Journal of Pharmaceutical Research International

Volume 34, Issue 63, Page 40-49, 2022; Article no.JPRI.95847
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Thermosensitive Liposomal Drug Delivery Systems: A Review

Sachin Lohe [a*] and Milind Umekar [a]

[a] *Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Dist-Nagpur, M.S., India.*

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i637288

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/95847

Review Article

Received: 25/10/2022
Accepted: 30/12/2022
Published: 31/12/2022

ABSTRACT

When combined with local hyperthermia or high intensity focused ultrasound, thermosensitive liposomes are a promising technique for externally directing medications to solid tumours. To selectively focus drug delivery to diseased or damaged tissue while reducing drug distribution to vital normal tissues is the main goal of liposomal drug delivery. An overview of temperature-sensitive liposomes is provided in this review. The ability to heat tumours with external energy sources in a controlled and predictable manner makes temperature-sensitive liposomes an especially alluring alternative. The lipids used to make conventional thermosensitive liposomes experience a gel-to-liquid phase shift many degrees above physiological temperature. Lysolipids and artificial temperature-sensitive polymers have recently been used to show how liposomes can be made to be sensitive to temperature. Thermosensitive liposomes (TSL) and localized hyperthermia are potent delivery vehicles for tumor-specific drugs. In addition to chemotherapy, hyperthermia is given to cancer patients to help certain chemotherapeutic medications work more effectively. Using temperature-sensitive liposomes in conjunction with localized hyperthermia, which specifically releases the medicine contained in the heated tumor tissue, can significantly increase the temperature-dependent effect.

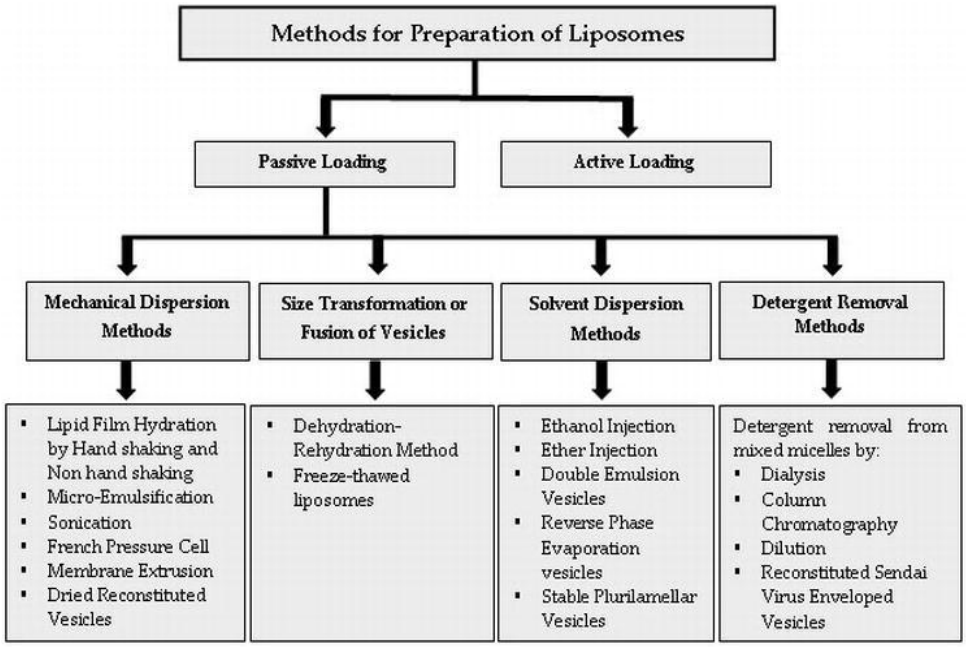
**Corresponding author: E-mail: Lohesachin@gmail.com;*

Keywords: Thermosensitive liposomal; drug delivery; temperature-sensitive polymers; tumor tissue; phospholipids.

1. INTRODUCTION

Typically made of phospholipids, liposomes are spherical vesicles that are generated by a membrane bilayer (Fig. 1). Hydrophilic pharmaceuticals can be enclosed in the membrane's aqueous core, whereas lipophilic medications can be integrated into the membrane. Liposomal formulations can be prepared using a variety of techniques, from laboratory size through Good Manufacturing Practice manufacture for clinical quantities [1]. Drug loading can be accomplished using active loading methods (Fig. 2A) or passive loading methods (Fig. 2B, Fig. 3).

