

# Advances in Thermosensitive Liposomes for Site-Specific Drug Release

Nagaraja Jarugula<sup>1\*</sup>, Pavan K Chennupati<sup>1,2</sup>, Rasheed Shaik<sup>1</sup>, M. Sireesha<sup>1</sup>, S. Chandra<sup>1</sup>

<sup>1</sup>Chennupati Indo American School of Pharmacy, Jonnalagadda, Andhra Pradesh, 522601

<sup>2</sup>Katalyst Healthcare & Life Sciences, Inc., South Plainfield, NJ 07080, USA.

\*Corresponding Email: [nagaraja.jarugula@gmail.com](mailto:nagaraja.jarugula@gmail.com)

## Abstract

Thermosensitive liposomes (TSLs) have emerged as a novel and adaptable platform in nanomedicine, enabling targeted and strategic drug delivery through their thermoresponsive release characteristics. Designed to remain stable at physiological temperatures and to undergo phase transitions at severe hyperthermia (41–43 °C), TSLs can release encapsulated therapeutic agents (e.g., doxorubicin, mitoxantrone, oxaliplatin) in controlled spatial and temporal concentrations to targeted tumors. Preclinical trials demonstrate that TSLs, particularly when combined with localized hyperthermia therapies such as focused ultrasound or radiofrequency heating, significantly enhance intratumoral drug delivery, improve therapeutic efficacy, and diminish systemic toxicity compared to standard chemotherapy. Strategic design changes, including adding lysolipids to lower phase transition temperatures and PEGylation to improve circulation and stem stability, can further improve pharmacokinetics and biocompatibility. A combination of real-time imaging measures gives us a greater chance to follow the liposomes' movement and release medications, which lets us tailor the therapy program to fit each patient. Even though these are good steps forward, there are still problems with standardizing formulations, keeping the temperature very stable throughout hyperthermia, and making preclinical research work for a lot of people in the clinic. Still, ongoing research that focuses on improving the formulation and combining it with other innovative treatments like immunotherapy, gene therapy, and non-invasive thermal procedures is essential to realize the full clinical potential of TSLs. In short, TSLs are a very promising idea for a safe and effective cancer treatment that can be targeted. They also make it possible to improve therapeutic results while keeping off-target side effects to a minimum.

## Key Words:

Thermosensitive Liposomes, Hyperthermia, Site-Specific Drug Delivery, Pegylation, Lysolipids, Tumor Targeting, Controlled Release, Preclinical Evaluation

## History:

Received: July, 28, 2025

Revised: Aug, 24, 2025

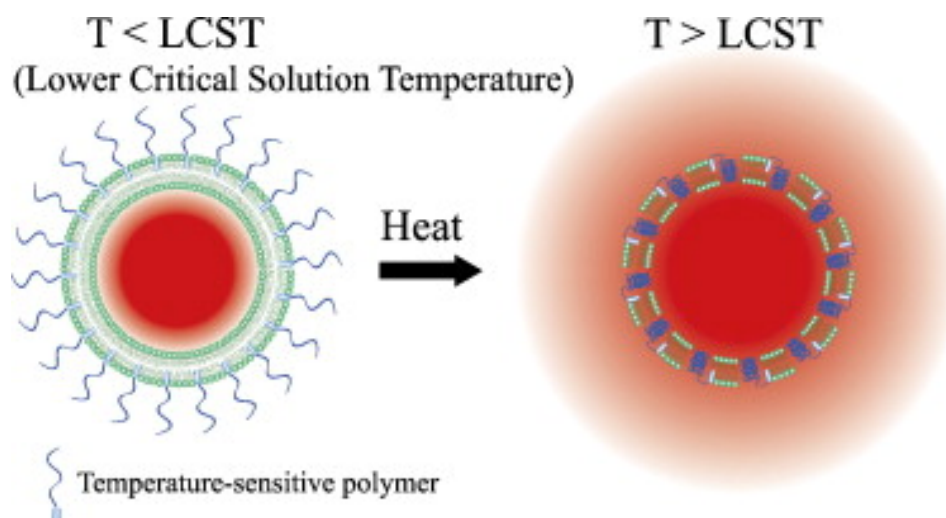
Accepted: Sep, 11, 2025

Published: Oct 28, 2025

DOI: <https://doi.org/10.64063/3049-1681.vol.2.issue10.3>

## I. INTRODUCTION

Liposomes are naturally detailed as efficient drug delivery vehicles owing to biocompatibility, drug encapsulation as well as regulating pharmacokinetics<sup>1</sup>. In recent decades, these nanocarriers are developed into more widely-used platforms and one of the outstanding innovations is thermosensitive liposomes (TSLs). As opposed to traditional liposomes, TSLs are designed to be stable at room temperature but undergo a phase transition during exposure to slightly elevated hyperthermia that is commonly 41°C to 43°C. This behavioral characteristic of the temperature-dependence makes possible the opportunity to release encapsulated drugs at a point of interest and applies spatial and temporal accuracy. Combination of TSLs and hyperthermia strategies detailed above i.e. local heating with radiofrequency or focused ultrasound has shown significant promise in increasing differences in delivery of drugs to the tumor, reducing systemic circulation and enhancing therapy effects.



