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SHORT COMMUNICATION

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DIFFUSION OF LIDOCAINE HYDROCHLORIDE FROM LIPID MICROPARTICLES

Lipid particles, as drug carriers, are of increasing research interest, because a sustained drug release and avoidance of side effects could be achieved by using them.

Lidocaine hydrochloride is a very efficient local anesthetic, but it has a short effect. The objective was to prolong the effect of the drug by encapsulating lidocaine hydrochloride in phospholipids microparticles.

Two different procedures were used for the preparation of phospholipids microparticles. In both cases, phosphatidylcholine and lysophosphatidylcholine were used for the preparation of microparticles in which 5 % w/w lidocaine hydrochloride solution was encapsulated.

The standard Franz diffusion cell was used for the experimental diffusion rate determination. The obtained results show that diffusion rate from microparticles is significantly lower than from the lidocaine hydrochloride solution, which means that this kind of microparticles could be used for the prolonged drug release. There was no much difference in diffusion rates from microparticles obtained by different procedures. That indicates that only the composition of the particles membrane has an influence on the lidocaine hydrochloride release rate.

Key words: microparticles; diffusion; phospholipids; lidocaine; Franz cell.

Phospholipids particles for drug-delivery applications are now the most widely investigated area of their practical application [1-3]. These drug vesicles are self-assembled particles that even occur naturally [4].

Phospholipids possess a polar and a non-polar group on the same molecule and they represent amphiphiles. Adding a small water amount to phospholipids will cause their self-organization into a lamellar phase. In this self-assembled structure the molecules are oriented in such a way that the polar part of the molecule is in contact with the water and shields the non-polar portion. The additional dilution in the excess water and a mechanical energy input will cause the formation of stable colloidal microparticles. These microparticles are hollow spheres which could be used as drug carriers, for hydrophilic and hydrophobic molecules [5,6].

Lidocaine hydrochloride was chosen as a drug which will be encapsulated in phospholipids micropar-

ticles. Lidocaine hydrochloride is a local anesthetic the use of which is limited by the relatively short action of the drug compared with the potential duration of the pain. This drug is water soluble and could be incorporated into the aqueous phase of phospholipids microparticles. By encapsulation of lidocaine hydrochloride a slow release could be achieved and the action of the drug will be prolonged [7].

EXPERIMENTAL

Microparticles were prepared by two different methods.

For the first method, Prolipo S (Lucas Meyer GmbH&Co) was used. Microparticles were prepared by simple vortex mixing [8]. First, Prolipo S was measured and put in a small glass. Lidocaine hydrochloride was dissolved in distilled water and then added in the first phase. The mixture was agitated by the propeller mixer on 1208 rpm for 20 min, at the room temperature which was the transition temperature of an unsaturated phosphatidylcholine phase. By this mixing, the energy was brought into dispersion and it was used for closing bilayers in spherical microparticles. The concentrated dispersion of microparticles was obtained. Distilled water and DMDM hydant-

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toin (preservative) were added in the concentrated dispersion and it was agitated on 505 rpm for 10 min. The homogeneous dispersion with 5 % w/w encapsulated lidocaine hydrochloride was obtained.

The second method of the microparticle preparation was a thin film method [9]. Lipoid S 75, which was kindly donated by Lipoid AG (Germany), was dissolved in chloroform and transferred into a round-bottom flask. The solvent was evaporated in a rotary evaporator at 40 °C and 350 mbar. The thin film formed was hydrated with 5 % w/w solution of lidocaine hydrochloride in water and then hand shaken. Small PET particles were added to intensify the mixing.

In both cases, a microparticles membrane consists mostly of phosphatidylcholine, with small amounts of lysophosphatidylcholine present. Prolipo S contents 30 % w/w of phosphatidylcholine and 0.5 % w/w lysophosphatidylcholine, while Lipoid S75 has 73 % w/w of phosphatidylcholine, 9 % w/w of phosphatidylethanolamine and 1.5 % w/w lysophosphatidylcholine. All phospholipids are unsaturated.

Particles were analyzed using an optical microscopy with magnification of 1500 \times .

In order to study the release of lidocaine hydrochloride from the prepared phospholipids microparticles a jacketed Franz-type cell 25 mm in diameter (donation of PermeGear, Inc., USA) was used (Figure 1). A static diffusion cell comprised two compartments with a membrane between the donor and the receptor sections. The receptor compartment had a fixed volume (20 ml) and it was kept at 37 °C with the water bath. The receptor fluid (distilled water) was mixed with a magnetic bar stirrer.

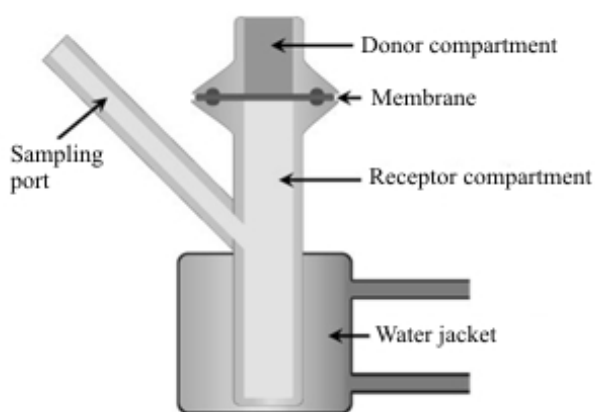


Figure 1. Jacketed Franz diffusion cell.

