Profiles of Drug Substances, Excipients, and Related Methodology Volume 34

Profiles of
DRUG SUBSTANCES, EXCIPIENTS, AND RELATED METHODOLOGY

VOLUME 34

Edited by

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Profiles of
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VOLUME 34

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PREFACE TO VOLUME 34

The comprehensive profiling of drug substances and pharmaceutical excipients as to their physical and analytical characteristics remains at the core of pharmaceutical development. As a result, the compilation and publication of comprehensive summaries of physical and chemical data, analytical methods, routes of compound preparation, degradation pathways, uses and applications, *etc.*, have always been a vital function to both academia and industry.

As the science of pharmaceutics grows and matures, the need for information similarly expands along new fronts and causes equivalent growth in the vehicles where investigators find the information they need. The content of the ***Profiles*** series has expanded to meet this need, with chapters falling into one or more of the following main categories:

1. Comprehensive profiles of a drug substance or excipient
2. Physical characterization of a drug substance or excipient
3. Analytical methods for a drug substance or excipient
4. Detailed discussions of the clinical uses, pharmacology, pharmacokinetics, safety, or toxicity of a drug substance or excipient
5. Reviews of methodology useful for the characterization of drug substances or excipients
6. Annual reviews of areas of importance to pharmaceutical scientists

As it turns out, all of the chapters in the current volume are comprehensive in nature, and provide detailed profiles of the drug substances involved. Volumes in the recent past have contained reviews of methodology, and it is anticipated that future volumes in the of the ***Profiles*** series will contain similar reviews, as well as other types of review articles that summarize the current state in a particular field of pharmaceutics. As always, I welcome communications from anyone in the pharmaceutical community who might want to provide an opinion or a contribution.

Harry G. Brittain

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Excipients, and Related Methodology

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CHAPTER 1

Creatine Monohydrate

Somnath Singh and **Alekha K. Dash**

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1. HISTORY AND THERAPEUTIC ASPECTS

Creatine was discovered in 1832 by a French scientist, Michel Eugene Chevreul, who extracted a new organic constituent from meat and named it creatine after the Greek word for flesh, *Kreas*. Justus von Liebig, in 1847, confirmed that creatine was a regular constituent of animal flesh. In the mid-1880s, creatinine was discovered in the urine, and later researchers speculated that creatinine was derived from creatine and was related to total muscle mass. In the late 1920s, scientists found that the intramuscular stores of creatine can be increased by ingesting creatine in higher than normal amounts. Phosphocreatine (PCr), the phosphorylated form of creatine, was discovered in 1927 and found to be involved in exercise energy expenditure. Creatine kinase, the enzyme which catalyzes PCr, was discovered in 1934 [1].

Although creatine's influence on physical performance has been well documented since the early twentieth century, it came into public view following the 1992 Olympics in Barcelona, when several newspapers reported about the use of creatine by several gold medalists. Creatine supplements designed for strength enhancement were not commercially available until 1993 when a company called EAS (Experimental and Applied Sciences) introduced the compound to the sports nutrition market under the name Phosphagen. Since that time, numerous creatine supplements have been introduced, with the most notable advancements coming in 1998, with the launch of the first creatine–carbohydrate–alpha lipoic acid supplement, Cell-Tech, by MuscleTech Research and Development, and in 2003 with the introduction of the first creatine ethyl ester supplements. To date, the most extensively researched and proven brand-name creatine supplement is Cell-Tech [2], which remains one of the most-used creatine supplements in the world.

Creatine ethyl ester is also becoming a widely used form of creatine, with many companies now carrying both creatine monohydrate-based supplements and creatine ethyl ester supplements. Creatine monohydrate ($400 million in annual sales in the United States alone) still easily outsells all other forms of creatine [3].

