing metaxalone and one or more rate controlling polymers. The monolithic matrix may have drug release profile tailored in a fashion to provide both immediate and controlled release profile. The matrix may further include one or more pharmaceutically acceptable excipients.

In another embodiment, the matrix-type dosage forms may be a bilayered type formulation comprising at least two layers which includes an extended release layer, and an immediate release layer. The ratio of the immediate release metaxalone layer to the extended release metaxalone layer may range from about 20:80 to about 80:20 by weight.

The extended release layer may be a core and the immediate release layer may cover at least a portion of the core. The extended release core may be a matrix and the matrix may have a uniform mixture of the metaxalone and one or more rate controlling polymers.

In another embodiment, the controlled release metaxalone composition may be formulated as a multiple unit dosage form having plurality of discrete or aggregated particles, pellets, mini tablets, beads or granules.

It another general aspect there is provided a controlled release metaxalone composition, in multiple unit dosage form, comprising at least two types of metaxalone – containing units which includes one immediate release unit, and another controlled release unit. The ratio of first unit to the second unit may range from about 20:80 to about 80:20 by weight.

The units containing metaxalone may include other pharmaceutically acceptable excipients. The units can be filled into a capsule or compressed into a tablet dosage form. The units may be coated with one or more layers comprising film forming agents and/or pharmaceutically acceptable excipients.

In yet another aspect of the invention there is provided a controlled release metaxalone composition, in an osmotic dosage form, which includes a core comprising

metaxalone and a swelling agent, and a semi-permeable membrane coating surrounding the core and optionally, one or more additional layers of metaxalone below and/or above the semipermeable membrane for immediate release. The ratio of immediate release metaxalone layer to the metaxalone core may range from about 20:80 to about 80:20 by weight.

The dosage form may further include one or more other pharmaceutically acceptable excipients.

According to one of the embodiments, metaxalone may be included in one or more forms. For example, the metaxalone may be micronized or nanonized. It may be used as a metaxalone adsorbate, or as an admixture of metaxalone-cyclodextrin.

The rate controlling polymers may include one or more of hydrophilic polymers, hydrophobic polymers, or combinations thereof. The pharmaceutical composition may also include one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients may be fillers, binders, lubricants, glidants, colorants and flavoring agents.

In another general aspect there is provided a method of treating muscle spasm associated with acute, painful musculoskeletal conditions in a patient in need thereof. The method includes administering a a controlled release pharmaceutical composition of metaxalone that provides a constant release profile for a sustained period of time of up to at least twelve hours.

Embodiments of the method may include one or more of the following features. For example, the dosage form may further include a non steroidal anti-inflammatory drug, analgesics or other pharmaceutical agents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have developed a controlled release pharmaceutical composition for metaxalone that helps to achieve the constant release profile up to at least about 12 hours time period.

The term "controlled release" as used herein includes any type of controlled release such as prolonged release, sustained release, modified release and extended release.

The term "matrix" as used herein includes a uniform mixture of metaxalone, one or more rate controlling polymers and one or more pharmaceutically acceptable excipients.

The rate controlling polymers used in the matrix type dosage form may include one or more of hydrophilic polymers, hydrophobic polymers, or combinations thereof.

The hydrophilic rate-controlling polymers may include one or more of cellulose derivatives such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose, sodium carboxy methylcellulose or combinations thereof; polyvinylpyrrolidone, polysaccharides, polyalkylene glycols, starch and derivatives; or mixtures thereof.

The hydrophobic polymers may include one or more of ethyl cellulose, cellulose acetate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, poly (alkyl) methacrylate, and copolymers of acrylic or methacrylic acid esters, waxes, shellac and hydrogenated vegetable oils.

The osmotic controlled metaxalone dosage form may be prepared by blending metaxalone, at least one swelling agent, optionally an osmotic agent and one or more pharmaceutically acceptable inert excipient; and compressing the blend into a compact core; enclosing the core with a solution/dispersion of an enclosing composition comprising one or more semi-permeable membrane-forming polymers and other coating additives. The immediate release metaxalone layer may be layered to cover at least a portion of the core, using a conventional coating pan, a spray coater, a rotating perforated pan, or an automated system, such as a centrifugal fluidizing (CF) granulator, a fluidized bed process, or any other suitably automated coating equipment.

The swelling agents may include any pharmaceutically acceptable polymers, which swell in the presence of aqueous media. For example, cellulose derivatives, starch,

gums, alginates, acrylic acid derivatives, polyethylene oxides and carbohydrate based polymers.