**Figure 1:** Thermosensitive Liposomes for Site-Specific Drug Release<sup>2</sup>

The main aim of having studies in this category has been to maximize the design of TSL robotized lipid composition, PEGylation, and lysolipids inclusion to provide effective and localized drug delivery whilst retaining biocompatibility and overall circulation. Encapsulations of chemotherapeutic agents such as doxorubicin, mitoxantrone and oxaliplatin have been studied in preclinical models with the aim of evaluating efficacy and safety as well as safety and efficacy<sup>3</sup>. TSLs are important not solely due to their ability to deliver drugs to disease locations, they are an illustration of a precision approach to medicine and, treating diseases, require concentration at the effector sites, sparing normal tissues. TSLs have a tremendous potential in advancing nanomedicine category by improving the therapeutic index and decreasing the systemic toxicity

particularly with localized cases of cancer in which it is highly required to deliver drugs with a fair degree of control and targeted growth to the effect.

### **1.1. Background Information and Context**

The biosphere Liposomes are known to be a versatile nanocarrier used in drug delivery because of their biocompatibility, capacity to encapsulate a large diversity of therapeutic agents, and capability to enhance the characteristics of drug stability, solubility and pharmacokinetic characteristics<sup>4</sup>. Developments in the technology of liposomes over the years have resulted in creating specialized formulations, including thermosensitive liposomes (TSLs) which provide an extra level of accuracy in treatment. TSLs are designed to be stable at normal physiological temperatures to avoid untimely potentially premature drug release, but when subjected to a stage change to allow mild hyperthermia, which may be in a range between 41 -43C. This temperature-controlled reaction allows the release of the encapsulated drug in location-specific fashion and provides clinicians with the chance to regulate the place and timing of this release. This is especially useful in therapy of localized tumours, where it is very important to achieve high drug concentration at the tumour site and minimal drug exposure to the rest of the body to ensure improved drug and response effects and also to limit adverse effects. TSLs combine these properties with the targeted hyperthermia methods, which demonstrates that TSLs represent the future of precision medicine and drug delivery control.

### **1.2. Objectives of the Review**

- To summarize recent advances in the design and formulation of thermosensitive liposomes, including lysolipid incorporation and PEGylation strategies, for enhanced drug delivery.
- To evaluate preclinical studies on TSLs, focusing on hyperthermia-triggered drug release, tumor accumulation, therapeutic efficacy, and pharmacokinetic profiles.
- To analyze the safety and toxicity of TSLs in animal models, including systemic and localized effects, histopathology, and immune response.
- To assess the impact of hyperthermia techniques (local and systemic) and drug selection on the controlled release and site-specific delivery of chemotherapeutic agents.
- To identify current challenges, gaps, and future research directions in optimizing TSL performance, clinical translation, and combination with emerging therapies such as immunotherapy or gene therapy.

### **1.3. Importance of the Topic**

The role of thermosensitive liposomes (TSLs) in precision medicine is important as they have the highest capacities of delivering therapeutic agents at high levels to the site of disease with minimum exposure to the normal tissues. This targeted method does not only increase the index of a therapeutic level of anticancer drugs but also reduces considerably the systemic toxicity which is one of the greatest limitations of traditional chemotherapy. TSLs enable clinicians to measure

the when, where, and how of drug delivery process and boost the efficacy and safety of treatment through controlled and temperature-sensitive release, which enables finer adjustment in treatment timing and the location of drug administration; aiding treatment efficacy and patient safety<sup>5</sup>. Moreover, the TSLs are also compatible with hyperthermia therapies, allowing synergistic treatment to occur, which enhances tumor suppressive action. This further increases the circulation stability and accumulation in the tumor by their design flexibility, e.g. PEGylation or lysolipid addition. All in all, TSLs are one of the major contributions to nanomedicine and provide a proper foundation through which to develop better, safer, and personalised therapeutic approaches in treated cancers.

## 2. PRECLINICAL EVALUATION OF THERMOSENSITIVE LIPOSOMES

Preclinical animal experiments have confirmed that thermosensitive liposomes (TSLs) are very good in site-specific drug delivery over localized hyperthermia<sup>6</sup>. TSLs loaded with Doxorubicin-, mitoxantrone-, and oxaliplatin have a greater tumor deposition, effective controlled drug release, and effective tumor suppression in murinosattributes coupled with reduced systemic toxicity. Thin-film hydration is normally used to prepare these liposomes and characterize them in aspects such as size, encapsulation efficiency and thermosensitivity properties. In vivo studies based on imaging procedures substantiate accurate, hyperthermia-initiated drug movement. Although TSLs are a specific and on-demand therapeutic option, with better pharmacokinetics compared to other options, they face limitations in temperature regulation, technology formulation, and scalability<sup>7</sup>.

