METHOD FOR INCREASING THE RATE AND CONSISTENCY OF BIOAVAILABILITY OF SUPPLEMENTAL DIETARY INGREDIENTS

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ABSTRACT
The present invention relates to a method for increasing the rate of bioavailability of orally administered supplemental dietary ingredients through the process of fine-milling to increase the rate of dissolution of the ingredients. The ingredients to be fine-milled are ingredients suitable for use in supplemental dietary compositions.
METHOD FOR INCREASING THE RATE AND CONSISTENCY OF BIOAVAILABILITY OF SUPPLEMENTAL DIETARY INGREDIENTS

RELATED APPLICATIONS

[0001] The present application is related to and claims benefit of priority to U.S. Provisional Application No. 60/776,325, entitled “Compositions and method for increasing the rate of bioavailability of supplemental dietary ingredients” filed Feb. 23, 2006, the disclosure of which is hereby fully incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention relates to the process of particle milling, micronization, for the purposes of increasing the rate of bioavailability following oral administration of components comprising supplemental dietary compositions. The compositions and methods promote increased rate of bioavailability by increasing the total surface area of poorly soluble particles, thereby increasing the rate of absorption.

BACKGROUND OF THE INVENTION

[0003] Poorly-soluble compounds are described as either sparingly soluble or insoluble in polar or non-polar solvents depending on the hydrophilicity of lipophilicity of said compounds. Many compounds, particularly in the dietary supplement industry, fall into the class of low solubility. This not only presents a problem in terms of bioavailability but also in terms of reducing or preventing toxicity and irregular absorption in the intestinal tract (Shekunov B Y, Chattopadhyay P, Seitzinger J, Huff R. Nanoparticles of poorly water-soluble drugs prepared by supercritical fluid extraction of emulsions. Pharm Res. January 2006; 23(1):196-204). Therefore, it is a challenge to make these compounds, which will be used in a biological system, e.g., orally ingested by a human, such that they will be more readily bioavailable. Various methods have been explored to achieve this in the pharmaceutical industry including chemical methods, physiological procedures, and pharmaceutical methods (Müller R H, Benita S, Böhm B (eds.). Emulsions and Nanosuspensions for the Formulation of Poorly Soluble Drugs, pp 15, 16, 20. Medpharm GmbH Scientific Publishers, Stuttgart, Germany. 1998). As such, it is advantageous to increase the rate of dissolution in a liquid medium or gastric juices as a method to increase bioavailability.

SUMMARY OF THE INVENTION

[0004] The present invention relates to a method for increasing the rate of bioavailability of supplemental dietary ingredients in mammals. The rate of bioavailability is increased via a narrowing of particle size range and a concomitant reduction in the average particle size, improving the immediacy of absorption of said supplemental dietary ingredient. A further aspect of the present invention is to improve the consistency of dissolution, and thus the absorption of orally administered supplemental dietary ingredients.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0005] For the purposes of the present invention, the terms micronization, milling, particle-milling, and fine-milling are used interchangeably, wherein they refer to a technology, process and end-products involved in or leading to a narrowing of particle size range and a concomitant reduction in the average particle size. For the purposes of the present invention, acceptable milled-particle sizes are in the range of from about 1 nanometer to about 500 microns.

[0006] Although it is understood by the inventors that dietary supplements from natural sources must inherently undergo a degree of processing prior to use, as used herein the terms ‘unprocessed’ or ‘regular’ refer the physical state of ingredients or compounds which have not been subjected to a micronization process.

[0007] As used herein, the term ‘bioavailability’ refers to the amount of a substance available at a given site of physiological activity after administration. It is generally assumed that substances administered intravenously have a bioavailability of 100%. Bioavailability of a given substance is affected by a number of factors including but not limited to degradation and absorption of that substance. Orally administered substances are subject to excretion prior to complete absorption, thereby decreasing bioavailability as compared to other administration routes.

[0008] As used herein, the term ‘molecule’ refers to the smallest size attainable of a given substance wherein the chemical properties of said substance are retained. It is understood that such molecules are themselves comprised of smaller atoms, however, the forces required and involved in reductions beyond the molecule scale are not the subject of the present invention.

[0009] As used herein, the term ‘particle’ refers to chunks or clumps of a substance of varying size wherein said chunks or clumps are comprised of varying numbers of molecules of a given substance. By way of example, the term ‘particle of ice’ is used to refer to a block of ice. Said particle of ice is comprised of several individual water molecules. The block of ice may be incrementally broken into smaller chunks or particles of ice still comprised of water molecules.

