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POLYMERIC MICELLES: FUNDAMENTAL CONCEPTS AND EMERGING USES IN THERAPEUTICS

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Article History
Received: February 2025 | Accepted February 2025 | Published March 2025

ABSTRACT:
The clonal expansion of mature B lymphocytes is a common feature of small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL), two common neoplastic diseases. With a lifetime risk of about 0.57%, CLL is the most prevalent form of adult leukemia in the Western world. The condition usually manifests in men and is diagnosed in those between the ages of 70 and 72. The treatment landscape for sickle cell disease (CLL/SLL) has changed over time, bringing with it a variety of therapeutic alternatives such as immunotherapy, targeted medicines such BTK inhibitors, chemotherapy, and novel drug delivery techniques. A promising method for drug delivery that increases the solubility and bioavailability of anti-cancer drugs is the use of polymeric micelles. Due to the enhanced permeability and retention (EPR) effect in tumor tissues, which is caused by leaky blood vessels and impaired lymphatic drainage, these nanoscale structures—which are created by the self-assembly of amphiphilic block copolymers—allow targeted drug delivery. This paper discusses the fundamental concepts of polymeric micelles, their mechanisms of action, and their potential applications in improving therapeutic outcomes for CLL/SLL patients.

Keywords: *Polymeric Micelles, Targeted Drug Delivery, Nanomedicine.*

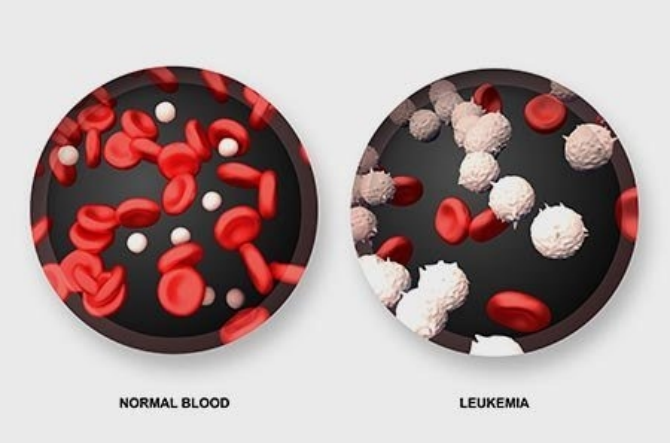
1.INTRODUCTION:

In the West, adult leukemia with Chronic Lymphocytic Leukemia (CLL) is the most common type; in Asia, however, it is less common and comparatively rare in Korea and Japan, even among Japanese visitors to the West. [1] For the general population, the lifetime risk of getting CLL is roughly 1 in 175 (0.57%). With roughly twice the risk of females, males have a slightly higher chance of developing CLL/SLL. The median age of diagnosis for CLL is between 70 and 72 years old, and the disease's risk rises with age. In adults under 40, CLL is infrequent and rare in children. The clonal expansion of mature B cells is a hallmark of small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL), two closely related neoplastic diseases [2]. These indolent malignancies are distinguished by the overproduction of dysfunctional B cells, often

leading to lymphadenopathy, splenomegaly, and cytopenias. [3] These malignancies are non-Hodgkin lymphoma (NHL) subtypes that target B lymphocytes, which are specific types of white blood cells [4] The spleen, lymph nodes, bone marrow, and peripheral blood are the main illness sites. There exist multiple therapeutic options, like as immunotherapy and chemotherapy, aimed at inhibiting the progression of CLL/SLL. CLL/SLL is a progressive, morbidity-causing disease if left untreated. as well as a rise in mortality [3].

For both systemic and local cancer therapy, oral drug delivery is the recommended method since it improves patient quality of life and lowers medical expenses [5]. Optimizing drug distribution to target cancer cells while reducing toxicity and off-target effects is a major problem in the treatment of CLL/SLL. The limited water solubility of several antineoplastic drugs limits their oral bioavailability [6,7]. Various approaches, such as size reduction, surfactant use, salt creation, pH adjustment, prodrug design, and integration into polymeric or lipid formulations, can be used to address issue and improve drug solubility and bioavailability. Drug solubility for CLL/SLL treatment can be effectively increased by formulation techniques like hydrogel-based forms, liposomes, cyclodextrins, polymeric/inorganic nanoparticles, lipid-based formulations, and nanoparticle encapsulation [8]

