Investigation and mathematical modelling of micellar preparation encapsulation

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Introduction

The goals of this work are investigation of encapsulation technology for temperature and ph-sensitive bioactive pharmaceutical products in an intestinally-soluble cover and mathematical modelling of this process. Production of peroral forms for such drugs is the perspective problem in modern pharmaceutics. The developed mathematical model allows to predict quality of medicinal agent in a product, and also to regulate active component's content efficiency using varying conditions of process.

The purpose of the present work is the development of tableting technology for production of micellar containing preparations which are the liver protectors with the directional pathogenetic effect. The preparation contains phospholipids (the main component is phosphatidylcholine) restoring the structure and functions of the damaged hepatocyte's membranes. Due to such pharmacological effect the loss of enzymes and other active substances by cells is prevented; albuminous, lipidic and adipose exchanges and detoxicational function of a liver are normalized; the formation of connective liver tissue is inhibited, the risk of a hepatic fibrosis and cirrhosis appearance is decreased. Phosphatidylcholine exists in the form of micellar structures, providing the micelle penetration to liver cells where they act as membrane glue. The size of micellar structures is 50 - 90 nanometers.

During the manufacture of phospholipid peroral forms there are many difficulties: micellas are destroyed under the action of gastric juice (the preparation should be soaked in intestines) and high temperature. Bioactive radicals of phosphatidylcholine are oxidized at opened air. The problem of preservation of pharmacological activity of the preparation and delivery in intestines has been solved at use of Encapsulation technology has been used to preserve the pharmacological activity of the preparation and to deliver it to intestines.

Material and methods

Placebo pellets: pellets of micro cellulose, 350 μm.

Encapsulated preparation: temperature and ph-sensitive bioactive pharmaceutical products containing micellar structures of phosphatidylcholine.

Cover material: intestinally-soluble cover.

The encapsulation consists of two consecutive stages: layering placebo pellets by pharmaceutical substance and coating the received microspheres by the intestinally-soluble polymeric media. Both technological stages have been carried out in the fluid-bed apparatus with bottom spray.

The pharmacological action of phospholipidic preparation is characterized by three major parameters: the abundance of phosphatidylcholine, the size of micellas and the oxidability degree of

phosphatidylcholine's radicals in encapsulated product. The complex of experimental and analytical investigations has been done. The experimental part was based on the full factorial plan. During layering the fluidized air temperature and the concentration of initial solution for coating have been varied.

The analytical investigations were: analysis of encapsulated microsphere surfaces; determination of grain-size distribution of a product; determination of the abundance of pharmaceutical substance in a product; oxidability degree of pharmaceutical substance after encapsulation; determination of the phospholipidic micella size in a product.

Results and Discussion

The uniformity of polymeric intestinally-soluble coating has been confirmed by the high resolution microscope (absence of breaks and cracks) at all experiments. The size of phosphatidylcholine particles has been defined by the photon correlated spectrometer. The analysis showed that the size of micellas after encapsulation has not changed practically and lies in the admissible range (figure 1).

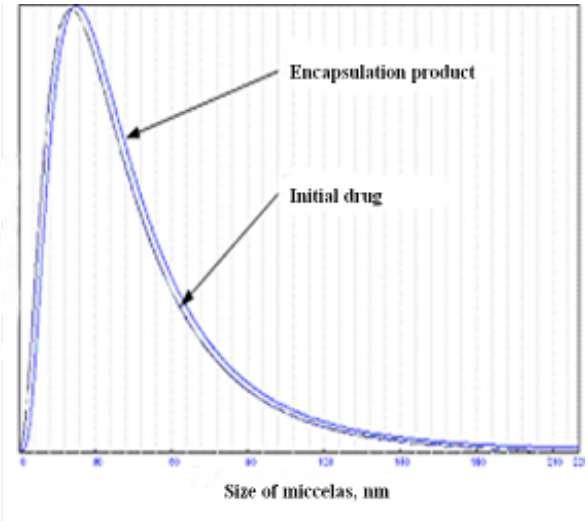

Figure 1: Grain-size distribution of phosphatidylcholine micellas before and after encapsulation

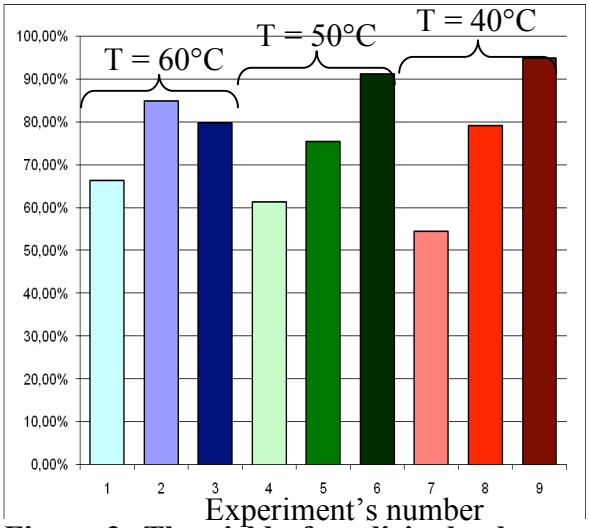

Figure 2: The yield of medicinal substance in a product against the total quantity of introduced preparation

The determination of oxidability index has been carried out by the spectrophotometer. The results confirm the pharmacological properties preservation for the encapsulated preparation (see table 1).

The abundance of pharmaceutical substance in the encapsulated pellets has been defined by UF-spectrophotometric method. The diagram (figure 2) illustrates influence of the coating operation parameters on yield of phospholipids.