[0010] As used herein, the term ‘solubility’ refers to the amount of or degree to which a substance or solute will dissolve within a given solvent. Several factors affect the solubility of a given substance. These factors include but are not limited to: specific properties of the solute and the solvent, polarity of the solute, the polarity of the solvent, the temperature and the pressure. The term ‘absolute solubility’, as used herein, refers to the solubility of a given substance under conditions in which time is not a factor, i.e. infinite time. It is understood that a substance may be in ‘suspension’ rather than solution but will appear to be in solution.

[0011] As used herein, the term ‘dissolution’ refers to the process of a solute going into solution or solubilizing. Dissolution is dependent upon several factors including but not limited to: temperature, agitation and surface area of a given particle.

[0012] It is herein understood that, due to the relationship between solubility and dissolution, the amount of a sub-
stance in solution at any given time is dependent upon both dissolution and solubility. Furthermore, it is understood by way of extension that increasing the rate of dissolution of a given substance may act to reduce the time to dissolution of a given solute or substance in a given solvent. However, the absolute solubility of said solute does not increase with infinite time. Thus, increasing the rate of dissolution of a substance will increase the amount of said substance in solution at earlier points in time, thus increasing the rate of bioavailability of said substance at earlier times upon oral administration.

As it relates to this invention, micronization techniques are employed to increase the rate of bioavailability of said poorly soluble supplemental dietary ingredients. The increase in the rate of bioavailability will allow better and quicker compound transfer to the systemic parts of the body following ingestion, and thus increase efficacy of the compositions comprising such supplemental dietary ingredients.

Micronization is a technique which has been used as a method of sizing solid compounds to fine powders. Following a micronization process, said poorly soluble compounds are transformed into fine powders which can then be transformed into suitable, stable and patent-compliant dosage forms. These forms, for the purposes of the present invention are derived for oral administration.

Micronization-technique treated poorly-soluble compounds or dietary supplement ingredients are preferred in the present invention in that they offer an advantage over larger forms of poorly soluble compounds—following micronization, compounds have higher surface area to volume ratio. This provides for, as compared to physically coarse compounds, an ultrafine micronized powder that has a significantly increased total surface area. Mathematically, cross-sectional surface area increases with the square of the radius, while volume increases with the cube of the radius. Therefore, as a particle becomes smaller, the volume of the particle decreases at a faster rate than the surface area leading to an increase in the ratio of surface area to volume. By way of theoretical calculations, decreasing the size of a particle can increase its rate of dissolution via increasing the surface area to volume ratio. In the case of solubility, this increase in relative surface area allows for greater interaction with solvent.

For example, consider 1 cm³ of coarse compound occupying a virtually spherical volume (V), for demonstration purposes, a single particle of any given substance. The surface area (SA) of this 1 cm³ particle is calculated using Formula I to solve for the radius (r). This value for r is used to calculate SA with Formula II:

\[ V = \frac{4}{3} \pi r^3 \]  
(1)

\[ SA = 4\pi r^2 \]  
(2)

Therefore, a particle with V of 1 cm³ has SA of approximately 4.8 cm². If this substance were milled to several particles each having a V of 0.5 mm³, each particle would have SA of approximately 0.03 cm². In this example, the volume of a single 1 cm³ particle could contain 2000 of the particles fine-milled to a size of 0.5 mm³ with a total SA of 2000 particles×0.03 cm² per particle which equals 60 cm² and therefore corresponds to a 60-fold increase in total SA. This increase in total SA would allow for greater access of solvent molecules to solute molecules, thus leading to a greater rate of dissolution.

Micronization or particle-milling for the purposes of the present invention is performed by a variety of methods. Dry milling or nanosuspensions are often made by air jet milling and wet milling in pearl mills and rotor-stator mills as commonly known in the art as part of the micronization process.

Methods of milling particles can also be those such as hammer mills, cryogenic hammer mills, fluid and air jet milling, jaw crushing, and high-pressure dispersion milling. These are methods of medialess milling. Hammer milling produces particles of typically 30-500 microns. At ambient temperatures, rotating hammers which strike the particles repeatedly reduce the particle size to a point where they can pass through a screen having a given mesh size. If required, the process can also be done at lower temperatures in cases where a reduced temperature is required to fracture a given particle.

During the process of jet milling, particles are suspended in flowing streams of air where they are targeted at either themselves or a stationary target. This results in a fine grind with a particle size of typically 1-10 microns being produced.