By preventing quick metabolism, stable drug encapsulation inside of a liposomal formulation lengthens the medication's half-life in the bloodstream following intravenous delivery. Additionally, since undesired distribution in various physiological compartments is prevented, there is a lower chance of drug-related side effects. The adaptability of liposomal drug delivery systems is due to the fact that the lipid composition and/or technique of synthesis can alter their biophysical properties, such as vesicle size, lamellarity, surface charge, membrane fluidity, and surface [2]. Liposomes are typically categorized as biocompatible due to the usage of naturally occurring chemicals as the primary components, such as (phospho) lipids and cholesterol. After distributing lecithin in an aqueous media, Bangham et al. described the spontaneous production of liquid crystals in 1965 [3]. This review's goal is to give a comprehensive overview of temperature-sensitive liposomes, with a focus on the Low Temperature-Sensitive Liposome (LTSL). This LTSL was created to release medication quickly in response to a temperature trigger at 41–42°C utilizing moderate hyperthermia. Its fundamental design relies on a wealth of knowledge about liposomes that was accumulated over a 40-year period in order to load and retain medication while dodging the body's defences [4]. The most cutting-edge nanoscale drug delivery technology in clinical therapy is a result of these studies, which also encompass basic research and preclinical and clinical investigations [5]. The addition of thermosensitive polymers to the formulation can also result in drug release from liposomes that are activated by heat [6]. However, in this study, we emphasize the impact of lipid composition on the in vitro and in vivo behavior of the TSL formulations currently being studied and concentrate on formulations where thermosensitivity is accomplished via the biophysical properties of the membrane-forming phospholipids [7].



Flow chart 1. Protocol for liposome preparation

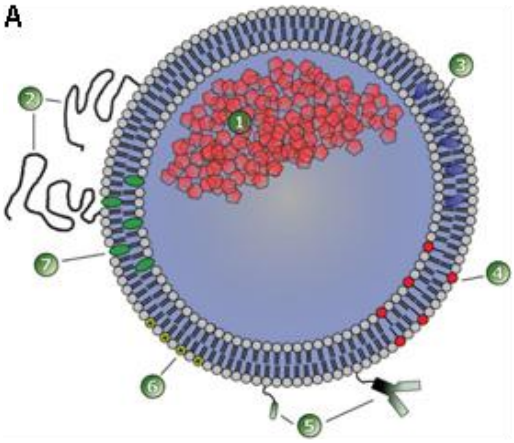


Fig. 1. Structure of liposomes

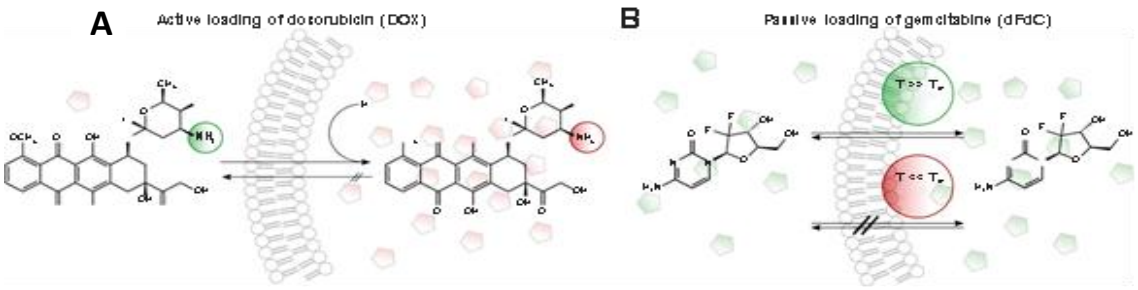


Fig. 2. Loading of drugs

2. A NOVEL APPROACH TO MEDICATION TARGETING: EXTERNAL TARGETING THAT TRIGGERS INTRAVASCULAR TEMPERATURE-TRIGGERED DRUG RELEASE

Due to the leaky tumor vasculature, traditional PEGylated long-circulating doxorubicin formulations like Doxil/Caelyx have been created to take advantage of the improved permeability and retention effect (Fig. 3A). “However, due to a number of drawbacks, passive drug targeting has not been able to outperform the free drug in terms of clinical efficacy in humans. The amount that accumulates varies on the particulars of the tumor's vasculature and could be boosted by heating the tumor tissue” [8,9] “Although less than 10% of the injected dose accumulates in the tumor, extravasation of vesicles is the rate-limiting step, and nanoparticles must circulate for days to accumulate in sufficiently high concentrations” [10]. This is because uptake in the liver and spleen competes with accumulation in tumor tissue [11] External targeting performed by temperature-triggered, localized intravascular drug release from TSL with focussed heating is a promising substitute, according to Manzoor et al (Fig. 3B) [12]. Doxorubicin was directly released into the bloodstream after reaching the heated tumor tissue, leading to a high intravascular drug concentration [12,13]. When compared to mice given with free doxorubicin or Doxil/Caelyx, this resulted in a much higher penetration depth of bioavailable doxorubicin into the tumor tissue [12]. With the use of this method, tumor sites with limited blood flow might also be treated, which is known to be more challenging because of a hypoxia-mediated resistance mechanism. Targeting more hydrophilic medicines, such as gemcitabine, under the idea of intravascular drug release. By controlling the heating focus and heating power, temperature-triggered drug targeting by TSL has the benefit of allowing external spatial and temporal control of drug release. In clinical practice, there are well-established devices for localized or regional heating of tumour tissue, including deep-seated tumour tissue, to 42°C (mild hyperthermia) [14]. As a result, frequently used TSL is made to release the medicine from the capsule between 39°C and 42°C.

