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The Use of Coating Agents to Enhance Liposomes Blood Circulation Time

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The efficient use of drugs requires that they must be delivered selectively to the site of action. This is especially true for potent drugs with strong side effects, such as anti-cancer drugs [1]. Nowadays, drug delivery systems (DDS) studies focus on achieving selective delivery and distribution of drugs to the target disease sites in order to enhance safety and effectiveness. Thus, several types of particulate systems such as liposomes, emulsions, and polymeric nanoparticles have been evaluated as effective DDS [2].

Clinical applications of liposomes as injectable drug carriers have been extensively investigated due to their biocompatibility and effective drug encapsulating property. However, liposomes that are administered through intravenous injection are rapidly uptaken by reticuloendothelial system (RES) cells in the liver and spleen [3]. Therefore, techniques based on surface modification have been developed for preventing the uptake by RES cells in order to increase the liposomes effectiveness. Polyethyleneglycol (PEG) has often been used to extend the circulation time of liposomes [3,4]. PEG is a highly hydrophilic polymer with very low toxicity; hence, PEG and its derivatives have been widely used to improve the stability and pharmacokinetics characteristics of drug carriers. A worth mentioning example is the doxorubicin-loaded PEGylated liposomes (Doxil®) which have a potent, yet low toxic, pharmacological effect. Thereby, PEGylated liposomes have been widely used in clinical applications and are approved in more than 80 countries for cancer treatment [4].

It is known that the incorporation of polyethyleneglycol on liposome surface leads to the formation of a fixed aqueous layer thickness (FALT) around the nanoparticle due to an interaction between the PEG-polymer and water molecules, which prevents the attraction of opsonins, since serum proteins are unable to bind to the water gathered on the surface of the liposomes [4,5]. As a result, PEG-modified liposomes avoid being captured by RES cells, thus having a prolonged circulation time and accumulating in tumors by passive targeting [5,6]. The size of FALT is influenced by the PEG molecular weight, so the FALT, typically, increases when a larger PEG is used [7]. Moreover, several studies indicate that a maximum FALT is found using a mixture of PEG with long and short chains of polymer. This mixture may favor the formation of 'brushes' structures (extended chain conformations determined by the interaction between neighboring chains), giving a greater steric barrier around the nanoparticle [5,7,8]. However, the amount of PEG inserted in the liposome membranes is limited, because there is a maximum concentration of PEG from which this polymer promotes destabilization of the lipid bilayer and as a consequence the FALT reaches plateau [9]. Also, since FALT around liposomes is shown to correlate with their biodistribution, FALT is a very important characteristic to be considered regarding PEG-coated liposomes specificity [10].

The incorporation of lipid-conjugated PEG into liposomal drug systems enhances the circulation time of liposomes, and in the absence of encapsulated or surface coupled proteins, PEGylated liposomes are generally considered to be non-immunogenic [11]. However, some studies have reported that upon repeated injection, PEGylated liposomes produce a strong immune response. The phenomenon involves sequential events, including induction of anti-PEG IgM antibody production in the spleen by the first dose of PEGylated liposomes, complement activation by the IgM antibody and opsonization by C3 fragments following the second dose of PEGylated liposomes, and their uptake by mononuclearphagocyte system [11-13]. This phenomenon, known as accelerated blood clearance (ABC) phenomenon, has been observed in rat, rhesus monkey and mouse. After repeated injections, circulation time of PEGylated liposomes decreases while their uptake by the liver increases concomitantly [11,14].

The exact mechanism involved in this phenomenon is not clear, but it was demonstrated that the magnitude of the ABC phenomenon depended on the properties of injected liposomes as a first dose, time interval between injections, lipid dose and drug encapsulation [15,16]. Wherein, studies showed a strong inverse correlation between the lipid dose of the first injection and the extent of the ABC phenomenon [17,18]. Moreover, the time between the injections can determine the occurrence or not of this reaction, yet, in general, the ABC effect occurs when dosages are administered in a lower interval of time (1-3 weeks). However, this phenomenon has not been reported to occur in patients; this fact could be explained by the fact that PEGylated drugs, such as Doxil®, are typically used in a longer interval of dose (3-6 weeks). In addition, the drug cytotoxicity can damage the immune system cells responsible for this phenomenon [18,19].

After the discovery of the ABC phenomenon, alternatives to the use of PEG emerged. One alternative is the development of PEG linked to lipids by ester bonds, so that, after the chemical bond being gradually cleaved, PEG would dissociate from the particle surface, preventing or reducing the occurrence of ABC phenomenon. Compared with the un-cleavable PEG-lipids, the advantage of esterase catalyzed cleavable PEG-Lipids rely on the fact that the synthesis of these compounds is very simple and esterase exists throughout the animal body. In addition, the cleavable PEG-lipid modified liposomes preserve the long circulation properties demonstrated by un-cleavable ones [12].