A further type of medialess milling which may be employed in the present invention is high pressure dispersion milling in which dispersions are pressurized to 10,000-50,000 psi. At this point, the pressure is rapidly released. This release in pressure causes cavitation and grinding. Particles of 0.5 to 1 micron are typically produced via this method (The Aveka Group, Specialists in Particle Processing, Grinding and Classification. www.aveka.com/grinding_and_classification.htm).

In the process known as media milling, balls, pebbles or other media such as sand are added in with material to be ground in order to reduce particle size. The collisions of the media with material to be ground results in the fracture of the large particles into smaller such particles. Using media milling, particles can be milled to average sizes of 0.1 micron with relative ease. Through control of the grinding time and force with which the material is ground, virtually any particle size can be obtained. Media mill can be used with or without any liquids additives, although water or other solvents are commonly used to produce the finest particle.

Until recently, the actual quantification of milling in terms of size distribution and the effects of process variables have been complicated. Mathematical models predicting the size and size distribution of milled particles have been developed (Pierre Chapelle, Nicholas Christakis, Hadi Abou-Chakra, Ian Bridle, M. S. A. Bradley, Mayur Patel, Mark Cross. Computational model for prediction of particle degradation during dilute phase pneumatic conveying: Modeling of dilute phase pneumatic conveying. Advanced Powder Technology, 2004 Vol 15, pp. 31-50) and deemed valid by the demonstrated agreement with laboratory results. For jet milling, for example, it is now known how variables such as feed rate, angle of inlet nozzle and air flow rate affect the process of micronization. This allows for a much greater control over resultant particle size with narrower size distribution.

Examples of mills and techniques for milling particles for the purposes of size reduction are disclosed in e.g.
For the purposes of various embodiments herein disclosed, but not limited to existing embodiments, the process of micronization is referred to as fine-milling. As used herein, fine-milling is a process employing current micronization techniques whereby the size of a particle is reduced to a range between 2 to 50 microns. Preferably, jet milling is used to produce fine-milled particles involving the steps of feeding the material into a hopper. The material to be fine-milled is then gravity fed into a pipe which employs an auger to propagate the material into the jet mill. Utilizing two opposing forces: free vortex resulting from centrifugal force imparted on the particles by the nozzles and drag force, created by the gas-flow as it spirals towards the centre of the mill, the particles are reduced in size as the nozzles are arranged tangentially in the peripheral wall of the grinding chamber. As the particle size is reduced, said particles are drawn to the centre of the mill where they leave the mill via a pneumatic conveyor and are collected in a bag filter. The gas is vented to waste.

Therefore, the present invention is directed at the process of fine-milling of supplemental dietary ingredients leading to a method of increasing the rate of bioavailability following oral administration. The increased rate of dissolution ensures an increased number of molecules in solution in a liquid supplemental dietary composition or gastric juices, thereby improving bioavailability. Since more molecules will be available in a readily absorbable state, and thus bio-absorption prior to excretion for an individual's body, the method of the present invention thereby improves bioavailability.

Moreover, with respect to the small particle size of fine-milled products, there may be an improved taste, flavor-enhancement, texture and palatability of compositions comprising poorly-soluble compounds which have been fine-milled owing to the improved rate of dissolution.

Experiments relating to fine-milling and bioavailability were undertaken by the inventors. Outlines and the result of said experiments are given below.

In order to determine the effect of fine-milling on the dissolution rate, initial testing was performed to examine the rate of dissolution of common supplemental dietary ingredients. For the purposes of this disclosure, the term “regular” as used herein makes reference to non-fine-milled particles.

Experimental Procedure:

100 mL of water was placed into a 250 mL beaker and a magnetic stirrer bar was added to the beaker. The beaker was then placed on a magnetic stirrer was set to constant speed. Increments of 2 g of regular ingredients were quickly added wherein the next increment was added after the previous increment visually appeared to dissolve until the mixture appeared saturated. The time required to dissolve was estimated by visual inspection. Equal amounts of the fine-milled ingredients were then added to the water and the time required to dissolve was estimated by visual inspection. The supplemental dietary ingredients used were Zinc Acetate, L-Arginine base, Creatine Ethyl Ester and Creatine Monohydrate.

Results

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Powder Type</th>
<th>Amount Added (g)</th>
<th>Time taken to dissolve (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc Acetate</td>
<td>Regular</td>
<td>18</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td>Fine-milled</td>
<td>18</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Arginine</td>
<td>Regular</td>
<td>16</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td>Fine-milled</td>
<td>16</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Creatine Ethyl Ester</td>
<td>Regular</td>
<td>22</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td>Fine-milled</td>
<td>22</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Creatine</td>
<td>Regular</td>
<td>2</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Monohydrate</td>
<td>Fine-milled</td>
<td>2</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Table 1 presents the observations made examining the time to dissolve for non-milled and fine-milled ingredients. In all cases, the fine-milled ingredients dissolved faster than the regular ingredients with the exception of Creatine Monohydrate. The Creatine Monohydrate sample appeared to dissolve at the same rate in both the fine-milled and regular formats.

