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LIPOSOME DELIVERY SYSTEMS CONTAINING IBUPROFEN

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ABSTRACT

Multilamellar liposome vescicles containing ibuprofen were successfully prepared by hydrating the lipids in the presence of organic solvent. The effects of varying the ratio of lipid to drug; the filter size; and the stirring period during hydration of the dried lipids layer were evaluated. Liposomes sample prepared by using a ratio of 3 lipid: 1 drug gave the highest entrapment efficiency of the drug and released all the drug over 12 hours of testing dissolution. Also the dissolution data showed that the drug release from large liposomes (5.0 μm) was 65.7% after 12 hours; 62.6% from medium size (0.8 μm) and 46.6% from small size liposomes (0.22 μm). Additionally, the increase of the stirring period during hydration of the dried lipid layer with the aqueous phase increased the release of the drug from the liposomes.

INTRODUCTION

Liposomes are microscopic vescicles consisting of one or more concentric spheres of lipid layers separated by water or aqueous buffer compartment (1). Clinical and animal studies have demonstrated the ability of liposomes

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to encapsulate and effectively deliver a diverse assortment of drugs (2-4).

The preparation of spontaneous liposome vescicles by dissolving a mixture of lipids in a suitable organic solvent and removing it by solvent vaporization or solvent sublimation are the most widely studied type of liposome (5-7). Stability and leakage of some liposome preparations were also studied by some authors (8-9).

The short serum half life of ibuprofen (1.8 to 2.0 hours), in addition to the adverse reactions and intestinal retention associated with carriers as polymeric materials have led this drug to be considered as a good candidate for entrapment into the liposome vesicles. The purpose of this study is to evaluate the process of preparing ibuprofen liposomes by hydration of the dried lipid film. Additionally to investigate the effect of parameters such as composition of the liposomes, size, and time of stirring during hydration of the dried lipids on the entrapment efficiency of the drug, physical properties and on drug release.

MATERIALS AND METHODS

Materials

Ibuprofen (supplied by UpJohn Inc., P.R.) was chosen as the drug model. The lipids selected were soy bean lecitin; cholesterol; and cholesteryl hemisuccinate (Sigma, USA). All other chemicals were of anlytical grades.

Preparation and characterization of liposomes

The composition of the different liposome formulations are shown in Table 1. Initially three different formulations composed of different ratios of lipid to drug (batch 1 to 3) were prepared in order to select the best formula, which will give highest entrapment efficiency and best release profile.

The aqueous phase was prepared by dissolving ibuprofen (4.5 g) in phosphate buffer pH 7.4, USP XXI (100 mL). The lipid phase was prepared by dissolving the lipid components in chloroform (300 mL). Subsequently the chloroform was evaporated (at 55^0 C) and a dried lipid mixture was produced.

The drug aqueous solution was incorporated into the dried lipid film at room temperature. The liposome dispersion was stirred for 5 hours using mixer set at 705.50 rpm (Dyna Mix, Fisher Scientific Instruments) to

TABLE 1

Composition Of The Different Liposome Formulations

Batch NO.:	Lipid:Drug Ratio	Filter Pore Diameter;μm	Stirring Time; Hours
1	1:1	0.22	5
2	2:1	0.22	5
3	3:1	0.22	5
4	3:1	5.0	5
5	3:1	0.80	5
6	3:1	0.22	2
7	3:1	0.22	12

help in the swelling process of the phospholipids. An extrusion technique was used to reduce the size of the vescicles. For extrusion the liposomes vescicles were placed in a dispensing pressure vessel and were extruded through polycarbonate membrane filter of 0.22 μm pore diameter (Millipore Inc.) using nitrogen gass under 80 psi.

Liposome formulation composed of 3 lipid to 1 drug ratio (batch No. 3) was selected to evaluate different parameters such as the effect of extrusion through different membrane filter of different opening diameter (5 μm and 0.8 μm); and the stirring period during the hydration of the dried lipid layer (2 hours and 12 hours).

Dissolution studies

The dissolution test was carried out in 500 ml phosphate buffer of pH 7.4 at 37±0.5°C using the rotating basket apparatus (Hanson Research, Model SR2,USA) at 50 rpm. A known quantity of liposome formulations (0.5 g) were placed in the basket and tested for dissolution over 12 hours. Filtered samples were withdrawn manually at pre-determined time intervals and assayed using a UV spectrophotometer (Beckman Instruments, Model DU 65, USA) at 223 nm. Three replicates were tested and their mean percent release calculated.

