

# Comparative Characteristics of Dosage Forms of $\alpha$ -Lipoic Acid

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**Abstract.**  $\alpha$ -Lipoic acid is a fatty acid, which in its physiological effect is on a par with vitamins and minerals, is a vitamin-like substance (vitamin N). A review of clinical trials of the effectiveness of  $\alpha$ -lipoic acid in evidence-based diseases is presented. It is proved that the main indication for the use of  $\alpha$ -lipoic acid is diabetes mellitus and complications associated with impaired glucose metabolism, including neuropathy, comprising children and adolescents. In addition,  $\alpha$ -lipoic acid can be used for medicinal purposes and for a number of other diseases.  $\alpha$ -Lipoic acid is an active substance with "critical bioavailability": when introduced into the interior, its inter- and intra-individual plasma levels can vary significantly. Therefore, the therapeutic effectiveness of lipoic acid preparations largely depends on its form. A comparative characteristic of solid dosage forms of  $\alpha$ -lipoic acid according to pharmacokinetic and clinical indicators is given. It was shown that the pharmacokinetic indices of the solid forms of  $\alpha$ -lipoic acid practically do not differ, and the bioavailability of all forms is in the range of 30-60%. The advantages (for manufacturers and consumers / patients) and the disadvantages of  $\alpha$ -lipoic acid drugs in solid forms - capsules and tablets are shown. Results proving the best therapeutic effect of  $\alpha$ -lipoic acid in micellar form are presented.

## 1 Introduction

Lipoic acid, thioctic acid (Thioctic acid is the internationally accepted name for the substance), 5- (2,3-dithiacyclopentyl) pentanoic acid, 6,8-dithiocanoic, 1,2-dithiolan-3-pentanoic acid is a fatty acid, a natural sulfur-containing compound. It was first isolated in 1951 in crystalline form from the lipid extract of the liver of cattle L. Reed and synthesized in 1953. By now, more than ten methods for its synthesis have been developed [10].  $\alpha$ -Lipoic acid is found in some products - in red meat, liver, green vegetables, potatoes, yeast; in a smaller amount - in spinach, broccoli, tomatoes, peas, Brussels sprouts, mainly in the form of strong complexes with protein. In addition,  $\alpha$ -lipoic acid can be synthesized in human cells de novo as a result of a number of biochemical processes in the liver and other tissues. The endogenous level of  $\alpha$ -lipoic acid of a healthy person is from 1 ng / ml to 25 ng / ml. Its synthesis decreases with the age, as well as in chronic diseases, including diabetes mellitus and its complications, for example, diabetic neuropathy [27].

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Available experimental data and results of clinical studies confirm the high therapeutic potential of  $\alpha$ -lipoic acid in various fields of medicine, due to its basic biological properties and metabolic effects [11, 25]. The main indication for the use of  $\alpha$ -lipoic acid is diabetes mellitus and complications associated with impaired glucose metabolism, including neuropathy, comprising children and adolescents [2, 3, 29]. Additionally, it can be noted that  $\alpha$ -lipoic acid helps to reduce the dependence of patients with diabetes on insulin.

Also,  $\alpha$ -lipoic acid can be used for medicinal purposes and for a number of other diseases. So, when considering the causes of the development of chronic fatigue syndrome, some researchers admit a possible role in changing the level of free radicals, which suggests the possibility of using antioxidant therapy. A clinical study (Canada, 2014-2016) found a positive effect of  $\alpha$ -lipoic acid and other antioxidants in the treatment of this syndrome [12]. Moreover, the difference between lipoic acid and other fatty acids is that its antioxidant properties are preserved in both aqueous and fatty media; both in oxidized and in reduced forms. This distinguishes it from the water-soluble antioxidant vitamin C and the fat-soluble antioxidant vitamin E [21]. The clinical study proved the effectiveness of  $\alpha$ -lipoic acid at all stages of alcoholic liver disease, manifested by a decrease in the severity of hepatocyte fatty degeneration and histological activity index [4]. It has been confirmed that the use of  $\alpha$ -lipoic acid (Espa-Lipon preparation) is a scientifically sound and effective method for the treatment of cognitive and asthenic disorders [5, 28]. According to the results of clinical observation of patients with moderate and severe ischemic stroke, it was shown that the severity of neurological deficit among patients who received standard treatment with Berlithion  $\alpha$ -lipoic acid decreased to a greater extent than in those who received only standard treatment [20].

