

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,000

Open access books available

148,000

International authors and editors

185M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



Chapter

# Perspective Chapter: Magnetoliposomes - A Recent Development as Recent Advances in the Field of Controlled Release Drug Delivery

*Edyta Maroń, Paweł Krysiński and Michał Chudy*

## Abstract

The authors of this chapter point out that, although liposomal vesicles are widely used in cancer drug delivery systems, their limitations are also known. Therefore, more recently, new developments in modifications of liposomes have rapidly appeared to improve their parameters, including the maintenance of drugs in their structure, accumulation in target sites, and the active mechanism of drug release. Research on the effectiveness of existing liposomal carriers through their functionalization, allowed to propose a promising candidate for multifunctional nanopatform based on liposomes and magnetic nanoparticles called magnetoliposomes. The presence of magnetic nanoparticles makes it possible to magnetically direct the liposomal carrier to the specific site, and appropriate magnetic field parameters can lead to controlled disintegration of the vesicle and release of the drug. The increasing variety of suggested platforms constantly provides new variants in the structure and mechanism of drug release, which enable the adjustment of the carrier's characteristics to the specific needs of cancer therapy.

**Keywords:** magnetoliposomes, drug delivery, controlled release, magnetic nanoparticles, magnetotherapy

## 1. Introduction

Cancer remains still a major problem worldwide, leading to many deaths. There are many available anticancer drugs that effectively work against tumors, but their dose in anticancer therapies is limited due to numerous side effects [1]. Currently, carriers known as drug delivery systems (DDS) are used to limit the administration of conventional drugs and improve the safety of pharmacological treatment of patients. According to the DDS definition, these are preparations that enable the controlled introduction and distribution of the drug in the organism [2]. The functionality and effectiveness of DDS consist of the stages related to the structure, that is, the

synthesis enabling to obtain specific physicochemical properties of the carrier, the method of immobilizing the drug inside the structure, administration, delivery, and release of the content at a specific place and time [3].

Drug delivery systems allow for better use of anticancer compounds and greater control of the drug while it is circulating in the bloodstream, thereby significantly reducing drug's side effects on healthy tissues. The advantage of such systems over the original form of drugs improves bioavailability and systemic clearance by achieving the optimal concentration of the drug in the target tissue. Additionally, entrapment of drugs in the form of carriers may solve problems with their stability and solubility [4–6].

## **2. Drug delivery systems**

Drug carriers are widely researched and used due to the wide variety of materials from which they can be proposed. Initially, the main challenge for DDS was to reduce the side effects of strong cytostatics that, in free form in the bloodstream, induced cytotoxic damage to healthy tissues, as well as in the target sites. Anthracyclines are the primary chemotherapy drugs used in breast cancer. Doxorubicin (DOX) is one example of an effective anticancer drug with adverse effects on many organs. The greatest clinical problem with the use of conventional anthracyclines is cardiovascular complications, which mainly concern patients with significant risk factors for the development of heart failure [7–9]. Pegylated liposomal doxorubicin under the name Doxil® is a commercially used form of an enclosed drug and was the first liposomal formulation approved by the US Food and Drug Administration (FDA) [10].

### **2.1 Liposomes**

Due to their structure and pharmacokinetics, liposomes are widely used as carriers for anticancer drugs and are particularly advantageous due to the possibility of encapsulating both hydrophilic and hydrophobic drugs [11]. Selective action of liposomes within the tumor can be achieved by passive accumulation associated with the enhanced permeability and retention (EPR) effect [12, 13]. Their phospholipid structure also allows for the slow release of the active substance. Studies of liposomal doxorubicin indicate the lack of initial high peak plasma concentrations of doxorubicin, while the actual peak concentration of the cardiotoxic metabolite occurs later and is lower compared to the conventional form [14, 15]. The encapsulation of doxorubicin in liposomes makes it practically impossible to penetrate the wall of properly functioning capillaries in healthy tissues [16, 17]. Research confirms that drug encapsulation causes significantly fewer cardiovascular complications than the conventional form [18].

Nevertheless, with the current advancement of research, liposomal vesicles are insufficient as an independent carrier due to slow action, susceptibility to phagocytosis, and insufficient drug release at the tumor site. Significant efforts in designing and developing novel drug delivery systems for targeted cancer chemotherapy remain a significant challenge. The main direction is to improve the drug delivery system, which includes two main approaches. The first concerns active approach, which is targeted guidance of the drug carrier to the target site. The second is passive approach, in which passive accumulation of liposomes by the EPR

Name of product	Name of drug	Cancer type	Main composition	Refs
DaunoXome®	Daunorubicin	AIDS-related Kaposi's sarcoma	DSPC:Chol	[26]
Doxil®	Doxorubicin	Ovarian, breast, Kaposi's sarcoma	HSPC:Chol: MPEG-DSPE	[10, 27]
DepoCyt®	Cytarabine	Acute leukemia, meningeal lymphoma	DOPC:DPPG: Chol:triolein	[28]
Myocet®	Doxorubicin	Metastatic breast, ovarian, multiple myeloma, Kaposi's sarcoma	EPC:Chol	[15, 29]
Mepact®	Mifamurtide	Osteosarcoma, bone	DOPS:POPC	[30]
Marqibo®	Vincristine	Acute lymphoblastic leukemia	SM:Chol	[31, 32]
Lipoplatin™	Cisplatin	Pancreatic, lung	DPPG:PC: MPEG- DSPE: Chol	[33]
Onivyde™	Irinotecan	Pancreatic	DSPC:MPEG- DSPE:Chol	[34]
ThermoDox®	Doxorubicin	Liver, breast	DPPC:MSPC: MPEG-DSPE	[35]
Visudyne®	Verteporfin	Choroidal neovascularisation	EPG:DMPC	[36]

*Abbreviations: distearoylphosphatidylcholine (DSPC); hydrogenated soy phosphatidylcholine (HSPC); methoxy polyethylene glycol (MPEG); distearoyl-sn-glycero-phosphoethanolamine (DSPE); dioleoylphosphatidylcholine (DOPC); dipalmitoylphosphatidylglycerol (DPPG); egg phosphatidylcholine (EPC); dioleoylphosphatidylserine (DOPS); palmitoyloleoylphosphatidylcholine (POPC); sphingomyelin (SM); phosphatidylcholine (PC); dipalmitoylphosphatidylcholine (DPPC); 1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholine (MSPC); egg phosphatidylglycerol (EPG); dimyristoyl phosphatidylcholine (DMPC).*

**Table 1.**  
 Summary of the commercial liposomal products.

effect is insufficient to ensure proper targeting due to imprecise and slow distribution. Moreover, not all tumors exhibit vascular porosity and a high degree of tumor vascularization [19–21]. Given the stability of the liposomal formulation, slow action prevents complete drug delivery and creates the need to optimize active targeting by functionalization with various targeting ligands, such as proteins, peptides, nucleic acids, or small molecules. The targeting strategy involving mainly ligand-coupled liposomes is based on obtaining tumor-specific targeting through the interaction between the ligand and the receptor overexpressed in cancer cells [22–25]. The potential of liposomes for such modifications has led to various patents, which are listed in **Table 1**.

