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DELIM

LABORATORIO FARMACEUTICO

DEVELOPMENT OF A CHOLINERGIC DRUG IN THE FORM OF ORODISPERSIBLE GRANULATE FOR THE TREATMENT OF COGNITIVE DECLINE

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01 INTRODUCTION

At the level of the central nervous system, the cholinergic transmission is involved in numerous processes that regulate the activity and main functions of the brain, such as attention, learning, memory, circadian rhythm, sensory information.
Recent studies on the brain of patients suffering from senile dementia have shown a marked loss of choline acetyltransferase, an enzyme involved in the synthesis of acetylcholine, and of nicotinic cholinergic receptors.
Acetylcholine therefore plays an important role in cognitive processes and its deficiency is found in Alzheimer's disease. The observation that central cholinergic antagonists can induce a confusional state supports the cholinergic hypothesis according to which acetylcholine deficiency is critical in the onset of symptoms of the disease.
Choline and phosphatidylcholine, a phospholipid containing choline, are essential for maintaining the integrity and structure of the cell membrane. In particular, choline, a precursor of acetylcholine, plays a role in transport in cells.
In this panorama, choline alfoscerate (L-alpha-glycerophosphorylcholine), known by the acronym GPC, has provided positive results in some preclinical -clinical studies, demonstrating moderate efficacy in the treatment of vascular origin forms of dementia. Furthermore, GPC, as a cholinergic precursor, guarantees higher plasma choline levels and greater activity on memory and cognitive parameters. The pharmaceutical formulations for oral administration based on choline alfoscerate currently on the market are in the form of tablets, soft capsules or syrup. However, GPC formulations in solid form are large in size and have low compliance as they are difficult to be swallowed especially by elderly subjects (over 70 y/o) who represent the main portion of the population targeted by the treatment.
There is a need to have solid oral pharmaceutical forms containing GPC with greater compliance.
However, the liquid physical state of choline alfoscerate, its high viscosity and hygroscopicity complicate the formulation of solid oral pharmaceutical forms alternative to those currently available.

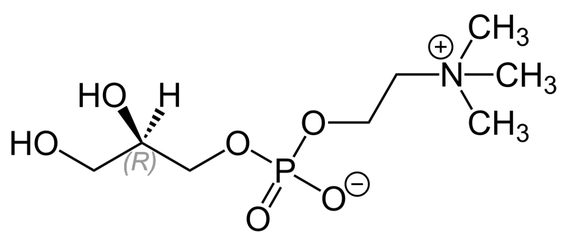

Figure 1. Structure of L-alpha-glycerophosphorylcholine

02 AIM OF THE PROJECT

It is a general aim of the present invention to provide an oral dosage form of orodispersible granules of choline alfoscerate, having improved compliance and high absorption in the gastrointestinal tract, as well as a rapid dissolution profile. The objective is to obtain a finished dose of 2 grams to be assumed without the use of water. This is a ready-to-use product with a portion of active ingredient (choline alfoscerate) equal to 600 mg, to be taken twice a day,. Formulating an active dose of 600 mg would reduce the number of daily intakes by the patient, maintaining good adherence to therapy compared to other marketed products containing 400 mg of active.
In accordance with the results of the present work, micronized colloidal silica is the key excipient suitable for obtaining an oral solid formulation in which choline alfoscerate is in the form of orodispersible granules.

03 MATERIALS AND METHODS

a. Granulate qualitative formulation:
Choline alfoscerate, mannitol, micronized colloidal silica, purified water, orange flavor, citric acid monohydrate.

b. Equipment:
High Shear Mixer, Trichop mgr-5, Lleal (Spain).