Creatine in its free or phosphorylated form plays an important role in the regulation and homeostasis of muscle energy metabolism [4]. Its popular role in sports performance enhancement is well documented [5–7]. Recently, creatine has been shown to occur throughout the brain, affecting energy metabolism by working as a neuromodulator [8]. Nervous tissue and the role of creatine supplementation are rapidly garnering more attention [9, 10]. Creatine is being looked at for its neuroprotective effects [11] because high energy phosphate metabolism plays a critical role in progression of neurodegenerative diseases. Huntington's disease [12, 13], Parkinson's disease, and amylotrophic lateral sclerosis [14–17] have all been investigated and appear to be beneficially affected by the consumption of creatine. While creatine may directly improve bioenergetic defects, it may also benefit other pathophysiological mechanisms associated with Huntington's disease. The major source of energy in the brain is ATP, which is tightly coupled to creatine and PCr levels within the cell. Creatine is shuttled across membranes via a sodium-dependent creatine transporter protein (CreaT) [18], which regulates tissue levels in response to low dietary intake or high endogenous creatine levels. Creatine kinase catalyzes the reversible transfer of a phosphoryl group from PCr to ADP, forming ATP. Thus, creatine offsets energy depletion by forming PCr, which provides a spatial energy buffer to rephosphorylate ADP to ATP at cellular sites of needed energy consumption and in the reversible reaction forming PCr and ADP from creatine and ATP [19]. Thereby, augmenting creatine levels in HD may therefore help to prevent reduced energy stores

and improve neuronal function. Another potential neuroprotective mechanism of creatine supplementation is the ability of PCr to stimulate synaptic glutamate uptake and thereby reduce extracellular glutamate [20]. In addition, creatine has also been reported to act as an antioxidant, scavenging reactive oxygen species [21].

Moreover, there are a number of researches using creatine in the treatment of various clinically relevant diseases such as arthritis [22], congestive heart failure [23], gyrate atrophy [24], disuse atrophy [25], McArdles disease [26], mitochondrial diseases [27, 28], and muscular dystrophy [29]. The aging process is associated with a reduction in total skeletal muscle mass and strength. The increase in total muscle creatine and PCr in response to dietary creatine monohydrate supplementation is higher in those with lower muscle concentration [30].

2. DESCRIPTION

2.1. Nomenclature

2.1.1. Chemical name

N-(Aminoiminomethyl)-*N*-methylglycine; *N*-amidinosarcosine; (α-methylguanido) acetic acid; *N*-methyl-*N*-guanylglycine; methylglycocyamine

2.1.2. Generic name

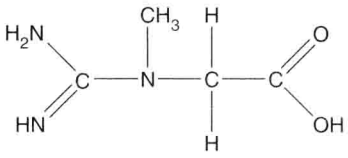
Creatine

2.2. Formulae

2.2.1. Empirical formula, molecular weight, CAS number

$C_4H_9N_3O_2$, 131.133 g/mol, CAS 57-00-1

2.2.2. Structural formula



2.3. Elemental composition[31]

The calculated elemental composition of creatine is as follows:

Carbon	36.64%
Hydrogen	6.92%

Nitrogen	32.04%
Oxygen	24.40%

2.4. Appearance, color and odor

Creatine is a white, crystalline, and odorless powder, which forms clear and colorless solution in water.

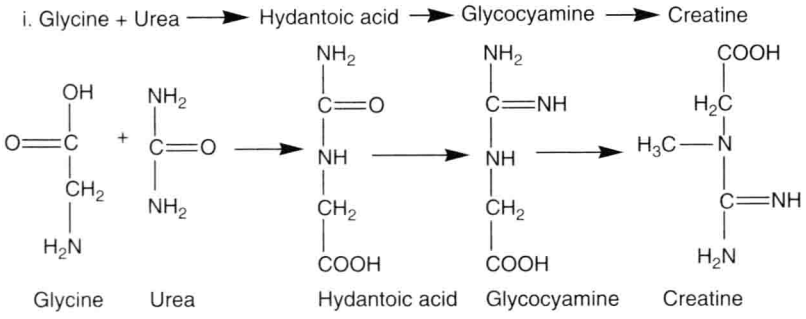
2.5. Pharmaceutical dosage forms

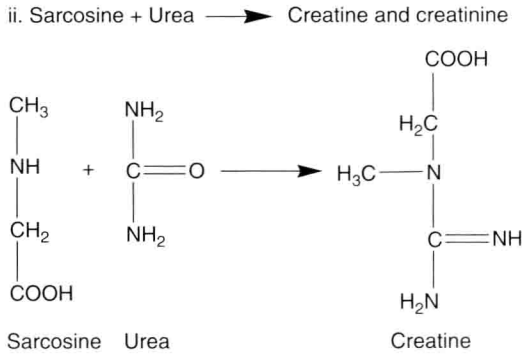
Table 1.1 shows the various dosage forms of creatine manufactured by various companies under different brand names:

