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Cover Story

Not all liposomes are created equal

Liposomes were first developed by Dr. Alec Bangham in the early 1960s, and they were initially called "Bangosomes." Since the introduction of liposomes for applications in life sciences, many groups have used these lipid vesicles for drug delivery. The initial assumption was simply that, like erythrocytes, liposomes in the blood stream would circulate for an extended period of time, thereby gradually delivering their cargo to the target sites. Early enthusiasm, however, declined quite fast upon noticing that plain liposomes are eliminated rapidly from the blood stream. In the last two decades, it was noticed that elimination from blood circulation could be delayed by modifying the liposome surface with poly(ethylene glycol) (PEG) through PEGylated lipids [1].

While PEGylated liposomes have been shown to increase the blood circulation time, not many studies have been done on the fate of the drug loaded inside the liposomes. Hydrophilic drugs incorporated in the aqueous core of the liposome are not expected to affect the characteristics of the liposomal carrier. After intravenous (i.v.) injection, liposomes can gain access to the target site and be ingested by target cells, upon which the drug can be released. On the contrary to the hydrophilic drugs present in the aqueous core, hydrophobic drugs, residing inside the liposomal lipid bilayer, behave as considerably more active passengers. In fact, not only might they change the physical properties of the lipid host, they are also prone to transfer to lipophilic binding sites in the blood [2]. This has been underestimated for a long time, as it was assumed that a lipophilic drug remains firmly associated with the hydrocarbon core of the hosting bilayer. Equally premature was the assumption that a more rigid bilayer provides a more stable binding site for the drug inside the membrane. In fact, the opposite was found upon measurements of drug transfer from donor to acceptor liposomes *in vitro* combined with corresponding modeling of the underlying kinetics [3]. Fluidity and high flexibility of the host bilayer appeared to provide a more favorable environment for a poorly water-soluble drug than a rigid bilayer, resulting in a tighter association. In some cases, drug molecules are separated to form aggregates or crystals. In other cases, the expelled drug molecules bind to the hydrophobic sites of blood proteins. Naturally, all this is strongly influenced by the specific structure of the lipophilic drug, but the influence of the bulk lipids is an equally crucial component that provides an opportunity to control the release kinetics.

Do these theoretical and *in vitro* considerations bear any relevance to an *in vivo* environment? The work published by Decker et al. in this issue of the Journal addresses this question. A very hydrophobic drug was incorporated into liposomes, and the independent pharmacokinetics of drug and liposome were studied in a rat model after i.v. injection. The individual elimination kinetics of drug and liposome were measured using radioactive labeling. Following the development of an appropriate kinetic modeling approach, the authors translated their data into a correlation coefficient indicating that there is always an amount of drug removed from the blood prior to the removal of the host liposomes. This amount is significant but strongly dependent on the composition and surface modification of the liposomes. The *in vivo* data lead to similar conclusions as in previously performed, corresponding *in vitro* model studies [3]. Specifically, liposomes with more rigid bilayers exhibit higher drug transfer rates to lipoproteins than liposomes with more flexible bilayers. Although PEGylation of the liposomes *per se*, as expected, does lead to longer circulation time, the lipophilic drug is released from these liposomes at a higher rate. This might be attributed to the formation of drug-carrying micelles from the PEGylated lipids or to a less tight secondary binding location of the drug within the PEG-containing liposomal bilayer. It is also noteworthy that liposomes containing polyglycerol-lipids, which prolong circulation time but do not form micelles do not exhibit such an enhanced drug release.

In retrospect, it should have been obvious that liposomal drug carriers lose the loaded drug by simple diffusion over time, and thus, the more drug loss occurs after longer blood circulation. The drug loss from liposomes becomes even more significant by the additional mechanisms of drug removal from the carriers. The *in vivo* study by Decker et al. [4] is highly valuable, because it is probably the first systematic attempt to link their results to preceding *in vitro* studies, combined with theoretical modeling. The study provides concrete mechanisms of the underlying drug transfer processes. These results could eventually lead to the design of liposome drug delivery systems with minimal loss of lipophilic drug to blood components. Maintaining the loaded drug inside the delivery vehicle is important not just for liposome formulations but also for all other i.v. administered formulations.

References

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