The osmotic agents may be one or more of water soluble salts of inorganic acids, water soluble salts of organic acids, non ionic organic compounds having high water solubility, water-soluble amino acids, urea and urea derivatives.

The semi-permeable membrane of the osmotic dosage form is permeable to the passage of an external fluid, such as water and biological fluids, but is substantially impermeable to the passage of components in the internal compartment. The materials useful for forming the wall are essentially nonerodible and are substantially insoluble in biological fluids during the life of the dosage form.

The semi-permeable membrane may be one or more of semi-permeable membrane-forming polymers and coating additives. The semi-permeable membrane-forming polymers may be one or more of cellulose derivatives, starch, gums, alginates, acrylic acid derivatives and carbohydrate based polymers.

Flux-regulating agents can be admixed with the semi-permeable membrane to modulate the fluid permeability of the wall. For example, agents that produce a marked increase in permeability to fluid such as water are often essentially hydrophilic, while those that produce a marked permeability decrease to water are essentially hydrophobic. Example of flux regulating agents include, but are not limited to, polyhydric alcohols, polyalkylene glycols and polyalkylenediols, polyesters of alkylene glycols.

The immediate release outer layer may further include film-forming polymers and optionally other pharmaceutically acceptable excipients.

The metaxalone used in the present invention may be in one or more forms such as metaxalone, micronized or nanonized metaxalone, metaxalone adsorbate and metaxalone-cyclodextrin admixture.

Due to poor bioavailability of metaxalone, it can be used in a micronized or nanonized form. The particle size of micronized or nanonized metaxalone may be in the range of 50nm to 50μm. The size reduction for micronization or nanonization may be carried out in any of the conventionally known methods using air jet mill, dyno mill, ball mill, colloid mill, grinding mill, roller mill, impact mill, etc.

The metaxalone adsorbate may be prepared by dissolving metaxalone and one or more of pharmaceutically acceptable surface modifiers in organic solvent and removing the solvent to co-precipitate the metaxalone adsorbate.

The pharmaceutically acceptable surface modifiers may be one or more of cellulose derivatives, starch, gums, sugars, saccharides, alcohols, alginates, surfactants, acrylic acid derivatives and carbohydrate based polymers.

Suitable examples of cellulosic polymers include, but are not limited to, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, cross-linked carboxymethylcellulose, hydroxymethylcellulose and hydroxyethylcellulose.

Suitable examples of acrylic acid derivatives include, but are not limited to, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D).

Suitable surfactants can be anionic, cationic, zwitterionic and nonionic surfactants. Particularly, the compositions include at least one anionic surfactant. Suitable anionic surfactants include but are not limited to alkyl sulfonates, alkyl phosphates, alkyl phosphonates, potassium laurate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidylinositol, diphosphatidylglycerol, phosphatidyl inosine, phosphatidylserine, phosphatidic acid and their salts, cholic acid and other bile acids (e.g., cholic acid, deoxycholic acid, glycocholic acid, taurocholic acid, glycodeoxycholic acid) and salts thereof (e.g., sodium deoxycholate, etc.).

Suitable examples of organic solvent may include one or more of ketones, such as acetone; alcohols, such as methanol, ethanol, isopropyl alcohol; and chlorinated hydrocarbons, such as methylene chloride.

Solvents may be removed by techniques known in the art, for example, one or more of distillation, distillation under vacuum, evaporation, and spray drying.

The metaxalone-cyclodextrin admixture may be prepared by blending metaxalone with cyclodextrin. The admixture may also include one or more other pharmaceutically acceptable excipients.

The cyclodextrin may be a naturally occurring dextrin and also the methylated derivatives of these natural products, especially of beta-cyclodextrin.

In addition to the metaxalone and rate-controlling polymers, the matrix may further include one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients may be fillers, binders, lubricants, glidants, colorants or flavoring agents.

Suitable examples of fillers include, but are not limited to, corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized, sucrose, and mixtures thereof.

Examples of binders include, but are not limited to, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, poloxamer, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullutan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and mixtures thereof.

Examples of lubricants and glidants include, but are not limited to, colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax, and mixtures thereof.

The coloring agents of the present invention may be selected from any FDA approved color for oral use.

The composition may be formulated into various pharmaceutical preparations for oral administration, e.g., in the form of a tablet or capsule in accordance with any of the conventional procedures known in the field of art, for example, simple granulation followed by sieving; extrusion and marumerization or spheronization; rotogranulation;

pelletization; micropelletization, compression, coating etc. These steps may be carried out in a conventional manner.

The bilayered or multilayered tablets prepared by the present invention may optionally be coated with one or more layers comprising film forming agents and/or pharmaceutically acceptable excipients.

