PHARMACEUTICAL NANOTECHNOLOGY

Drug Release from Differently Structured Monoolein/Poloxamer Nanodispersions Studied with Differential Pulse Polarography and Ultrafiltration at Low Pressure

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ABSTRACT: Aqueous colloidal monoolein/poloxamer dispersions are under investigation as drug delivery systems. Depending on the composition and preparation procedure these dispersions may either contain predominantly vesicular particles or nanoparticles of cubic inner structure. To study the influence of ultrastructure on drug release, corresponding dispersions loaded with the model drugs diazepam (two different concentrations) and chloramphenicol were prepared by high-pressure homogenization with or without subsequent heat treatment. The dispersions were characterized with regard to particle size and their ultrastructure was confirmed with small angle X-ray diffractometry. Two techniques with high time resolution, differential pulse polarography (DPP) and ultrafiltration at low pressure were compared for their suitability to monitor rapid release from the dispersions. Instantaneous release was found for both drugs independent on the type of particle structure with the amount of released drug being controlled by the partition coefficient. Both release methods were suitable to monitor the rapid appearance of the releasable drug in the release medium.
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INTRODUCTION

Monoolein/water mixtures can form different lyotropic liquid crystalline structures in dependence on concentration and temperature.[1] Especially the cubic phase, a highly ordered, three-dimensional structure of the bicontinuous type which contains high amounts of water (up to ~40%) is interesting for drug delivery. Hydrophilic, hydrophobic, and amphiphilic drugs can be incorporated in the different domains of the cubic phase. The bulk cubic phase can be used, for example, for topical administration[2] and is under intensive investigation for its drug release properties.[3–5] The cubic monoolein/water phase is stable in excess water and can be dispersed into colloidal particles with cubic inner structure by

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addition of a stabilizer (e.g., poloxamer 407) and high-pressure homogenization of the preequilibrated system[1,6–7] or alternative ways of preparation which avoid high shear forces.[8–9] Colloidal dispersions of cubic nanoparticles have been proposed as parenteral drug delivery system, including their use for intravenous administration,[10] but they are also under investigation with regard to peroral[9] and topical administration.[11] Depending on preparation parameters, not only cubic phase particles have been found in homogenized dispersions, but also a fraction of vesicular particles. In particular, the use of high concentrations of poloxamer in high-pressure homogenized systems results in dispersions containing mainly vesicular particles and only a small amount of internally structured particles.[12–13] The vesicular particles can be transformed into cubic particles by heat treatment, for example by autoclaving the dispersions at 121°C.[13] It is thus possible to prepare vesicular and cubic phase dispersions with exactly the same composition of ingredients. The vesicular to cubic phase transformation upon autoclaving does also take place in the presence of various drugs[14] (e.g., betamethasone valerate, chloramphenicol), although small differences in the particle size or the lattice constant of the autoclaved dispersions may occur.

The aim of the present study was to investigate the influence of the different internal structures of the dispersions (vesicular or cubic phase particles) on drug incorporation and especially on drug release upon dilution to simulate the release after intravenous administration.

A general problem of monitoring drug release from colloidal particles is that the nanoparticles interfere with many analytical techniques used to determine the drug content in the release medium. Therefore, separation of the drug-containing medium from the colloidal particles is usually required. Release methods using this principle include membrane diffusion techniques, sample and separation methods or continuous flow techniques.[15] As shown in several studies,[16–18] the convenient and frequently used dialysis bag membrane diffusion method (in which the dispersion is placed into a dialysis bag and the concentration of the drug in the dialysis buffer is monitored over time) leads to highly misleading drug release results since the particles are not in direct contact with the release medium. To obtain undistorted release profiles, the drug-containing dispersions must be diluted directly into the release medium. For the "sample and separation" (separation by filtration or centrifugation) and the "continuous flow" (e.g., use of an ultrafiltration cell with continuous analysis of the drug content) techniques the separation step is usually quite time consuming or the drug concentration increases with a lag time, respectively. Methods which do not require separation, that is, *in situ* techniques, are thus highly desirable. These can be, for example, electrochemical methods,[19–20] where the drug concentration is directly measured in the release medium also containing the drug carrier.

It has been shown previously that colloidal lipid dispersions like submicron emulsions containing liquid or liquid crystalline particles release incorporated lipophilic substances rapidly.[16,19,21] Based on these previous results we assumed that the drug release from vesicular and cubic phase monoolein/poloxamer particles would be quite fast. We were thus aiming at selecting release methods which provide very fast and accurate measurements and would be able to reveal possibly small differences in release behavior between vesicles and cubic particles. In the present study two methods were tested and compared for their suitability of monitoring rapid drug release and for the use with vesicular and cubic phase monoolein particles. One technique is ultrafiltration at low pressure[21] where the dispersion is diluted in the release medium and the released drug is subsequently separated from the dispersion by an ultrafiltration membrane. Drug analysis was done with UV spectroscopy and high performance liquid chromatography (HPLC), respectively. The ultrafiltration technique was chosen because it offers the possibility of a comparatively fast separation of drug from the carrier. The second method is an electrochemical *in situ* technique, differential pulse polarography (DPP), which does not require separation of drug containing release medium from the carrier. Therefore, it should be a suitable method for measuring fast release. The principle of polarography is the reduction of drug substances, which reach the dropping mercury electrode by diffusion.[22] This is only possible for the free drug in the release medium, but not for drug incorporated in the nanoparticles.[23] DPP is also a very specific and sensitive technique, which offers the possibility to determine traces of drug in a highly diluted dispersion. The method is limited to electrochemically active substances, but there is a wide range of different drugs which