Thus,  $\alpha$ -lipoic acid, being a natural antioxidant, affects cellular metabolism at various levels. High efficiency, good tolerance, the absence or low severity of side effects are factors that determine its choice in the treatment of patients with chronic liver diseases, diabetes mellitus, with various intoxications, as well as lesions of the peripheral nervous system. However, the effectiveness of a drug depends to a large extent on its form and biopharmaceutical properties, which do not provide optimal absorption and bioavailability, which ultimately can have a significant influence on the pharmacotherapeutic effect until it is lost [19].

The aim of the work was to study the pharmacokinetic parameters of solid forms of  $\alpha$ -lipoic acid to identify their advantages and disadvantages, and to predict maximum therapeutic efficacy.

## 2 Materials and methods

The objects of the study were pharmaceutical information sources - instructions for the use of pharmaceutical preparations of solid forms of  $\alpha$ -lipoic acid of Russian and foreign manufacturers: coated tablets: Lipoic acid (Uralbiopharm, Russia), Lipoic acid (Marbiopharm, Russia), Oktolipen® (Pharmstandard, Russia), Thioctic acid (Atoll, Russia), Thioctic acid-Vial (VIAL, Russia), Tiolept® (Canonfarmaproduction, Russia), Berlithion®300, 600 (Berlin-Chemie, Germany), Thiogamma® (WÖRWAG Pharma, Germany), Espa-Lipon® (Esparma GmbH, Germany), Thioctacid®600 HR (MEDA Pharmaceuticals GmbH, Germany), Neuro lipon ("FARMAK", Ukraine) and gelatin capsules: Oktolipen® ("Pharmstandard", Russia), Lipoic acid ("Marbiofarm", Russia), Neyrolipon ("FARMAK", Ukraine). The listed drugs are taken orally. The oral route of administration of  $\alpha$ -lipoic acid drugs has a number of obvious advantages compared with injection, rectal and others: the most physiological route of administration is the simplest and most obvious; The presence of a medical professional, special equipment or skills are not required; economically and conveniently both to dose and accept; low cost; does not require sterile conditions. At the

same time, the following objective disadvantages of tablets and capsules of  $\alpha$ -lipoic acid for oral administration shouldn't go unnoticed: absorption is unstable and incomplete, since the drug can be poorly soluble, slowly absorbed, destroyed under the influence of hydrochloric acid of the stomach and intestinal enzymes; the relationship of the effectiveness of the drug with food intake and other pharmacological preparations; irritates the mucous membrane of the gastrointestinal tract; cannot be used with unconsciousness and with vomiting; slow onset of effect, which is ineffective in providing emergency care.

Also the objects of the study were published scientific data representing the results of clinical studies to prove the versatile therapeutic efficacy of  $\alpha$ -lipoic acid.

The study was performed using analytical methods for selecting and evaluating the given sources of information that are used in the interaction: analysis, systematization, generalization. So, the pharmaceutical information has been analyzed according to the main pharmacokinetic indicators of the preparations of solid forms of  $\alpha$ -lipoic acid and is summarized in tabular format. Information on clinical trials, extracted from world databases and scientific electronic libraries of ISI Web of Knowledge, Science Direct, Google Scholar, Cyberleninka, etc., is systematized according to the therapeutic potential of  $\alpha$ -lipoic acid in various diseases and is presented in a narrative review. Using the methods of systematization and generalization of the extracted information, the advantages and disadvantages of solid forms and formats of  $\alpha$ -lipoic acid are identified from the point of view of the consumer / patient and manufacturer of drugs, presented in a tabular format.

### 3 Results and Discussion

On the world pharmaceutical market, preparations of  $\alpha$ -lipoic acid are presented in the form of dosage forms: liquid - solutions and concentrates for injections and droppers and solid - in the vast majority of tablets, coated tablets and gelatin capsules.

It should be noted that when comparing the forms of the drug, the following pharmacokinetic indicators are the most important and informative: absorption and distribution — relative bioavailability (F), maximum concentration (C<sub>max</sub>), time to reach maximum concentration (T<sub>max</sub>); metabolism and excretion - the mechanism of metabolism, total plasma clearance (Cl), elimination half-life (T<sub>1/2</sub>) and others. In addition, when comparing the forms of the drug, the main clinical indicators are used: effectiveness, tolerability (side effects, tolerable / intolerable) and integral indicators that depend on effectiveness / tolerance: duration of retention on therapy, quality of life, patient preference, etc. [26]. It should be noted that the indicators of this group can be considered subjective; however, based on the feedback from patients, it seems possible to determine their values.

The analysis of instructions for the use of drugs of  $\alpha$ -lipoic acid, allowed us to determine the main values of the pharmacokinetic parameters of drugs of solid forms of  $\alpha$ -lipoic acid, summarized in table.