Scanning electron microscope

The surface morphology of the different liposome formulations was investigated by scanning electron microscope (Autoscan, ETEC) with magnification of 5000X.

RESULTS AND DISCUSSION

Liposomes from the different formulations were prepared successfully. Figure 1 showed the scanning electron photomicrograph of liposome before extrusion prepared at a ratio of 3 lipids:1 drug. The liposome vescicle is spherical and the lipid bilayer compartment is clear.

Figure 2 showed that the percent of ibuprofen released from liposomes containing 1 lipid:1 drug was 35% after 12 hours of testing dissolution, while liposomes containing 2 lipids:1 drug released only 89%. Liposomes prepared at a ratio of 3 lipids:1 drug were of the highest entrapment efficiency of the drug and they released all the drug after 12 hours of testing dissolution.

As shown in Figure 3, the size of liposomes was decreased as the size of filter (opening) used for extrusion was decreased. Figure 4 showed that the drug release from liposome extruded through filter of large opening size (5 μm) was 65.7%; For medium opening size filter (0.8 μm) was 62.62%; and For small size opening filter (0.22 μm) was 46.6%. As the opening size of the filter increased, the drug release from the liposomes increased, due to the fact that large size liposomes entrapped more drug.

The period of mixing during the hydration of the dried lipid layer with the aqueous phase had significant effect on the drug release from the prepared liposomes. As shown in Figure 5, the drug release from liposomes prepared by mixing for 2 hours was 54.48%, while the drug release from liposomes of the same composition but prepared by mixing for 12 hours was 100.7% after 12 hours of testing dissolution. Figure 6 showed that as the stirring time during hydration of the lipid layer was increased, the liposome size was decreased.

CONCLUSIONS

In conclusion, this work presents some new evidence that tends to confirm recent findings in the sense that it is possible to modify the drug release from liposome

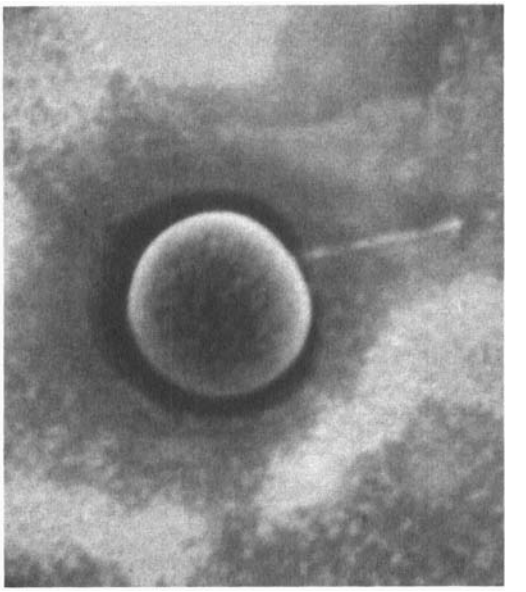

FIGURE 1

Scanning Electron Micrograph of Ibuprofen Liposomes Containing 3 Lipid:1 Drug; 5000 X.