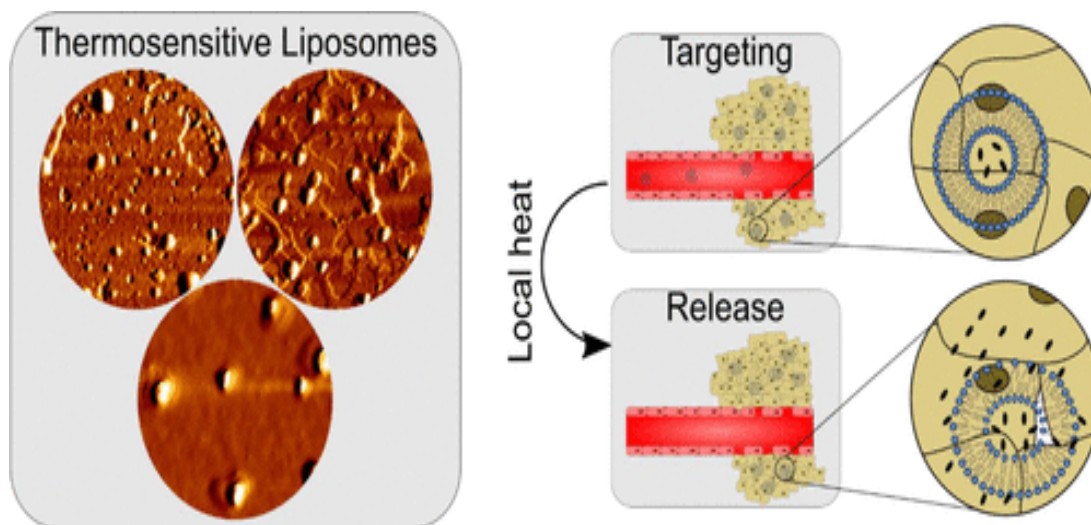


Figure 2: thermosensitive liposomes Encapsulating<sup>8</sup>

### 2.1. Key Research Studies

- **Doxorubicin-Loaded TSLs:** The preclinical trials in animals have shown potential of doxorubicin loaded thermosensitive liposomes (TSLs)<sup>9</sup>. In addition to having localised

hyperthermia, these liposomes greatly improve the accumulation of drugs in tumors as well as inhibiting the illness in murines. The condition brought about by hyperthermia induces a liposomal membrane phase transition, which releases doxorubicin locally at the tumor region<sup>10</sup>. This localized release does not only enhance the antitumor capability, but also reduces the systemic toxicity and hence provides a better targeted form of therapy as opposed to the conventional chemotherapy.

- **Mitoxantrone-Loaded TSLs:** Mitoxantrone-impregnated TSLs have been demonstrated in the laboratory to have fast and controllable drug release when autostimulated to release drugs in mild hyperthermia in BDF1 mouse implants with RM-1 prostate tumors. There was a high encapsulation efficiency of the formulation and stable circulation and a good deal of tumor suppression was possible. These results show that TSLs can maximize the pharmacodynamic properties of chemotherapeutic agents and it offers an added benefit of control over location of release.
- **Oxaliplatin-Loaded TSLs:** PEGylated TSLs containing oxaliplatin have been tested in animals with regard to antitumor activity. In mild hyperthermia, these liposomes selectively release the oxaliplatin at tumor sites thus positively influencing therapy outcomes and, in the process, eliminating systemic toxicity<sup>11</sup>. PEGylation increases liposome stability, longevity, and dropouts at early stages, and it provides a better functional formulation by enhancing the controlled and localized treatment with chemotherapy.

## 2.2. Methodologies and Findings

- **Preparation and Characterization:** Thermosensitive liposomes are usually synthesized through the use of thin-film hydration method and afterwards extruded or sonicated in order to produce uniform-sized particles<sup>12</sup>. Upon preparation, TSLs are strictly defined on the basis of particle size, zeta potential, drug encapsulation efficiency, and chemosensitivity, in such a way that the liposomes can be spared that can be stable in physiological settings and release drugs in reaction to hyperthermia.
- **In Vivo Evaluation:** The use of animal modes is widely applicable in the process of assessing the pharmacokinetic, tumor accumulation, kinetic of drug release, and the overall therapeutic efficacy of TSLs<sup>13</sup>. Models of imaging, such as magnetic resonance imaging (MRI) and fluorescence imaging can be used as real-time to monitor liposome distribution and release of drugs and thereby accurately correlate the use of hyperthermia with local drug delivery.
- **Findings:** The combined findings of these publications all point to the fact that when using hyperthermia-induced TSLs universal delivery of drugs, enhanced tumor control and reduced systemic toxicity are among the announced (as compared to the free drug delivery)<sup>14</sup>. The controlled release mechanism is one of the mechanisms that make sure that the therapeutic growths of the drug are attained at the specific site where the tumors are and not to the healthy tissues.

### 2.3. Critical Evaluation: Strengths and Weaknesses

- **Strengths:** The benefit of thermosensitive liposomes enables to target, at a specific location of the target type, the chemotherapeutic agent, thus minimizing the off-target effects and enhancing the overall effectiveness of the therapeutic product<sup>15</sup>. TSLs combined with hyperthermia permit on-demand localized administration of drugs. Overall, PEGylation is another formulation strategy that could increase the stability of the liposomes, their longevity circulating within the body and their elimination, increasing treatment efficacy further.
- **Weaknesses:** Irrespective of their benefits, there are a number of drawbacks that restrict the clinical adaptation of TSLs. Controlled temperature is essential to cause the activation of drug release and the inconsistency in tumor heating may lead to unequal treatment time. The fact that it requires advanced machines to deliver hyperthermia alongside liposomal treatment make it complicated. In addition to that, TSL formulations should undergo further investigation of long-term safety, greater manufacturing in scale and reproducibility before they can be fully used in a clinical setup<sup>16</sup>.