The bilayered or multilayered tablets may be prepared by multiple-compression tablets comprising an inner core and an outer coat of metaxalone, and may be prepared such that one surface of the inner core is exposed. These types of tablets are also referred to as inlay or bull's-eye tablets and these are similar to compression-coated tablets except that one surface of the coating is eliminated.

Suitable film forming polymers include one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, waxes, methacrylic acid polymers such as Eudragit® RL and RS, and mixtures thereof. The coating can also be performed using any commercially available ready to coat preparations such as opadry-AMB, opadry-white, opadry-clear, etc.

Suitable solvents used for making a solution/suspension of film forming polymer include one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

The controlled release pharmaceutical composition for metaxalone of the present invention may be used for treating muscle spasm associated with painful musculoskeletal conditions in humans, by administering a controlled release pharmaceutical composition for metaxalone that provides a constant release profile for a sustained period of time up to at least twelve hours.

The method may further include administering in combination with other medicines, for example, other non-steroidal anti-inflammatory agents (NSAIDs), any analgesics or other pharmaceutically active agents, etc.

The following examples illustrate various aspects of the present inventions. These examples are for illustration only and do not limit the scope of the inventions.

Example 1:

PREPARATION OF METAXALONE EXTENDED RELEASE TABLETS

Ingredients	percent w/w
A. Extended Release Layer	
Metaxalone (micronized or nanosized)*	21.05
Poloxamer	2.10
Polyvinyl pyrrolidone	2.64
Lactose Monohydrate	2.38
Microcrystalline Cellulose	2.38
Hydroxypropyl methylcellulose	7.37
Magnesium stearate	0.53
Colloidal anhydrous silica	0.26
Talc	0.26
B. Immediate Release Layer	
Metaxalone (micronized or nanosized)*	42.10
Poloxamer	3.15
Polyvinyl pyrrolidone	2.64
Lactose Monohydrate	3.15
Sodium Starch Glycolate	4.21
Microcrystalline Cellulose	5.26
Magnesium stearate	0.21
Colloidal anhydrous silica	0.31

(*prepared by using Air jet mill)

Process:

Granulation of Extended Release layer

1. Metaxalone, poloxamer, lactose monohydrate, microcrystalline cellulose and hydroxypropyl methylcellulose were mixed well and granulated with polyvinyl pyrrolidone solution.
2. The granules were dried and mixed with magnesium stearate, colloidal anhydrous silica and talc.

Granulation of Immediate Release layer

1. Metaxalone, poloxamer, lactose monohydrate, microcrystalline cellulose and sodium starch glycollate were mixed well and granulated with polyvinyl pyrrolidone solution.
2. The dried granules were mixed with magnesium stearate and colloidal anhydrous silica.

Compression

Both the layers were compressed to give bilayered or press coated tablets using appropriate tooling.

Example 2:

PREPARATION OF METAXALONE ADSORBATE

Ingredients	percent w/w
Metaxalone	47.6
Povidone	4.8
Cross-linked carboxymethylcellulose	47.6
Methylene chloride	q.s.

Metaxalone was dissolved in methylene chloride with constant stirring. Polyvinyl pyrrolidone and cross-linked carboxymethylcellulose were dispersed in it. Methylene chloride was removed to obtain metaxalone adsorbate for further formulation work.

Example 3:

PREPARATION OF METAXALONE EXTENDED RELEASE TABLETS

Ingredients	percent w/w
A. Extended Release Layer	
Metaxalone adsorbate of example 2	21.05
Poloxamer	2.10
Polyvinyl pyrrolidone	2.64
Lactose Monohydrate	2.38
Microcrystalline Cellulose	2.38

Ingredients	percent w/w
Hydroxypropyl methylcellulose	7.37
Magnesium stearate	0.53
Colloidal anhydrous silica	0.26
Talc	0.26
B. Immediate Release Layer	
Metaxalone adsorbate of example 2	42.10
Poloxamer	3.15
Polyvinyl pyrrolidone	2.64
Lactose Monohydrate	3.15
Sodium Starch Glycolate	4.21
Microcrystalline Cellulose	5.26
Magnesium stearate	0.21
Colloidal anhydrous silica	0.31

Process:

Granulation of Extended Release layer

1. Metaxalone adsorbate of example 2, poloxamer, lactose monohydrate, microcrystalline cellulose and hydroxypropyl methylcellulose were mixed well and granulated with polyvinyl pyrrolidone solution.
2. The granules were dried and blended with magnesium stearate, colloidal anhydrous silica and talc.