A second approach to increase the efficiency of drug delivery using conventional liposomes is to induce a controlled release of the drug at a specific location and time using an internally or externally guided mechanism. The capsule disintegration mechanism is initiated by stimuli and is strictly dependent on the lipids building liposomal carriers. Thus, controlled leakage of drugs at the target site can be caused by specific external stimuli applied to specific liposomes sensitive to ultrasound, light, and temperature or by the use of specific biological features in tumor microenvironment such as low pH, enzymes, redox potential and hypoxia [37, 38].

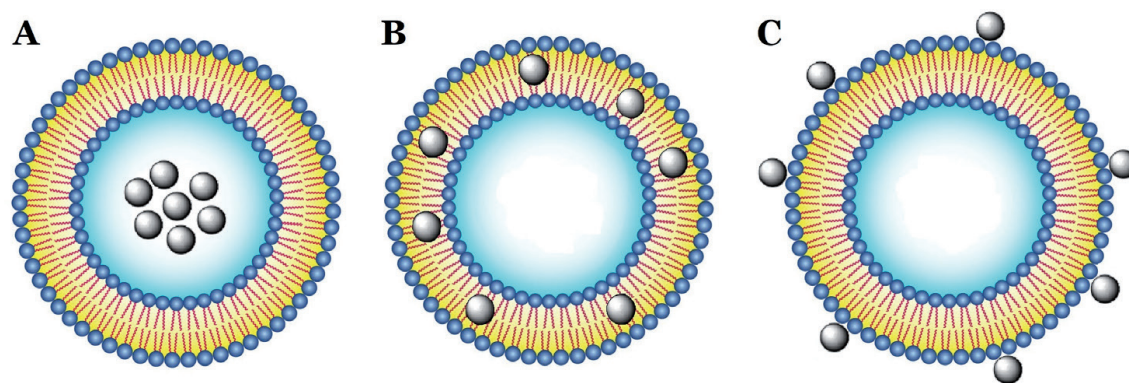
### **3. Magnetoliposomes**

In recent years, increasing attention has been paid to the application of an external magnetic field in directing the drug carriers to the target tissue with subsequent stimulated drug release from the carriers in this tissue. The great potential in this regard has led to the connection of liposomes with magnetic nanoparticles (MNP) forming nanostructures called magnetoliposomes (MLP). Their size ranges from 100 to 150 nm, but the final size depends on the method of liposome synthesis [39]. The potential applications of these relatively new carriers are increasingly recognized as providing significant biomedical possibilities both in the diagnosis and treatment of cancer and in monitoring the effectiveness of the therapy. The presence of magnetic nanoparticles enables magnetic targeting based on the selective guidance of the MLP to the target site and maintenance of the drug in the diseased tissue by applying a permanent magnet there. In addition, an alternating magnetic field (AMF) can be used as an exogenous stimulus to trigger a controlled drug release due to carrier degradation. Hereby, magnetoliposomes are an area of strong interest and research for the development and creation of new multifunctional magnetic nanomaterials with complex functions in drug delivery systems. This literature review is devoted to issues related to the types and methods of obtaining magnetoliposomes, and the next section is devoted to the advances and recent achievements in the field of controlled-release drug delivery with the use of magnetoliposomes [40, 41].

#### **3.1 Types of magnetoliposomes**

The magnetic properties of MLP allow magnetic targeting with a permanent magnet. For nanoparticles to meet specific properties and show a specific susceptibility to MF, it is important, however, that they have a strong magnetic moment randomly oriented at room temperature in the absence of the external magnetic field. This means using MNP, which are superparamagnetic, makes them prone to strong magnetization. When the magnetic field is applied, nanoparticles orient themselves towards the field but do not maintain permanent magnetization in the absence of MF. This behavior is due to the small size of nanoparticles, up to 10 nm, where these nanoparticles are single-domain with a single magnetic moment. In such a system, interactions between particles are weak, therefore, after removing the magnetic field, nanoparticles can return to the state of disorder. MNP also have other interesting features regarding their ability to modify the surface and create unique structures tailored to the variability of the magnetic field strength, which determines the specific mechanism of drug release from the carrier [42, 43].

Magnetic nanoparticles can be arranged differently in the structure of liposomes depending on the nature of their surface. Magnetoliposomes can be formed using three different approaches: encapsulation of hydrophilic nanoparticles in the aqueous core of liposomes, incorporation of hydrophobic nanoparticles into a phospholipid bilayer, and binding magnetic nanoparticles to the surface of liposomes (**Figure 1**). The above-mentioned designs should be selected according to the application, as each has its own advantages and disadvantages. For example, the presence of both nanoparticles and drug inside liposomes reduces the drug loading capacity of such carriers. However, this is the most well-known method due to the ease of incorporation of nanoparticles. In turn, the deposition of nanoparticles in the membrane poses some limitations concerning the capacity and size of the bilayer. Its thickness varies



**Figure 1.** Schematic representation of the main types of magnetoliposome structure related to the distribution of magnetic nanoparticles: encapsulation of hydrophilic nanoparticles in the aqueous core of the liposomes (A); incorporation of hydrophobic nanoparticles in the phospholipid bilayer (B); and bonding of magnetic nanoparticles on the surface of liposomes (C).

around 6 nm, so only suitably small and well-separated nanoparticles are introduced. Under the influence of the presence of nanoparticles, the bilayer convenges and becomes stiffer. Regardless of the point of introduction, it is necessary to coat the nanoparticles to prevent their aggregation and to improve the efficiency of incorporation into liposomes. MNP are most often coated with citric acid as hydrophilic introduced inside liposomes or with oleic acid, oleylamine as hydrophobic in the phospholipid bilayer [44, 45].

### 3.2 Methods of magnetoliposomes preparation

The preparation of magnetoliposomes is divided into two separate steps, involving the initial synthesis of magnetic nanoparticles and the subsequent combination with lipids in the proper synthesis of magnetoliposomes [46].