Discussion:

In three of the four cases examined, the fine-milled ingredients took less time to dissolve according to visual inspection. For Zinc Acetate, Arginine and Creatine Ethyl Ester the fine-milled samples dissolved within 10 minutes, whereas the non-milled versions of these ingredients all required greater than 10 minutes. Creatine Monohydrate, which is known to be of relatively low solubility, did not display a difference dependent on particle size.

A second experiment relating to fine-milling and potential increase in bioavailability was conducted. In order to test the capacity of fine-milling to improve the rate bioavailability of substances, a simple test was performed. The test was conceived to mimic various elements involved in the processes of oral administration of a nutritional supplement. The key parameters involved were rate of dissolution and solubility, as it is understood that an ingested nutrient must be dissolved or reduced to a bio-transportable size in order to be utilized biochemically by the body.

Digestion converts complex foods into nutrients usable by cells. As such, digestion can be divided into
distinct processes including ingestion, mechanical digestion, chemical digestion and absorption. Orally consumed substances are first broken down in the mouth by a combination of physical forces (chewing) and salivary enzymes. In the stomach, substances are further broken down by churning and mixing with more enzymes and acid. Partially digested substances then pass to the small intestine where more enzymes complete digestion. In the case of many supplemental dietary ingredients enzymatic digestion does not occur, therefore another method of bioavailability must occur. In the present invention, bioavailability of these substances is improved by fine-milling. The increase in the dissolution rate, it is understood by the inventors, to lead to and increase in bioavailability by increasing the likelihood that a given molecule is absorbed by the body of an individual prior to excretion. In the case of poorly-soluble substances, the substance may be excreted before it is absorbed if it is not fine-milled, thereby decreasing bioavailability. Absorption of digested substances begins in the stomach and occurs mainly in the small intestine and is facilitated by diffusion and active transport. Water is typically an important component of these processes as the enzymatic reactions often require that substances be in solution, e.g., dissolved.

Experimental Procedure

The rates of dissolution and solubility of regular common nutritional supplements were compared to fine-milled versions within a fixed time. The substances tested were whey protein concentrate, creatine monohydrate, L-arginine, and glycine-L-arginine-alpha-ketoisocaproic acid calcium. 100 mL of water was added to a 250 mL beaker and a magnetic stirring bar was placed in the beaker. The beaker was placed on a magnetic stirrer and stirred with low speed. 1 g of a given supplemental dietary ingredient powder was added incrementally to the beaker with the stirring speed constant until the solution visually appeared saturated. The solution was filtered by gravity through a pre-weighed filter paper (Whatman 41, particle retention 20-25 µm). The filter paper was allowed to dry completely and weighed to measure the amount of substance remaining on the filter paper.

Table 2 presents the results of the solubility test designed to mimic bioavailability to compare regular substances to their fine-milled counterparts. The 'Fold Change' represents the change in the amount of substance unable to pass through the filter as calculated by the amount of unfiltered regular substance divided by the amount of filtered fine-milled substance and represents the potential theoretical improvement in bioavailability. The approximate molecular weight is also shown for comparison.

Discussion

In analogy to digestion, the experimental test system employed herein assesses bioavailability in relation to rate of dissolution and solubility on the premise that unsolved substances will be excreted from the body of an individual and not be absorbed. The mixing of the samples with a magnetic stir bar is analogous to mechanical digestion in the mouth and stomach. Passage of the samples through the filter paper is also analogous to the absorption of nutrients through cell membranes. In both cases (digestion and the current experimental test system), the rate of dissolution and solubility are factors. It is important to understand that molecules in solution are individual molecules. Those substances in powder form, and by extension substances in solid forms derived from powdered substances such as tablets and capsules, typically must be dissolved before they can effectively pass through a membrane. Furthermore, it is important to understand that substances in powder form are present in chunks or clumps of molecules with a distribution of particle sizes. The goal of micronization or milling for the purposes of the present invention is to reduce the average particle size, ideally to the smallest size attainable, e.g., a single molecule. It is understood that the absolute solubility is not affected by reduced particle size whereas the rate of dissolution is drastically increased or improved by a fine-milling process.

