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SCIENTIFIC PAPER

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IN VITRO EVALUATION OF THE CONTROLLED RELEASE OF ANTIBIOTICS FROM LIPOSOMES

Results of this study have shown significantly prolonged release of selected antibiotic from liposome dispersion as compared to free antibiotic solution of the same initial concentration. Two models of non–steady, one–dimensional diffusion were successfully applied to the experimental data and the antibiotic diffusion coefficients were estimated. In addition, the mass transfer resistance of the membrane was shown to be insignificant confirming the suitability of the applied experimental system.
Since liposomes are known as systems with slower drug release, then, when it comes to their incorporation in the final form of a preparation for further experiments in vivo, the system of choice would be liposomes with an encapsulated antibiotic drug. The established experimental system could be extended to other liposome formulations with respect to the release rate of the active components.

In the last ten years the general trend in immobilization and encapsulation biotechnology has been obtaining very small uniform microparticles for the purpose of cell and active substance immobilization. Various techniques and methods have been developed for this purpose. Hydrogel mirocapsules and microbeads have been produced via the dripping mode (droplet gelation technique) using different types of external forces such as air flow, electrostatic force [1–5], vibration [6,7] and jet cutting [8,9].

The main disadvantage of the above mentioned techniques is a limited down to microbead size of a maximum of 50 μm [1]. In order to overcome this, we applied the emulsification technique for the production of nano vesicles with an average diameter of less than 0.2 microns.

Liposomes, small spherical particles that consist of lipid bilayers, have become a very interesting topic for many researchers during the past few decades. Especially attractive is the application of liposomes as carriers of different active principles in the field of cosmetics and pharmacy. According to the literature, it may be concluded that serious work has been done in developing new formulations for topical use, where liposomes are incorporated as a system for the sustained delivery of drugs to the skin [10–12]. All relevant results have shown that liposomes have a capacity to encapsulate a wide range of hydrophobic and hydrophilic active substances. Specific formulations intended for the treatment of certain skin disorders have been developed with the aim of achieving several benefits, such as the better accumulation of the drug on the specific site of action [13] and the reduction of toxic effects [10,12]. Liposome formulations can provide better efficiency of the treatment by localization of the active components on the skin and prolonged drug release [12].

The advantages of liposome formulations for medical applications have been considered in a number of articles published in the past ten years, dealing with different aspects of liposome use as a system for the sustained delivery of drugs in topical preparations for the treatment of certain skin disorders [14].

Characterization of the obtained formulations is one of the main issues regarding their commercial use, and there is still a lack of standardized methods and procedures applicable to all liposome systems. Generally, the characterization of carrier systems should include assays for drug release [15]. In Franz–type diffusion cells, which are described in the literature [16] and have been used in many articles for the evaluation of the controlled delivery of active components to the skin [17–19], the controlled release of the active material from the selected carrier can be monitored through different mammalian skin samples [17,19] or suitable synthetic membranes [19]. Beside the Franz diffusion cell, other membrane systems can also be applied for *in vitro* release studies [14,20].

In this work, an effort was made towards the evaluation of the controlled release process of a selected antibiotic from a liposome dispersion designed to be incorporated in a final preparation for topical use in the form of a gel. However, we have focused on the controlled release from the liposome dispersion per se, in order to understand the basic mechanism of that part of the process itself. For this purpose, a specific experimental system was designed. The system

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consisted of a cylindrical module with cellulose acetate membranes with 0.2 μm pore size. A simple experimental protocol was proposed for the comparison of different liposome formulations with respect to the release rate of the encapsulated material.

MATERIALS AND METHODS

Materials

A special blend of soya phospholipids (20%) in the form of hydrated bilayers suspended in a minimal amount of hydrophilic medium (Lucas Meyer, France S.A.) was used for the production of liposomes with an encapsulated antibiotic. All other chemicals were of reagent grade of pharmacopoeal purity, except the acetonitrile used for liquid chromatography (HPLC grade).