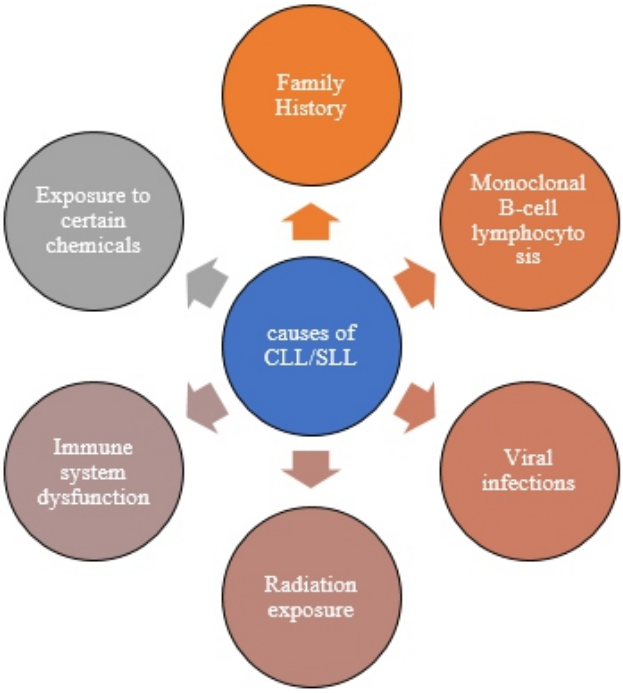
Figure : Comparison of (A) Normal blood (B) Patient having CLL/SLL Blood



2. CAUSES OF CLL/SLL:

Throughout a person's lifespan, specific chromosomes and genes might mutate or change, which can result in chronic lymphocytic leukemia. The precise origins of CLL are unknown, while some circumstances can induce the disease, and medical professionals are unsure of what causes these changes. raise the likelihood of getting the illness. Qualities that raise the risk include the following as follows in *Figure 2*:

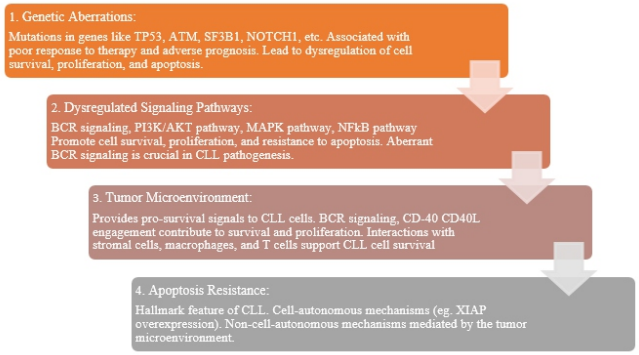
Figure: Causes of (CLL) / (SLL)



3. PATHOGENESIS OF CLL/SLL:

Mature CD5+ B cells accumulate in peripheral blood, bone marrow, and secondary lymphoid organs in chronic lymphocytic leukemia (CLL), a clonal lymphoproliferative disease. Leukemogenesis is facilitated by a complicated interaction between hereditary and non-genetic variables in the pathophysiology of CLL. The multistep mechanism of CLL development has been clarified by the identification of recurrent mutations and clonal evolution. The pathophysiology of CLL is largely determined by genetic anomalies, dysregulated signaling

pathways, and interactions with the tumor microenvironment. Apoptosis, NF-κB signaling, inflammatory pathways, RNA and ribosome processing, NOTCH1 signaling, BCR signaling, DNA damage response, genome/chromatin structure, and cell cycle regulation are some of these processes [9].