The greatest yield of preparation while the most diluted initial liquid has been observed at temperature 60°C (figure 2 – exp. 1). The greatest yield at the most concentrated solution for coating has been observed at temperature 40°C (figure 2 – exp. 9).

At temperature 40°C and low concentration of preparation in initial solution the drop has no enough time to achieve the sufficient viscosity for successful adhesion before collision with a particle. After

collision with particle the greater part of a drop is spattered and the small fraction fines are passed away together with the drying agent from the chamber (low yield in exp. 7 in fig. 2).

Sample	Oxidability index
Source phospholipid	0.21
After encapsulation	0.73±0.05
Permissible oxidability degree	1.2

Table 1: Oxidability index of the phospholipids

At the high concentration and temperature 40°C the drop has sufficient viscosity – and the greater part of drops successfully collides with a surface of microsphere (high yield in exp. 9 in fig. 2). However, at this temperature the drying velocity is too low and the microspheres are located into the high compactness zone with high surface stickiness – two peaks on the grain-size distribution plot (fig. 3). It means a lot of particles stuck together.

At temperature 60°C and low concentration of a preparation in initial solution the drop has time to get dry for successful collision with microsphere. And at the same time the drop has good flowability, which positively exerts on quality of coating. At high concentration of phosphatidylcholine the drop gets excessive hardness before collision with microsphere that promotes the rebound of drop from pellet.

The analysis of product grain-size distribution showed the influence of initial preparation concentration and fluidizing air temperature on coating quality.

Conclusions

On the basis of complex analysis of product grain-size distribution and preparation yield the encapsulation conditions have been recommended. The high yield with minimum of particles stuck together is reached under the fluidizing air temperature is 60°C and the initial phospholipid concentration equal 29.41 %.

The experimental data analysis has showed the influence of fluidized air temperature and initial solution concentration on product yield. The dependence has been found by the statistical methods and can be expressed as the second order regression equation:

$$G_{out} = 918{,}67 - 5.235T - 47.551C + 0.197C \cdot \dot{O} + 0{,}566 \cdot \tilde{N}^2 - 6{,}483 \cdot 10^{-3} \cdot \dot{O}^2,$$

$$G_l = 100 - G_{out},$$

where Gout - phosphatidylcholine yield, % mass; Gl - a share of losses applied substances, % mass; C – initial phosphatidylcholine concentration, % mass; T - fluidized air temperature, °C.

The diagram of pharmaceutical product losses because of varied operation parameters is presented on fig. 3 (the experimental data are noted by points).

According to the block approach (Kafarov 1976) the mathematical model of micellar pharmaceutical substance encapsulation to intestinally-soluble capsule at the fluid-bed dryer has

been developed. The model allows to predict the quantitative yield of micellar preparation and to select the optimum operation parameters to preserve the pharmacological properties of phosphatidylcholine.

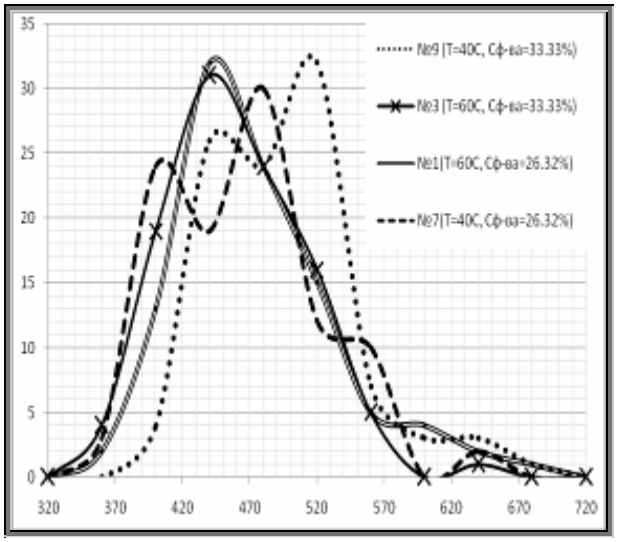

Figure 1 : Grain-size istribution of encapsulated product

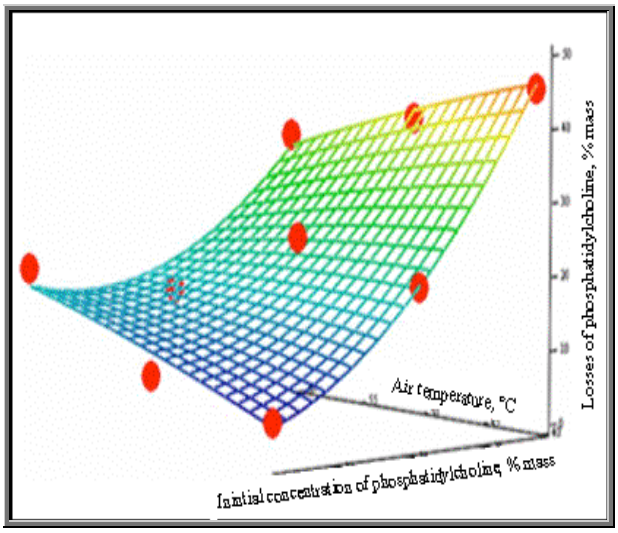

Figure 4. Share of phosphatidylcholine losses at encapsulation in fluid-bed

The analytical investigations have shown the applicability of encapsulation technology to produce the intestinally-soluble dosage forms containing micellar structures which are sensitive to temperature and oxygen. It has been confirmed by admissible values of oxidability index and preservation of micella size in a product.

References

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