Differential scanning calorimetry

Differential–scanning calorimetry (DSC2–Perkin Elmer) was applied to determine the phase transition temperature of a mixture of hydrogenated phospholipids used for the formation of liposome membranes, [21]. Measurements were performed in nitrogen atmosphere, at a heating rate of 5°C/min.

The phase transition temperature of a selected mixture of hydrogenated soya phospholipids was 49.4±2.5°C. For the same phospholipid mixture purified in chloroform, chosen as a suitable organic solvent it was 45.8±1.7°C.

Since purification of the selected phospholipid mixture in chloroform led to a decrease in the phase transition temperature, the thin film method, in which this purification step is included during the removal of organic solvent in a rotary vacuum evaporator, was applied for the production of liposomes. In addition, considering the fact that the phase transition temperature must be reached for the liposomes to encapsulate the selected material, the temperature of 45°C was chosen as the working condition for the liposome preparation process.

Preparation of liposomes

The liposomes were prepared using the technique first reported by Bangham et al. (1965), known as the thin film method [22,23], followed by sonication. A suitable amount of hydrogenated soya phospholipids in chloroform (5:1) was subjected to treatment in a rotary vacuum evaporator, BÜCHI Rotavapor R–124 (BÜCHI Labortechnik AG, Flawil, Switzerland), at 45°C until the solvent had been completely removed. After the formation of a thin phospholipid film, an aqueous solution of the selected antibiotic was added to the flask to obtain the final concentration of 4% w/w in the liposome dispersion, and liposomes were formed during mild agitation.

A bath–type NEY ULTRAsonic™ 104 X sonicator (Neytech, Bloomfield, CT) was used to achieve liposome size reduction as previously reported (24), and partial homogenization of the obtained dispersion. The liposomes were then passed through a Microfluidizer® Processor (Model HC–5000, Microfluidics Corporation, Newton, MA), in five cycles under a working pressure of approximately 85 bar. The resulting product should have an even liposome size distribution and uniform deagglomeration [25]. Size analysis of the liposomes was performed on a CILAS Granulometer HR 850 (CILAS, Marcoussis, France), using the laser light scattering method (26), after sonication and homogenization in the Microfluidizer® Processor.

Characterization of the obtained liposome dispersion

A method of agar diffusion (Ph. Eur. III, 2.7.2) was used to determine the total antibiotic content in the liposome dispersion after five passes through a homogenizing module. Medium A (Ph. Eur. III) was sterilized at 121°C/15 min in an autoclave and inoculated with a test microorganism (*Sarcina lutea* ATCC 9341). Pretreated samples (100 μl) of the liposome dispersion and standard solutions of defined final concentrations were placed on perforated plates. After 30 min of prediffusion at room temperature and incubation at 35°C/16–18 h, the inhibition zones were measured. The total antibiotic concentration in the liposome dispersion was calculated according to the following equations (Ph. Eur. III, 5.3):

$$(\Sigma T_2 + \Sigma T_1) - (\Sigma S_2 + \Sigma S_1) = D \quad (1)$$

$$(\Sigma T_2 - \Sigma T_1) + (\Sigma S_2 - \Sigma S_1) = B \quad (2)$$

$$\%\text{Expected conc. in the sample} = 10^{D/B \cdot 0{,}301} \cdot 100 \quad (3)$$

T_1 and T_2 are the different final concentrations, i.e. the inhibition zone diameters of the pretreated sample, while S_1 and S_2 are the final concentrations (inhibition zone diameters) of the pretreated standard solution.

Determination of antibiotic concentration in aqueous solution

A reference solution for HPLC was prepared by dissolving 75.0 mg of standard substance in 25 ml of the mobile phase. The HPLC conditions were: C8 column, flow rate 1 ml/min, UV detector wavelength 210 nm and loop injector (20 μl). The mobile phase was a mixture of acetonitrile/KH_2PO_4 solution of pH 2.5 preadjusted with phosphoric acid.