#### 3.2.1 Synthesis of magnetic nanoparticles

The methods of producing nanoparticles can be divided into bottom-up methods, consisting in building a nanometric structure from individual atoms or molecules, and top-down methods, consisting in grinding a micrometric structure to the nanometric scale. To obtain metal nanoparticles with high stability and high chemical purity, as well as of the desired sizes, bottom-up methods are used, including chemical strategies, such as co-precipitation, thermal decomposition, sol-gel, hydrothermal and solvothermal methods, and the synthesis of microemulsions [47, 48]. Co-precipitation is the most common method because it is characterized by simplicity, high efficiency, and low cost. Undoubtedly, its advantage is also the possibility of producing nanoparticles of different chemical compositions and controlling the size of the obtained nanoparticles, which determines the achievement of the desired superparamagnetic properties. The morphology of nanoparticles and their stability can be controlled by selecting appropriate synthesis parameters, such as metal salt concentration, stabilizer concentration, and the molar ratio of the reducer and metal salt. For example, by increasing the molar ratio of salt to the reductant, it is possible to create many nuclei and, as a result, to obtain small, monodisperse nanoparticles [49].

Iron oxide-based nanoparticles are a class of great biomedical importance due to their good magnetic properties, stability, biocompatibility, and the possibility of chemical modification [50]. These nanoparticles are most often obtained by the aforementioned co-precipitation method, which consists of the co-precipitation of a stoichiometric mixture of iron and ferrous salts in an aqueous medium and the absence of oxygen. Carefully planned synthesis procedures (water-phase co-precipitation and thermal decomposition from organic precursors) will yield iron-based magnetic nanoparticles with controlled sizes and surface properties suitable for later use as a “vector” to guide drug-loaded magnetoliposomes in an external magnetic field and initiate drug release in an alternating magnetic field [51]. For example, various ferrite nanoparticles were synthesized by co-precipitation, including ferrites doped with manganese, calcium, magnesium, and nickel [52]. The previously prepared magnetic nanoparticles are supplied with lipids during liposome synthesis and, depending on the surface nature, hydrophilic or hydrophobic, are incorporated into the interior or bilayers of magnetoliposomes, respectively [53].

### *3.2.2 Synthesis of liposomes and magnetic liposomes*

Magnetoliposomes are created during the synthesis of liposomes, which are modified with magnetic nanoparticles by administering them together with a lipid mixture. The choice of the method of liposome preparation depends on the method of using the obtained vesicles. The simplest and most used technique is the hydration of a thin lipid/nanoparticle film. In this process, lipids and MNP are first dissolved in a volatile organic solvent and a thin layer is formed at the bottom of the container after the solvent is evaporated under nitrogen. The sample is then rehydrated with a phosphate buffer. Using this method, a heterogeneous suspension of multilayer magnetoliposomes with a diameter of 0.1  $\mu\text{m}$  to 10  $\mu\text{m}$  is obtained. However, the main disadvantage of this synthesis is the low encapsulation efficiency of hydrophilic drugs (5–20%) [54, 55]. Next method of magnetic liposome preparation includes, among others, evaporation using the reverse phase technique, in which a mixture consisting of two phases: lipids and nanoparticles are dissolved in an organic solvent and a buffer is subjected to short sonication. The solvent is then removed under low pressure to form a sticky gel. The final step of the procedure, involving the removal of residual solvent on a rotary evaporator under reduced pressure, produces bubbles with a large size distribution. They are characterized by a high encapsulation efficiency of up to 65% in a solution with low ionic strength. The disadvantage of the method, however, is that the entrapped drug dissolved in the buffer contacts the organic phase. Additionally, intensive sonication may damage the structure of the closed substance [56]. Another method of magnetoliposomes preparation is the rapid injection of lipids with magnetic nanoparticles dissolved in ethanol into the aqueous solution. This procedure results in a heterogeneous suspension of vesicles with a diameter of 30 to 110 nm. The obtained magnetic liposome suspension is diluted and may contain traces of ethanol [55, 57]. In turn, the freeze-thaw technique allows one to obtain small single-layer magnetoliposomes. After sonication, they are quickly frozen in liquid nitrogen and slowly thawed in water, as a result of this process liposomes fuse and are characterized by a loading efficiency of 20–30% [57]. Similar to the ethanol injection described above, an ether solution or ether/methanol solution of lipids and MNP can be slowly injected into the buffer at elevated temperature under reduced pressure. A heterogeneous suspension of magnetoliposomes with a diameter of 70 to 190 nm is formed. As with the reverse phase evaporation technique, the enclosed

drug is exposed to phase mixing with an organic solvent at high temperatures [56, 57]. Some of the above MLP preparation techniques result in multilayer and single-layer vesicles with a large size distribution. Due to the efficient permeability of small carriers to tumor cells, homogeneous vesicles in the range of 100–200 nm are preferred. In order to homogenize the obtained heterogeneous mixture, MLP extrusion through polycarbonate membrane filters with a defined pore diameter is used. As a result, the obtained phospholipid vesicles are characterized by a small size distribution. Additionally, this method is fast, cheap, and allows obtaining even small, unilamellar liposomes of 100 nm in size. The breaking down of the vesicles into smaller structures can also be obtained by the action of ultrasound, which can complement the above techniques to increase the effectiveness of MLP preparation [55].

The discussed methods assume the closure of compounds during the synthesis of magnetoliposomes. In this case, we can talk about the so-called passive loading. However, some compounds have ionizable groups that exhibit hydrophobic and hydrophilic properties depending on the pH of the solution and may not be efficiently encapsulated in liposomes due to their diffusion through the phospholipid membrane. In such a case, they can be encapsulated in liposomes with high efficiency, even above 90%, after the formation of the liposomes using the active loading technique. In this method, liposomes are prepared with their internal pH suitable for ionizing the drug, which in this non-ionized form can passively diffuse through the lipid membrane from the external solution into the liposomes. As a result, the drug after penetration into the liposome becomes ionized and is no longer able to re-diffuse through the phospholipid bilayer [58, 59].

### **3.3 Mechanisms of drug release from magnetoliposomes**

So far, in the chapter, we discussed the methodology of magnetoliposomes and their modification to obtain an effective magnetic field-assisted drug delivery system. In addition to the selective action of the constant magnetic field, enabling the efficient accumulation of carriers within the tumor tissue, it is possible to obtain, on-demand, the release of drugs enclosed in the carriers. Then, an alternating magnetic field is used which, by changing the behavior of nanoparticles, initiates the degradation of the carrier and the outflow of the drug. The susceptibility of nanoparticles to AMF results from their superparamagnetic behavior, for which the physicochemical properties of these nanomaterials and strict control of parameters during synthesis are responsible. Only superparamagnetic nanoparticles are capable of efficient, local release of the drug from the carriers. How the degradation of the magnetoliposomes takes place depends on the parameters of the magnetic field, where special attention is focused on the use of low or high frequency [60].