Therefore, sample material remaining on the filter paper represents two non-mutually exclusive cases. One case is that soluble molecules are too large to pass through the pores of the filter. In this case, none of the solubilized molecules will pass through the pores of the filter paper. The second case is that the material represents insoluble or yet-undissolved sample material present as particles that are too large to pass through the pores of the filter. It is understood that insoluble particles comprised of numerous single molecules in suspension may be deemed to be in solution by the naked eye under visual inspection, however, they are in fact not actually in solution.

In all cases the fine-milled samples passed through the filter paper more readily and effectively than did the regular samples, i.e. more of the regular samples remained on the filter than the fine-milled samples. It was also observed that in all cases the regular samples took more time to filter than the fine-milled samples (data not shown). These data suggest that the dissolution rate of the substances was increased by fine-milling via decreasing average particle size.

It is interesting to note that the ‘Fold Change’ appears to be correlated to two parameters. The substance that was least soluble (creatinine) showed the most significant improvement (19-fold), while the most soluble (glycine-L-arginine-alpha-ketoisocaproic acid calcium and L-arginine) showed the least improvement (1.4-fold). Also, the molecular weight may contribute to the efficacy afforded by fine-milling as evidenced by the lowest molecular weight sub-

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Powder Type</th>
<th>Max Amount Dissolved (g)</th>
<th>Dry Powder On Filter (g)</th>
<th>Fold Change</th>
<th>Approx. Molecular Mass (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whey Protein</td>
<td>Regular</td>
<td>12</td>
<td>0.79</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fine-milled</td>
<td>12</td>
<td>0.15</td>
<td>5.3</td>
<td>149</td>
</tr>
<tr>
<td>Creatine</td>
<td>Regular</td>
<td>2</td>
<td>0.19</td>
<td>19.0</td>
<td>418</td>
</tr>
<tr>
<td></td>
<td>Fine-milled</td>
<td>2</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Monohydrate glycine-L-arginine-alpha-ketoisocaproic acid calcium</td>
<td>Regular</td>
<td>18</td>
<td>0.42</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fine-milled</td>
<td>18</td>
<td>0.31</td>
<td>1.4</td>
<td>174</td>
</tr>
</tbody>
</table>

Table 2 presents the results of the solubility test designed to mimic bioavailability to compare regular substances to their fine-milled counterparts. The 'Fold Change' represents the change in the amount of substance unable to pass through the filter as calculated by the amount of unfiltered regular substance divided by the amount of unfiltered fine-milled substance and represents the potential theoretical improvement in bioavailability. The approximate molecular weight is also shown for comparison.
stance (creatine) showing the largest improvement. It should be noted that the molecular weight of the whey protein concentrate is not listed as it is a distribution of multiple protein fractions but the average is most likely significantly larger than the other substances tested and does not therefore likely follow this second potential correlate. However, the theoretical smallest size of a protein particle is the size of an individual amino acid or L-arginine, which constitutes the protein. Therefore, significant improvement for whey protein (5.3-fold) is not surprising.

Further to improving bioavailability, it is understood by the inventors that increased solubility resulting from fine-milling will lead to improvements in characteristics in which solubility and reduced particle size likely play a role. For example, a fine-milled ingredient used in the formulation of a nutritional bar will be less course in texture and more palatable than a non-fine-milled ingredient. Likewise, a fine-milled ingredient used in the formulation of a nutritional beverage will be less ‘gritty’ due to reduced particle size and increased rate of dissolution.

In order to expand on the results of the aforementioned experiments, a kinetic experiment was conducted to examine the change in the dissolution rate over short time periods.

Experimental Procedure

Following the same method as immediately above experiment, the solubility of non-milled or regular Creatine Monohydrate was compared to that of fine-milled Creatine Monohydrate. 1 g of sample was added to 50 ml. water in a flask with a magnetic stir bar on a stirrer set at constant speed. Separate samples were filtered at 1 and 5 minutes. The pre-weighed filter papers (Whatman 41, particle retention 20-25 µm) were allowed to dry and the amount of sample remaining on the filter paper was determined.