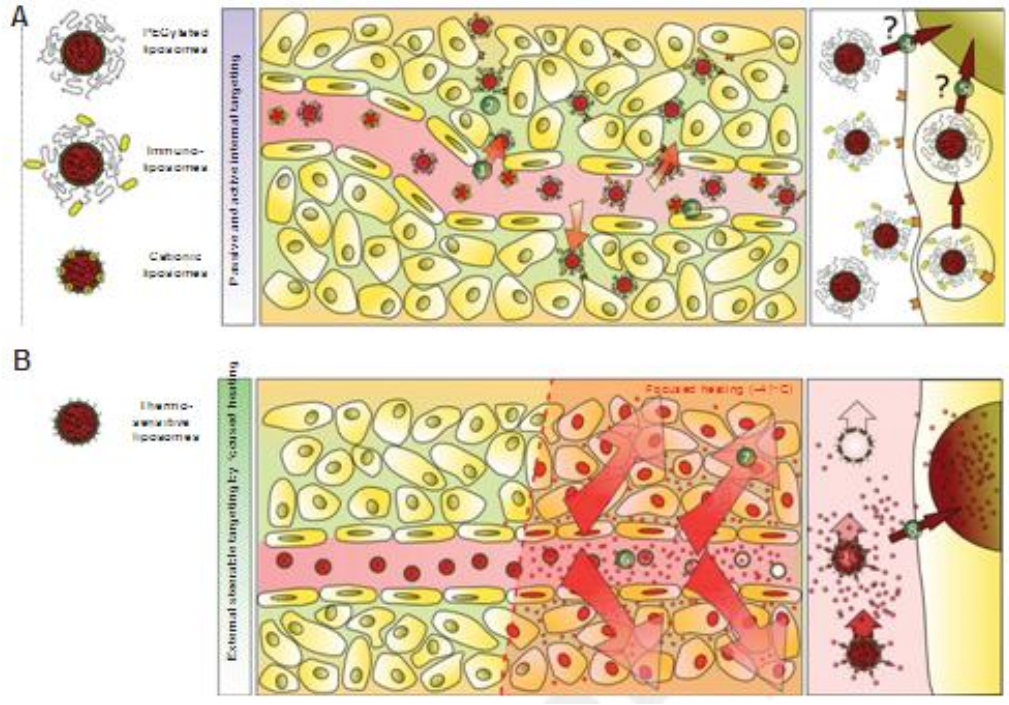


Fig. 3. Schematic illustration of targeting concepts with liposomes

3. INFLUENCE OF LIPID COMPOSITION ON DRUG RELEASE

"At the lipid bilayer's melting phase transition temperature (Tm), encapsulated hydrophilic medicines are released from TSL. When the changeover from a solid gel phase (L) to a liquid-crystalline phase (L) happens at Tm, the structure of the lipid bilayer changes (Fig. 4). When the membrane is in the liquid-crystalline phase as opposed to the gel phase, it is more permeable to water and hydrophilic medicines" [15,16]. Because membrane portions from both phases coexist and form grain boundaries at temperatures close to the Tm, hydrophilic medicines have the highest permeability at these temperatures [17,18].

4. TRADITIONAL TEMPERATURE-SENSITIVE LIPOSOMES

"The effect of cholesterol and PEG-phosphatidylethanolamine on stabilizing TSL formulations in vitro" was described by Gaber et al. in 1995 [19]. Cholesterol at a concentration of 30 mol% was added to TSL formulations to abolish Tm by converting the membrane's phase state to a liquid-ordered phase. "For MRI-guided delivery of doxorubicin, a conventional temperature-sensitive liposome (TTSL) formulation with co-encapsulated doxorubicin and a gadolinium-based contrast agent is being researched" [20–23]. "Because it is more stable than low temperature-sensitive liposome (LTSL) formulations that contain lysolipid, the TTSL formulation was chosen for this research" [20].

5. LYSOLIPID-CONTAINING LOW TEMPERATURE-SENSITIVE LIPOSOMES

"As stated by Needham et al. in 2000, the integration of lysolipids into the membrane bilayer represented a breakthrough in the production of clinically useful TSL formulations. The first TSL formulation suited for the intravascular drug release strategy was LTSL" [24]. "Although the use of surfactants reduces vesicle stability around Tm, this formulation is distinguished by extremely rapid drug release upon heating" [25]. "In addition, it was discovered that 70% of the lysolipid dissociated from the formulation within an hour of injection" [26].