#### *3.3.1 Magnetic hyperthermia*

In magnetic hyperthermia, the exposure of magnetic nanoparticles to the magnetic field will result in their magnetization, and the supplied amount of magnetic field energy will be converted into heat. In the case of single-domain, superparamagnetic iron oxide nanoparticles (SPION), relaxation losses related to the rotation of the magnetic moment inside the nanoparticle (Nelson) and a lesser extent to the physical rotation of the entire nanoparticle (Brown) may cause local heating of the magnetoliposomes. Taking into account the short relaxation time, an alternating high-frequency magnetic field (AMF-HF), 50–400 kHz, is used [61]. In this case,

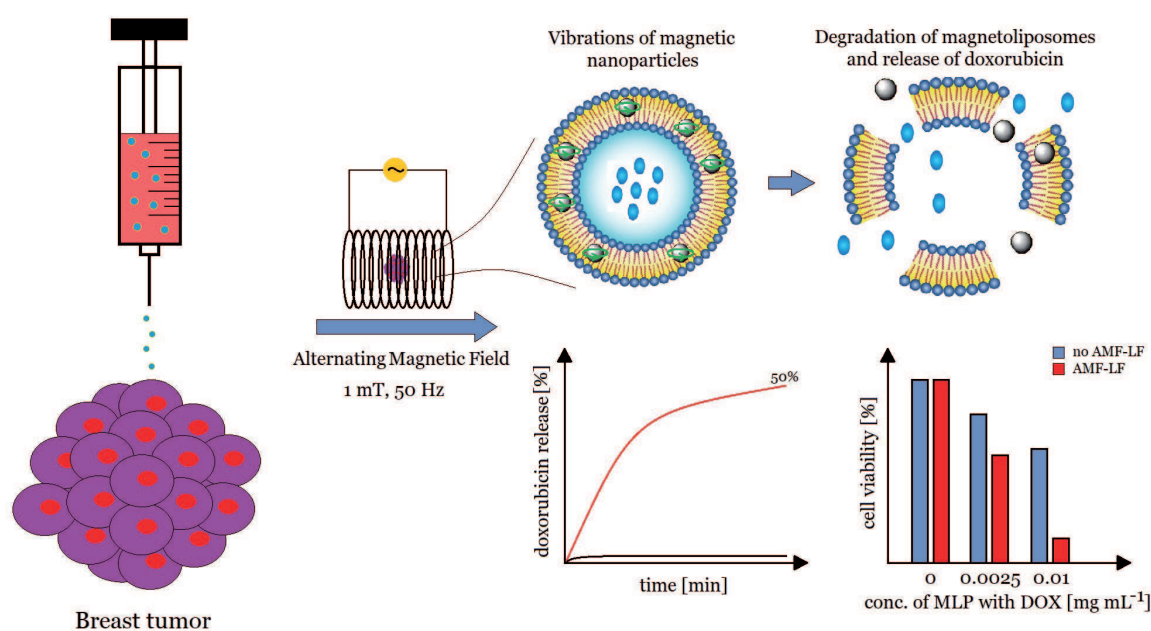


the heat released under the influence of nanoparticles placed in a magnetic field is a factor that initiates the degradation of the liposomal carrier. Liposomes are characterized by a phase transition temperature that keeps the drug inside the structure. When these liposomes are loaded with magnetic nanoparticles and drugs, an interesting drug delivery system can be created. The energy supplied from the magnetic system in the form of heat, after exceeding the threshold value  $T_m$ , causes a phase transition in the phospholipid bilayer. This magnetocaloric effect enables the activation of drug release from MLP in the presence of AMF by locally increasing the temperature in the membrane and inducing changes in liposome permeability, which changes with increasing temperature. Under these conditions, the order of phospholipid molecules changes, which results in destabilization and an increase in the fluidity of the membrane. Leaks, that appear as a result of such changes, allow dissolved drugs to pass through the membrane. The packing of lipids depends on the degree of saturation of fatty acid residues and the number of carbon atoms that build them, which translates into different  $T_m$  values of individual lipids. Therefore, when designing carriers, thermosensitive lipids are selected that are able to release the drug even with a slight increase in temperature. Magnetic nanoparticles can be used to generate both mild hyperthermia (42–46°C) and high-temperature hyperthermia (> 46°C). However, even under milder conditions of temperature increase, neoplastic tissues are exposed to it, because they are more sensitive to higher temperatures than normal cells, and as a result, local hypoxia and acidification of the tumor occur, and eventually apoptosis. Higher temperature hyperthermia causes immediate tissue necrosis through dehydration, protein denaturation, and damage to cell membranes (thermal ablation) and is rarely used due to its negative impact on the viability of healthy cells. The undoubted advantage of using magnetic hyperthermia among magnetoliposomes is the possibility of inducing heat only in a strictly defined volume, in which magnetic nanoparticles are located. However, it should be noted that a living organism cannot be exposed to an alternating magnetic field of any high-intensity  $H$  and frequency  $f$ , because eddy currents can be induced in it, leading to heating of the whole body or a significant part of it. Therefore, in treatments with the use of AMF, these values are strictly limited to the safe range, in accordance with the Brezovich criterion, which requires  $H \cdot f < 4.85 \times 10^8 \text{ Am}^{-1} \text{ s}^{-1}$  [62–64].

### *3.3.2 Mechanical degradation*

An alternative, relatively new approach to activating drug release from magnetoliposomes in the presence of AMF is the degradation of the carrier by mechanical means. This manner of controlled drug release is effected by using a low-frequency alternating magnetic field (AMF-LF). Under the influence of a low-frequency < 50 Hz, the movements of the superparamagnetic magnetic nanoparticles become dominant, which leads to the mechanical disruption of the lipid bilayer of the vesicles and the release of the drug from the liposomes. Currently, there is growing interest in research on the controlled release of a drug from magnetic carriers under the influence of AMF-LF. The disintegration process takes place without sudden increases in temperature and without magnetically induced eddy currents, preventing damage and reducing the viability of healthy cells surrounding the tumor. A significant advantage of this mechanism over magnetic hyperthermia is also a significant reduction in the parameters of the magnetic field, which in this case are within the acceptable ranges of conventional magnetotherapy, and therefore can be considered a safe dose [37, 65].