Results

1-Minute Interval:

Regular Creatine Monohydrate

- weight of empty filter paper=2.30 g
- weight of filter paper after=2.62 g
- weight of unfiltered sample=0.32 g
- time to filter=2 minutes

Fine-Milled Creatine Monohydrate

- weight of empty filter paper=2.26 g
- weight of filter paper after=2.59 g
- weight of unfiltered sample=0.33 g
- time to filter=3.5 to 4 minutes

5-Minute Interval:

Regular Creatine Monohydrate

- weight of empty filter paper=2.29 g
- weight of filter paper after=2.69 g
- weight of unfiltered sample=0.40 g
- time to filter=1 to 1.5 minutes

Fine-Milled Creatine Monohydrate

- weight of empty filter paper=2.22 g
- weight of filter paper after=2.49 g
- weight of unfiltered sample=0.27 g
- time to filter=2 to 2.5 minutes

Discussion

At the 1-minute interval, essentially equal amounts of regular and fine-milled creatine were retained by the filter paper (0.33 g and 0.32 g). However, at the 5-minute interval, more of the regular creatine was retained by the filter paper than fine-milled creatine (0.40 g versus 0.27 g). This suggests that more of the fine-milled creatine was able to pass through the filter paper after 5 minutes i.e. more was in solution. The time to filter was consistently longer for the fine-milled samples. This may be explained by the ability of the smaller fine-milled particles to become entombed within the pores of the filter paper, thus slowing the rate of solvent passage. It is commonly known in the area of column chromatography that molecules too large to enter the pores of the separation matrix do not usually impede the rate of flow of solvent, while molecules small enough to enter the porous matrix become trapped and may impede the solvent flow rate.

In the present invention as a first example embodiment of a supplemental dietary composition that comprises the use of a ketoacid in combination with one or more monobasic amino acids as disclosed in U.S. application Ser. No. 11/595,170 incorporated herein in its entirety by reference, is provided. With respect to the instant composition, poorly-soluble monobasic, dibasic, and tribasic amino acids and ketoacid are treated fine-milled to increase solubility and thus bioavailability. An embodiment comprising present invention is set forth in greater detail in Example 1.

Furthermore, the present disclosure provides a second example embodiment of a supplemental dietary composition that comprises the use of a ketoacid in combination with one or more cationic or dibasic amino acids as disclosed in U.S. Pat. No. 6,100,287 incorporated herein in its entirety by reference wherein at least one of the components is fine-milled. With respect to this composition, cationic and dibasic amino acids and ketoacids are fine-milled to increase solubility, and thus bioavailability. An embodiment comprising present invention is set forth in greater detail in Example 2.

Additionally, the present disclosure provides a third example embodiment of a supplemental dietary composition that comprises the use of Creatine-Ethyl Ester, Creatine Alpha-ketoglutarate and Alpha-lipoic acid as disclosed in U.S. application Ser. No. 11/399,885 incorporated herein in its entirety by reference. With respect to this composition, the components which comprise this example are fine-milled to increase solubility and thus bioavailability. An embodiment comprising present invention is set forth in greater detail in Example 3.

An aspect of the present invention is the inclusion of fine-milled supplemental dietary ingredients as part of a greater composition comprising like and additional ingredients. As part of the greater composition the fine-milled ingredients may be present in ratios from about 50:1 to about 4:1.
Although the following examples illustrate the practice of the present invention in three of its embodiments, the examples should not be construed as limiting the scope of the invention. Other embodiments will be apparent to one skilled in the art from consideration of the specification and the following examples.

**EXAMPLE 1**

In Powdered Form

A dietary supplement comprising the following ingredients per serving is prepared for consumption one time per day per individual:

- about 2.0 g of fine-milled Glycine, about 2.0 g of regular Glycine, about 5.0 g of fine-milled L-Arginine, about 5.0 g of regular L-Arginine, about 3.0 g of fine-milled Calcium-KIC, about 3.0 g of regular Calcium-KIC, about 2.0 g of Maltodextrin, about 1.5 g of Citric Acid, about 80 g of Dextrose, about 0.5 g of Sodium Citrate, about 0.3 g of Sodium Gluconate, about 0.4 g of Polyvinylpyrrolidone, about 0.1 g of Modified Food Starch, about 0.4 g of Syrup Solids, about 0.03 g of Gum Acacia, about 0.05 g of Silicon Dioxide, about 0.027 g of Acesulfame-Potassium, and about 0.01 g FD&C Red #40.

Preferably, the nutritional composition is consumed in accordance with the following directions:

**Directions:** As a dietary supplement, take one serving (35 g) of product before a high-intensity workout. Mix in a shaker cup with 8 oz. of water. Swallow immediately. Consume ten 8 oz. glasses of water daily for general good health.

In Caplet Form

A dietary supplement comprising the following ingredients per serving is prepared for consumption one time per day per individual:

- about 2.0 g of fine-milled Glycine, about 2.0 g of regular Glycine, about 5.0 g of fine-milled L-Arginine, about 5.0 g of regular L-Arginine, about 3.0 g of fine-milled Calcium-KIC, about 3.0 g of regular Calcium-KIC, about 1.5 g Microcrystalline Cellulose, about 0.88 g Hydroxypropyl Cellulose, about 0.6 g Coating [Partially Hydrolyzed Polyvinyl Alcohol, Polyethylene Glycol, Hydroxypropyl Cellulose, Titanium Dioxide, Soy Lecithin, Polysorbate 80, Colourings], about 0.176 g Croscarmellose Sodium, about 0.176 g Stearic Acid, about 0.088 g Magnesium Stearate, about 0.044 g Silica and about 0.43 mg Acesulfame-potassium.