Diffusion experiments

Cellulose acetate disc membranes (ø142 mm; Sartorius AG, Göttingen, Germany) were placed on each side of a cylindrical module (Figure 1), which consisted of three concentric steel rings (114 mm, i.d.), so that the total membrane surface area available for mass

transport was 204 cm^2. The width of the module, i.e. the distance between the two membranes was δ = 10 mm.

The experimental system shown in Figure 2 was used for measurements of the diffusion rates of the selected antibiotic from 1) the liposome dispersion and 2) a free antibiotic solution used as the reference. The initial antibiotic concentrations in the both liposome dispersion and reference solution were adjusted to 4% w/w. The experiments were performed at room temperature.

In the experiment with encapsulated liposomes, the dispersion was poured in the module before the upper membrane was placed between the middle and the upper ring of the cylindrical module (Figure 1). In the experiment with the reference solution, the solution was poured into the space between two membranes through a side hole on the middle ring of the cylindrical module (Figure 1). In both experiments, the module was placed in a glass container (10 l) filled with WFI and stirred with an IKAMAG® RCT basic stirrer, at a rate of 800 min^{-1}, and a Eurostar power control–visc propeller stirrer (IKA–Werke GmbH & Co. KG, Staufen, Germany), at a rate of 900 min^{-1}. Samples of water (1.5 ml) were taken at predetermined time intervals and the antibiotic concentration was determined by HPLC (EP – 1997, 2.2.29). In the experiment with the liposome dispersion, the liposomes were retained within the module, while small molecules of the released antibiotic could easily pass through the membrane pores into the aqueous solution in which the cumulative change in antibiotic concentration was measured.

At the end of the experiment with encapsulated liposomes, a sample (1.25 g) was taken from the module, and the content of the remaining antibiotic in the liposome dispersion was determined by a microbiological method, as described above.

RESULTS

Characterization of the obtained liposome dispersion

The antibiotic concentration in the liposome dispersion determined by the microbiological method,

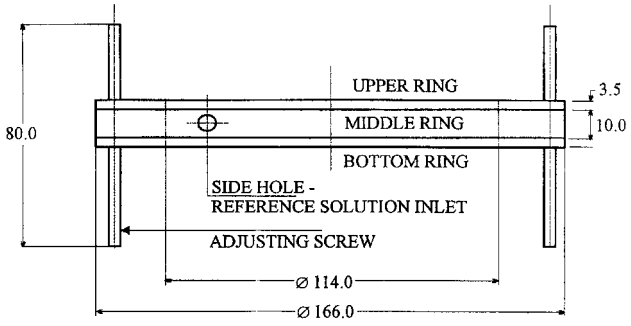

Figure 1. Cylindrical module applied for in vitro diffusion experiments (all dimensions are given in mm)

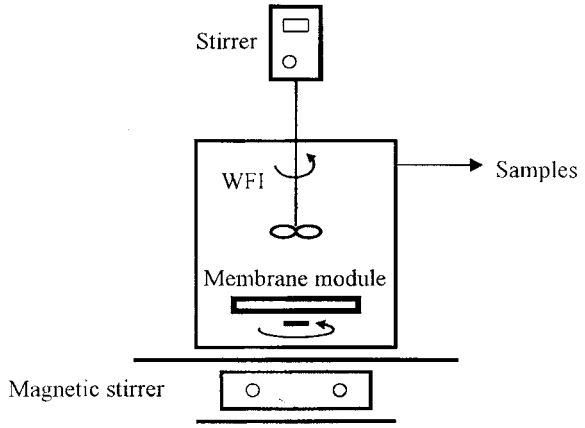

Figure 2. Experimental membrane system for evaluation of the controlled release of antibiotic from the selected liposome dispersion

was 95.8 % of the expected value (4% w/w), i.e. 3.83% w/w.

Figures 3 and 4 show the particle size distributions in the liposome dispersion after sonication, and after further homogenization in the Microfluidizer® Processor, respectively. It can be seen that the median liposome size after sonication was 0.9 μm, while after five passes through a homogenizing module under a working pressure of 85 bar, an even particle size distribution was obtained as expected, and the mean liposome diameter decreased to 0.38 μm.