The above reasons prompted us to develop a selective delivery of doxorubicin to cancer cells supported by a low-frequency magnetic field with the use of magnetoliposomes as drug carriers [66]. To the best of our knowledge, the magnetoliposome design we propose has been optimized and adapted to a specific application. Moreover, the physicochemical characteristics of the carrier met the criteria for drug delivery systems, which are discussed in more detail in our article. The main research object was the use of magnetomechanical activation for controlled drug release, which we reported for the first time in 2016 by Joniec et al., see [67]. For further purposes and biological studies, degradation of the carrier under unheated conditions was desirable to avoid synergistic cytotoxic effects caused by released doxorubicin and elevated temperature. The selection of lipids took into account the possibility of obtaining MLP with appropriate physicochemical properties and good stability in the conditions of cell culture, as well as different conditions in the tumor environment. We used passive loading of the drug into the aqueous phase of the liposome, which compared to active loading has a lower efficiency of drug encapsulation. Thus, in order to increase this final efficiency, we synthesized hydrophobic SPION. As a result, during the incorporation into liposomes, they locate in the hydrophobic phospholipid bilayer, leaving a free internal space for the drug. Moreover, such separation may prevent interaction between the vibrating SPION and the drug. For loaded to the interior of the liposome bilayer, their magnetic movement, limited only to the membrane, may facilitate the degradation of the carrier and thus increase the drug release efficiency. We have successfully tested the *in vitro* effect of magnetoliposomes loaded with doxorubicin as a potent cytostatic drug, on a cancerous human breast cell line. The obtained nanocarriers were susceptible to an alternating magnetic field in low frequency, released a significant amount of drug, and caused a highly efficient reduction in the viability of cancerous cells in comparison to control without exposure to this magnetic field (Figure 2).



**Figure 2.** Schematic illustration showing the research concept of magnetoliposomes as magnetically assisted drug nanocarriers.

#### **4. Advances in anticancer drug delivery system using magnetoliposomes**

In recent years, the worldwide progress in research has been significant and has led to new advances in the field of controlled-release drug delivery using magnetoliposomes. Modifications in the design of carrier structures tended to create multifunctional platforms to improve parameters, including drug maintenance, target accumulation, and active drug release mechanism. Several innovative solutions from the last 3 years are presented below.

The research presented in the article by Cintra et al. in 2022, see [68] demonstrates the antitumor properties of magnetoliposomes that have been functionalized with a selective ligand to actively target the tumor. Folic acid was used to modify the surface of magnetoliposomes. The potential effect of drug accumulation into neoplastic cells is related to the overexpression of folic acid receptors by some neoplasms, including ovarian cancer [69]. The release of the drug from MLP took place with the participation of heat released by an alternating magnetic field under magnetic hyperthermia.

Another example of the use of magnetoliposomes and magnetic hyperthermia was the study by Riberio et al. in 2020, see [70]. In this example, an interesting approach was the multi-drug loading into magnetoliposomes. Magnetic nanoparticles, gemcitabine, and paclitaxel were encapsulated in thermosensitive liposomes with high efficiency and showed equally efficient drug release from preparations exposed to AMF-HF. In addition, the separated and combined cytotoxic effects of loaded magnetoliposomes and magnetic hyperthermia on breast cancer cells were investigated. Based on the presented work, the authors stated that drug-loaded magnetoliposomes may have the potential for combination therapy, including hyperthermia and controlled release of chemotherapeutic drugs.

The development of stimulus-sensitive DDS is a current area of cancer therapy research by Riberio et al., see [71]. The authors have developed magnetic liposomes adequate for temperature and pH-triggered anticancer drug release in the tumor environment in conjunction with magnetic hyperthermia. Two new anticancer thienopyridine derivatives have been successfully enclosed in magnetoliposomes and the results have confirmed the efficiency of drug delivery by loaded nanocarriers under various pH and temperature conditions.

Departing from the use of AMF-HF and magnetic hyperthermia to release encapsulated compounds on demand, Trilli et al., see [72] proposed magnetoliposomes sensitive to low-intensity magnetic fields. The use of low-intensity pulsed electromagnetic fields (PEMF) provided magnetomechanical activation and efficient content release. In particular, the authors devoted attention to investigating the effect of bilayer packing on the ability of MLP with oleic acid-coated MNP enclosed in a bilayer to respond to PEMF application. For this purpose, magnetoliposomes with different lipid composition and the degree of order of the phospholipid bilayer were compared. The effectiveness of the magnetic triggering was greatest with highly ordered bilayers that are unable to suppress the disturbance caused by MNP movement.

#### **5. Conclusion**

In summary, the growing variety of proposed platforms constantly provides new variants in the structure and mechanism of drug release, which enable the adaptation of the carrier to the specific needs of the therapy. The number of literature reports on the development of new multifunctional drug carriers is constantly growing.

However, due to the development of more precise anticancer therapies, increasingly advanced solutions are being sought. Nanotechnology can offer many opportunities, progress in this field is constantly developing methods of producing and studying magnetoliposomes.

## Acknowledgements

This work was implemented as a part of Operational Project Knowledge Education Development 2014–2020 cofinanced by the European Social Fund.

This work has been supported by Warsaw University of Technology and University of Warsaw.

## Conflict of interest

The authors declare no conflict of interest.

## Author details

Edyta Maroń<sup>1,2</sup>, Paweł Krysiński<sup>2</sup> and Michał Chudy<sup>1\*</sup>


1 Faculty of Chemistry, Warsaw University of Technology, Chair of Medical Biotechnology, Warsaw, Poland

2 Faculty of Chemistry, University of Warsaw, Laboratory of Electrochemistry, Warsaw, Poland

\*Address all correspondence to: [chudziak@ch.pw.edu.pl](mailto:chudziak@ch.pw.edu.pl)