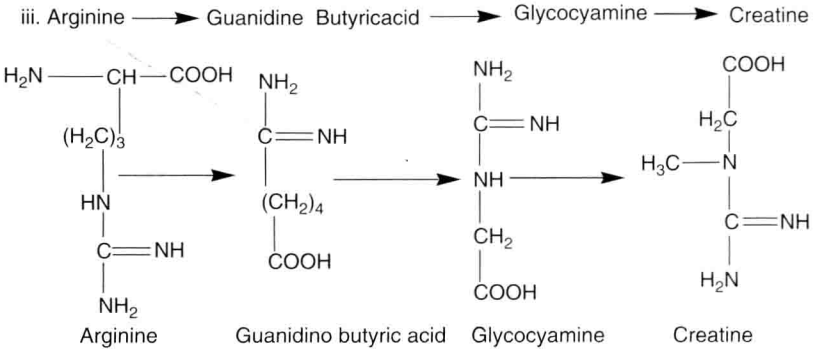
3. SYNTHESIS

Creatine is synthesized in the liver and kidneys and released into the blood stream to be taken up into muscle cells via a protein-based transport system. The liver produces creatine in a two step process: (1) Glycine and arginine are reacted to form guanidinoacetate and ornithine, and then (2) guanidinoacetate is methylated to creatine and released into the blood. The transport protein on the cell membrane has a high affinity for creatine and easily transports it into the cell.

Early researchers used creatine extracted from animal flesh, which was an expensive process. Today, commercial creatine is produced through chemical synthesis, which uses various muscle-related compounds as the principal starting materials as shown below [32]:







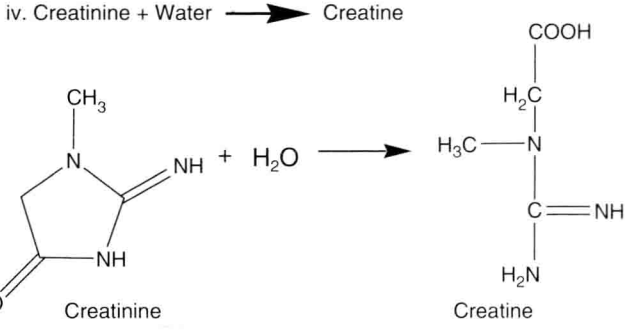


Figure 1.1 shows the biosynthesis of creatine using three amino acids as starting materials [33]. L-Argininеglycine amidinotransferase (AGAT) catalyzes reaction 1, which is the rate-limiting step in the creatine biosynthesis. AGAT expression is also reduced by the presence of creatine,

TABLE 1.1 List of different dosage forms of creatine available under various brand names

Chemical form	Brand name	Dosage form	Company
Micronized Creatine	AST Micronized Creatine	Powder	AST Sports Science
Creatine Monohydrate	Creatine Monohydrate Powder	Powder	ProLab
Creatine Monohydrate	American Creatine Powder	Powder	American Sports Nutrition
Creatine Monohydrate	Pure Creatine Monohydrate	Powder	Inter-Sport Technology
Creatine Monohydrate	IST Pure Creatine	Powder	Optimum Nutrition
Creatine Monohydrate	Mega Creatine Fuel	Capsule	Twin Lab
Creatine	Cell Pro	Powder	Universal Nutrition
Creatine Monohydrate	Cell-Tech	Powder	Muscle Tech
Creatine Monohydrate	ATP Advantage Creatine Serum	Liquid (sublingual)	Muscle Marketing USA
Micronized Creatine	Creatine Effervescent	Effervescent powder	ISS Research Monohydrate
Creatine Monohydrate	Creatine Edge powder	Effervescent	FSI Nutrition
Di-Creatine Citrate	Creatine Clear	Effervescent powder	FSI Nutrition
Creatine Monohydrate	Betagen	Powder	EAS
Creatine	Creatine Gum	Chewing Gum	NuCare

which raises concerns that prolonged creatine supplementation might inhibit endogenous creatine synthesis for an indefinite period of time. This synthetic scheme shows that at last, glycine is completely incorporated into the creatine backbone while arginine and methionine only contribute side groups.