Granulation of Immediate Release layer

1. Metaxalone adsorbate of example 2, poloxamer, lactose monohydrate, microcrystalline cellulose and sodium starch glycollate were mixed well and granulated with polyvinyl pyrrolidone solution.
2. The dried granules were mixed with magnesium stearate and colloidal anhydrous silica.

Compression

The two types of granules were compressed into bilayered tablets using appropriate tooling.

Example 4:

PREPARATION OF METAXALONE EXTENDED RELEASE CAPSULES

Ingredients	percent w/w
A. Extended Release Layer	
Metaxalone (micronized or nanosized)*	26.46
Sugar spheres # 40-60	11.91
Hydroxypropyl methylcellulose	1.33
Ethyl cellulose	3.97
Triacetin	q.s.
B. Immediate Release Layer	
Metaxalone (micronized or nanosized)*	52.91
Hydroxypropyl methylcellulose	2.64
Colloidal silicone dioxide	0.52
Talc	0.26

(*prepared by using Air jet mill)

Process:

1. Metaxalone and hydroxypropyl methylcellulose were mixed well and layered over the sugar spheres
2. Ethylcellulose, hydroxypropyl methylcellulose and triacetin are mixed and coated over the metaxalone layered sugar spheres
3. The immediate release layer of metaxalone was provided by again layering metaxalone and hydroxypropyl methylcellulose over the coated spheres of step 2.
4. The prepared spheres were blended in a desired weight ratio and filled in appropriate size capsule.

Example 5:

PREPARATION OF METAXALONE EXTENDED RELEASE CAPSULES

Ingredients	percent w/w
A. EXTENDED RELEASE LAYER	
Metaxalone (micronized or nanosized)*	26.46
Sugar spheres # 40-60	11.91
Hydroxypropyl methylcellulose	1.33
Ethyl cellulose	3.97
Triacetin	q.s.
B. IMMEDIATE RELEASE LAYER	
Metaxalone (micronized or nanosized)*	52.91
Hydroxypropyl methylcellulose	2.64
Colloidal silicone dioxide	0.52
Talc	0.26

(*prepared by using Air jet mill)

Process:

Preparation of Extended Release pellets

1. Metaxalone and Hydroxypropyl methylcellulose were mixed well and layered over the sugar spheres
2. Ethylcellulose, hydroxypropyl methylcellulose and triacetin were mixed and coated over the metaxalone layered sugar spheres

Preparation of Immediate Release pellets

Metaxalone and Hydroxypropyl methylcellulose were mixed well and layered over the sugar spheres

Preparation of finished product

The two types of pellets were blended in a desired weight ratio and filled in to the capsules of suitable size.

Example 6:

PREPARATION OF BILAYERED TABLETS

Ingredients	percent w/w
A. Extended release layer	
Metaxalone	55
Lactose	5.6
Sodium lauryl sulphate	1
Hydroxypropyl methylcellulose	11
Polyvinylpyrrolidone	3.4
Colloidal Sillicon dioxide	0.3
Magnesium Stearate	0.6
B. Immediate release layer	
Metaxalone	18.4
Microcrystlline Cellulose	1.9
Sodium Starch Glycolate	0.9
Sodium Lauryl Sulfate	0.4
Polyvinylpyrrolidone	0.9
Colloidal Sillicon dioxide	0.2
Magnesium Stearate	0.4

Process:

Granulation of Extended Release layer

1. Metaxalone, Lactose, sodium lauryl sulphate, and Hydroxypropyl methylcellulose were blended well and granulated with Polyvinylpyrrolidone solution.
2. The granules were dried and mixed with magnesium stearate and colloidal anhydrous silica.

Granulation of Immediate Release layer

1. Metaxalone, microcrystalline cellulose, sodium lauryl sulphate, and sodium starch glycollate were blended well and granulated with Polyvinylpyrrolidone solution.

2. The granules were dried and mixed with magnesium stearate and colloidal anhydrous silica.

Compression

Both the granules were compressed using appropriate tooling.

Examples 7-10:

PREPARATION OF MONOLITHIC MATRIX TABLETS

Ingredients	Example 7 (percent w/w)	Example 8 (percent w/w)	Example 9 (percent w/w)	Example 10 (percent w/w)
Metaxalone	71.3	74.2	72.6	72.6
Lactose	7.2	7.4	7.3	7.3
Sodium lauryl sulphate	1.6	1.5	-	-
Hydroxypropyl methylcellulose (Methocel K4M)	14.8	11.2	14.5	-
Hydroxypropyl methylcellulose (Methocel K100M)	-	-	-	14.5
Polyvinylpyrrolidone	4.6	4.7	4.5	4.5
Colloidal silicon dioxide	0.5	0.4	0.4	0.4
Mag stearate	0.8	0.6	0.7	0.7

Process:

1. Metaxalone, Lactose, sodium lauryl sulphate (in case of Example 7 & 8), and Hydroxypropyl methylcellulose were mixed well and granulated with Polyvinylpyrrolidone solution.
2. The granules were dried and mixed with magnesium stearate and colloidal anhydrous silica.
3. Lubricated granules were compressed into tablets.

