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(57) Abstract

Pharmaceutical compositions in form of nanoparticles comprising a composite material, consisting of at least one lipidic substance and of at least one amphiphilic substance, and of a pharmaceutically active principle. Said compositions, thanks to the surface and mass properties of said composite material, show an improvement in the incorporation of the active principles and an increase in the bioavailability of the poorly absorbable active principles.

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PHARMACEUTICAL COMPOSITIONS IN FORM OF NANOPARTICLES COMPRISING LIPIDIC SUBSTANCES AND AMPHIPHILIC SUBSTANCES AND RELATED PREPARATION PROCESS

Prior art

In the research field of the new vehicles suitable to the administration of active principles, a great interest has been directed towards the polymeric systems having size in the micrometer range and to the polymeric systems having size in the nanometer range.

Among the mostly used polymers the polyalkylcyanoacrylates and the poly-lactic acid (PLA) and poly-lactic glycolic acid (PLA-PLGA) derivatives are to remember. Such systems show however some disadvantages.

For example the polyalkylcyanoacrylates are metabolized by the organism in a 24 hours interval and release formaldehyde, a potentially toxic derivative; the PLA and PLA-PLGA polymers do not produce toxic metabolites but they have long degradation times ranging from some weeks to some months, and then they may show dangerous accumulation phenomena.

Moreover, the preparation methods of these systems need the use of potentially toxic organic solvents which may remain in traces in the final form.

In the end, the size of the majority of said systems exclude their use for intravenous way because extraneous bodies having size higher than 5 μm injected in vein may cause embolisms.

These negative aspects generated greater attention for administration systems having greater biocompatibility and lower toxicity: the first among all these are the lipidic colloidal systems such as oil/water emulsions, liposomes, lipidic micro- and nanoparticles.

Oil/water emulsions, consisting of lipidic droplets having size in the range of nanometers, dispersed in an external aqueous phase, have been used as a vehicle for the parenteral feeding (JP Patent No. 55,476, 1979, Okamota, Tsuda and Yokoama).

Oil/water emulsions containing active principles have been described in the Patent WO 91/02517, 1991, Davis and Washington. Such systems have a high capacity

to incorporate active principles in the internal lipidic phase, but the active principles easily diffuse from such phase towards the external phase originating stability problems and limitations for the optional development of a protracted release form.

The liposomes are colloidal structures having an aqueous internal phase sorrounded by one or more layers of phospholipids. The use of liposomes as vehicles for the administration of drugs is described for example in the U.S. Patent No. 3,993,754 (1976, Rahman and Cerny).

However typically, such systems show stability problems during the stocking, a poorly reproducible preparation method and a low potentiality to incorporate and retain active principles.

Fountain and others invented lipidic microparticles in globular form having size ranging from 0.5 μm to 100 μm as vehicles for the administration of active principles. Such invention is disclosed in the U.S. Patent No. 4,610,868 (1986).

Domb and others (US Patent 435,546) invented the Liposheres™, insoluble particles having size about equal to 40 μm, suspended in an aqueous environment, consisting of a lipophilic internal phase surrounded by external layers of phospholipids, added to the composition and adsorbed on the surface of the particles themselves. These systems were developed for the controlled release of anaesthetic drugs (Domb and others, US Patent 5227165) and of active principles having insecticide and pesticide activity (Domb and others US Patent 5227535). However the technique for the preparation of such systems requires the help of solvents which remain in traces in the final form.

The per os administration turns out to be difficult for active principles which are not much soluble, not much absorbed in the gastroenteric tract or which are sensible to the pH or the action of the proteolytic enzymes (proteins and peptides). The incorporation of such substances in lipidic nanoparticles allows to overcome such difficulties because these nanoparticle systems may be absorbed along the gastrointestinal tract. Their reduced size allow to exploit the mechanisms of the passive transmucosal absorption, or to pass through the intercellular junctions or the ionic channels or to use the endocytosis mechanism or to enter the lymphatic

flux.

Solid lipidic systems consisting of nanopellets were developed by Speiser and others (US Patent 4,880,634, 1989), and destined to the oral administration of poorly absorbed drugs. The lipidic pellets are prepared emulsifying lipidic substances in an aqueous environment with a high energy mixer, then cooling the emulsion at room temperature and obtaining the pellets by sonication.

Gasco (EP 0526666A1, 05/08/1991) invented a technique for the preparation of lipidic nanoparticles. A microemulsion is prepared adding to an aqueous phase a lipid melted in the presence of surfactants and cosurfactants, which is then dispersed in an aqueous environment maintained at a temperature around 10 °C. The solid nanoparticles are obtained in an aqueous suspension, but may be subsequently deprived of the residual surfactants by ultrafiltration and recovered by filtration or freeze-drying.

Such technique turns out to be advantageous from the point of view of the saving of energy with respect to the high energy homogenization, it allows to obtain smaller nanoparticles, having average diameters ranging from 90 nm to 900 nm, with a more uniform size distribution and a low polydispersion index. However the preparation of a microemulsion needs the melting of the lipidic material which is for most used lipidic substances about 70 °C, which limits the use of such technique for the thermolable substances.

Summary of the invention

The invention relates to pharmaceutical compositions in form of nanoparticles, having a diameter lower than 1000 nm and preferably ranging from 50 to 500 nm, comprising a composite material, consisting of at least one lipidic substance and at least one amphiphilic substance, and a pharmaceutically active principle.

We have unexpectedly found that, operating according to the present invention, said composite material and the relative particles have characteristics not achievable by an usual mixing of a lipidic substance with an amphiphilic substance or by the adsorption of an amphiphilic substance on lipidic particles.

The amphiphilic substance may be preferentially distributed on the surface of the nanoparticles or it may be preferentially distributed inside the nanoparticles or it

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