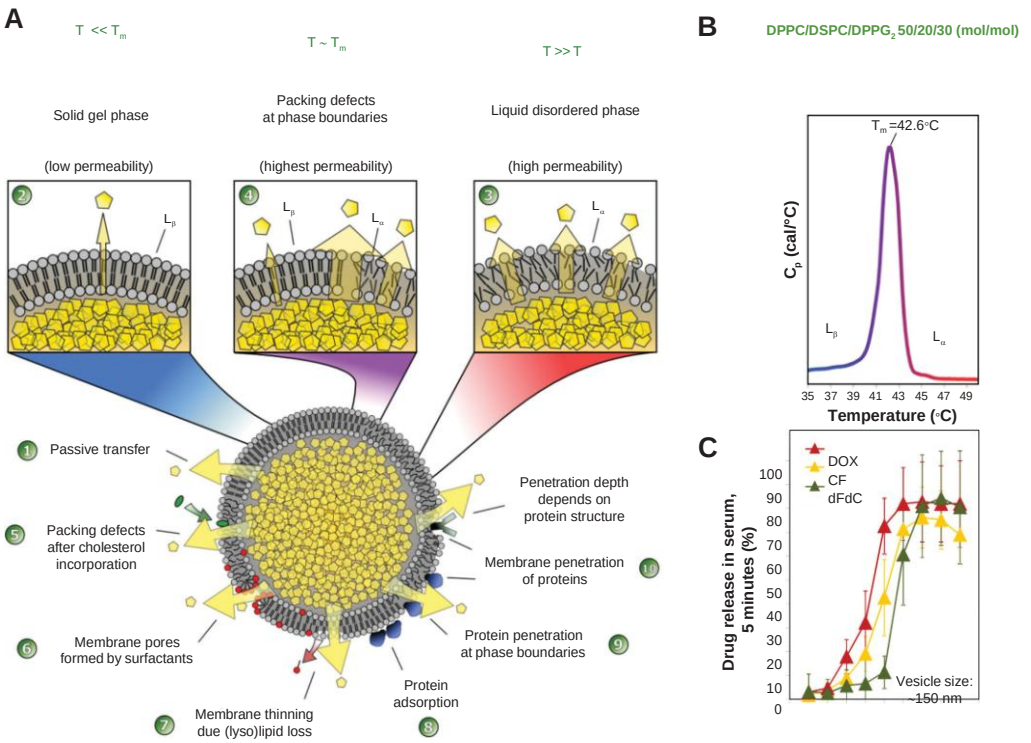


Fig. 4. Factors affecting drug release from thermosensitive liposomes

6. $DPPG_2$ -THERMOSENSITIVE LIPOSOME

In 2004, Lindner et al. reported on a novel liposomal formulation (DPPG2 -TSL) made up of the phospholipids DPPC, DSPC, and 1,2-dipalmitoyl-sn-glycero-3-phosphodiglycerol(DPPG2) [27]. Because only one extra glycerol molecule is connected to the head group via an ether bond, DPPG2 is a synthetic phospholipid with a molecular weight that is similar to that of naturally occurring 1,2-dipalmitoyl-sn-glycerol-3-phosphoglycerol [27]. Similar to PEGylated lipids, the molecular family of oligoglycerols was created to lengthen the half-life of vesicles in circulation. In both non-thermosensitive [28] and thermosensitive [29,27] formulations, the addition of DPPG2 resulted in a lengthened circulation time. In DPPG2 -TSL-encapsulated carboxy -fluorescein, the plasma half-life was observed to be 9.6 hours in hamsters and 5 hours in rats [27]. Surfactants were not included in the DPPG2 -TSL formulation, in contrast to the LTSL formulation. Although the release rates of doxorubicin and carboxyfluorescein from DPPG2 -TSL were as quick as those observed with the LTSL formulation [30], the drug release from the DPPG2 -TSL formulation began at a temperature that was about one degree higher [30]. When compared to LTSL, DPPG2 -TSL demonstrated improved in vitro stability in full serum [31]. In contrast to LTSL, the formulation was stabilized throughout time by the presence of serum components at 37°C.

7. STEALTH TSL

By incorporating DSPE-PEG2000 into the original Yatvin formulation, a sterically stabilized TSL formulation (Stealth TSL; Table 1) was created that allowed the passive accumulation of TSL in tumor tissue and had a better in vivo half-life than the LTSL formulation [32]. Li et al. showed that Stealth TSL had better in vitro stability at 37°C in serum when comparing it to LTSL [28] At 42°C, Stealth TSL released doxorubicin at its highest rate [28]. The release of doxorubicin from Stealth TSL begins at a greater temperature (39°C versus 37°C) than LTSL [28].

8. HYPERTHERMIA-ACTIVATED CYTO-TOXIC FORMULATION

The hyperthermia-activated cytotoxic (HaT) liposome formulation published by Tagami et al. is another TSL formulation containing encapsulated doxorubicin that is currently being

studied (Table 1). [33] DPPC and the non-ionic surfactant polyoxyethylene (20) stearyl ether make up HaT. (Brij78). It was assumed that since Brij78 had a PEGylated acyl chain, it may perform the same role as lyso-PC and DSPE-PEG2000 in the LTSL formulation [33,34]. At 40°C–42°C in buffer, the HaT formulation demonstrated 100% doxorubicin release in 3 minutes [34]. HaT demonstrated increased drug release rates at 40°C and comparable blood pharmacokinetics when compared to LTSL [33]. A blood circulation half-life of roughly 0.5 hours was noted for both formulations following injection [33]. When compared to LTSL, a single intravenous treatment with HaT at a doxorubicin dose of 3 mg/kg body weight in conjunction with local heat demonstrated improved tumor reduction [33].