Preferably, the nutritional composition is consumed in accordance with the following directions:

**Directions:** As a dietary supplement, take one serving (8 caplets) per day before a high-intensity workout. Do not exceed one serving in a 24-hour period. Consume ten 8 oz. glasses of water daily for general good health.

**EXAMPLE 2**

A dietary supplement comprising the following ingredients per serving is prepared for consumption one to four times per day per individual:

- about 7.5 g Leucine, about 0.0004 g fine-milled Leucine, about 0.05 g Calcium-KIC, about 0.45 g Hydroxypropyl Cellulose, about 1.75 g Microcrystalline Cellulose, about 0.18 g Croscarmellose Sodium, about 0.03 g Calcium Carbonate, about 0.12 g Vegetable Stearines, about 0.06 g Magnesium Stearate, about 0.06 g Silica, about 0.03 g Magnesium Silicate, about 0.306 g Coating [Polyvinyl Alcohol, Polyethylene Glycol, Talc, Titanium Dioxide, Riboflavin, Soy Lecithin, Polysorbate 80, Hydroxypropyl methylcellulose, Coloring], about 0.001 g Lysine Ketaisocaproyl Acid and about 0.0004 g Sweeteners.

Preferably, the nutritional composition is consumed in accordance with the following directions:

**Directions:** As a dietary supplement, take 1 serving (6 caplets) first thing in the morning. On workout days, take 1 serving immediately before your workout. For extreme results, take twice a day. Consume ten 8 oz. glasses of water daily for general good health.

**EXAMPLE 3**

A dietary supplement comprising the following ingredients per serving is prepared for consumption one to four times per day per individual:

- about 2.0 g regular Creatine-Ethyl Ester HCl, about 0.001 g fine-milled Creatine-Ethyl Ester HCl, about 0.1 g Creatine Alpha-ketoglutarate and about 0.1 g Alpha-lipoic Acid.

Preferably, the nutritional composition is consumed in accordance with the following directions:

**Directions:** As a dietary supplement, take two servings per day, e.g., one serving (2 caplets) in the morning and one serving (2 caplets) in the afternoon. Consume 10 8 oz. Glasses of water daily. To maximize results, use in conjunction with weight training.

**What is claimed:**

1. A method for increasing the rate of bioavailability of a supplemental dietary ingredient in a mammal, the method comprising the step of:
   - fine-milling said ingredient such that, upon administration of said fine-milled ingredient to said mammal, the immediacy of absorption of said supplemental dietary ingredient in said mammal is improved as compared to an immediacy of absorption of said ingredient when said ingredient is in a regular form.
   - The method of claim 1, whereby the improved immediacy of absorption is the result of an increased rate of dissolution of said supplemental dietary ingredient in said mammal, thereby increasing the rate of bioavailability of said supplemental dietary ingredient.
   - The method of claim 1, wherein said fine-milled supplemental dietary ingredient is suitable to be orally administered.
   - The method of claim 1, further comprising the step of:
     - providing said fine-milled supplemental dietary ingredient in a composition, the composition including said ingredient in a regular form.
   - The method of claim 1, wherein the ratio of regular form to fine-milled form of said supplemental dietary ingredient is from about 5:1 to about 10,000:1.
6. The method of claim 1, wherein said fine-milled particles have an average size range of between from about 2 to about 50 microns.

7. A method for improving the consistency of the rate of digestive absorption of a supplemental dietary ingredient in a mammal, the method comprising the step of:

    fine-milling said ingredient so as to improve a uniformity of particles sizes of said ingredient, such that, upon administration of said fine-milled ingredient to said mammal, the consistency of the rate of digestive absorption is improved as compared to a rate of digestive absorption of said ingredient in regular form due to said improved uniformity of the particle size.

8. The method of claim 7, wherein said fine-milled particles have an average size range of between about 2 to about 50 microns.

9. A method for manufacturing a supplemental dietary composition suitable for ingestion by a mammal, the method comprising the step of:

    providing in the supplemental dietary composition an ingredient, the ingredient being fine-milled such that, upon administration of said fine-milled ingredient to said mammal, a rate of bioavailability of said ingredient is improved as compared to a rate of bioavailability of said ingredient when said ingredient is in a regular form.