4. TREATMENT OF CLL/SLL:

For CLL/SLL, conventional therapies consist of surgery, radiation, chemotherapy, or a mix of these. Although parenteral administration is a common practice in traditional chemotherapy, Oral delivery of polymeric micelles has gained popularity because it can enhance patient compliance and address issue related to low bioavailability and short half-life as polymeric micelles have hydrophilic corona which makes it suitable candidate to eliminate the process of opsonization and hence it may lead to a greater bioavailability. Innovative dosage forms such as prodrugs, solid dispersions, microparticles, nanomicelles, nanodispersions, nanocapsules, and nanosuspensions offer intriguing ways to get around the drawbacks and improve the effectiveness of oral drug delivery in the treatment of CLL/SLL [10,11]. Significant progress has been made in the therapeutic landscape for CLL/SLL, offering patients a variety of treatment alternatives. Conventional methods encompass chemotherapy, targeted therapy (like BTK inhibitors), immunotherapy (like monoclonal antibodies), and stem cell transplantation for qualified patients. Chemotherapy is the process of targeting and killing cancer cells by administering anti-cancer medications parenterally or orally. Purine analogs, alkylating drugs, and corticosteroids are common chemotherapeutic treatments for CLL, with fludarabine typically being the first-line option. Through the use of laboratory-engineered immune components or by boosting the patient's own immune response, immunotherapy uses the immune system to fight cancer cells. Monoclonal antibodies such as ribauximab and obinutuzumab are utilized in CLL immunotherapy [3,12]. Biologically active substances known as "targeted therapies" specifically target particular molecular changes in cancer cells to encourage the proliferation of those cells. Targeted therapies, as opposed to traditional chemotherapeutic medications, aim to interfere with one or more particular proteins implicated in the etiology of chronic lymphocytic leukemia (CLL). Certain CLL cells require a protein called Bruton's tyrosine kinase (BTK) in order to proliferate and survive. BTK inhibitors are a type of targeted treatments that are frequently used as a first-line treatment for CLL. Furthermore, cutting-edge therapies including chimeric antigen receptor (CAR) T-cell therapy have shown promise in the treatment of CLL/SLL [12,13].

5. MODERN PHARMACOLOGIC THERAPIES FOR CHRONIC LYMPHOCYTIC LEUKEMIA:

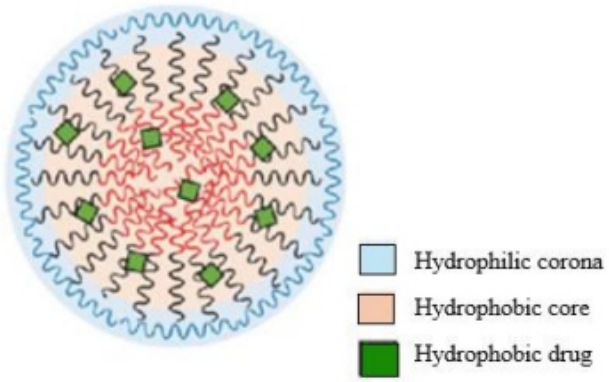
Table 1: Modern pharmacologic therapies for Chronic Lymphocytic Leukemia

Sr No.	Classification	Drug Name	Mechanism of Action
1.	Chemotherapy		
	Alkylating Agents	Bendamustine	Inhibits the expression of genes involved in DNA repair
		Chlorambucil	DNA replication and RNA transcription inhibitor
		Cyclophosphamide	DNA synthesis inhibitor

	Purine Analogs	Fludarabine	DNA polymerase and ribonucleotide reductase inhibitor
		Pentostatin	adenosine deaminase inhibitor
		Cladribine	DNA synthesis inhibitor
	Monoclonal antibodies	rituximab	Anti-CD20 Monoclonal Antibodies
		ofatumumab	
		Obinutuzumab	
		Alemtuzumab	
2.	**Targeted Therapy Drugs**		
	Bruton's tyrosine kinase (BTK) inhibitor	Ibrutinib	Bruton's tyrosine kinase (BTK) inhibitor
		Acalabrutinib	BTK inhibitor
		Zanubrutinib	
		Pirtobrutinib	
	PI3K inhibitors	Idelalisib	phosphatidylinositol 3-kinase inhibitor
		Duvelisib	
3.	B-cell lymphoma 2 inhibitor	Venetoclax	BCL-2 Inhibitor

6. POLYMERIC MICELLES:

Polymeric micelles are nanoscale structures composed of a core-shell architecture formed by the spontaneous assembly of amphiphilic block copolymers in aqueous solutions. Amphiphilic copolymers possess both hydrophobic and hydrophilic segments within the same molecule, which, when present at or above the critical micelle concentration (CMC), self-assemble into a dynamic micellar structure with a core-shell morphology. Because of its unique features, which include nanoscale dimensions, ease of synthesis, superior solubilization qualities, biocompatibility, low toxicity, core-shell architecture, micellar association, form, and relative stability, polymeric micelles are used in drug administration. The hydrophobic core of polymeric micelles encloses and shields the drug, while the hydrophilic shell provides stability and support for the drug in the aqueous medium. This facilitates drug administration and increases the polymers' solubility in water. Polymeric micelles are useful in medicine for many reasons, such as improving drug solubility and safeguarding encapsulated medications [15,16].