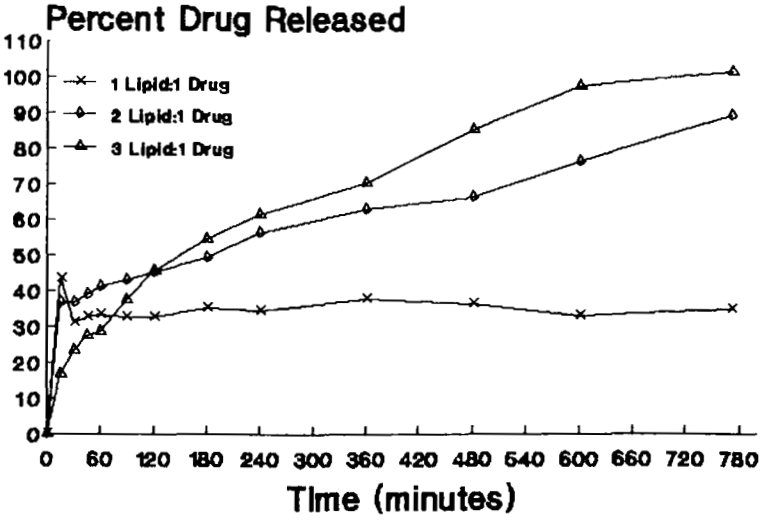

FIGURE 2

Effect Of Varying The Lipid:Drug Ratio On Ibuprofen Release

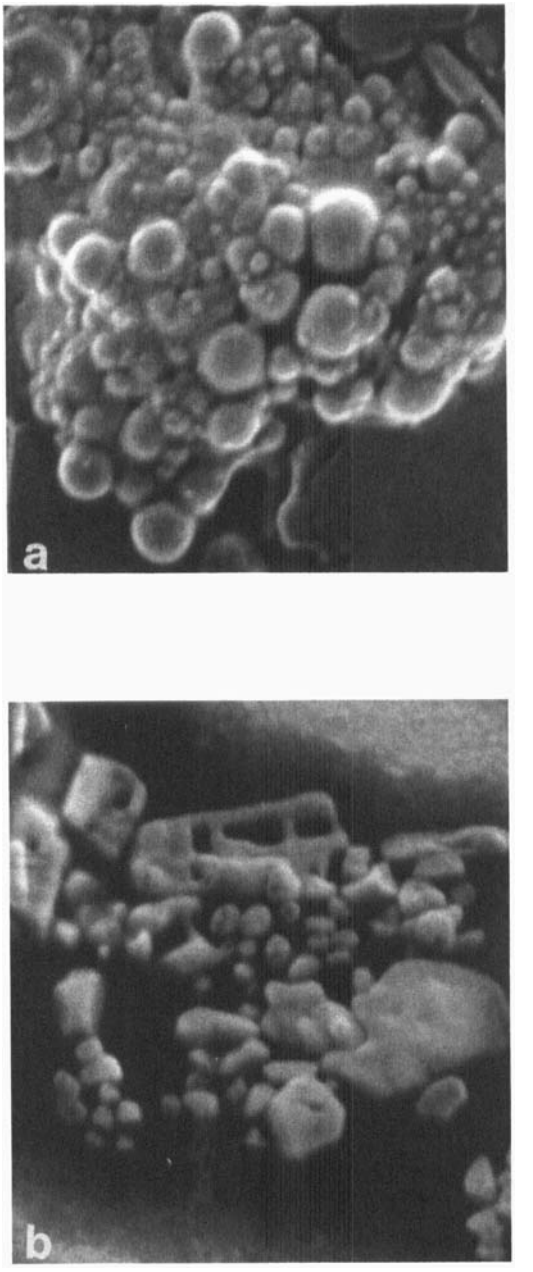

FIGURE 3

Scanning Electron Micrographs Of Ibuprofen Liposomes Containing 3 Lipid:1 Drug. (A) 5 μm Filter Size; (B) 0.22 μm Filter Size; 5000 X