## IntechOpen

---

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Bargahi N, Ghasemali S, Jahandar-Lashaki S, Nazari A. Recent advances for cancer detection and treatment by microfluidic technology, review and update. *Biol. Proced. Online.* 2022;**24**(1):5. DOI: 10.1186/s12575-022-00166-y
- [2] Jain KK. An overview of drug delivery systems. In: Jain KK, editor. *Drug Delivery Systems.* Method Mol. Biol. New York: Humana; 2020. p. 2059. DOI: 10.1007/978-1-4939-9798-5\_1
- [3] Boverhof DR, Bramante CM, Butala JH, Clancy SF, Lafranconi M, West J, et al. Comparative assessment of na-nomaterial definitions and safety evaluation considerations. *Regulatory Toxicology and Pharmacology.* 2015;**73**:137-150. DOI: 10.1016/j.yrtph.2015.06.001
- [4] Lavik EB, Kuppermann BD, Humayun MS. Drug delivery. In: Hinton DR, editor. *Basic Science and Translation to Therapy.* United States: W.B. Saunders; 2013. pp. 734-745. DOI: 10.1016/B978-1-4557-0737-9.00038-2
- [5] Garg NK, Tandel N, Jadon RS, Tyagi RK, Katare OP. Lipid-polymer hybrid nanocarrier-mediated cancer therapeutics: Current status and future directions. *Drug Discovery Today.* 2018;**23**(9):1610-1621. DOI: 10.1016/j.drudis.2018.05.033
- [6] Sohail M, Guo W, Li Z, Xu H, Zhao F, Chen D, et al. Nanocarrier-based drug delivery system for cancer therapeutics: A review of the last decade. *Current Medicinal Chemistry.* 2021;**28**(19):3753-3772. DOI: 10.2174/0929867327666201005111722
- [7] Tacar O, Sriamornsak P, Dass CR. Doxorubicin: An update on anticancer molecular action, toxicity and novel drug delivery systems. *The Journal of Pharmacy and Pharmacology.* 2013;**65**(2):157-170. DOI: 10.1111/j.2042-7158.2012.01567.x
- [8] Malato A, Saccullo G, Fazio G, Vergara B, Raso S, Guarneri GP, et al. Drug-related cardiotoxicity for the treatment of haematological malignancies in elderly. *Current Pharmaceutical Design.* 2010;**16**(26):2872-2879. DOI: 10.2174/138161210793176446
- [9] Trucillo P. Drug carriers: Classification, administration, release profiles, and industrial approach. *PRO.* 2021;**9**:470. DOI: 10.3390/pr9030470
- [10] Porche DJ. Liposomal doxorubicin (Doxil). *The Journal of the Association of Nurses in AIDS Care.* 1996;**7**(2):55-59. DOI: 10.1016/S1055-3290(96)80016-1
- [11] Abu Lila AS, Ishida T. Liposomal delivery systems: Design optimization and current applications. *Biological & Pharmaceutical Bulletin.* 2017;**40**(1):1-10. DOI: 10.1248/bpb.b16-00624
- [12] Danhier F. To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine? *Journal of Controlled Release.* 2016;**28**(244):108-121. DOI: 10.1016/j.jconrel.2016.11.015
- [13] Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: A review. *Journal of Controlled Release.* 2000;**65**(1-2):271-284. DOI: 10.1016/S0168-3659(99)00248-5
- [14] Mayer LD, Tai LC, Bally MB, Mitilenes GN, Ginsberg RS, Cullis PR.

Characterization of liposomal systems containing doxorubicin entrapped in response to pH gradients. *Biochimica et Biophysica Acta*. 1990;**1025**:143-151. DOI: 10.1016/0005-2736(90)90091-2

[15] Marty M. Liposomal doxorubicin (Myocet™) and conventional anthracyclines: A comparison. *The Breast*. 2001;**10**:28-33. DOI: 10.1016/S0960-9776(01)80005-9

[16] Tardi PG, Boman NL, Cullis PR. Liposomal doxorubicin. *Journal of Drug Targeting*. 1996;**4**(3):129-140. DOI: 10.3109/10611869609015970

[17] Makwana V, Karanjia J, Haselhorst T, Anoopkumar-Dukie S, Rudrawar S. Liposomal doxorubicin as targeted delivery platform: Current trends in surface functionalization. *International Journal of Pharmaceutics*. 2021;**25**(593):120117. DOI: 10.1016/j.ijpharm.2020.120117

[18] Batist G, Harris L, Azarnia N, Lee LW, Daza-Ramirez P. Improved anti-tumor response rate with decreased cardiotoxicity of non-pegylated liposomal doxorubicin compared with conventional doxorubicin in first-line treatment of metastatic breast cancer in patients who had received prior adjuvant doxorubicin: Results of a retrospective analysis. *Anti-Cancer Drugs*. 2006;**17**(5):587-595. DOI:10.1097/00001813-200606000-00014

[19] Qamar Z, Qizilbash FF, Iqbal MK, Ali A, Narang JK, Ali J, et al. Nano-based drug delivery system: Recent strategies for the treatment of ocular disease and future perspective. *Recent Patents on Drug Delivery & Formulation*. 2019;**13**(4):246-254. DOI: 10.2174/1872211314666191224115211

[20] Meng W, He C, Hao Y, Wang L, Li L, Zhu G. Prospects and challenges of extracellular vesicle-based drug

delivery system: Considering cell source. *Drug Delivery*. 2020;**27**(1):585-598. DOI: 10.1080/10717544.2020.1748758

[21] Heidarli E, Dadashzadeh S, Haeri A. State of the art of stimuli-responsive liposomes for cancer therapy. *Iran. J. Pharm. Res*. 2017;**16**(4):1273-1304. DOI: PMID: PMC5843293

[22] Mertz D, Sandre O, Bégin-Colin S. Drug releasing nanoplatfoms activated by alternating magnetic fields. *Biochimica et Biophysica Acta - General Subjects*. 2017;**1861**(6):1617-1641. DOI: 10.1016/j.bbagen.2017.02.025

[23] Yang B, Song BP, Shankar S, Guller A, Deng W. Recent advances in liposome formulations for breast cancer therapeutics. *Cellular and Molecular Life Sciences*. 2021;**78**(13):5225-5243. DOI: 10.1007/s00018-021-03850-6

[24] Veloso SRS, Andrade RGD, Castanheira EMS. Magnetoliposomes: Recent advances in the field of controlled drug delivery. *Expert Opinion on Drug Delivery*. 2021;**18**(10):1323-1334. DOI: 10.1080/17425247.2021.1915983

[25] Rajabi M, Mousa SA. Lipid nanoparticles and their application in Nanomedicine. *Current Pharmaceutical Biotechnology*. 2016;**17**(8):662-672. DOI: 10.2174/1389201017666160415155457

[26] Offidani M, Corvatta L, Centurioni R, Leoni F, Malerba L, Mele A, et al. High-dose daunorubicin as liposomal compound (Daunoxome) in elderly patients with acute lymphoblastic leukemia. *The Hematology Journal*. 2003;**4**(1):47-53. DOI: 10.1038/sj.thj.6200222