Three different diffusion experiments were done in the same way. The first experiment endured 4.5 h and the second and the third 12 h. For all the runs a Franz cell with the receptor solution in both compart-

ments first was thermostated in the water bath at 37 °C for 30 min.

Between the donor and the receptor compartments the acetate-cellulose membrane with a pore size of 0.45 μm was placed.

In the first experiment, 5 % w/w solution of lidocaine hydrochloride in water was used as a donor phase. In the second and the third experiment, the obtained liposomal dispersions with encapsulated lidocaine hydrochloride were used as a donor phase.

The samples were withdrawn periodically, first two after 15 min, next three after 30 min and then after 60 min. In all cases, the receptor compartment was fully discharged, the sample(s) weight was measured and a new receptor solution, preheated at 37 °C, was added to the receptor compartment.

The concentration of lidocaine hydrochloride in the water solution was determined spectrophotometrically measuring the absorbance at 262.2 nm. The correlation between the absorbance and the lidocaine hydrochloride concentration was determined measuring the absorbance at 262.2 nm for concentrations of lidocaine hydrochloride from 0.01 to 0.11 % w/w. This correlation was linear:

$$A = 15.034 \tilde{x}$$

where A is the absorbance and \tilde{x} is w/w concentration of lidocaine hydrochloride expressed as a percent mass concentration. This correlation with experimentally obtained points was shown in Figure 2.

RESULTS AND DISCUSSION

The mean diameter of microparticles was about 800 nm in both cases. The largest particles were with diameter of 17.4 μm and they were lonely in dispersion. Both particles dispersions were stored at 4 °C for 90 days and they did not change their structures and that was the evidence of their stability.

On the bases of the measured samples weight and the concentration of lidocaine hydrochloride in the receptor compartment, a cumulative weight of lidocaine hydrochloride which permeated the membrane was calculated. The results of the diffusion across the membrane of lidocaine hydrochloride from the water solution and microparticles dispersions obtained by two different methods were shown in Figure 3.

It could be seen that the diffusion is much faster from the solution than from microparticles dispersions. There is almost no difference in a diffusion rate for different microparticles dispersions.

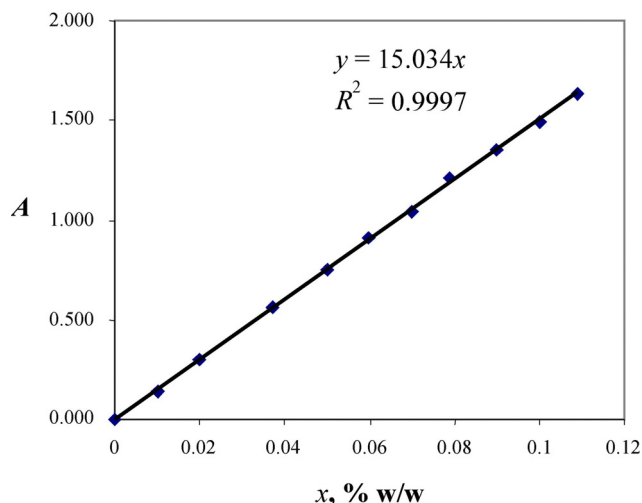


Figure 2. The absorbance of lidocaine hydrochloride water solution of different concentrations.

Therefore, phospholipids microparticles could successfully be used for a prolonged release of lidocaine hydrochloride. The microparticles preparation method has no influence on the release rate of an active, especially because a mean particle diameter was almost the same in both experiments.

CONCLUSION

Phospholipids microparticles are a promising device for the prolonged release of local anesthetics. The diffusion from this kind of particles is significantly slower than from the drug solution. This finding is in accordance with the literature data for lidocaine hydrochloride [10].

Microparticles dispersions are stable for at least 3 months.

The diffusion rate is determined by the particle size and the membrane composition. For both preparation method the membrane of particles was mainly of phosphatidylcholine, and the diffusion of an active could be further modified only by using hydrogenated

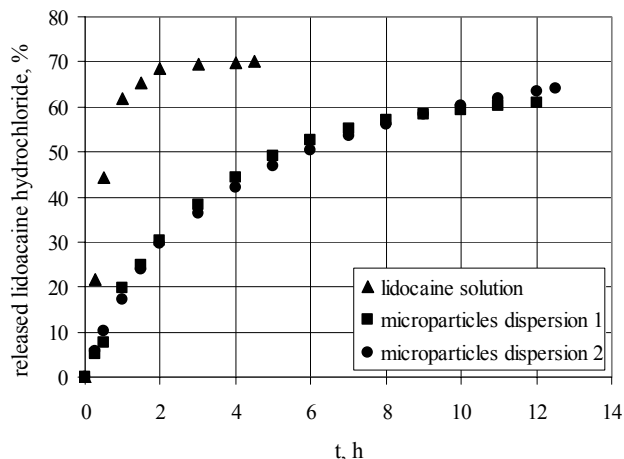


Figure 3. The diffusion of lidocaine hydrochloride from the solution and microparticles dispersions.

phospholipids and cholesterol as the membrane constituents.

Nomenclature

- A Absorbance
 \tilde{x} Lidocaine concentration w/w, %.

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