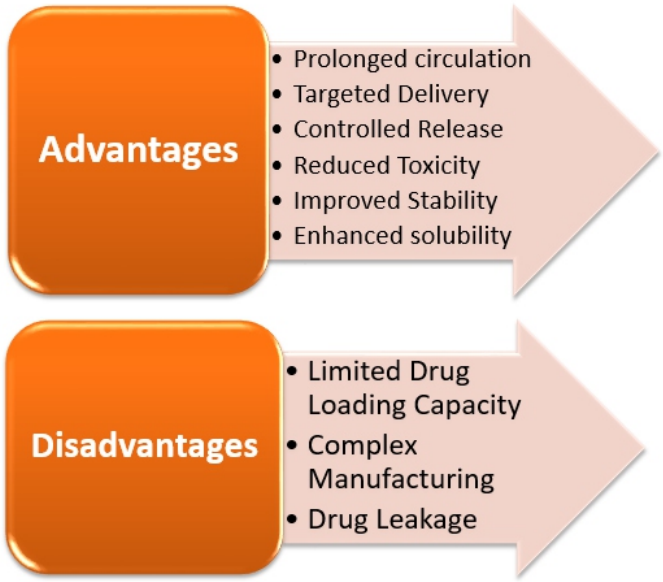


6.1. The Mechanism of Polymeric Micelle Permeation:

Polymeric micelles penetrate tissues through both passive and active processes, which are carefully adjusted to promote therapeutic effects. Passively, their nanoscale size take advantage of the enhanced permeability and retention (EPR) effect, which is particularly strong in tumor tissues and inflamed areas with irregular, highly permeable vasculature, allowing for preferential accumulation. The hydrophilic outer layer of micelles provides steric stability, reduces opsonization, and increases circulation time.

Active micelle penetration into cells is required for subcellular drug delivery, which is predominantly accomplished by endocytosis. Micelles engage with the cell membrane to start this process, which is then internalized and translocated by endosomes into the cytoplasm. Micelles may deconstruct at the plasma membrane or degrade in lysosomes upon entry, resulting in drug release within or outside of cells, as well as drug accumulation at the plasma membrane or in other cellular compartments. Micelles are gaining popularity due to their capacity to circumvent ATP-dependent efflux pumps via endocytosis, which aids in the fight against drug and multidrug resistance. This effect is frequently generated by unimers causing increased membrane fluidity below the critical micelle concentration (CMC), resulting in ATP depletion and lower ATPase activity, which enhances efflux pump inhibition [16].

6.2. Advantage and Disadvantage of Polymeric Micelles:



6.3. COMPOSITION OF POLYMERIC MICELLES:

Table 2:Composition of Polymeric Micelles

Amphiphilics block polymer	Organic Solvents	Aqueous Solvents	Surfactants
Pluoronic (poloxamer)	Acetonitrile	Phosphate buffer	Tween 80
PEG-PLGA	Chloroform	saline	Sodium Dodecyl Sulfate
PEG-PCL	Acetone	water	
PEG-PLA	Dichloromethane		

6.4. Preparation Methods of Polymeric Micelles:

6.4.1. Thin Film Hydration Method

The medication and polymer are dissolved in an organic solvent using this approach. A rotary vacuum evaporator is then used to extract the solvent at a regulated temperature. To guarantee that all solvent remains are completely eliminated, vacuum drying is next performed. This technique produces a thin vesicular film, which is subsequently hydrated with saline phosphate buffer or Milli-Q water by rotating the flask in the evaporator at a predetermined temperature. Micelles are created and kept for future research. The medicine is integrated according to its solubility in organic or aqueous solution [18].

6.4.2. Direct Dissolution Method

This is the most common technique for micelle production. It uses block copolymers with great aqueous solubility. To help the drug load into the micelle, the drug and polymer are dissolved in water, stirred, and heated. Micelle production happens as the core-forming blocks are dehydrated. This process involves dissolving the polymer and medication separately in aqueous solutions, which are then mixed in the proper ratio to generate micelles [18].

6.4.3. Dialysis Method

This method dissolves the hydrophilic and hydrophobic segments of the drug and polymer by dissolving them in a water-miscible solvent. Water can enter the dialysis bag when the solution is dialyzed against it, which starts the block copolymer's self-assembly into micelles. The dialysis bag's semipermeable membrane allows free medication to be released while preserving the micelles inside [19].