[27] Barenholz Y. Doxil® — The first FDA-approved nano-drug: Lessons learned. *Journal of Controlled Release*. 2012;**160**(2):117-134. DOI: 10.1016/j.jconrel.2012.03.020

- [28] Murry DJ, Blaney SM. Clinical pharmacology of encapsulated sustained-release cytarabine. *The Annals of Pharmacotherapy*. 2000;**34**(10):1173-1178. DOI: 10.1345/aph.19347
- [29] Balazsovits JA, Mayer LD, Bally MB, Cullis PR, McDonell M, Ginsberg RS, et al. Analysis of the effect of liposome encapsulation on the vesicant properties, acute and cardiac toxicities, and antitumor efficacy of doxorubicin. *Cancer Chemotherapy and Pharmacology*. 1989;**23**(2):81-86. DOI: 10.1007/BF00273522
- [30] Vail DM, MacEwen EG, Kurzman ID, Dubielzig RR, Helfand SC, Kisseberth WC, et al. Liposome-encapsulated muramyl tripeptide phosphatidylethanolamine adjuvant immunotherapy for splenic hemangiosarcoma in the dog: A randomized multi-institutional clinical trial. *Clinical Cancer Research*. 1995;**1**(10):1165-1170
- [31] Silverman JA, Deitcher SR. Marqibo® (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemotherapy and Pharmacology*. 2013;**71**(3):555-564. DOI: 10.1007/s00280-012-2042-4
- [32] Johnston MJ, Semple SC, Klimuk SK, Edwards K, Eisenhardt ML, Leng EC, et al. Therapeutically optimized rates of drug release can be achieved by varying the drug-to-lipid ratio in liposomal vincristine formulations. *Biochimica et Biophysica Acta*. 2006;**1758**(1):55-64. DOI: 10.1016/j.bbame.2006.01.009
- [33] Stathopoulos GP, Boulikas T, Vougiouka M, Deliconstantinos G, Rigatos S, Darli E, et al. Pharmacokinetics and adverse reactions of a new liposomal cisplatin (Lipoplatin): Phase I study. *Oncology Reports*. 2005;**13**(4):589-595
- [34] Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: An updated review. *Pharmaceutics*. 2017;**9**(2):12. DOI: 10.3390/pharmaceutics9020012
- [35] Chen J, He CQ, Lin AH, Gu W, Chen ZP, Li W, et al. Thermosensitive liposomes with higher phase transition temperature for targeted drug delivery to tumor. *International Journal of Pharmaceutics*. 2014;**475**(1-2):408-415. DOI: 10.1016/j.ijpharm.2014.09.009
- [36] Saraf S, Jain A, Tiwari A, Verma A, Panda PK, Jain SK. Advances in liposomal drug delivery to cancer: An overview. *J. Drug Deliv. Sci. Technol.* 2020;**56**:101549. DOI: 10.1016/j.jddst.2020.101549
- [37] Nappini S, Bonini M, Bombelli FB, Pineider F, Sangregorio C, Baglioni P, et al. Controlled drug release under a low frequency magnetic field: Effect of the citrate coating on magnetoliposomes stability. *Soft Matter*. 2011;**7**:1025-1037. DOI: 10.1039/C0SM00789G
- [38] Guo H, Chen W, Sun X, Liu YN, Li J, Wang J. Theranostic magnetoliposomes coated by carboxymethyl dextran with controlled release by low-frequency alternating magnetic field. *Carbohydrate Polymers*. 2015;**118**:209-217. DOI: 10.1016/j.carbpol.2014.10.076
- [39] Bakandritsos A, Fatourou AG, Fatouros DG. Magnetoliposomes and their potential in the intelligent drug-delivery field. *Therapeutic Delivery*. 2012;**3**(12):1469-1482. DOI: 10.4155/tde.12.129
- [40] Nappini S, Fogli S, Castroflorio B, Bonini M, Baldelli Bombelli F, Baglioni P. Magnetic field responsive drug release from magnetoliposomes in biological fluids. *Journal of Materials Chemistry B*. 2016;**4**(4):716-725. DOI: 10.1039/c5tb02191j

- [41] Rodrigues ARO, Almeida BG, Rodrigues JM, Queiroz MJRP, Calhella RC, Ferreira ICFR, et al. Magnetoliposomes as carriers for promising antitumor thieno[3,2-b]pyridin-7-arylamines: Photophysical and biological studies. *RSC Advances*. 2017;7:15352-15361. DOI: 10.1039/C7RA00447H
- [42] Tomitaka A, Takemura Y, Huang Z, Roy U, Nair M. Magnetoliposomes in controlled-release drug delivery systems. *Critical Reviews in Biomedical Engineering*. 2019;47(6):495-505. DOI: 10.1615/CritRevBiomedEng.2020033002
- [43] Wahajuddin AS. Superparamagnetic iron oxide nanoparticles: Magnetic nanoplatforms as drug carriers. *International Journal of Nanomedicine*. 2012;7:3445-3471. DOI: 10.2147/IJN.S30320
- [44] Monnier CA, Burnand D, Rothen-Rutishauser B, Lattuada M, Petri-Fink A. Magnetoliposomes: Opportunities and challenges. *Eur. J. Nanomed*. 2014;6:201-215. DOI: 10.1515/ejnm-2014-0042
- [45] Soenen SJ, Velde GV, Ketkar-Atre A, Himmelreich U, De Cuyper M. Magnetoliposomes as magnetic resonance imaging contrast agents. *Wires. Nanomed. Nanobi*. 2011;3(2):197-211. DOI: 10.1002/wnan.122
- [46] Faria MR, Cruz MM, Gonçalves MC, Carvalho A, Feio G, Martins MB. Synthesis and characterization of magnetoliposomes for MRI contrast enhancement. *International Journal of Pharmaceutics*. 2013;446(1-2):183-190. DOI: 10.1016/j.ijpharm.2013.02.025
- [47] Majidi S, Sehrig FZ, Farkhani SM, Goloujeh MS, Akbarzadeh A. Current methods for synthesis of magnetic nanoparticles. *Artif. Cells Nanomed. Biotechnol*. 2016;44(2):722-734. DOI: 10.3109/21691401.2014.982802
- [48] Ramimoghdam D, Bagheri S, Hamid SBA. Progress in electrochemical synthesis of magnetic iron oxide nanoparticles. *Journal of Magnetism and Magnetic Materials*. 2014;368:207-229. DOI: 10.1016/j.jmmm.2014.05.015
- [49] Babooram K. Novel solution routes to ferroelectrics and relaxors. In: Ye Z-G, editor. *Handbook of Advanced Dielectric, Piezoelectric and Ferroelectric Materials*. Materials Science. Cambridge, England: Woodhead Publishing; 2008. p. 852. DOI: 10.1533/9781845694005.7.852
- [50] Lattuada M, Hatton TA. Functionalization of monodisperse magnetic nanoparticles. *Langmuir*. 2007;23(4):2158-2168. DOI: 10.1021/la062092x
- [51] Mahdavi M, Ahmad MB, Haron MJ, Namvar F, Nadi B, Rahman MZ, et al. Synthesis, surface modification and characterisation of biocompatible magnetic iron oxide nanoparticles for biomedical applications. *Molecules*. 2013;18(7):7533-7548. DOI: 10.3390/molecules18077533
- [52] Cardoso BD, Rio ISR, Rodrigues ARO, et al. Magnetoliposomes containing magnesium ferrite nanoparticles as nanocarriers for the model drug curcumin. *Royal Society Open Science*. 2018;5(10):181017. DOI: 10.1098/rsos.181017
- [53] Amstad E, Gillich T, Bilecka I, Textor M, Reimhult E. Ultrastable iron oxide nanoparticle colloidal suspensions using dispersants with catechol-derived anchor groups. *Nano Letters*. 2009;9(12):4042-4048. DOI: 10.1021/nl902212q