### 3. DESIGN STRATEGIES AND HYPERTHERMIA APPROACHES FOR THERMOSENSITIVE LIPOSOMES

Thermosensitive liposomes (TSLs) are constructed to achieve an optimal delivery of drugs by designing its formulation, hyperthermia application and under selection of the drug<sup>17</sup>. TSLs having lysolipids reduce the phase transition temperature to release the drug quickly and at mildly hyperthermic temperatures, whereas PEGylation greatly increases the circulatory life span and the AD rate of accumulation to the tumor, which works with the EPR effect. Site-selective release of drugs is facilitated by local hyperthermia, such as focused ultrasound or laser, but is too perilous to be sensitive enough to treat more than one location of tumour, but systemic hyperthermia can treat many locations of tumour, but it must be selectively targeted. The efficiency of their encapsulation, activation under complete control, aggregation within the intratumor mass, and a minimum of side effects under administration, a combination of chemotherapeutic agents with ATPA is the most effective approach to administer therapy to animals systems<sup>18</sup>.

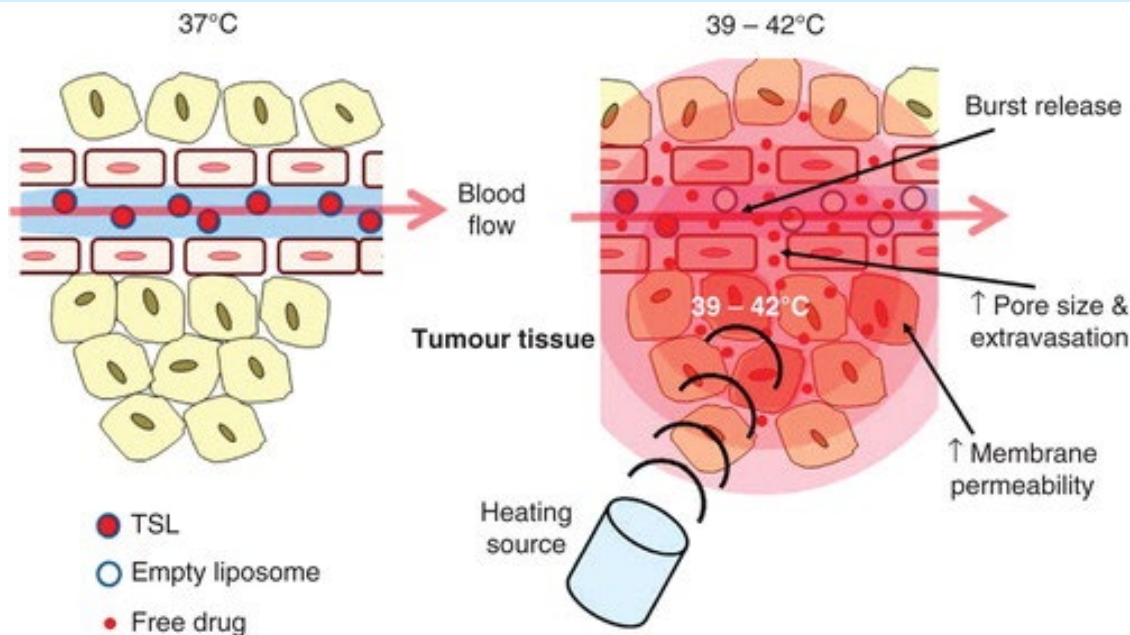


Figure 3: Hyperthermia Drug Targeted<sup>19</sup>

### 3.1. Thermosensitive Liposome Formulations

- Lysolipid-Containing TSLs:** These solutions incorporate lysolipids to the liposomal membrane in effect reducing the phase transition temperature ( $T_m$ ) in order to release drugs at mildly elevated hyperthermic (approximately 39-41 °C) temperatures. This design is better in trying to increase responsiveness of liposomes to local heating, causing quick and efficient drug delivery to the tumor site. Animal experiments have shown that, TSLs which contain lysosaccharides, have better drug release, increased tumor drug delivery and therapeutic outcome in comparison with other liposomes<sup>20</sup>. Lysolipids also ensure membrane stability even at normal physiological temperatures resulting in a decrease in early drug leakage.
- PEGylated TSLs:** PEGylating the liposomes creates a hydrophilic (stealth) layer to enhance circulation time of the liposomes, which leads to the accumulation of the liposomes at the tumor site through growth of an enhanced permeability and retention (EPR) effect. PEGylated TSLs enable the duration of exposure of the encapsulated drug to the target tissue and decrease reticuloendothelial clearance. Animals have also been reported to respond to PEGylated TSLs with effective results in terms of slower toxicity in the body and stable encapsulation of the drug, which makes them best in repeated or extended treatment procedures<sup>21</sup>.