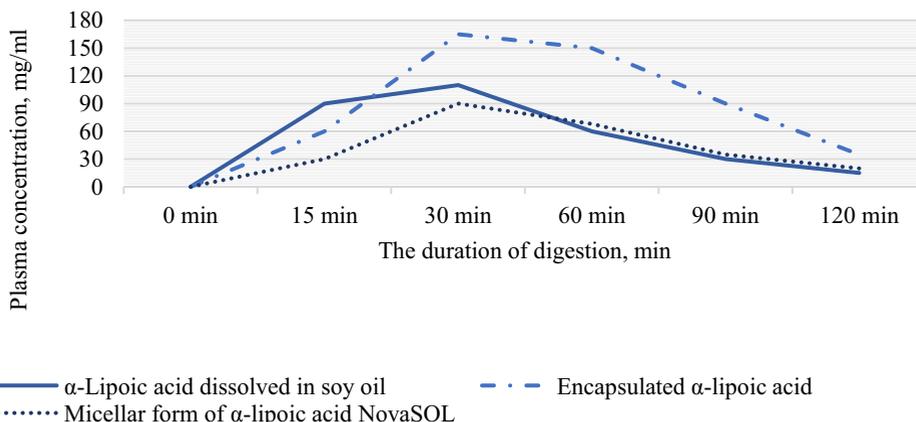
**Table 1.** Pharmacokinetic parameters of drugs of solid forms of  $\alpha$ -lipoic acid

Indicators	Pills	Capsules	Capsules with micellar $\alpha$ -lipoic acid
1	2	3	4
Pharmacokinetic			
Relative bioavailability (F),%	30-60 27-55 [7]	30-60	30-60
Maximum concentration (C <sub>max</sub> ), mcg / ml	4,0	4,5	

Time to reach maximum concentration (T <sub>max</sub> ), min	40-60	25-60	30-60
Metabolic mechanism	in the liver by oxidation of the side chain and conjugation		
Distribution mechanism	has a "first pass effect" through the liver "		
Total plasma clearance (Cl), ml / min	10-15	10-15	
The half-life (T <sub>1 / 2</sub> ), min	20-50	20-50	
Clinical			
Efficiency (achieving a therapeutic effect)	good in RR (rapid release) technology	good due to higher absorption rate and sufficient bioavailability	the best in metabolic and energy processes in cells [18, 23]; [1, 13-16] *
Tolerance	good		
Features of taking medication	In the morning, on an empty stomach, 30 minutes before the first meal, without chewing, with a small amount of liquid; 600 mg / day.	in the morning, on an empty stomach, 30-60 minutes before the first meal, without chewing, with a small amount of liquid	
Side effects	when exceeding the recommended daily dose, the most common: itching, rash, other allergic reactions and nausea, abdominal pain, headache, deterioration of general well-being. Patients with diabetes mellitus are advised to check their sugar levels regularly while taking lipoic acid [27].		
	In the Sydney 2 study, side effects (nausea, diarrhea, and dizziness), most often nausea, were noted at a dose of ALA of 600 mg in 13% of cases, at a dose of 1,200 mg in 21% of cases, and at a dose of 1,800 mg in 48% [22].		
Treatment duration	the doctor determines, based on the disease, as a rule, at least 2-3 months.		
Dosage	For diabetes, the recommended dose is 300-600 mg / day. For antioxidant support 20-50 mg / day is taken [27].		
* literature data on other preparations in micellar form			

As can be seen from the data presented, the pharmacokinetic indices of the solid forms of  $\alpha$ -lipoic acid practically do not differ, and the bioavailability of its solid forms (due to low solubility in water and fast binding to proteins) is in the range of 30-60%. Which, in turn, causes large doses of tablets and capsules of  $\alpha$ -lipoic acid for patients to take for a long time (treatment period), and / or its intravenous administration is practiced.

However, there are results proving the best therapeutic effect of  $\alpha$ -lipoic acid in micellar form [18]. So, thanks to the micellar form,  $\alpha$ -lipoic acid has not only increased bioavailability, but also a higher plasma content for a longer time (Fig. 1).



**Fig. 1.** Bioavailability of  $\alpha$ -lipoic acid [6]

According to the data presented, the concentration of  $\alpha$ -lipoic acid in blood plasma reaches a maximum after 30 minutes of administration, regardless of the form of the drug, however, the content of the active substance in micellar form is 75% higher than for the encapsulated analog and 60% for its solution in soybean oil. At the same time, a high concentration of  $\alpha$ -lipoic acid in the micellar form remains in the blood plasma for another half an hour, and only after that it gradually decreases, while for other forms there is a sharp drop in concentration immediately after reaching a maximum.