Diffusion experiments

Cumulative changes in the concentration of the released antibiotic with time obtained for the liposome dispersion and the reference free antibiotic solution, are shown in Figure 5. The initial concentration of the selected antibiotic in the reference free antibiotic solution in the module was 37.25 mg/ml (3,72% w/w), determined by HPLC. The initial antibiotic concentrations in the liposome dispersion and the reference solution differed by approximately 0,1%.

The final antibiotic concentration remaining in the liposome dispersion at the end of diffusion experiment was determined by the microbiological method to be 1.04% w/w.

Two mathematical models were used to describe the experimental data gathered in both diffusion experiments. In both models, the liposome dispersion was regarded as a quasi–homogeneous medium, which was described by a single diffusion coefficient, similarly to the free antibiotic solution. In that way, the influence of the liposomes on mass transfer affected only the value of the diffusion coefficient [27]. Only diffusion in the axial direction was considered, while the concentration gradient in the radial direction was neglected.

The first model (model I) was a one–parameter, non–stationary, one dimensional model, in which all

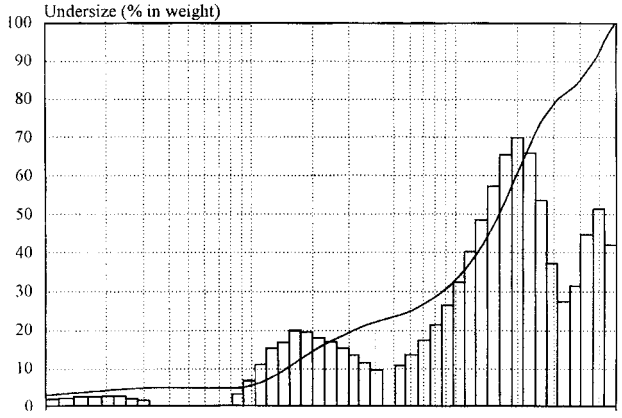

Figure 3. Particle size distribution in the liposome dispersion after sonication

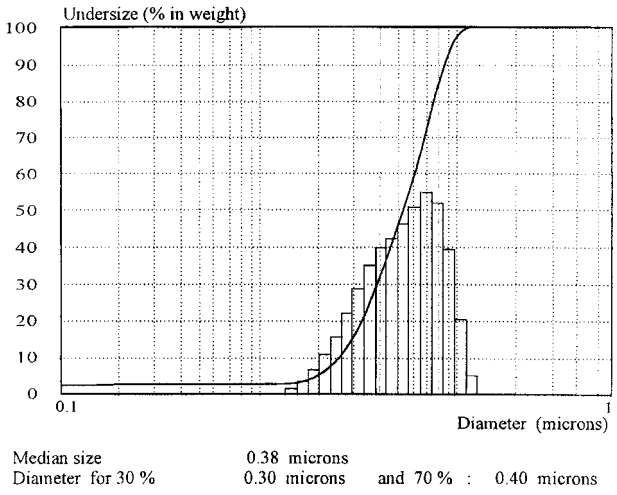

Figure 4. Particle size distribution in the liposome dispersion after homogenization in the Microfluidizer® Processor (5 cycles, 85 bar)

mass transfer resistances of the membrane and the boundary layers on both its sides were neglected.

The second (model II) model was a two–parameter model, which took into consideration the mass transfer resistances of the membrane and the fluid films on both of its sides. All these resistances were lumped in a single mass transfer coefficient.