### 3.2. Hyperthermia Techniques

- **Local Hyperthermia:** This mode implies the direct application of heat onto the location of the tumor to induce thermosensitive DNA triggering of drugs release by TSLs. One of the applied techniques is the radiofrequency ablation, which is conducted in animal models using focused ultrasound, laser-induced hyperthermia, and other techniques to achieve specific temperatures. Local hyperthermia will provide such that the release of drugs will be delivered consequently mostly at the tumor location consuming minimal systemic exposure and adverse effects. Combination of TSLs and localized hyperthermia have also proved to have better tumor suppression and greater intratumor drug concentrations.
- **Systemic Hyperthermia:** Another method of stimulating the drug delivery out of the TSLs in the body is whole-body heating. Although systemic hyperthermia is able to induce release of drugs at a range of tumor sites within the body, it has an augmented prospect of inducing systemic toxicity owing to non-selective drugs release<sup>22</sup>. Overall, it is important to have a very close monitoring and measure of the temperature to strike a balance between therapeutic measures and safety. It has been proposed that systemic hyperthermia is effective in some models of metastatic tumors, or conveyed diffuse tumors with some optimization of heating regimens anticipated to generate adverse effects.

### 3.3. Drug Selection for Encapsulation

A very important element of TSL efficacy is the choice of a chemotherapeutic agent. Doxorubicin, mitoxantrone and oxaliplatin are drugs that can be used widely due to the potent anticancer effect and the suitability with liposomal encapsulation<sup>23</sup>. The main physicochemical characteristics such as molecular size, charge, and lipophilicity affect the ability of encapsulation, membrane interference and release rate under hyperthermic conditions. It has been shown in animal studies that drug-liposomes are most effectively combined so that intratumoral deposition is maximum, treatment is advantageous and systemic toxicity is reduced. There is also a need to select drugs taking their room stability, chances of premature leakages, sensitiveness to temperature signals among others to maintain uniform performance both preclinical and clinical<sup>24</sup>.

## 4. SAFETY AND TOXICITY EVALUATION IN ANIMAL MODELS

Thermosensitive liposomes (TSLs) are aimed at increasing site-specific administration of drugs to reduce systemic exposure. Nevertheless, their safety profile needs to be rigorously evaluated during clinical translation<sup>25</sup>. Animal research has emphasized both acute and chronic toxicology analysis, which includes hematological, biochemical, organ histopathology and immune systems. The studies can give insights on the interaction between TSLs by biology system, so that targeted drug delivery will not impair the overall health.

The majority of studies also suggest that TSLs, particularly PEGylated formulations show low systemic toxicity in therapeutic concentrations. PEGylation prolongs the circulation time and an

aspect known as stealth effect, which reinforces the reticuloendothelial avoidance, reducing accidents of the reticuloendothelial system and causing off-target effects in the human body<sup>26</sup>. In general, in the case of major organs (liver, kidneys, spleen, and heart), histopathological tests do not indicate any severe structural damage, which proves the biocompatibility of such liposomal formulations. According to hematological and biochemical measurements, there exists only weak, momentary changes that in the largest part does not need any treatment, clear up into itself.

Hyperthermia is localized to cause drug release in TSLs and it is safe with regular tolerance except in circumstances where rare tissue irritation or short-lived inflammatory reactions at the site of therapy develop<sup>27</sup>. Many of them are reversible and can be treated by proper regulation of temperature and exposure time. The animal experiment analyses highlight the need of maximizing hyperthermia procedures in order to achieve adequate drug delivery as well as reducing thermal load or harm on tissues.

The current research is still continuing to bypass the TSL composition and hyperthermia with an aim of maximizing the therapeutic effects but keeping to a positive safety profile. They involve the strategies of modifying lipid composition, PEGylation density, and lysolipid content, and the exploration of the alternative method of non-invasive hyperthermia like focused ultrasound. All these studies together clarify that TSLs will provide a highly promising, safe, and efficient platform of drug delivery through controlled delivery on a properly constructed platform<sup>28</sup>.

**Table 1:** Summary of Recent Studies on Advanced Drug Delivery Systems<sup>29</sup>

Author(s) & Year	Study	Focus Area	Methodology	Key Findings
Rastogi et al., (2020) <sup>30</sup>	Lipopharmaceuticals: A critical review focused on recent advances in liposomal drug delivery	Liposomal drug delivery	Literature review of liposomal formulations	Liposomes improved drug solubility, bioavailability, and reduced systemic toxicity; PEGylation and ligand modifications enhanced stability and targeting efficiency