- [54] Shashi K, Satinder K, Bharat P. A complete review on: Liposomes. *Int. Res. J. Pharm.* 2012;**3**:10-16. DOI: 10.46956/ijhd.vi.116
- [55] Vishvakrama P, Sharma S. Liposomes: An overview. *J. Drug Deliv. Ther.* 2014;**4**:47-55. DOI: 10.22270/jddt.v0i0.843
- [56] Dua JS, Rana AC, Bhandari AK. Liposome: Methods of preparation and applications. *Int. J. Pharm. Stud. Res.* 2012;**3**:14-20
- [57] Allen TM, Cullis PR. Liposomal drug delivery systems: From concept to clinical applications. *Advanced Drug Delivery Reviews.* 2013;**65**(1):36-48. DOI: 10.1016/j.addr.2012.09.037
- [58] Gubernator J. Active methods of drug loading into liposomes: Recent strategies for stable drug entrapment and increased in vivo activity. *Expert Opinion on Drug Delivery.* 2011;**8**(5):565-580. DOI: 10.1517/17425247.2011.566552
- [59] Sharma A, Sharma US. Liposomes in drug delivery: Progress and limitations. *International Journal of Pharmaceutics.* 1997;**54**(2):123-140. DOI: 10.1016/S0378-5173(97)00135-X
- [60] McNeil SE. Nanoparticle therapeutics: A personal perspective. *Wires. Nanomed. Nanobi.* 2009;**1**(3):264-271. DOI: 10.1002/wnan.6
- [61] Rosensweig RE. Heating magnetic fluid with alternating magnetic field. *Journal of Magnetism and Magnetic Materials.* 2002;**252**:370-374. DOI: 10.1016/S0304-8853(02)00706-0
- [62] Robinson R, Gerlach W, Ghandehari H. Comparative effect of gold nanorods and nanocages for prostate tumor hyperthermia. *Journal of Controlled Release.* 2015;**220**:245-252. DOI: 10.1016/j.jconrel.2015.10.036
- [63] Guo Y, Zhang Y, Ma J, Li Q, Li Y, Zhou X, et al. Light/magnetic hyperthermia triggered drug released from multi-functional thermo-sensitive magnetoliposomes for precise cancer synergetic theranostics. *Journal of Controlled Release.* 2018;**28**(272):145-158. DOI: 10.1016/j.jconrel.2017.04.028
- [64] Rodrigues ARO, Ramos JMF, Gomes IT, Almeida BG, Araújo JP, Queiroz M-JRP, et al. Magnetoliposomes based on manganese ferrite nanoparticles as nanocarriers for antitumor drugs. *RSC Advances.* 2016;**6**:17302-17313. DOI: 10.1039/C5RA27058H
- [65] Nappini S, Al Kayal T, Berti D, Norden B, Baglioni P. Magnetically triggered release from Giant Unilamellar vesicles: Visualization by means of confocal microscopy. *Journal of Physical Chemistry Letters.* 2011;**2**:713-718. DOI: 10.1021/jz2000936
- [66] Szuplewska A, Rekorajska A, Pocztańska E, Krysiński P, Dybko A, Chudy M. Magnetic field-assisted selective delivery of doxorubicin to cancer cells using magnetoliposomes as drug nanocarriers. *Nanotechnology.* 2019;**30**:315101. DOI: 10.1088/1361-6528/ab19d3
- [67] Joniec A, Sek S, Krysinski P. Magnetoliposomes as potential carriers of doxorubicin to Tumours. *Chemistry.* 2016;**22**(49):17715-17724. DOI: 10.1002/chem.201602809
- [68] Cintra ER, Hayasaki TG, Sousa-Junior AA, Silva ACG, Valadares MC, Bakuzis AF, et al. Folate-targeted PEGylated Magnetoliposomes for hyperthermia-mediated controlled release of doxorubicin. *Frontiers*

in *Pharmacology*. 2022;**13**:854430.  
DOI: 10.3389/fphar.2022.854430

[69] Kukowska-Latallo JF, Candido KA, Cao Z, Nigavekar SS, Majoros IJ, Thomas TP, et al. Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. *Cancer Research*. 2005;**65**:5317-5324. DOI: 10.1158/0008-5472.CAN-04-3921

[70] Ribeiro RFL, Ferreira RV, Pedersoli DC, Paiva PRP, Cunha PS, Goes AM, et al. Cytotoxic effect of thermosensitive magnetoliposomes loaded with gemcitabine and paclitaxel on human primary breast cancer cells (MGSO-3 line). *Journal of Nanoparticle Research*. 2020;**22**:172. DOI: 10.1007/s11051-020-04833-7

[71] Ribeiro BC, Alvarez CAR, Alves BC, Rodrigues JM, Queiroz MJRP, Almeida BG, et al. Development of Thermo- and pH-sensitive liposomal magnetic carriers for new potential antitumor Thienopyridine derivatives. *Materials (Basel)*. 2022;**15**(5):1737. DOI: 10.3390/ma15051737

[72] Trilli J, Caramazza L, Paolicelli P, Casadei MA, Liberti M, Apollonio F, et al. The impact of bilayer rigidity on the release from Magnetoliposomes vesicles controlled by PEMFs. *Pharmaceutics*. 2021;**13**(10):1712. DOI: 10.3390/pharmaceutics13101712