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Juliana de Oliveira Silva and André Luís Branco de Barros*

Department of Clinical and Toxicological Analyses, Faculty of Pharmacy, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

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***Corresponding author:** André Luís Branco de Barros, Department of Clinical and Toxicological Analyses, Faculty of Pharmacy, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, Tel: +55 31 34096840; E-mail: brancodebarros@yahoo.com.br

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Editorial

Toxicological Issues Faced after Liposomes Administration

Abbreviations

HSRs: Hypersensitivity Reactions; C: Complement system; PEG: Polyethyleneglycol; PE: Phosphatidylethanolamine

Editorial

Nanoparticles are defined as structures in nanometric range - often smaller than 100 nm [1-4]. These particles can be made of sundry materials, the most common being metals, metal oxides, silicates, polymers, carbon, lipids and biomolecules. In addition, they can assume different shapes such as spheres, cylinders, platelets, tubes, etc. The study of these structures in living organisms, for diagnosis, monitoring physical and pathologic processes, therapy and control of biological systems is known as nanomedicine [1].

The study and development of these nanoparticles, mainly lipid carriers, has gained great notoriety for many uses, especially due to their potential as cytotoxic drugs carriers. Over the years, many lipid nanosystems have been developed and applied for different purposes. Liposomes are one of the most studied nanocarrier since Bangham and colleagues [5] reported their preparation in 1965. Afterwards, several kinds of enclosed phospholipid bilayer structures, formed by single bilayers, were described. In this scenario, Gregory Gregoriadis established a new concept that liposomes could entrap drugs, being promising drug delivery systems [6]. Moreover, other researchers showed that liposomes could change the in vivo distribution of entrapped drugs leading to better pharmacokinetics compared to free drugs [7-9]. As a result, these systems may have some advantages, such as the improvement of physicochemical characteristics of the drugs, the delivery to a specific site and controlled release of these molecules. These factors lead to a positive impact on the safety profile. Currently, there are over ten liposomal formulations approved for human use, apart from many preparations in advanced stage of clinical study [8].

Due to the clinical importance of these nanocarriers, the study of their relative toxicity in living organisms is essential for assuring the safety of these systems. These studies are called nanotoxicology [10]. Despite these nanoparticles being considered biocompatible and biodegradable, they can promote activation of the innate immune system [11]. Acute hypersensitivity reactions (HSRs) to liposomes and other lipid excipient-based therapeutic products have been reported from time to time, ever since these formulations were introduced in the clinics. Liposome reactions were reported as early as 1986, when large doses of liposomes were infused in cancer patients in the first human study [11,12].

Previous studies highlighted the anaphylactoid nature of liposome reactions, pointing to activation of the complement (C) system as probably the underlying cause [13]. It was also established earlier that multilamellarity, large size, and the presence of very high amounts of cholesterol in the bilayer membrane are likely one of the main cause of C activation and anaphylactoid reactions. More recently, the causal role in C activation of acidic phosphate groups on polyethyleneglycol conjugated (PEGylated) phosphatidylethanolamine (PE) has been demonstrated [14-16].

Other studies described that liposomes are predicted to activate the immune system and then induce the release of cytokines. This release may contribute to the inflammation-like side effects presented in some cases of liposome administration. However, data on determining if that release of cytokines is induced by liposome stimulation is quite limited. One hypothesis to this stimulation take place on the idea that liposomes might interact with cells surface, which leads to signal transduction and secretion of cytokines. However, the precise mechanism is not clear. Nevertheless, it might be possible to regulate cytokine release by changing physical or chemical properties of liposomes, such as size and lipid composition [17].

In conclusion, although therapeutic benefits brought by liposomes lead to many already approved formulations by clinical use and others by clinical trials, much remains to be done, such as long-term toxicological studies, to confirm the safety of these lipid-based systems.

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References

1. Moghimi SM, Hunter AC, Murray JC (2005) Nanomedicine: current status and future prospects. FASEB J 19: 311-330.
2. Mailänder V, Landfester K (2009) Interactions of nanoparticles with cells. Biomacromolecules 10: 2379-2400.
3. Wagner V, Dullaart A, Bock AK, Zweck A (2006) The emerging nanomedicine landscape. Nat Biotechnol 24: 1211-1217.
4. Kim BYS, Rutka JT, Chan WCW (2010) Nanomedicine: current concepts. N Engl J Med 363: 2434-2443.
5. Bangham AD, Standish MM, Watkins JC (1965) Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol 13: 238-252.

6. Gregoriadis G, Ryman BE (1971) Liposomes as carriers of enzymes or drugs: a new approach to the treatment of storage diseases. Biochem J 124: 58p.

7. Kimelberg HK, Tracy TF, Biddlecome SM, Bourke RS (1976) The effect of entrapment in liposomes on the in vivo distribution of 3H-methotrexate in a primate 36: 2949-2957.

8. Allen TM, Cullis PR (2013) Liposomal drug delivery systems: From concept to clinical applications. Adv Drug Deliv Rev 65: 36-48.

9. Kraft JC, Freeling JP, Wang Z, Ho RJY (2014) Emerging Research and Clinical Development Trends of Liposome and Lipid Nanoparticle Drug Delivery Systems J Pharm Sci 103: 29-52.

10. Oberdörster G (2009) Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Intern Med 267: 89-105.

11. Szebeni J, Muggia F, Gabizon A, Barenholz Y (2011) Activation of complement by therapeutic liposomes and other lipid excipient-based therapeutic products: Prediction and prevention. Adv Drug Deliv Rev 63: 1020-1030.

12. Sculier JP, Coune A, Brassinne C, Laduron C, Atassi G et al. (1986) Intravenous infusion of high doses of liposomes containing NSC 251635, a water-insoluble cytostatic agent. A pilot study with pharmacokinetic data. J Clin Oncol 4: 789-797.

13. Szebeni J (1998) The interaction of liposomes with the complement system. Crit Rev Ther Drug Carrier Syst 15: 57-88.

14. Szebeni J, Baranyi B, Savay S, Bodo M, Morse DS et al. (2000) Liposome-induced pulmonary hypertension: properties and mechanism of a complement-mediated pseudoallergic reaction. Am J Physiol 279: H1319-1328.

15. Moghimi SM, Hamad I, Andresen TL, Jörgensen K, Szebeni J (2006) Methylation of the phosphate oxygen moiety of phospholipid- methoxy-(polyethylene glycol) conjugate prevents PEGylated liposome-mediated complement activation and anaphylatoxin production. FASEB J 20: 2591-2593.

16. Szebeni J, Bed?cs P, Rozsnyay Z, Weiszhár Z, Urbanics R, et al. (2012) Liposome-induced complement activation and related cardiopulmonary distress in pigs: factors promoting reactogenicity of Doxil and AmBisome. Nanomed Nanotech Biol Med 8: 176-184.

17. Yamamoto S, Ishida T, Inoue A, Mikami J, Muraguchi M et al. (2002) HEPC-based liposomes trigger cytokine release from peripheral blood cells: effects of liposomal size, dose and lipid composition. Int J Pharm 236: 125-133.

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