Other approaches have been using different polymers as an alternative for preparing long-circulating liposomes [20,21]. Non-biodegradables polymers, such as PEG itself, are not easily degraded inside the cells; this might impair the cell function. In order to avoid that, Metselaar et al., developed liposomes coated with biodegradable and biocompatible polymers, based on hydroxyalkyl derivatives of L-glutamine and

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L-asparagine as monomers. Results indicated that this new formulation possess similar circulation time when compared to PEG-liposomes. This finding suggests that biodegradable polymers can also be a good alternative to improve nanoparticles circulation [20]. In addition to synthetic polymers, the use of natural hydrophilic compounds such as carbohydrates has also been investigated. The inclusion of certain gangliosides, such as monosialoganglioside (GM1), which confer to the liposome surface a negative charge and increased water-solubility, might enhance liposome stability in plasma and prolongs liposome half-life in blood with a concomitant decrease in liver and spleen uptake. These approaches might also be alternatives to using PEG [22,23].

In conclusion, to this date, PEG-liposomes are the only polymer-coated liposomes that have been approved for clinical use. Despite the occurrence of ABC phenomenon reported after PEG-liposomes applications, to the best of our knowledge no new coating molecule showed strong evidence that they present superior characteristics than those described for PEG-liposomes. The benefits, in terms of pharmacokinetic profiles and therapeutic effects, possessed by the use of PEG, make this polymer the best choice for coating long-circulating liposomes. Still, research in order to develop new polymer derivatives or even other molecules that can surpass the advantages brought by the use of PEG should be encouraged. However, although many molecules have been reported as an alternative for improving liposomes circulation time, much remains to be done to obtain new formulations with suitable pharmacokinetic properties, acceptable therapeutic efficacy, and also, low or none toxicity. With that in mind, new formulations must be developed and evaluated to be used in clinical trials in a near future.

References

1. Panagi Z, Beletsi A, Evangelatos G, Livaniou E, Ithakissios DS, et al. (2001) International Journal of Pharmaceutics 221: 143-152.
2. Yoshino K, Nakamura K, Terajima Y, Kurita A, Matsuzaki T, et al. (2012) Biochimica et Biophysica Acta 1818: 2901-2907.
3. Sadzuka Y, Nakai S, Miyagishima A, Nozawa Y, Hirota S (1995) J Drug Targeting 3: 31-37.
4. Shimada K, Miyagishima A, Sadzuka Y, Nozawa Y, Mochizuki Y, et al. (1995) J Drug Targeting 3: 283-289.
5. Sugiyama Y, Sadzuka Y (2007) Biol Pharm Bull 30: 208-211.
6. Sadzuka Y, Nakade A, Hirama R, Miyagishima A, Nozawa Y, et al. (2002) Int J Pharm 238: 171-180.
7. Schmitz S, Allen T M, Jimbow K (1992) Cancer Res 52: 6638-6645.
8. Sadzuka Y, Nakade A, Tsuruda T, Sonobe T (2003) J Control Release 91: 271-280.
9. Sugiyama I, Sadzuka I (2013) Int J Pharm 441: 279-284.
10. Sadzuka Y, Nakai S, Miyagishima A, Nozawa Y, Hirot S (1997) Cancer Lett 111: 77-86.
11. Ishida T, Atobe K, Wang X, Kiwada H (2006) Anti-PEG IgM Response against PEGylated Liposomes in Mice and Rats. J Control Release115: 251-258.
12. Xu H, Wang KQ, Deng YH, Chen DW (2010) Biomaterials 31: 4757-4763.
13. Lu W, Wan J, She Z, Jiang X (2007) Brain delivery property and accelerated blood clearance of cationic albumin conjugated pegylated nanoparticle. J Control Release 118: 38-53.
14. Ishida T, Ichihara M, Wang X, Kiwada H (2006) J Controlled Release 115: 243-250.
15. Li C, Zhao X, Wang Y, Yang H, Li H, et al. (2013) Int J Pharm 443: 1-2,17-25.
16. Laverman P, Carstens MG, Boerman OC, Dams, ET, Oyen WJ, et al. (2001) J Pharmacol Exp 298: 607-612.
17. Dams ET, Laverman P, Oyen WJ, Storm G, Scherphof GL, et al. (2000) Accelerated blood clearance and altered biodistribution of repeated injections of sterically stabilized liposomes. J Pharmacol Exp Ther 292: 1071-1079.
18. Laverman P et al. (2001) Factors Affecting the Accelerated Blood Clearance of Polyethylene Glycol-Liposomes upon Repeated Injection 298: 607-612.
19. Ishida T, Masuda K, Ichikawa T, Ichihara M, Irimura K (2003) Anti-PEG IgM Response against PEGylated Liposomes in Mice and Rats. Int J Pharm 255: 167-174.
20. Metselaar JM, Bruin P, De Boer LWT, De Vringer T, Snel C, et al. (2003) A novel family of L-amino acid-based biodegradable polymer-lipid conjugates for the development of long-circulating liposomes with effective drug-targeting capacity. Bioconjug Chem 14:1156-1164.
21. Torchilin VP, Levchenko TS, Whiteman KR, Yaroslavov AA, Tsatsakis AM, et al. (2001) Biomaterials 22: 3035-3044.
22. Gabizon A, Papahadjopoulos D (1988) Proc Natl Acad Sci 85: 6949-6953.
23. Liu A, Mori L, Huang (1991) Biochim Biophys Acta 1066: 159-65.