9. STL Formulation

Another stabilized formulation containing encapsulated doxorubicin was described by Park et al. in 2013 and included DPPC, DSPE-PEG2000, cholesterol, and fatty acid-conjugated elastin-like polypeptide 55:2:15:0.4125 (mol/mol) (STL) (Table 1) [35]. Doxorubicin encapsulated in STL and LTSL, [35]. respectively, had plasma half-lives of 2.03 hours and 0.92 hours, according to pharmacokinetic tests in mice. When combined with high-intensity focused ultrasound, STL considerably outperformed LTSL in terms of tumor growth delay seven days after injection [35].

10. THERMOSENSITIVE LIPOSOMES FOR MRI-GUIDED DRUG DELIVERY

The preferred technique for image-guided medication distribution with TSL is MRI. It is an accepted clinical practice due to its well-known capabilities for morphological and functional tumor characterization without exposure to ionizing radiation. Additionally, MRI thermometry is established for the management of thermotherapies such high intensity-focused ultrasound and radiofrequency hyperthermia. Clinical applications have already adopted specialized hybrid systems [15,36,37]. Using MRI to modulate hyperthermia, localized drug release from TSL has been proven in rodents [38,39] and nonrodents [40–42]. Encapsulating MRI contrast agents in TSL formulations enables for additional characterization of the drug administration that is only possible in humans when utilizing MRI, in addition to managing the heating volume.

11. SIGNAL MECHANISM

The most common MRI-active contrast agents for encapsulating in TSL formulations are paramagnetic gadolinium chelates [54,41,43-45], and manganese ions [46-49] (Table 1). The fundamental source of the MRI signal is not the contrast agent itself, but rather the nuclear magnetic resonance of water protons. Only the ability of MRI contrast agents to speed up the water proton relaxation around the molecules of the contrast agent allows for their visualization. The contrast agent molecule must be given the opportunity to interact with a significant number of water protons in order for this indirect signal-producing contrast process to work. The contrast agent must be enclosed inside the TSL in order to visualize temperature-induced release [50–54]. Because there is little water interaction with the TSL's exterior below the Tm, the agent mostly interacts with the water inside of the TSL. As a result, as compared to contrast agents that are free, the contrast agent is less visible. T1-weighted pictures show an increase in signal as one gets closer to the Tm due to the increase in water exchange [49]. The contrast agent is released around the Tm, causing a maximal signal change that is comparable to the signal change produced by the free contrast agent [53]. This enables significant temperature-based modification of an MRI signal [54].

12. APPLICATIONS

A technique for quality control in thermotherapy for patients, TSL can be used with an encapsulating contrast agent to discriminate heated from unheated tissue [39,53] or to quantify absolute temperatures as a supplement to conventional MRI thermometry methods [54,55] The toxicity of manganese is the main disadvantage of the aforementioned strategy (II). Other studies are utilizing gadolinium-based contrast compounds that have received clinical approval to get around this. Hossann et al. looked examined six of these contrast agents for DPPG2 -TSL encapsulation and found that a non-ionic contrast agent with little osmolality contribution was the best option [40] Using gadolinium-based contrast agents, two encapsulation techniques are conceivable, but the release kinetics and signal mechanisms for the contrast agent and medication must be taken into account. Combining two TSL subsets, one of which contains only the contrast agent and the other of which contains only the medication, is one tactic [56]. By using this technique, more

Table 1. Overview of thermosensitive liposomes

Abbreviation	Membrane composition	First publication	T_m (encapsulated doxorubicin)	Encapsulated drugs	Encapsulated MRI contrast agent	Targeting principle
First TSL	DPPC/DSPC 3:1 (mol/mol)	1978[9]	–	Neomycin[9] Methotrexate[9]	–	
TTSL	DPPC/HSPC/Chol/ DPPE-PEG 50:25:15:3 (mol/mol)	1995[45]	40.9°C[54]	Doxorubicin[45,54]	Gd-based[54]	Passive targeting before heat-triggered, interstitial drug release
LTSL	DPPC/*lyso*-PC/DSPE-PEG_{2000} 90:10:4 (mol/mol)	2000[11]	40.8°C[10]	Doxorubicin[11] Cisplatinum[65]	Gd-based and Mn-based[54,87-89]	Intravascular drug release
$DPPG_2$-TSL	DPPC/DSPC/ $DPPG_2$ 50:20:30 (mol/mol)	2004[67]	41.9°C	Doxorubicin[46] Gemcitabine[28] Miltefosine[71]	Gd- and Mn-based[84-86,90,93]	Intravascular drug release
Stealth TSL	DPPC/DSPC/ DSPE-PEG_{2000} 80:15:5 (mol/mol)	2007[46]	43.0°C[72]	Doxorubicin[27,72]	–	Passive targeting before heat-triggered, interstitial drug release
HaT	DPPC/Brij78 96:4 (mol/mol)	2011[73]	41.0°C[74]	Doxorubicin[73] Gemcitabine[75] Oxaliplatin[75]	Gd-based[97]	Intravascular drug release
STL	DPPC/DSPE-PEG_{2000}/ Chol/ELP 55:2:15:0.4125 (mol/mol)	2013[77]	–	Doxorubicin[77]	–	Intravascular drug release