<b>Raza et al., (2019)<sup>31</sup></b>	Endogenous and exogenous stimuli-responsive drug delivery systems for programmed site-specific release	Stimuli-responsive drug delivery	Literature review on endogenous and exogenous triggers	Systems responded to pH, temperature, enzymes, and redox conditions; improved targeted drug delivery and minimized off-target effects
<b>Reddy &amp; Reddy, (2025)<sup>32</sup></b>	Recent breakthroughs in drug delivery systems for targeted cancer therapy: an overview	Targeted cancer therapy	Review of novel drug carriers	Nanoparticles, liposomes, and polymer-based systems enhanced tumor targeting, circulation time, and reduced side effects; multifunctional carriers improved delivery specificity
<b>Santhamoorthy et al., (2025)<sup>33</sup></b>	Recent advancements of polymer-modified mesoporous silica nanoparticles for drug delivery under stimuli-trigger	Polymer-modified mesoporous silica nanoparticles	Literature review of hybrid nanoparticle systems	Hybrid systems combined high loading capacity with stimuli responsiveness; polymer modifications improved biocompatibility, stability, and controlled release
<b>Sharifi-Azad et al., (2022)<sup>34</sup></b>	Recent advances in targeted drug delivery systems for resistant colorectal cancer	Drug delivery for resistant	Review of targeted delivery platforms	Nanoparticles, liposomes, and polymeric carriers overcame drug

		colorectal cancer		resistance; ligand-mediated targeting and stimuli-responsive mechanisms improved drug accumulation
--	--	-------------------	--	--

## 5. DISCUSSION

The results of animal investigations as well as preclinical assessments point at the feasibility of thermosensitive liposomes (TSLs) as exceptionally efficient pharmaceutical delivery methodologies in association with hyperthermia<sup>35</sup>. These experiments show that TSLs have accurate site-specific drug delivery that results in enhanced tumor abatement and decreased systemic toxicity in comparison to current therapies. Real-time imaging also contributes to the expanded capability of tracking of drug delivery and release and provides prospects of individualized and optimized therapeutic schedules. But in spite of these encouraging findings there are still challenges to ensure reproducibility, standardization and overall applicability in clinical settings and it is argued that further research is required to overcome these constraints and fully utilize the clinical potential of TSL-based therapies<sup>36</sup>.

### 5.1. Interpretation and Analysis of Findings

Preclinical trials show that TSLs are effective in using mild hyperthermia in order to induce targeted drug release to optimize therapeutic levels in tumor focused areas with sparing of healthy tissues. The animal models show that this will enhance the total efficacy of the treatment as well as decrease the off target toxic effect<sup>37</sup>. Liposome distribution and release kinetic information yielded through imaging (MRI and fluorescence monitoring) techniques has supported the reality of controlled and on-demand drug delivery in vivo.

### 5.2. Implications and Significance

The combination of TSLs and hyperthermia is an important breakthrough in precision medicine. TSLs can increase the therapeutic index of chemotherapeutic agents and provide more convenient, safer and effective approaches to treatment because they permit orders of methodical release of the drugs in space and time. Individualized therapy is also easily achieved with this technology, with the drug release measured and decreased in line with the individual tumor reaction in real-time<sup>38</sup>. The use of TSLs along with hyperthermic targeting stresses their possibilities to transform local cancer therapy.

### 5.3. Gaps and Future Research Directions

Although these results appear promising, the inconsistency among in studies can be detrimental due to variability of TSL formulation and lipid profile and varying hyperthermal protocols used in other studies<sup>39</sup>. Additional studies should be conducted to normalize the preparation procedures, perfect phase transition temperature, and enhance stability and circulation of TSLs. It is also hoped that in future studies integrating TSLs with developing therapy options, including immunotherapy, gene therapy or a combination of chemotherapy versus other modalities should be studied to achieve tumor feeding, as well. Discussing long-term safety, scalability and clinical translation issues will also be essential to developing TSLs beyond preclinical models to the normal clinical practice<sup>40</sup>.

## 6. CONCLUSION

Thermosensitive liposomes (TSLs) have become an exciting line of research within site-specific drug delivery surrounded by controlled hyperthermia-sensitive release of drug treatment following the tumors in the least toxicity and some systemic exposure. Animal trials in preclinical trials with the use of TSLs regularly show that with variable localized hyperthermia, metatumoral concentration of drugs is higher, released at desired times, with exhaustive tumor growth inhibiting occurrence. Further optimization of therapeutic efficacy and biocompatibility has been achieved by the development of strategies of liposomal design, including incorporation of lysolipids to reduce phase transition temperature, PEGylation to extend circulation and increase stability. In addition, the combination of imaging modalities will lead to immediate tracking of the allocation and release of drugs, personalized and response-based treatment plans. Notwithstanding these encouraging results, there are obstacles, such as inconsistency in formulation strategies, thermostat in hyperthermia and clinical scale-up. The next phase of utilizing the clinical capability of TSLs and standardizing the compositions of TSLs as well as exploration of combinatoric therapies including immunotherapy or gene therapy will be essential in order to explore the full potential of TSLs in the clinic. Altogether, TSLs are an extremely versatile, and prospective platform of nanomedicine, an insightful and safe way to deliver targeted cancer therapy, which could greatly enhance the patient outcomes.

## REFERENCES

1. Abuwatfa, W. H., Awad, N. S., Pitt, W. G., & Hussein, G. A. (2022). Thermosensitive polymers and thermo-responsive liposomal drug delivery systems. *Polymers*, 14(5), 925.
2. Aghdam, M. A., Bagheri, R., Mosafer, J., Baradaran, B., Hashemzaei, M., Baghbanzadeh, A., ... & Mokhtarzadeh, A. (2019). Recent advances on thermosensitive and pH-sensitive liposomes employed in controlled release. *Journal of controlled release*, 315, 1-22.

