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(54) **CREATINE ORAL SUPPLEMENTATION USING CREATINE HYDROCHLORIDE SALT**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 12/477,413, filed on Jun. 3, 2009, now Pat. No. 8,026,385, which is a continuation of application No. 10/846,782, filed on May 14, 2004, now Pat. No. 7,608,641.

(60) Provisional application No. 60/470,356, filed on May 15, 2003.

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A61K 31/195 (2006.01)

(52) **U.S. Cl.** **514/565**

(58) **Field of Classification Search** 514/565
See application file for complete search history.

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(57) **ABSTRACT**

The present invention is directed to a third generation form of creatine, specifically a creatine hydrochloride salt, that drives significant improvements in muscle development and recovery due to its enhanced bio-availability, while causing fewer negative side effects compared to previous forms of creatine.

20 Claims, 1 Drawing Sheet

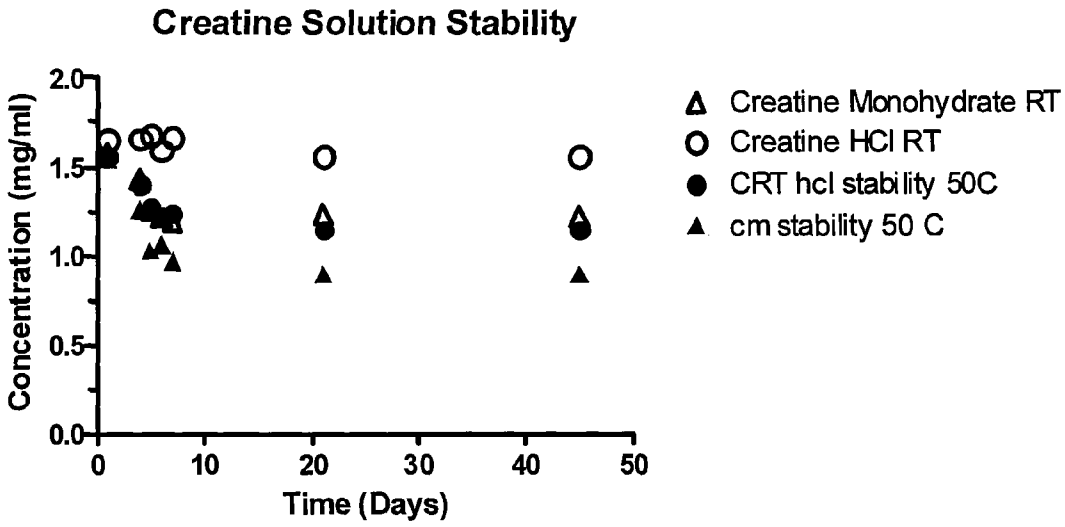

Figure 1

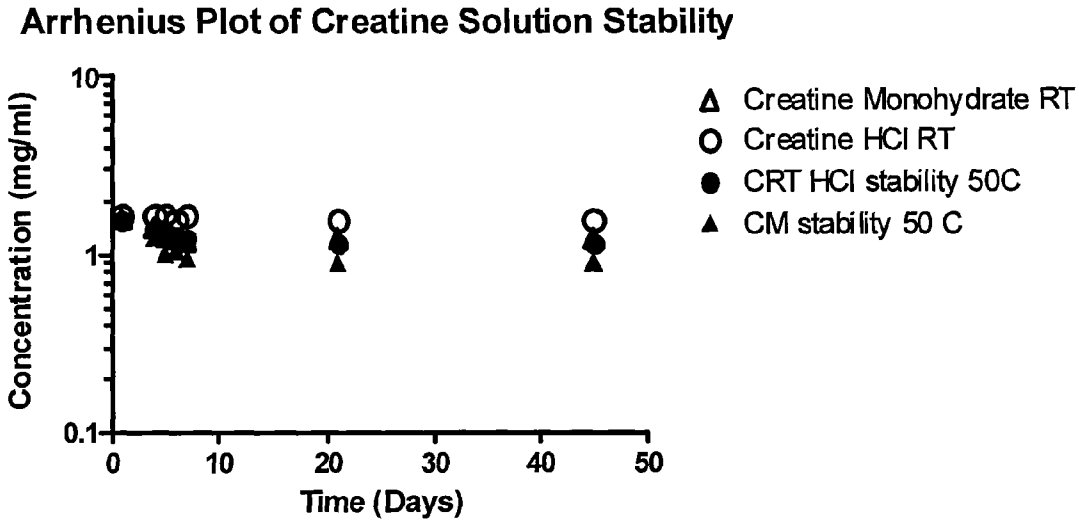

Figure 2

CREATINE ORAL SUPPLEMENTATION USING CREATINE HYDROCHLORIDE SALT

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation-in-part of U.S. patent application Ser. No. 12/477,413, filed Jun. 3, 2009, now pending, which is a continuation of U.S. patent application Ser. No. 10/846,782, filed May 14, 2004, now U.S. Pat. No. 7,608,641, which claims priority to U.S. Provisional Application 60/470,356, filed May 15, 2003, the entirety of which is incorporated herein.

FIELD OF THE INVENTION

The present invention is directed to a form of creatine that has increased aqueous solubility, increased plasma uptake at low dosage amounts, and improved stability and half-life. In particular, the present invention relates to a creatine supplement that, when compared to creatine monohydrate, has an increased aqueous solubility of at least an order of magnitude, a bioavailability or plasma uptake level of at least 50 percent greater than creatine monohydrate, and a shelf-life of more than double the shelf-life of creatine monohydrate.

BACKGROUND OF THE INVENTION

Creatine is a naturally occurring nitrogenous compound found in the skeletal muscles of vertebrates that plays an important role in protein metabolism and other bio-chemical functions. For example, creatine is taken up into muscle cells by specific receptors and converted to phosphocreatine by creatine kinase.

Both creatine and phosphocreatine play an important role in the anaerobic production of ATP during short and intensive exertions, via the creatine kinase system. Specifically, during muscle contraction, there is an increase in the amount of phosphocreatine (which is generated from creatine) and consequently in ATP. The amount of phosphocreatine in the muscle cell determines the amount of time it takes for a muscle to recover from activity; thus, supplementing the diet with creatine can increase the concentration of phosphocreatine in muscles by 6 percent to 16 percent, with a consequent increase in the ATP turnover during physical exertion.