For completeness of the comparative characteristics of solid forms and formats of  $\alpha$ -lipoic acid, data on their advantages and disadvantages are systematized from the point of view of the consumer / patient and the manufacturer of drugs (Table 2).

**Table 2.** Advantages and disadvantages of solid forms of drugs  $\alpha$ -lipoic acid

Type of solid form $\alpha$ -lipoic acid	pill	Capsules	Micellar $\alpha$ -lipoic acid capsule
1	2	3	4
<i>Benefits for the consumer / patient</i>			
Ergonomic (usability) 3	Rapidity of medication taking, availability, cheaper. Small volume (portability).	Rapidity of medication taking, availability, stability of the active substance. There is no problem swallowing, as the gelatin capsule becomes slippery when wet and passes easily into the esophagus and stomach.	
Organoleptic perception	The coating of $\alpha$ -lipoic acid tablets provides less discomfort to the taste or smell of the drug.	Nice appearance. Capsules mask the smell or taste of a drug.	
The mechanism of assimilation (bioavailability)	It is poorly absorbed in the gastrointestinal tract, since usually the drug continuously moves along the gastrointestinal tract together with the food lump or chyme, it is difficult to determine the time and place of absorption of the active substance, that is, a delay in the release of the active substance	The capsule format protects the mucous membrane of the digestive tract from irritation or staining. Medicinal substances pass through the stomach unchanged. The ability to swell quickly, dissolve and absorb. Higher bioavailability. They are coated, which makes them invisible to phagocytic cells, and ensures their best preservation in the bloodstream when transported to the target organ.	

	inevitably shifts the release site down the digestive tract		
<i>Benefits for the manufacturer</i>			
	Dosing accuracy of active ingredients in mass production. Convenience of transportation and storage (tablets less than other solid forms are exposed to moisture, air and light), which leads to a shelf life of 3 years, subject to standard values of the climatic conditions of storage - prolonged action of drugs.	Dosing accuracy of active ingredients in mass production. Protection of the medicinal substance from exposure to light, air and moisture, which leads to a shelf life of 5 years, subject to standard values of the parameters of the climatic storage regime.	High chemical and physical stability during storage.
<i>Disadvantages</i>			
	They begin to act more slowly than other forms, since the tablets must first disintegrate and only then the medicinal substances begin to dissolve and absorb in the body. With prolonged storage of tablets, chemical changes can occur in them. In some cases, tablets lose their ability to disintegrate in the digestive tract. Tablets can cause mechanical or chemical irritation of the mucous membrane of the digestive tract. Tablets cannot be prescribed to children and people who do not know how to swallow them or who have lost this ability due to various reasons.	With increasing storage temperature, the shells may "melt" due to the high hygroscopicity of gelatin. Difficulty in swallowing (by reviews)	With increasing storage temperature, the shells may "melt" due to the high hygroscopicity of gelatin. Higher cost, since the drug is relatively new and the first time in sales is aimed at a niche market.

Almost all studies of drugs whose active substances are enclosed in micelles confirm that micellar forms are superior to traditional analogues in efficiency, which, in turn, improves such clinical indicators as quality of life and patient preference [1, 8, 9, 17, 18, 24]. This fact gives confidence to predict the maximum effectiveness of the micellar form of  $\alpha$ -lipoic acid.

## 4 Conclusion

The analysis of pharmaceutical and clinical information allows us to conclude that the pharmacokinetic parameters of the solid forms of  $\alpha$ -lipoic acid are practically the same, and the bioavailability of all forms is in the range of 30-60%, regardless of the patient's disease. At the same time, the best therapeutic effect of  $\alpha$ -lipoic acid in micellar form has been proved, which makes it possible to consider capsules with micellar  $\alpha$ -lipoic acid as the most effective solid form, since the size of micelles is, as a rule, significantly smaller than the size of liposomes used to encapsulate drugs. It was shown that the micellar form of  $\alpha$ -lipoic acid has the best therapeutic effect in the metabolic and energy processes in cells, and from the point of view of biological compatibility, micelles obtained from natural plant lipids are non-toxic and do not cause unwanted immune reactions. Of particular value is that micelles undergo gradual natural degradation without the occurrence of toxic products, and their metabolites are eliminated from the body almost completely, being included in the usual metabolic pathways. The advantages (for manufacturers and consumers / patients) and the disadvantages of  $\alpha$ -lipoic acid drugs in solid forms - capsules and tablets are summarized.

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