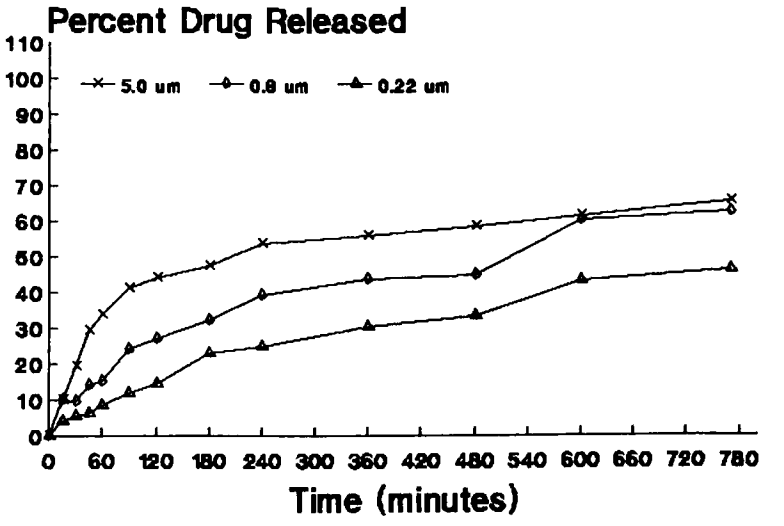

FIGURE 4

Ibuprofen Release From Liposomes Of Different Sizes

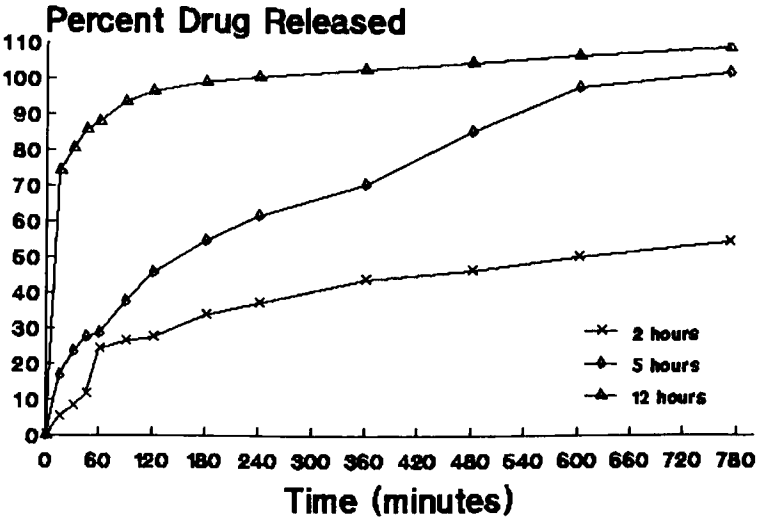

FIGURE 5

Effect Of Varying The Stirring Time On Ibuprofen Release

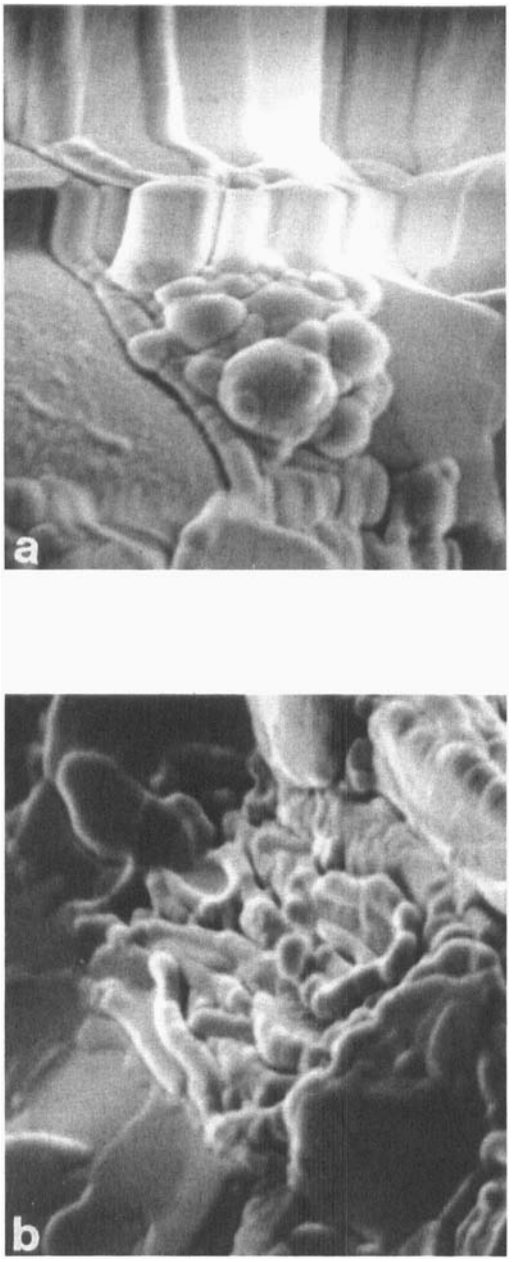

FIGURE 6

Scanning Electron Micographs of Ibuprofen Liposomes Containing 3 Lipid:1 Drug Prepared At Different Stirring Time. (A) 5 Hours; (B) 12 Hours; 5000 X.

vescicles by controlling the stirring period during hydration of the dried lipids; varying both drug and lipid levels; size (opening diameter) of the membrane filter used in the extrusion process; and also by varing the ratio of the components of the lipid phase.

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