Creatine-containing supplements have been shown to increase lean body mass, high intensity power output, and overall physical strength. By virtue of these characteristics, creatine has met with enormous success among professional and recreational athletes, as well as professional and amateur bodybuilders, in recent years as a dietary supplement.

Increasing creatine levels in muscle through dietary supplementation has proven effective at enhancing athletic performance, increasing muscle workload and shortening muscle recovery time. In addition, there is increasing interest in creatine dietary supplements for a variety of therapeutic indications, including muscular dystrophy, cardiovascular diseases, neurodegenerative disorders, and mental retardation. The zwitterionic creatine monohydrate has been the standard creatine salt of choice for commercial creatine supplement formulations.

However, creatine supplements containing creatine monohydrate are not ideal dietary supplements due to their low aqueous solubility. In other words, relatively large doses of creatine monohydrate must be consumed with large amounts

trointestinal problems due to the large dosages. In addition, the relatively high doses of creatine monohydrate required to produce the desired biological effects suggest that the oral bioavailability of creatine monohydrate is low and that more efficient dosage forms may provide better desired results accompanied by fewer gastrointestinal side effects.

There are other known salt forms of creatine including creatine citrate (creatine effervescent) and creatine pyruvate that have been patented and marketed as improvements over creatine monohydrate. However, despite the various salt forms currently marketed, there remains a need in the art for a more improved form of creatine with improved solubility and bioavailability characteristics that can be consumed in smaller dosage forms.

SUMMARY OF THE INVENTION

The present invention is directed to a supplement that includes creatine HCl, wherein the creatine HCl possesses a solubility of at least 600 mg/mL in water at 25° C. In one embodiment, the creatine HCl is at least 95 percent free of contaminants. In another embodiment, the recommended dosage range for the creatine HCl is between about one quarter teaspoon to about one tablespoon per hundred pounds body weight.

In this aspect of the invention, the supplement may be being taken orally. In one embodiment, the creatine HCl has a shelf-life of at least about 45 days in aqueous solution at room temperature. In another embodiment, an effective dosage of the supplement is about 500 mg to about 1500 mg of creatine HCl per 100 pounds body weight. In yet another embodiment, the creatine HCl further comprises an additive or feed supplement for livestock.