10. The method of claim 9, wherein said supplemental dietary composition having said ingredient is suitable to be ingested orally.

11. The method of claim 9, further comprising the step of providing in the supplemental dietary composition said ingredient in a regular form.

12. The method of claim 11, wherein the ratio of regular form to fine-milled form of said ingredient is from about 5:1 to about 10,000:1.

13. The method of claim 9, wherein said fine-milled ingredient includes particles having an average size range between about 2 and about 50 microns.

14. A method for manufacturing a supplemental dietary composition suitable for ingestion by a mammal, the method comprising the step of:

    providing in the supplemental dietary composition an ingredient, the ingredient being fine-milled such that, upon administration of said fine-milled ingredient to said mammal, an immediacy of absorption of said ingredient is improved as compared to an immediacy of absorption of said ingredient when said ingredient is in a regular form.

15. The method of claim 14, wherein said supplemental dietary composition having said ingredient is suitable to be ingested orally.

16. The method of claim 14, further comprising the step of providing in the supplemental dietary composition said ingredient in a regular form.

17. The method of claim 16, wherein the ratio of regular form to fine-milled form of said ingredient is from about 5:1 to about 10,000:1.

18. The method of claim 14, wherein said fine-milled ingredient includes particles having an average size range between about 2 and about 50 microns.

19. A method for manufacturing a supplemental dietary composition suitable for ingestion by a mammal, the method comprising the step of:

    providing in the supplemental dietary composition an ingredient, the ingredient being fine-milled such that, upon administration of said fine-milled ingredient to said mammal, a rate of dissolution of said ingredient is improved as compared to a rate of dissolution of said ingredient when said ingredient is in a regular form.

20. The method of claim 19, wherein said supplemental dietary composition having said ingredient is suitable to be ingested orally.

21. The method of claim 19, further comprising the step of providing in the supplemental dietary composition said ingredient in a regular form.

22. The method of claim 21, wherein the ratio of regular form to fine-milled form of said ingredient is from about 5:1 to about 10,000:1.

23. The method of claim 19, wherein said fine-milled ingredient includes particles having an average size range between about 2 and about 50 microns.

24. A method for manufacturing a supplemental dietary composition suitable for ingestion by a mammal, the method comprising the step of:

    providing in the supplemental dietary composition an ingredient, the ingredient being fine-milled such that, upon administration of said fine-milled ingredient to said mammal, a consistency of the rate of digestive absorption of the ingredient is improved as compared to a consistency of the rate of digestive absorption of the ingredient when said ingredient is in a regular form.

25. The method of claim 24, wherein said supplemental dietary composition having said ingredient is suitable to be ingested orally.

26. The method of claim 24, further comprising the step of providing in the supplemental dietary composition said ingredient in a regular form.

27. The method of claim 26, wherein the ratio of regular form to fine-milled form of said ingredient is from about 5:1 to about 10,000:1.

28. The method of claim 24, wherein said fine-milled ingredient includes particles having an average size range between about 2 and about 50 microns.

29. A method for manufacturing a supplemental dietary composition suitable for ingestion by a mammal, the method comprising the step of:

    providing in the supplemental dietary composition an ingredient, the ingredient being fine-milled such that a uniformity of particles sizes of said ingredient is improved as compared to a uniformity of particles sizes of said ingredient when said ingredient is in a regular form.

30. The method of claim 29, wherein said supplemental dietary composition having said ingredient is suitable to be ingested orally.

31. The method of claim 29, further comprising the step of providing in the supplemental dietary composition said ingredient in a regular form.

32. The method of claim 31, wherein the ratio of regular form to fine-milled form of said ingredient is from about 5:1 to about 10,000:1.

33. The method of claim 29, wherein said fine-milled ingredient includes particles having an average size range between about 2 and about 50 microns.
34. A supplemental dietary composition suitable for ingestion by a mammal, comprising:
    a fine-milled ingredient which, upon administration of said fine-milled ingredient to said mammal, has a rate of bioavailability that is improved as compared to a rate of bioavailability of said ingredient when said ingredient is in a regular form.
35. The method of claim 34, wherein said supplemental dietary composition having said ingredient is suitable to be ingested orally.

36. The method of claim 34, further comprising the step of providing in the supplemental dietary composition said ingredient in a regular form.
37. The method of claim 36, wherein the ratio of regular form to fine-milled form of said ingredient is from about 5:1 to about 10,000:1.
38. The method of claim 34, wherein said fine-milled ingredient includes particles having an average size range between about 2 and about 50 microns.

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