Comparison of the model predictions (solid lines for model I and dashed lines for model II) with the experimental data (symbols) is given in Figure 6 for the experiment with the liposome dispersion and in Figure 7 for the experiment with the reference solution. For better insight into the results, part of Figure 6, corresponding to the beginning of the experiment, was enlarged and presented separately in Figure 8. By inspection of Figures 6 to 8, and the least square sums [27] it may easily be concluded that both models fit the experimental values well, although the two–parameter model II is slightly better, especially in describing the

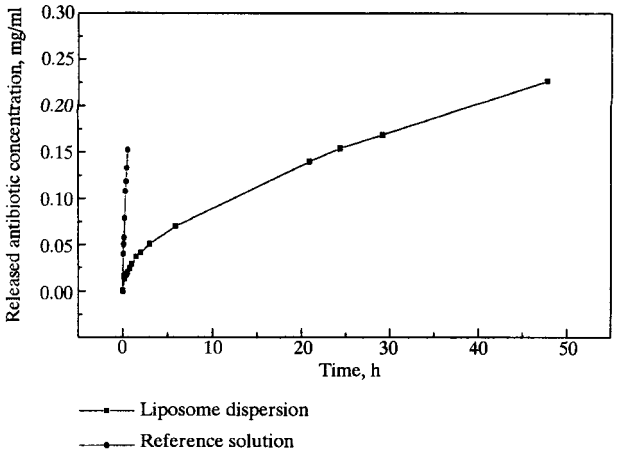

Figure 5. Cumulative changes in the concentration of the released antibiotic from the encapsulated liposome dispersion and the reference solution over time

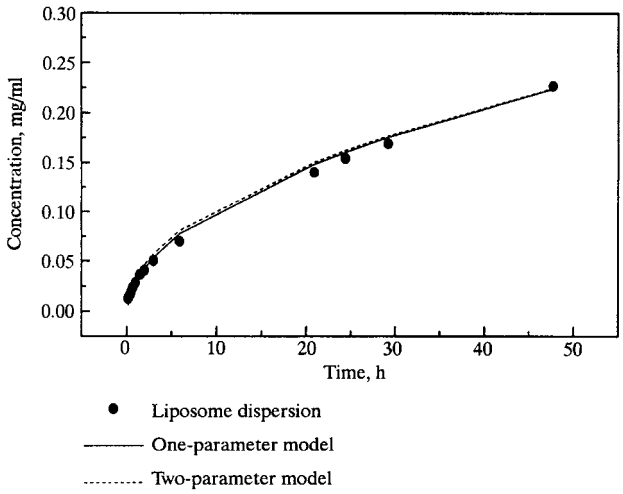

Figure 6. Comparison of the two diffusion models applied to the controlled release of antibiotic from the liposome dispersion in the experimental membrane system

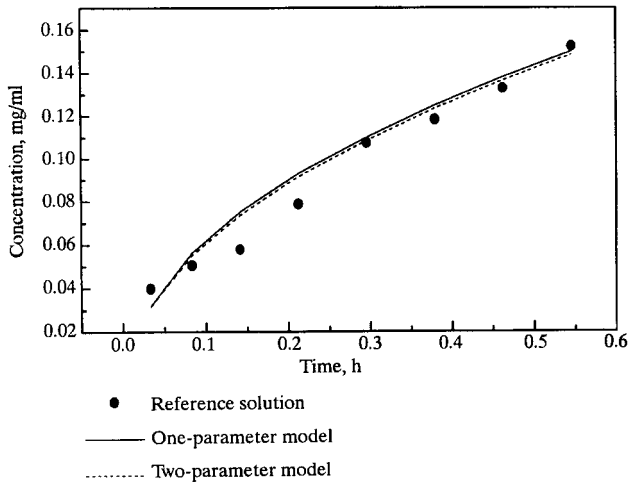

Figure 7. Comparison of the two mathematical models applied to antibiotic diffusion from the reference solution in the experimental membrane system