The present invention is also directed to a formula used to enhance athletic performance including creatine HCl, wherein the creatine HCl exhibits an aqueous solubility that is at least about 15 times greater than that of creatine monohydrate. In one embodiment, the formula also includes additional species of creatine selected from the group comprising creatine esters, creatine pyruvate, creatine phosphate, creatine alpha-ketoglutarate, creatine citrate, and combinations thereof. In another embodiment, the formula also includes additional supplements selected from the group comprising carbonate salts, methylsulfonylmethane, glucosamine, and chondroitin.

In yet another embodiment, the formula also includes compounds selected from the group comprising proteins, amino acid supplements, carbohydrates, D-Ribose, fats, fiber and combinations thereof. In still another embodiment, the formula also includes sweeteners selected from the group comprising sucralose, aspartame, saccharin, acesulfame potassium, neohesperidin dihydrochalcone, glycyrrhizin, thaumatin, alitame, stevioside, and combinations thereof. In one embodiment, the formula further includes a supplement selected from the group comprising sports bars, nutritional bars, powders, liquids, gels, sports drinks, and beverages. In another embodiment, the formula also includes flavoring agents selected from the group comprising cocoa, yogurt, peanut butter, mint, cheesecake, hazelnut paste, almonds, granola, coconut, strawberry, banana, cherry, plum, raspberry, lemon, orange, lime, pineapple, blueberry and other fruit flavors, coffee, or cremes and jellies, and combinations thereof.

alcohol, an acid catalyst, and creatine monohydrate, wherein the solubility of the creatine HCl product is at least about 650 mg/ml.

In this aspect of the invention, the alcohol may be selected from the group consisting of ethanol, methanol, butanol, and isopropanol. In one embodiment, the reaction is a super-saturated reaction including ethanol, acetyl chloride, and creatine monohydrate. In one embodiment, the volume of ethanol used is between about 4 and 5 L per kg of creatine monohydrate and the quantity of acetyl chloride used is between about 1.0 to about 1.1 mole equivalents of creatine monohydrate.

In another embodiment, the super-saturated reaction further includes the steps of mixing the alcohol and acetyl chloride in a reactor that is cooled to between about 0° C. and 20° C.; allowing the temperature of the reactor to increase to about 38° C.; adding creatine monohydrate; and maintaining a temperature of between about 30° C. and about 40° C. The creatine HCl product is preferably at least 95 percent free of contaminants.

BRIEF DESCRIPTION OF THE DRAWINGS

Further features and advantages of the invention can be ascertained from the following detailed description that is provided in connection with the drawing(s) described below:

FIG. **1** is a graphical representation in linear form of the stability of creatine HCl in aqueous solution as compared to creatine monohydrate; and

FIG. **2** is a graphical representation in log form of the stability of creatine HCl in aqueous solution as compared to creatine monohydrate.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a third generation form of creatine, specifically a creatine hydrochloride salt ("creatine HCl") that has improved aqueous solubility, plasma uptake, and shelf-life over that of previous forms of creatine. The present invention further contemplates suitable methods to produce the creatine HCl in a granular precipitate form with high purity and yield.

The creatine HCl of the present invention may be used as a nutritional supplement for enhancing muscle performance and muscle mass in both humans and livestock, including muscle quality in livestock. In this regard, based on the known beneficial qualities of creatine with regard to muscle development and recovery, it is believed that the improvements in solubility and plasma uptake of the creatine HCl of the present invention also lead to significant improvements in muscle development and recovery as compared to creatine monohydrate. Moreover, without being bound to any particular theory, the improvements in the solubility and plasma uptake also reduce or essentially eliminate the negative side effects typically associated with previous forms of creatine.

Creatine HCl Solubility

The creatine HCl of the present invention represents an improvement on prior forms of creatine due to is its remarkably high aqueous solubility. As the low oral absorption of creatine supplements are believed to be attributable at least in part to reduced solubility, the creatine HCl of the present invention is also expected to have better oral absorption properties compared to other forms of creatine.

The creatine HCl of the invention preferably has an aqueous solubility of at least about 150 mg/ml at room temperature. In another embodiment, the aqueous solubility of the creatine HCl of the invention is at least about 250 mg/mL or greater, more preferably of about 480 mg/mL or greater, and more preferably of about 800 mg/mL or greater. In another embodiment, the aqueous solubility of the creatine HCl of the invention ranges from about 250 mg/ml to about 1000 mg/ml. In yet another embodiment, the creatine HCl has an aqueous solubility of about 400 mg/ml to about 1000 mg/ml. In still another embodiment, the aqueous solubility of the creatine HCl of the invention is at least about 650 mg/ml, preferably at least about 675 mg/ml. For example, the aqueous solubility of the creatine HCl is preferably 679±18 mg/ml when tested at room temperature (25° C.) after a time period of about 1.5 hours.