04 MANUFACTURING PROCESS

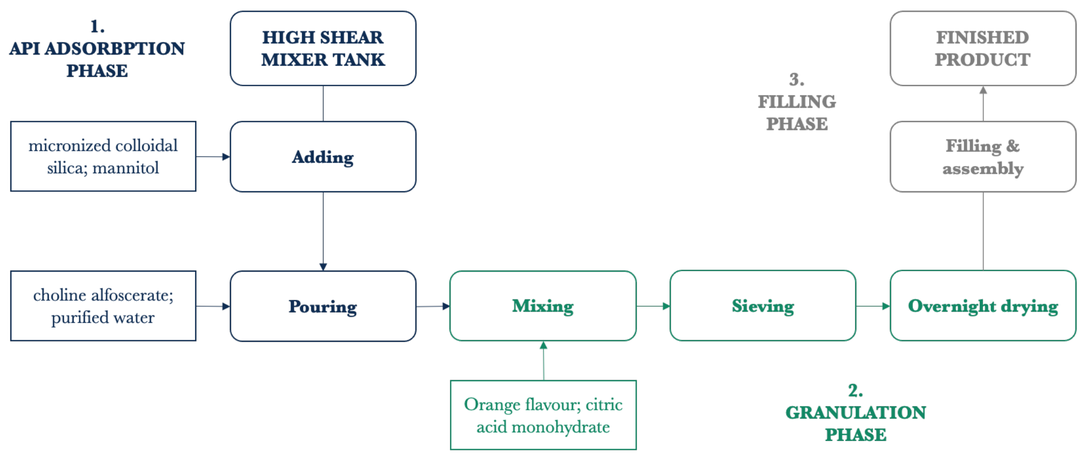

Figure 2. Manufacturing process of choline alfoscerate orodispersible granules

05 RESULTS

Starting from the stickiness and hygroscopic characteristics of choline alfoscerate, preliminary tests were carried out to identify excipients that combine high adsorbent properties and overcome the formulation challenges.
After an initial screening among excipients commonly used in pharmaceutical technology, the most promising were chosen: silica, anhydrous lactose, hydroxypropyl-β-cyclodextrin, mannitol, mannitol-sodium crosscaramellose mixture, micronized colloidal silica.
These excipients were subjected to tests aimed at verifying the adsorption of choline alfoscerate and the formation of a suitable orodispersible granular dosage form.
Comparative adsorption tests of choline alfoscerate on binary and ternary mixtures composed of the different selected excipients have led to defining the ideal candidates for formulating the active ingredient. Exploiting their peculiar technical characteristics allows the formulation problems of choline alfoscerate to be overcome. The micronized colloidal silica is the key excipient in the dosage form described herein; effectively it adsorbs choline alfoscerate and acting as a thixotropic agent produce a thickening effect. The selection of the bulking agent fell on mannitol thanks to its properties of high solubility in water and its sweetening capacity; actually it is also used in diabetic foods as it is poorly absorbed from the intestine, a considerable advantage since patients over 70 y/o could present further health issues. Moreover it is formulated maintaining a daily dose lower than the amount manifesting laxative effects. Beneficially, the combination of micronized silica and mannitol perform an easily processable granulate with a good flowability which facilitates the fabricating of an orodispersible pharmaceutical form and its filling in packaging, for example in sachets. According to some embodiments, the dosage form described herein contains granules with an average particle size preferably less than 800 microns. The selection of the size of the granules is done using sieves with desired mesh sizes.

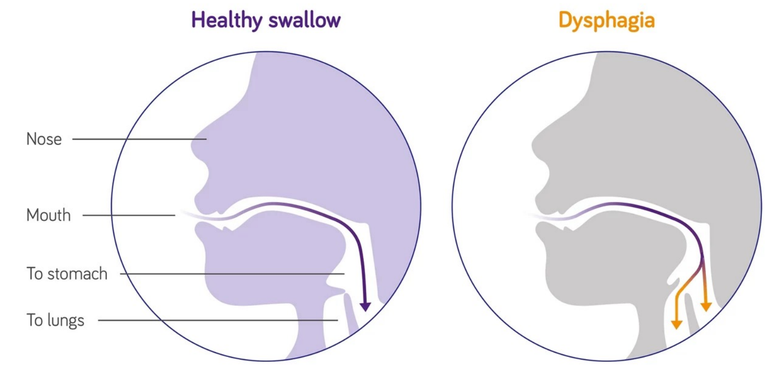

Figure 3. Complications of oropharyngeal dysphagia: risk of aspiration of ingested material and/or oral secretions into the trachea

Disintegration rate

In order to evaluate the disintegration time, a dose of granular finished product equal to 2 grams was weighed. Few milliliters of water to simulate saliva were added under gentle stirring, observing a very short disintegration time, in less than 10 seconds.

Palatability

Subsequently the finished product was evaluated in terms of palatability, which, thanks to the presence of orange aroma, citric acid monohydrate and the sweetish taste of mannitol, gives a positive feeling to the patient and dissolves in the mouth quickly, only with the help of saliva.

06 CONCLUSIONS

The over described formulation of choline alfoscerate is an advantageous alternative to the dosage forms available on the market, as well as a valid support against problems related to dysphagia. The API adsorption process guarantees the formation of a granulate with good flowability, useful for process workability. The high rate of disintegration in a small volume of saliva does not compromise patient compliance.

07 CURRENT AND FUTURE DEVELOPMENT

The current status of the project foresees the first industrial-scale production and a clinical trial (i.e. PK study) which will involve volunteer patients. This invention is subject to patent coverage and it is considered adaptable to new API frontiers.

08 REFERENCES

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09 CONTACTS

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