3. Alrbyawi, H., Poudel, I., Annaji, M., Arnold, R. D., Tiwari, A. K., & Babu, R. J. (2022). Recent advancements of stimuli-responsive targeted liposomal formulations for cancer drug delivery. *Pharmaceutical Nanotechnology*, 10(1), 3-23.
4. Amin, M., Huang, W., Seynhaeve, A. L., & Ten Hagen, T. L. (2020). Hyperthermia and temperature-sensitive nanomaterials for spatiotemporal drug delivery to solid tumors. *Pharmaceutics*, 12(11), 1007.
5. Amin, M., Lammers, T., & Ten Hagen, T. L. (2022). Temperature-sensitive polymers to promote heat-triggered drug release from liposomes: Towards bypassing EPR. *Advanced Drug Delivery Reviews*, 189, 114503.
6. Basak, S., & Das, T. K. (2024). Zwitterionic, stimuli-responsive liposomes for curcumin drug delivery: enhancing M2 macrophage polarization and reducing oxidative stress through enzyme-specific and hyperthermia-triggered release. *ACS Applied Bio Materials*, 8(1), 726-740.
7. Bi, H., Xue, J., Jiang, H., Gao, S., Yang, D., Fang, Y., & Shi, K. (2019). Current developments in drug delivery with thermosensitive liposomes. *Asian journal of pharmaceutical sciences*, 14(4), 365-379.
8. Choudhury, A., Kirti, A., Lenka, S. S., Naser, S. S., Sinha, A., Kumari, S., ... & Verma, S. K. (2025). Strategic advances in liposomes technology: translational paradigm in transdermal delivery for skin dermatosis. *Journal of Nanobiotechnology*, 23(1), 576.
9. Desai, K. G. H. (2018). Polymeric drug delivery systems for intraoral site-specific chemoprevention of oral cancer. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 106(3), 1383-1413.
10. Ezike, T. C., Okpala, U. S., Onoja, U. L., Nwike, C. P., Ezeako, E. C., Okpara, O. J., ... & Nwanguma, B. C. (2023). Advances in drug delivery systems, challenges and future directions. *Heliyon*, 9(6).
11. Fernandez, L. (2025). Advances in Liposomal Drug Delivery Systems. *American Journal Of Pharmacy And Pharmacology*, 6(1), 17-29.
12. Gawai, A. Y., Hatwar, P. R., Bakal, R. L., Nehar, K. N., & Bhujade, P. R. (2025). Stimuli-Responsive Nanocarriers for Site-Specific Drug Delivery System. *Asian Journal of Pharmaceutical Research and Development*, 13(2), 100-106.
13. Goel, H., Razdan, K., Singla, R., Talegaonkar, S., Khurana, R. K., Tiwary, A. K., ... & Singh, K. K. (2020). Engineered site-specific vesicular systems for colonic delivery: trends and implications. *Current Pharmaceutical Design*, 26(42), 5441-5455.
14. Hamzy, I. A., Alqhoson, A. I., Aljarbou, A. M., & Alhajri, M. A. (2024). Advancements in intelligent drug delivery systems and their clinical applications. *International journal of health sciences*, 1(S1), 1-27.
15. Hegde, M. M., Prabhu, S., Mutalik, S., Chatterjee, A., Goda, J. S., & Satish Rao, B. S. (2022). Multifunctional lipidic nanocarriers for effective therapy of glioblastoma: recent advances in