Example 11:

PREPARATION OF MONOLITHIC MATRIX TABLETS

Ingredients	percent w/w
Metaxalone adsorbate of example 2	71.6
Lactose	7.1
Sodium lauryl sulphate	1.4
Hydroxypropyl methylcellulose (Methocel K4M)	14.3
Polyvinylpyrrolidone	4.5
Colloidal silicon dioxide	0.4
Mag stearate	0.7

Process:

1. Metaxalone adsorbate of example 2, Lactose, sodium lauryl sulphate, and Hydroxypropyl methylcellulose were mixed well and granulated with Polyvinylpyrrolidone solution.
2. The granules were dried and mixed with magnesium stearate and colloidal anhydrous silica.
3. The granules of step 2 were then compressed into tablets.

In-vitro Dissolution for Example 6

The tablets prepared in the example 6 were subjected to in-vitro dissolution under the following conditions:

Media: Phosphate buffer pH 6.8 and

0.5% Sodium lauryl sulphate (SLS) - 900 ml

Apparatus: USP-2/100 rpm

The results are shown in Table 1.

Table 1:

Time (h)	Percent drug Released
0	0
1	34
2	42
4	57
6	69
8	80
10	88
12	95

In-vitro Dissolution for Example 7 –10

The tablets prepared in the example 7 - 10 were subjected to in-vitro dissolution under the following conditions:

Media: Phosphate buffer pH 6.8 and

0.5% Sodium lauryl sulphate (SLS) - 900 ml

Apparatus: USP-2/100 rpm

The results are shown in Table 2.

Table 2:

Time (h)	Percent Drug Released			
	Example 7	Example 8	Example 9	Example 10
0	0	0	0	0
1	12	14	12	12
2	24	28	26	27
4	48	55	52	57
6	66	77	69	74
8	79	92	85	87
10	92	105	93	98
12	105	114	105	103

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions.

We claim:

1. A controlled release pharmaceutical composition for metaxalone comprising a therapeutically effective amount of metaxalone and at least one rate controlling polymer, wherein the composition provides a constant release profile for a sustained period of time of up to at least twelve hours.

2. The composition according to claim 1, wherein the composition is in the form of a matrix type dosage form, multiple unit dosage form or osmotic dosage form.

3. The composition according to claim 2, wherein the matrix type dosage form comprises a single monolithic matrix, bilayered matrix and multi-layered matrix.

4. The composition according to claim 1, wherein the metaxalone is in one or more forms comprising metaxalone, micronized or nanonized metaxalone, metaxalone adsorbate and metaxalone-cyclodextrin admixture.

5. The composition according to claim 1, wherein the rate controlling polymer comprises one or more of hydrophilic polymers, hydrophobic polymers or a combination thereof.

6. The composition according to claim 5, wherein the hydrophilic polymers comprise one or more of cellulose derivatives comprising hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose or combinations thereof; polyvinylpyrrolidone, polysaccharides, polyalkylene glycols, starch and derivatives thereof.

7. The composition according to claim 5, wherein the hydrophobic polymers comprise one or more of ethyl cellulose, cellulose acetate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, poly (alkyl) methacrylate, and copolymers of acrylic or methacrylic acid esters, waxes, shellac and hydrogenated vegetable oils.

8. The composition according to claim 1, further comprising one or more pharmaceutically acceptable excipients.

9. The composition according to claim 8, wherein the one or more pharmaceutically acceptable excipients comprise fillers, binders, lubricants, glidants, colorants and flavoring agents.

10. The composition according to claim 1, wherein the composition is in the form of a tablet, capsule, aggregated particle, pellet, mini tablet, bead or granule.

11. The composition according to claim 10, further comprising one or more layers of film forming agents.

12. A method of treating muscle spam associated with painful musculoskeletal conditions in a patient in need thereof, the method comprising administering a controlled release pharmaceutical composition of metaxalone that provides a constant release profile for a sustained period of time of up to at least twelve hours.

13. The method according to claim 12, wherein the controlled release pharmaceutical composition of metaxalone further comprises one or more non-steroidal anti-inflammatory agents, analgesics and other pharmaceutical agents.