In comparison, the aqueous solubility of other forms of creatine including creatine monohydrate and creatine citrate salt typically ranges from about 10 to about 16 mg/mL. Accordingly, the creatine HCl of the present invention exhibits an aqueous solubility that is at least about 15 times greater than that of creatine monohydrate. In one embodiment, the aqueous solubility of the creatine HCl is at least about 20 times greater than that of creatine monohydrate, preferably at least about 30 times greater than that of creatine monohydrate. In another embodiment, the creatine HCl has an aqueous solubility that is at least about 40 times greater than that of creatine monohydrate, preferably at least about 50 times greater than that of creatine monohydrate. For example, the aqueous solubility of the creatine HCl is preferably 42 times greater than that of creatine monohydrate when tested at room temperature (25° C.) after a time period of about 1.5 hours.

Creatine HCl Bioavailability

The creatine HCl of the present invention exhibits improved bioavailability compared to creatine monohydrate. As used herein, the term "bioavailability" refers to the rate and amount of a drug (or in this case a supplement) that reaches the systemic circulation of a patient following administration of the drug or prodrug thereof to the patient. Accordingly, bioavailability is one of the principal pharmacokinetic properties of drugs and can be determined by evaluating, for example, the plasma or blood concentration-versus-time profile for a drug. Parameters useful in characterizing a plasma or blood concentration-versus-time curve include the area under the curve (AUC), the maximum drug concentration (C_{max}), and the time to maximum concentration (T_{max}).

As used herein, the term "AUC" refers to the area under a curve representing the concentration of a compound or metabolite thereof in a biological fluid, e.g., plasma and blood, in a patient as a function of time following administration of the compound to the patient. The AUC may be determined by measuring the concentration of a compound or metabolite thereof in a biological fluid using methods such as liquid chromatography-tandem mass spectrometry (LC/MS/MS), at various time intervals, and calculating the area under the plasma concentration-versus-time curve. Suitable methods for calculating the AUC from a drug concentration-versus-time curve are well known in the art.

C_{max} is the maximum concentration of a drug in the plasma or blood of a patient following administration of a dose of the drug or form of drug to the patient. T_{max} is the time to the maximum concentration (C_{max}) of a drug in the plasma or blood of a patient following administration of a dose of the drug or form of drug to the patient.

By definition, when a medication is administered intravenously, its bioavailability is 100 percent. However, when a medication is administered via other routes (such as orally), its bioavailability decreases (due to incomplete absorption and first-pass metabolism). More specifically, bioavailability

administration of a standard formulation. Frequently, the "standard formulation" used in assessing bioavailability is the aqueous solution of the drug, given intravenously.

The amount of drug absorbed is taken as a measure of the ability of the formulation to deliver drug to the sites of drug action; obviously—depending on such factors as disintegration and dissolution properties of the dosage form, and the rate of biotransformation relative to the rate of absorption-dosage forms containing identical amounts of active drug may differ markedly in their abilities to make drug available, and therefore, in their abilities to permit the drug to manifest its expected pharmacodynamic and therapeutic properties. The "amount absorbed" is conventionally measured by one of two criteria, either the area under the time-plasma concentration curve (AUC) or the total (cumulative) amount of drug excreted in the urine following drug administration.

A linear relationship exists between the AUC and dose when the fraction of the drug absorbed is independent of dose, and elimination rate (half-life) and volume of distribution are independent of dose and dosage form. However, when AUC is dependent on dose, as occurs when, for example, there is saturable absorption, significant metabolism, or poor solubility of the drug in the GI tract, a non-linear relationship exists between AUC and dose.

In order to compare the relative bioavailability of various forms of creatine and to correct for the slightly different doses of creatine administered with various forms due to the different molecular weights of the salt forms, the AUC plasma uptake values observed for creatine monohydrate and creatine HCl are entered into the following equation to produce a ratio:

$$\frac{(AUC_{SampleA} * Dose_B)}{AUC_{SampleB} * Dose_A}$$

Based on this relationship, the relative bioavailability of creatine HCl to creatine monohydrate is preferably about 1.5 or greater, more preferably about 1.55 or greater, and even more preferably about 1.65 or greater. In one embodiment, the ratio is about 1.70 or greater.