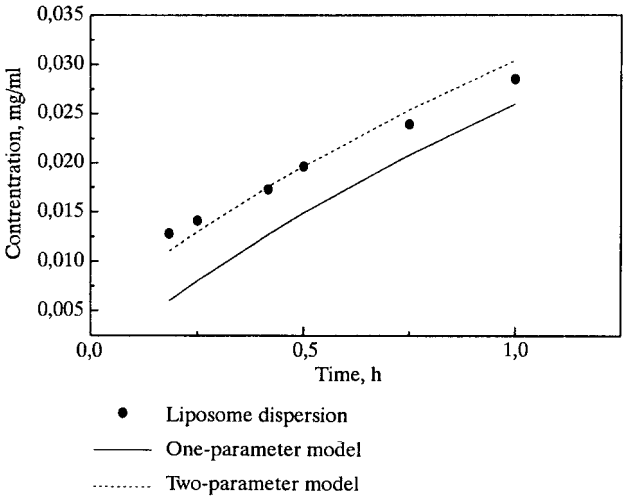

Figure 8. Comparison of the two mathematical models applied to antibiotic diffusion from the liposome dispersion at the beginning of the experiment

initial part of the experiment with the liposome dispersion (Figure 8).

Inspection of the estimated model parameters [27] shows a large difference in the diffusion coefficient obtained for the liposome dispersion and for the reference solution. This large decrease of the diffusion coefficient obtained in the liposome dispersion is actually a measure of the retention and prolonged release of the antibiotic encapsulated inside the liposomes. Another important result is that the same values of the diffusion coefficients were obtained with both models. Introduction of the additional parameter into model II only improved the fit of the experimental data, but did not influence the value of the diffusion parameter. Also, the same values of the mass transfer resistance coefficients were obtained for the liposome dispersion and for the reference solution. This suggests that the presence of liposomes on the inner membrane surface did not significantly affect the antibiotic transfer through the membrane.

DISCUSSION

In this study, we investigated the controlled release of a selected antibiotic from a liposome dispersion as a suitable carrier system, designed to be incorporated in the final form of a preparation for topical use. For this purpose, liposomes were prepared by the thin film method, using a special blend of hydrogenated soya phospholipids as the starting material, at exactly determined conditions, as shown previously.

Prior to liposome production, differential scanning calorimetry (DSC) was performed in order to determine the phase transition temperature of the selected phospholipid mixture, before and after purification in chloroform. The results of DSC revealed that the purification step slightly decreased the phase transition temperature of the phospholipid mixture, from 49.4°C to 45.8°C (mean values). In some cases, this property may be convenient for liposome preparations, since the phase transition temperature must be reached in the hydration process (addition of buffered aqueous solution of the active component). Thus, it can be concluded that the formation of thin film by chloroform removal in a rotary vacuum evaporator may be applied as a reasonable method in the first stage of the liposome production process, starting with the special blend of hydrogenated soya phospholipids used in this work.

Laser scattering results (Figures 3 and 4) showed that further homogenization of the liposome dispersion in the Microfluidizer® Processor (five cycles under a working pressure of 85 bar) led to a significant decrease in the mean liposome diameter, from 0.9 mm after sonication to 0.38 μm after homogenization. In addition, a very narrow size distribution of fine particles was obtained after five passes through the Microfluidizer® (Figure 4). As the working pressure was increased, more energy was imparted to the system, and smaller liposomes were produced [28]. On the other hand, the more passes through the homogenizing module, the more uniform they became. The liposome size distribution should be included in a more complex diffusion model and the correlation with the antibiotic release rate can be studied in the course of future experimental work.

Liposomes exhibited significantly slower antibiotic release from the dispersion in comparison with the reference solution, as shown in Figure 5. Examination of the antibiotic diffusion coefficients obtained by parameter estimation for both diffusion models, revealed that diffusion from the liposome dispersion was about 50 times slower than from the reference free antibiotic solution of the same initial concentration. Figures 6 and 7 present the comparison of two diffusion models applied to antibiotic release from the liposome dispersion and reference solution in the experimental system, respectively. Good agreement with experimental data was achieved using both models. Thus, the assumptions made in order to simplify the problem, by which liposomes were regarded as a quasi–homogenous medium, could be considered as justified. Furthermore, the difference between the two mathematical models was negligible for the liposome dispersion, as well as for the reference free antibiotic solution. This fact led to the conclusion that the one–parameter model was satisfactory when it came to approximation of the experimental data gathered in the course of this study. Also, since k > D, the released antibiotic diffused rapidly into the sink solution, indicating that the membrane was not the rate–limiting step under the experimental conditions used.