Abbreviations: Brij78, polyoxyethylene (20) stearyl ether; DPPE-PEG, 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-N-methoxy(PEG); $DPPG_2$, 1,2-dipalmitoyl-*sn*-glycero-3-phosphodiglycerol; DSPC, 1,2-distearoyl-*sn*-glycero-3-phosphocholine; DSPE-PEG_{2000}, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-methoxy(PEG)-2000; ELP, fatty acid conjugated elastin-like polypeptide; Gd, gadolinium; HaT, liposome hyperthermia-activated cytotoxic formulation; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; HSPC, hydrogenated soy phosphatidylcholine; LTSL, lysolipid-containing low-temperature sensitive liposomes; Mn, manganese; MRI, magnetic resonance imaging; TTSL, traditional temperature-sensitive liposome; TSL, thermosensitive liposome; Chol, cholesterol; T_m, phase transition temperature.

contrast agents and medication can be encapsulated without experiencing osmotic consequences [40]. The second technique, which limits the amount of both components in each TSL, is to encapsulate the medication and the contrast agent in the same TSL. The temperature-dependent medication release rate and MRI signal change must, however, be correlated for both procedures [57].

13. CONCLUSION

Together with local hyperthermia or high-intensity focused ultrasound, TSL is a promising method for external medication targeting solid tumors.

There have been several formulations created, one of which is currently undergoing clinical testing. Results from in vivo experiments provide compelling evidence that external targeting of extremely stable long-circulating medication formulations is preferable to passive targeting. Additionally, MRI-guided drug delivery opens up the possibility of online heating focus monitoring, determining the concentrations of drugs released locally, and externally managing drug release by adjusting the heating focus and power. The distinguishing feature of this nanotechnology-based medical strategy will be the integration of MRI-guided drug administration and external targeting with TSL.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wagner A, Vorauer-Uhl K. Liposome technology for industrial purposes. J Drug Deliv. 2011;2011:591325
2. Limmer S, Hahn J, Schmidt R, et al. Gemcitabine treatment of rat soft tissue sarcoma with phosphatidyldiglycerol-based thermosensitive liposomes. Pharm Res. Epub 2014 March 6.
3. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol. 1965;13:238–252.
4. Li L, ten Hagen TL, Schipper D, et al. Triggered content release from optimized stealth thermosensitive liposomes using mild hyperthermia. J Control Release. 2010;143:274–279.
5. Immordino ML, Dosio F, Cattel L. Stealth liposomes: Review of the basic science, rationale, and clinical applications, existing and potential. Int J Nanomedicine. 2006;1: 297–315.
6. van Elk M, Deckers R, Oerlemans C, et al. Triggered release of doxorubicin from temperature-sensitive poly(N-(2-hydroxypropyl)- methacrylamide mono/dilactate) grafted liposomes. Biomacromolecules. 2014;15:1002–1009.
   May JP, Li SD. Hyperthermia-induced drug targeting. Expert Opin Drug Deliv. 2013;10: 511–527.

7. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul. 2001;41:189–207.
8. Kong G, Anyarambhatla G, Petros WP, et al. Efficacy of liposomes and hyperthermia in a human tumor xenograft model: Importance of triggered drug release. Cancer Res. 2000; 60:6950–6957. 19.
9. Li L, ten Hagen TL, Bolkestein M, et al. Improved intratumoral nanoparticle extravasation and penetration by mild hyperthermia. J Control Release. 2013; 167:130–137. 20.
10. Harrington KJ, Mohammadtaghi S, Uster PS, et al. Effective targeting of solid tumors in patients with locally advanced cancers by radiolabelled pegylated liposomes. Clin Cancer Res. 2001;7: 243–254.
11. Harrington KJ, Mohammadtaghi S, Uster PS, et al. Effective targeting of solid tumors in patients with locally advanced cancers by radiolabeledpegylated liposomes. Clin Cancer Res. 2001; 7:243–254.
12. Manzoor AA, Lindner LH, Landon CD, et al. Overcoming limitations in nanoparticle drug delivery: triggered, intravascular release to improve drug penetration into tumors. Cancer Res. 2012;72: 5566–5575.
13. Li L, ten Hagen TL, Hossann M, et al. Mild hyperthermia triggered doxorubicin release from optimized stealth thermosensitive liposomes improves intratumoral drug delivery and efficacy. J Control Release. 2013;168:142–150.
14. Issels RD, Lindner LH, Verweij J, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: A randomised phase 3 multicentre study. Lancet Oncol. 2010;11: 561–570.
15. Grüll H, Langereis S. Hyperthermia-triggered drug delivery from temperature-sensitive liposomes using MRI-guided high intensity focused ultrasound. J Control Release. 2012; 161:317–327.
16. Evans E, Needham D. Physical properties of surfactant bilayermembranes – thermal transitions, elasticity, rigidity, cohesion, and colloidal interactions. J Phys Chem. 1987;91:4219–4228.
17. Mouritsen OG, Zuckermann MJ. Model of interfacial melting. Phys Rev Lett. 1987; 58:389–392.
18. Kaasgaard T, Leidy C, Crowe JH, Mouritsen OG, Jorgensen K. Temperature-controlled structure and kinetics of ripple phases in one- and two-component supported lipid bilayers. Biophys J. 2003;85: 350–360.
19. Gaber MH, Hong K, Huang SK, Papahadjopoulos D. Thermosensitive sterically stabilized liposomes: formulation and in vitro studies on mechanism of doxorubicin release by bovine serum and human plasma. Pharm Res. 1995; 12:1407–1416.
20. de Smet M, Langereis S, van den Bosch S, Grüll H. Temperaturesensitive liposomes for doxorubicin delivery under MRI guidance. J Control Release. 2010; 143:120–127.
21. de Smet M, Heijman E, Langereis S, Hijnen NM, Grüll H. Magnetic resonance imaging of high intensity focused ultrasound mediated drug delivery from temperature-sensitive liposomes: an in vivo proof-ofconcept study. J Control Release; 2011.
22. de Smet M, Hijnen NM, Langereis S, et al. Magnetic resonance guided high-intensity focused ultrasound mediated hyperthermia improves the intratumoral distribution of temperature-sensitive liposomal doxorubicin. Invest Radiol. 2013;48:395–405.
23. de Smet M, Langereis S, van den Bosch S, et al. SPECT/CT imaging of temperature-sensitive liposomes for MR-image guided drug delivery with high intensity focused ultrasound. J Control Release. 2013;169:82–90.
24. Needham D, Anyarambhatla G, Kong G, Dewhirst MW. A new temperature-sensitive liposome for use with mild hyperthermia: characterization and testing in a human tumor xenograft model. Cancer Res. 2000;60:1197–1201.
25. Ickenstein LM, Arfvidsson MC, Needham D, Mayer LD, Edwards K. Disc formation in cholesterol-free liposomes during phase transition. BiochimBiophysActa. 2003;1614:135–138.
26. Banno B, Ickenstein LM, Chiu GN, et al. The functional roles of poly (ethylene glycol)-lipid and lysolipid in the drug retention and release from lysolipid-containing thermosensitive liposomes in vitro and in vivo. J Pharm Sci. 2010;99:2295–2308.

27. Lindner LH, Eichhorn ME, Eibl H, et al. Novel temperature-sensitive liposomes with prolonged circulation time. Clin Cancer Res. 2004;10:2168–2178
28. Schagon O. Liposomenalspotentielle Arzneistoffträger: Variation der biopharmazeutischen Eigenschaftendurch 1,2-Dipalmitoyl-sn-glycero-oligoglycerine. [Liposomes as drug carriers - variation of biopharmaceutical characteristics by incorporation of 1,2-dipalmitoyl-sn-glycero-3-phosphooligo.
29. Limmer S, Hahn J, Schmidt R, et al. Gemcitabine treatment of rat soft tissue sarcoma with phosphatidyldiglycerol-based thermosensitive liposomes. Pharm Res. Epub 2014 March 6.
30. Hossann M, Wiggenhorn M, Schwerdt A, et al. *In vitro* stability and content release properties of phosphatidylglyceroglycerol containing thermosensitive liposomes. Biochim Biophys Acta. 2007;1768: 2491–2499.
31. Hossann M, Syunyaeva Z, Schmidt R, Zengerle A, Eibl H, Issels RD, Lindner LH. Proteins and cholesterol lipid vesicles are mediators of drug release from thermosensitive liposomes. Journal of controlled release. 2012;162(2):400-6.
32. Li L, ten Hagen TL, Bolkestein M, et al. Improved intratumoral nanoparticle extravasation and penetration by mild hyperthermia. J Control Release. 2013;167:130–137.
33. Tagami T, Ernsting MJ, Li SD. Efficient tumor regression by a single and low dose treatment with a novel and enhanced formulation of thermosensitive liposomal doxorubicin. Journal of Controlled Release. 2011;152(2):303-9.
34. Tagami T, Ernsting MJ, Li SD. Optimization of a novel and improved thermosensitive liposome formulated with DPPC and a Brij surfactant using a robust in vitro system. J Control Release. 2011;154:290–297.
35. Park SM, Kim MS, Park SJ, et al. Novel temperature-triggered liposome with high stability: formulation, in vitro evaluation, and in vivo study combined with high-intensity focused ultrasound (HIFU). J Control Release. 2013; 170:373–379
36. Peller M, Löffler R, Baur A, Turner P, Abdel-Rahman S, Futschik G, Santl M, Hiddemann W, Reiser M, Issels R. MRI-controlled regional hyperthermia. Der Radiologe. 1999;39(9):756-63.
37. Gellermann J, Wlodarczyk W, Hildebrandt B, et al. Noninvasive magnetic resonance thermography of recurrent rectal carcinoma in a 1.5 Tesla hybrid system. Cancer Res. 2005; 65:5872–5880.
38. de Smet M, Heijman E, Langereis S, Hijnen NM, Grüll H. Magnetic resonance imaging of high intensity focused ultrasound mediated drug delivery from temperature-sensitive liposomes: an *In vivo* proof-of-concept study. Journal of Controlled Release. 2011;150(1): 102-10.
39. Hijnen NM, Heijman E, Kohler MO, et al. Tumour hyperthermia and ablation in rats using a clinical MR-HIFU system equipped with a dedicated small animal set-up. Int J Hyperthermia. 2012; 28:141–155.
40. Staruch R, Chopra R, Hynynen K. Localised drug release using MRIcontrolled focused ultrasound hyperthermia. Int J Hyperthermia. 2011; 27:156–171
41. Negussie AH, Yarmolenko PS, Partanen A, et al. Formulation and characterisation of magnetic resonance imageable thermally sensitive liposomes for use with magnetic resonance-guided high intensity focused ultrasound. Int J Hyperthermia. 2011;27:140–155.
42. Ranjan A, Jacobs GC, Woods DL, et al. Image-guided drug delivery with magnetic resonance guided high intensity focused ultrasound and temperature sensitive liposomes in a rabbit Vx2 tumor model. J Control Release. 2012;158:487–494.
43. Lindner LH, Reinl HM, Schlemmer M, Stahl R, Peller M. Paramagnetic thermosensitive liposomes for MR-thermometry. Int J Hyperthermia. 2005;21:575–588.
44. Wang TT, Hossann M, Reinl HM, et al. In vitro characterization of phosphatidylglyceroglycerol-based thermosensitive liposomes with encapsulated H-1 MR T-1-shortening gadodiamide. Contrast Media Mol Imaging. 2008;3:19–26.
45. Peller M, Schwerdt A, Hossann M, et al. MR characterization of mild hyperthermia-induced gadodiamide release from thermosensitive liposomes in solid tumors. Invest Radiol. 2008;43:877–892.
46. Hossann M, Wang T, Syunyaeva Z, et al. Non-ionic Gd-based MRI contrast agents are optimal for encapsulation into phosphatidyldiglycerol-based