6.4.4. Emulsion Method

This approach uses water-insoluble solvents, including acetone, chloroform, or tetrahydrofuran, to dissolve the medication and polymer. Water is gradually mixed with the solution while being vigorously stirred. This creates an emulsion in which the water is the continuous phase and the organic solvent is the internal phase. The solvent is progressively removed by lyophilization or evaporation, which encourages the block copolymers to spontaneously self-assemble into micelles [18].

6.4.5. Drug-Encapsulation Method by Agitation

To make sure homogeneous dispersion, water is added to the drug and block copolymer residue

that remains after the solvent is removed, and the mixture is agitated at temperatures lower than 30°C. This approach creates micelles with over 73% encapsulation effectiveness and can be sterilized using a 0.22 µm filter [18].

6.5. APPLICATION OF POLYMERIC MICELLES:

The various applications of Polymeric micelles are listed in Table 3 [19,20].

Table 3: Application of Polymeric micelles in different diseases

Sr.no.	Name of disease	Application
1	Cancer	**Chemotherapy:** Enhances solubility and provides targeted delivery of hydrophobic anticancer drugs like paclitaxel and doxorubicin, minimizing systemic toxicity.
		Photodynamic Therapy (PDT): Improves efficacy by delivering photosensitizers directly to tumors.
2	Cardiovascular Diseases	**Atherosclerosis:** Targets delivery of anti-inflammatory or cholesterol-lowering drugs to atherosclerotic plaques, improving treatment and reducing systemic side effects.
		Heart Failure: Facilitates delivery of cardioprotective drugs to heart tissue, potentially improving function and reducing damage post-myocardial infarction.
3	Infectious Diseases	**Antibiotic Delivery:** Enhances antibiotic delivery to infected tissues, improving effectiveness against resistant bacterial strains and minimizing side effects.
		Antiviral Therapy: Directly delivers antiviral drugs to infected cells, increasing concentration at the infection site and reducing systemic toxicity.
4	Neurological Disorders	**Alzheimer's Disease:** Improves drug delivery across the blood-brain barrier, targeting brain tissues for better treatment of neurodegenerative diseases.
		Parkinson's Disease: Delivers neuroprotective agents or dopamine precursors to the brain, potentially slowing disease progression and improving symptoms.
5	Dermatological Conditions	**Psoriasis and Eczema:** Targets delivery of anti-inflammatory drugs to the skin, enhancing therapeutic outcomes and reducing systemic drug exposure.
6	Eye Diseases	**Macular Degeneration:** Provides targeted drug delivery to the retina for treating age-related macular degeneration.
		Glaucoma: Delivers drugs to lower intraocular pressure, increasing effectiveness and reducing side effects.
7	Autoimmune Diseases	Rheumatoid Arthritis: Targets delivery of anti-inflammatory drugs to inflamed joints, improving therapy and minimizing systemic immunosuppression.

7. Conclusion:

The utilization of polymeric micelles in the treatment of CLL/SLL represents a significant advancement in drug delivery systems. Their distinct core-shell structure improves oral bioavailability and therapeutic efficacy by making poorly water-soluble medications more soluble. The ability of micelles to bypass ATP-dependent efflux pumps through endocytosis addresses the challenge of drug resistance, a common issue in cancer therapy. Furthermore, the passive and active permeation mechanisms of polymeric micelles enable targeted delivery to tumor sites, maximizing therapeutic effects while minimizing systemic toxicity. As research progresses, the integration of polymeric micelles with existing treatment modalities, including CAR T-cell therapy and targeted therapies, holds promise for improving patient outcomes in CLL/SLL. To get over the present barriers to cancer treatment and enhance patient quality of life, more research into these novel drug delivery methods is essential. The results highlight the importance of creating sophisticated formulations that can successfully handle the difficulties of cancer treatment and provide fresh approaches to therapeutic intervention.

8. References:

[1]. Taneja A, Rettew AC, Master SR. Cancer, Chronic Lymphocytic Leukemia (CLL) [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2020. Available from:https://www.ncbi.nlm.nih.gov/books/NBK470433/

[2]. Anon, Treating Chronic Lymphocytic Leukemia [Internet]. www.cancer.org. Available from: https://www.cancer.org/cancer/types/chronic-lymphocyticleukemia/treating.html

[3]. Chronic Lymphocytic Leukemia (CLL) [Internet]. www.cancer.org. Available from: https://www.cancer.org/cancer/types/chronic-lymphocyticleukemia.html

[4]. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma - Cancer Stat Facts [Internet]. SEER. Available from: https://seer.cancer.gov/statfacts/html/cllsll.html

[5]. Suksiriworapong, J., Rungvimolsin, T., A-gomol, A., Junyaprasert, V. B., & Chantasart, D. (2014). Development and characterization of lyophilized diazepam-loaded polymeric micelles. Aaps PharmScitech, 15, 52-64.