Nevertheless, the second two–parameter model gave a slightly better fit of experimental data, especially in the case of antibiotic release from the liposome dispersion, at the beginning of the experiment (Figure 8). Since the presence of liposomes in the cylindrical module did not affect the mass transport through the

cellulose acetate membrane and boundary layers, the established experimental system could be successfully used for kinetic studies of antibiotic release from the investigated liposome dispersion.

CONCLUSIONS

An experimental protocol was established for evaluation of the controlled release of a selected antibiotic from a liposome dispersion obtained by the thin film method, followed by sonication and further homogenization in the Microfluidizer® Processor.

Suitable methods for characterization of the examined liposome dispersion were applied. The liposome size distribution was one of the most important parameters measured and the obtained results showed an extremely uniform distribution of fine particles (0.38 μm in diameter) after five passes through the homogenizer, under a working pressure of 85 bar. Thus, the applied process conditions led to satisfactory homogenization of the encapsulated liposome dispersion.

The controlled release rate from the liposome dispersion was studied using a cylindrical membrane module and by measuring cumulative changes in the concentration of the released antibiotic with time. The results showed significantly prolonged release of the selected antibiotic from the liposome dispersion as compared to the reference free antibiotic solution of the same initial concentration.

The experimental protocol established in this work could be extended to other liposome dispersions obtained using different production methods, with different active components and under different experimental conditions. Furthermore, the simple experimental system established in this work could be applied for *in vitro* evaluation of different liposome formulations, and the best carrier system, with respect to the release rate of the encapsulated material, could be selected for finalization of the product and further experiments in vivo.

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IZVOD

IN VITRO ISPITIVANJE KONTROLISANOG OTPUŠTANJA ANTIBIOTIKA IZ LIPOSOMA

(Naučni rad)

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Rezultati su pokazali značajan efekat produženog oslobađanja odabranog antibiotika iz lipidnih vezikula u membranskom sistemu sa cilindričnim modulom (namenski dizajniran u cilju mimike sistema primene topičnog preparata na koži) u poređenju sa rastvorom leka iste inicijalne koncentracije koji je podvrgnut istim eksperimentalnim uslovima. Dva modela nestacionarne, jednodimenzione difuzije primenjena su za predviđanje brzine oslobađanja leka iz lipidnih vezikula u cilindričnom membranskom modulu. Oba modela su pokazala dobro slaganje sa eksperimentalnim rezultatima i predskazala približno pedeset puta sporije otpuštanje iz lipidnih vezikula u poređenju sa čistim rastvorom leka. Osim toga, rezultati matematičkog modelovanja su pokazali da celulozno–acetatna membrana ima zanemarljiv uticaj na ukupnu brzinu oslobađanja leka. Ovakav rezultat potvrdio je pogodnost primenjenog eksperimentalnog sistema za ispitivanje kinetike otpuštanja odabranog antibiotika iz lipidnih vezikula.

Kako se pokazalo da je otpuštanje leka iz disperzije lipidnih vezikula sporije u poređenju sa čistim rastvorom antibiotika, ovakav sistem nosača sa inkapsuliranim antibiotskim agensom ima prednost kada je u pitanju njegovo ugrađivanje u finalni oblik topičnog preparata za dalja ispitivanja *in vivo*. Odabrani eksperimentalni sistem se može primeniti i na druge formulacije na bazi lipidnih vezikula, za ispitivanje kinetike otpuštanja inkapsuliranih aktivnih supstanci. Na taj način bi se mogla uspostaviti relevantna metoda za *in vitro* karakterizaciju i poređenje različitih sistema nosača aktivnih komponenti.

Key words: Membrane module • Controlled release • Liposomes • Diffusion • Modeling •
Ključne reči: Membrana • Kontrolisano otpuštanje • Lipidne vezikule • Difuzija • Modelovanje •