thermosensitive liposomes. J Control Release. 2013;166:22–29.
47. Viglianti BL, Abraham SA, Michelich CR, et al. In vivo monitoring of tissue pharmacokinetics of liposome/drug using MRI: Illustration of targeted delivery. Magn Reson Med. 2004;51:1153–1162.
48. Viglianti BL, Ponce AM, Michelich CR, et al. Chemodosimetry of *In vivo* tumor liposomal drug concentration using MRI. Magn Reson Med. 2006;56:1011–1018.
49. Ponce AM, Viglianti BL, Yu D, et al. Magnetic resonance imaging of temperature-sensitive liposome release: drug dose painting and antitumor effects. J
50. Reinl HM, Hossann M, Lindner LH, Reiser M. Thermosensitive Mn2+ liposomes for MR-guided hyperthermia – solvent-dependent Mn2+ release. IFMBE Proc. 2010;25:21–24.
51. Fossheim SL, Fahlvik AK, Klaveness J, Muller RN. Paramagnetic liposomes as MRI contrast agents: influence of liposomal physicochemical properties on *the In vitro* relaxivity. Magn Reson Imaging. 1999;17:83–89
52. Fossheim SL, Il'yasov KA, Hennig J, Bjornerud A. Thermosensitive paramagnetic liposomes for temperature control during MR imaging-guided hyperthermia: *In vitro* feasibility studies. AcadRadiol. 2000;7:1107–1115.
53. Reinl HM, Lindner LH, Schneider P, et al. New thermosensitive liposomes for MR-guided hyperthermia. Proc Intl Soc Mag Reson Med. 2003;11:1209.
54. McDannold N, Fossheim SL, Rasmussen H, Martin H, Vykhodtseva N, Hynynen K. Heat-activated liposomal MR contrast agent: initial in vivo results in rabbit liver and kidney. Radiology. 2004;230: 743–752.
55. Hey S, de Smet M, Stehning C, et al. Simultaneous T1 measurements and proton resonance frequency shift-based thermometry using variable flip angles. Magn Reson Med. 2012;67:457–463.
56. Wang T, Hossann M, Peller M, Reinl HM, Reiser M, Issels RD, Lindner LH. Dual phosphatidylglyceroglycerol-based thermosensitive liposomes for MR-guided chemothermotherapy. InWorld Congress on Medical Physics and Biomedical Engineering, September 7-12, 2009, Munich, Germany: Vol. 25/8 Micro-and Nanosystems in Medicine, Active Implants, Biosensors. Springer Berlin Heidelberg. 2010;259-260.
57. Tagami T, Foltz WD, Ernsting MJ, et al. MRI monitoring of intratumoral drug delivery and prediction of the therapeutic effect with a multifunctional thermosensitive liposome. Biomaterials. 2011;32:6570–6578.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/95847