[6]. Patil, P. H., Wankhede, P. R., Mahajan, H. S., & Zawar, L. R. (2018). Aripiprazole-loaded polymeric micelles: fabrication, optimization and evaluation using response surface method. Recent patents on drug delivery & formulation, 12(1), 53-64.

[7]. Vinchurkar, R. H., & Kuchekar, A. B. (2021). Polymeric micelles: a novel approach towards nano-drug delivery system. Biosciences Biotechnology Research Asia, 18(4), 629-649.

[8]. Rarokar, N., Agrawal, R., Yadav, S., Khedekar, P., Ravikumar, C., Telange, D., & Gurav, S. (2023). Pteroyl-γ-l-glutamate/Pluronic® F68 modified polymeric micelles loaded with docetaxel for targeted delivery and reduced toxicity. Journal of Molecular Liquids, 369, 120842.

[9]. Wei Z, Hao J, Yuan S, Li Y, Juan W, Sha X, et al. Paclitaxel-loaded Pluronic P123/F127 mixed polymeric micelles: Formulation, optimization and in vitro characterization. International Journal of Pharmaceutics. 2009 Jul;376(1-2):176–85.

[10]. Abdul Hussein HA, Maraie NK. Tenoxicam-loaded polymeric micelles material: Formulation, optimization, and evaluation. Materials Today: Proceedings. 2021 Sep.

[11]. DrugBank. go.drugbank.com. 2022. Available from: https://go.drugbank.com/

[12]. Wei Z, Hao J, Yuan S, Li Y, Juan W, Sha X, et al. Paclitaxel-loaded Pluronic P123/F127 mixed polymeric micelles: Formulation, optimization and in vitro characterization. International Journal of Pharmaceutics. 2009 Jul;376(1-2):176–85.

[13]. Patil PH, Wankhede PR, Mahajan HS, Zawar LR. Aripiprazole-Loaded Polymeric Micelles: Fabrication, Optimization and Evaluation using Response Surface Method. Recent Patents on Drug Delivery & Formulation. 2018 May 29;12(1):53–64.

[14]. Bromberg, L. (2008). Polymeric micelles in oral chemotherapy. Journal of controlled release, 128(2), 99-112.

[15]. Noh, G., Keum, T., Seo, J. E., Choi, J., Rakesh, B., Shrawani, L., ... & Lee, S. (2018). Development and evaluation of a water soluble fluorometholone eye drop formulation employing polymeric micelle. Pharmaceutics, 10(4), 208.

[16]. Ghezzi, M., Pescina, S., Padula, C., Santi, P., Del Favero, E., Cantù, L., & Nicoli, S. (2021). Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. In Journal of Controlled Release (Vol. 332, pp. 312–336). Elsevier B.V. https://doi.org/10.1016/j.jconrel.2021.02.031

[17]. Kapse, A., Anup, N., Patel, V., Saraogi, G. K., Mishra, D. K., & Tekade, R. K. (2019). Polymeric micelles: A ray of hope among new drug delivery systems. In Drug Delivery Systems (pp. 235–289). Elsevier. https://doi.org/10.1016/B978-0-12-814487-9.00006-5

[18]. Hemant Vinchurkar, R., & Bhanudas Kuchekar, A. (2021). Polymeric Micelles: A Novel Approach towards Nano-Drug Delivery System. BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, 18(4), 629–649. https://doi.org/10.13005/bbra/2947

[19]. Bai, K., & Wang, A. (2021). Polymeric Micelles: Morphology, Synthesis, and Pharmaceutical Application. E3S Web of Conferences, 290. https://doi.org/10.1051/e3sconf/202129001029

[20]. Kotta, S., Aldawsari, H. M., Badr-Eldin, S. M., Nair, A. B., & YT, K. (2022). Progress in Polymeric Micelles for Drug Delivery Applications. In Pharmaceutics (Vol. 14, Issue 8). MDPI. https://doi.org/10.3390/pharmaceutics14081636