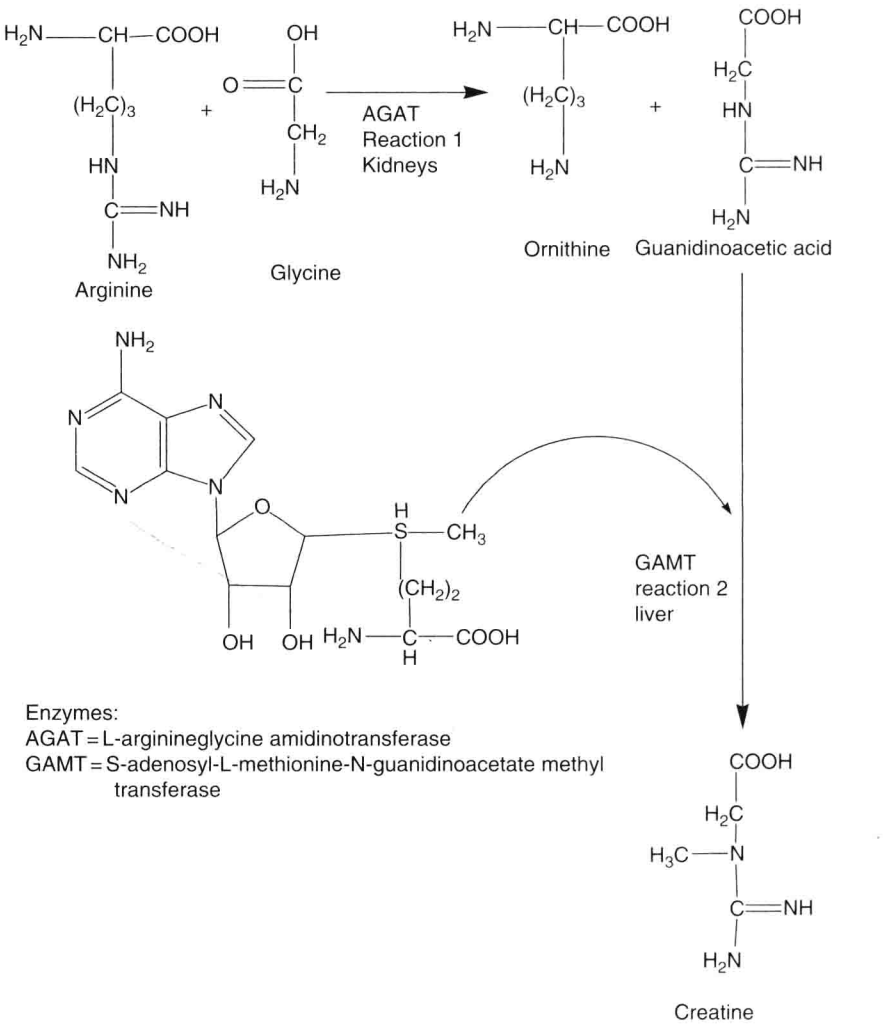


FIGURE 1.1 Synthesis of creatine from amino acids.

4. PHYSICAL PROPERTIES

4.1. Infrared spectrum

Figure 1.2 shows the infrared absorption spectrum [34] of creatine measured on dispersive instruments in carefully selected solvents, and hence may differ in detail from measurements on a FTIR instrument or in other chemical environments [35]. No band appears at 3520 cm^{-1}, which could be due to dimerization of carboxylic acid groups caused by strong hydrogen bonds between OH group of one carboxylic acid and C=O