- stimuli-responsive, receptor and subcellular targeted approaches. *Journal of Pharmaceutical Investigation*, 52(1), 49-74.
16. Ho, L., Bokharaei, M., & Li, S. D. (2018). Current update of a thermosensitive liposomes composed of DPPC and Brij78. *Journal of Drug Targeting*, 26(5-6), 407-419.
  17. Jain, A., & Jain, S. K. (2018). Advances in tumor targeted liposomes. *Current molecular medicine*, 18(1), 44-57.
  18. Jain, A., Raikwar, S., Bidla, P., & Jain, S. K. (2020). Liposomes for Advanced Drug Delivery. *Advanced Biopolymeric Systems for Drug Delivery*, 317.
  19. Jani, R. K., Gohil, K. M., & Kaushalkumar Jani, R. (2018). Liposomal formulations in cancer therapy: Basic concepts to advanced strategies. *Int. J. Pharm. Sci. Drug Res*, 10, 386-393.
  20. Kaur, S., & Singh, D. (2023). A sojourn on liposomal delivery system: recent advances and future prospects. *ASSAY and Drug Development Technologies*, 21(2), 48-64.
  21. Lu, J., Guo, T., Fan, Y., Li, Z., He, Z., Yin, S., & Feng, N. (2021). Recent developments in the principles, modification and application prospects of functionalized ethosomes for topical delivery. *Current drug delivery*, 18(5), 570-582.
  22. Mazzotta, E., Tavano, L., & Muzzalupo, R. (2018). Thermo-sensitive vesicles in controlled drug delivery for chemotherapy. *Pharmaceutics*, 10(3), 150.
  23. Narwade, M., Shaikh, A., Gajbhiye, K. R., Kesharwani, P., & Gajbhiye, V. (2023). Advanced cancer targeting using aptamer functionalized nanocarriers for site-specific cargo delivery. *Biomaterials Research*, 27(1), 42.
  24. Nasra, S., Bhatia, D., & Kumar, A. (2022). Recent advances in nanoparticle-based drug delivery systems for rheumatoid arthritis treatment. *Nanoscale advances*, 4(17), 3479-3494.
  25. Nayak, A. K., Ahmad, S. A., Beg, S., Ara, T. J., & Hasnain, M. S. (2018). Drug delivery: Present, past, and future of medicine. In *Applications of nanocomposite materials in drug delivery* (pp. 255-282). Woodhead Publishing.
  26. Nazir, F., Tabish, T. A., Tariq, F., Iftikhar, S., Wasim, R., & Shahnaz, G. (2022). Stimuli-sensitive drug delivery systems for site-specific antibiotic release. *Drug Discovery Today*, 27(6), 1698-1705.
  27. Nikolova, M. P., Kumar, E. M., & Chavali, M. S. (2022). Updates on responsive drug delivery based on liposome vehicles for cancer treatment. *Pharmaceutics*, 14(10), 2195.
  28. Qu, F., Geng, R., Liu, Y., & Zhu, J. (2022). Advanced nanocarrier-and microneedle-based transdermal drug delivery strategies for skin diseases treatment. *Theranostics*, 12(7), 3372.
  29. Rasel, M. S. I., Mohona, F. A., Akter, W., Kabir, S., Chowdhury, A. A., Chowdhury, J. A., ... & Amran, M. S. (2022). Exploration of Site-Specific Drug Targeting—A Review on EPR-, Stimuli-, Chemical-, and Receptor-Based Approaches as Potential Drug Targeting Methods in Cancer Treatment. *Journal of Oncology*, 2022(1), 9396760.

30. Rastogi, H., Shree, M., Srivastava, S., & Kaur, D. (2020). Lipopharmaceuticals: A critical review focused on recent advances in liposomal drug delivery. *J. Pharmaceut. Educ. Res*, 2, 7-11.
31. Raza, A., Rasheed, T., Nabeel, F., Hayat, U., Bilal, M., & Iqbal, H. M. (2019). Endogenous and exogenous stimuli-responsive drug delivery systems for programmed site-specific release. *Molecules*, 24(6), 1117.
32. Reddy, K. T. K., & Reddy, A. S. (2025). Recent breakthroughs in drug delivery systems for targeted cancer therapy: an overview. *Cellular, Molecular and Biomedical Reports*, 5(1), 13-27.
33. Santhamoorthy, M., Asaithambi, P., Ramkumar, V., Elangovan, N., Perumal, I., & Kim, S. C. (2025). A Review on the Recent Advancements of Polymer-Modified Mesoporous Silica Nanoparticles for Drug Delivery Under Stimuli-Trigger. *Polymers*, 17(12), 1640.
34. Sharifi-Azad, M., Fathi, M., Cho, W. C., Barzegari, A., Dadashi, H., Dadashpour, M., & Jahanban-Esfahlan, R. (2022). Recent advances in targeted drug delivery systems for resistant colorectal cancer. *Cancer Cell International*, 22(1), 196.
35. Sobol, Ž., Chiczewski, R., & Wątróbska-Świetlikowska, D. (2025). Advances in Liposomal Drug Delivery: Multidirectional Perspectives on Overcoming Biological Barriers. *Pharmaceutics*, 17(7), 885.
36. Torres, J., Valenzuela Oses, J. K., Rabasco-Álvarez, A. M., González-Rodríguez, M. L., & García, M. C. (2025). Innovations in Cancer Therapy: Endogenous Stimuli-Responsive Liposomes as Advanced Nanocarriers. *Pharmaceutics*, 17(2), 245.
37. Verma, A., Tiwari, A., Panda, P. K., Saraf, S., Jain, A., Raikwar, S., ... & Jain, S. K. (2020). Liposomes for advanced drug delivery. In *Advanced Biopolymeric Systems for Drug Delivery* (pp. 317-338). Cham: Springer International Publishing.
38. Yadav, A., Singh, S., Sohi, H., & Dang, S. (2021). Advances in delivery of chemotherapeutic agents for cancer treatment. *Aaps Pharmscitech*, 23(1), 25.
39. Yang, Q., Luo, S., Tong, S., Zhao, H., Chen, R., Song, B., & Wu, J. (2024). Advances in the study of liposomes gel with stimulus responsiveness in disease treatment. *Journal of Cluster Science*, 35(3), 701-714.
40. Yaramiri, A., Asalh, R. A., Asalh, M. A., AlSawaftah, N., Abuwatfa, W. H., & Husseini, G. A. (2025). A Comprehensive Review of Smart Thermosensitive Nanocarriers for Precision Cancer Therapy. *International Journal of Molecular Sciences*, 26(15), 7322.