In other words, the relative bioavailability of creatine HCl is preferably about 50 percent greater than creatine monohydrate, more preferably about 55 percent greater than creatine monohydrate and most preferably about 60 percent greater than creatine monohydrate. In one embodiment, the bioavailability of the creatine HCl is at least about 65 percent greater than bioavailability of creatine monohydrate. In another embodiment, the creatine HCl has a bioavailability of at least about 70 percent greater relative to creatine monohydrate.

Creatine HCl Stability

The half-life of other known forms of creatine in blood plasma is short (approximately 1-1.5 hours). Thus, to be effective, the creatine formulation must be able to reach desired blood plasma levels rapidly. In view of the bioavailability of previously known forms of creatine, such desired blood plasma levels can be obtained only by the administration of high doses of creatine, e.g., 5 to 10 g for mean body weights of about 70 kg.

In contrast, the creatine HCl of the invention is able to obtain high blood plasma levels at low doses at least in part due to its increased stability. In addition, due to the overall increase in stability, the creatine HCl of the invention is capable of maintaining a minimal creatine blood serum level

With regard to latent product storage, standard shelf-life according to the FDA is considered to be the time it takes for 10 percent of the starting material to degrade in a given sample. Creatine monohydrate typically exhibits a shelf-life of about one week when stored in aqueous solution at room temperature. In contrast, the creatine HCl of the present invention possesses a shelf-life of about 45 days or greater in aqueous solution. In one embodiment, the shelf-life of the creatine HCl of the invention in aqueous solution is at least about 60 days, preferably at least about 75 days. In another embodiment, the creatine HCl of the invention possesses a shelf-life of about 90 days or greater in aqueous solution.

As will be understood by those of ordinary skill in the art, higher temperatures accelerate degradation of all forms of creatine, including the creatine HCl of the invention. However, when exposed to higher temperatures, creatine monohydrate still degrades at a much higher rate than creatine HCl. In one embodiment, the shelf life of creatine HCl in aqueous solution at a temperature ranging from about 10 to 20 degrees (° C.) higher than room temperature is at least about 14 days, preferably at least about 25 days, and more preferably at least about 30 days. In another embodiment, the shelf life of the creatine HCl at 50° C. is at least about 1 day, preferably at least about 2 days, and more preferably at least about 5 days.

Supplement Forms

Due to its enhanced properties, the effective dose of creatine HCl is much less than other forms of creatine. In order to increase muscle mass and strength, compositions of creatine monohydrate are generally dosed in an amount from about 5 g to about 10 g per 150 pounds body weight. Contrastingly, in one embodiment of the present invention, the effective dose may range from about one quarter teaspoon to about one tablespoon per hundred pounds body weight, more preferably between about one quarter teaspoon to about one teaspoon per hundred pounds body weight, and most preferably between about one quarter teaspoon to about one half teaspoon per hundred pounds body weight.

In this aspect of the invention, the effective dose may range from about 500 mg to about 1500 mg per 100 pounds body weight. For example, in one embodiment, the effective dose may be from about 1500 mg to about 3000 mg for a subject that weighs up to 250 pounds. In one embodiment, the effective dose is from about 2250 mg to about 4500 mg for a subject that weighs over 250 pounds. In another embodiment, the effective dose is from about 750 mg to about 1500 mg per 100 pounds body weight.

In comparison to creatine monohydrate, the effective dose of creatine HCl is at least about 50 percent less than the effective dose of creatine monohydrate. In another embodiment, the effective dose of creatine HCl is at least about 55 percent less than the effective dose of creatine monohydrate. In yet another embodiment, the effective dose of creatine HCl is at least about 60 percent less, preferably at least about 65 percent less, than the effective dose of creatine monohydrate. For example, the effective dose of creatine HCl is preferably about 70 percent less than the effective dose of creatine monohydrate.

In one embodiment of the invention, creatine HCl may be provided in a liquid, gel, or powder form, with powders suitable for mixing with water or other liquids being preferred. These formulations may be added into a beverage. In addition, the creatine HCl may be provided as an ingredient premixed in a beverage. Examples of beverages contemplated by the invention include, but are not limited to, sports drinks and liquid meal replacements.

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