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## Impact of Micellar Characteristics on the Dissolution and Efficacy of Anticancer Agents: A Review

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# Impact of Micellar Characteristics on the Dissolution and Efficacy of Anticancer Agents: A Review

## Abstract

Micellar drug delivery system is one of the potentially efficient methods for increasing the solubility, stability, and bioavailability of hydrophobic anticancer agents. This review study investigates the effects of major micellar properties on the solubility and therapeutic effectiveness of anticancer medications, including size, shape, surface charge, and stability. The non-spherical micelles may increase cellular uptake and lengthen circulation time, while smaller micelles may improve drug solubility and tumor penetration as various studies suggested. The surface charge of particles is also a critical factor to determine how they interact with cells. The stable micelles improve therapeutic results by delaying the onset of drug release. Furthermore, controlled release of encapsulated medications is possible with micelles, enhancing targeted delivery to tumor sites. Notwithstanding the advantages, problems like long-term stability and early medication release still exist. The results of this review study highlight the possibility of enhancing micellar properties to raise the effectiveness of anticancer treatments, opening the door to more potent and focused cancer therapies.

**Keywords:** Micellar Characteristics, Dissolution, Drug delivery, Anticancer Agents, Surface charge.

## Introduction

The poor solubility and limited bioavailability are common problems that anticancer agents face and can significantly reduce their therapeutic efficacy and poses challenges in drug delivery. Looking to the solution of these problems, micellar drug delivery systems have gained popularity among researchers significantly. The micelles which are amphiphilic molecule-based colloidal carriers and can improve the solubility, stability and targeting of hydrophobic anticancer medications. In this review study, we have examined the effects of micellar properties on anticancer agent dissolution and therapeutic efficacy, including size, shape, surface charge, and stability. According to study, micelles, by encapsulating hydrophobic drugs, enhance solubility, improve controlled release and target specific tissues, thereby increasing drug efficiency and minimizing systemic toxicity (Jose, et al. 2014). In another study, a core-shell structure reported as a characteristic of several polymeric micelles. In the pharmaceutical industry, majority of polymeric micelle research has focused on A-B diblock copolymers, where A is the hydrophilic polymer (shell) and B is the hydrophobic polymer (core) (Discher et al. 1999) as revealed in figure 1.

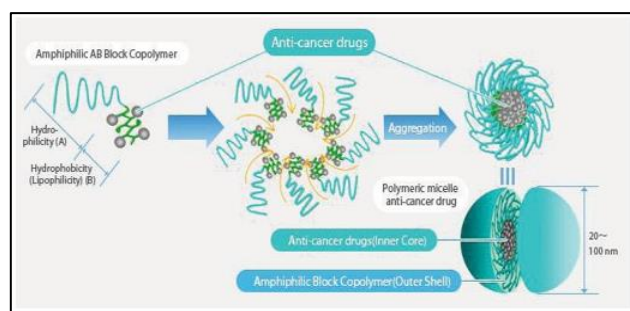


Figure 1: Amphiphilic block copolymeric micelle (Discher, et al. 1999)

The hydrophobic core, usually made of a biodegradable polymer such as poly ( $\beta$ -benzyl-L-aspartate) (PBLA), poly (DL-lactic acid) (PDLLA), or poly ( $\epsilon$ -caprolactone) (PCL), protects the insoluble medication from the aqueous environment & keeps it in reserve. The core may also consist of a water-soluble polymer, like poly(aspartic acid; P(Asp)), that has been chemically linked with a

hydrophobic drug to render it resistant (Mara, et al., 2015). The polymers are found in very small amounts as mono chains. Chains of polymer start to come together to form micelles when concentration hits a threshold value called the CAC. This guarantees that the copolymer's hydrophobic component remains distinct from the aqueous medium in which it is diluted as illustrated below in figure 2.

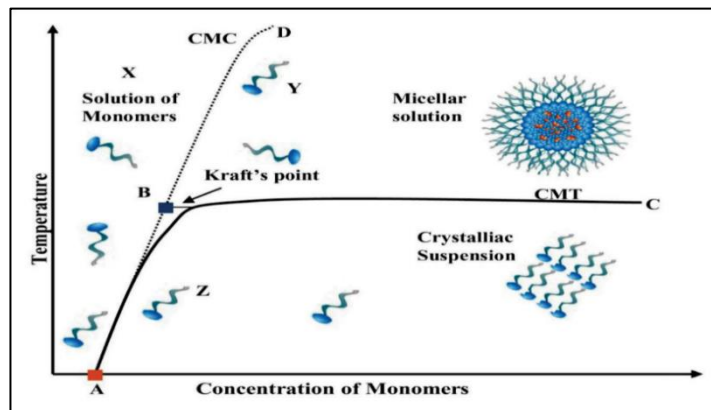


Figure 2: CMCs (Critical Micelle Concentrations) of the biodegradable block copolymers (Mohanty et al. 2014)

Micelles as described loose aggregates are with larger sizes than micelles produced at higher concentrations, and a significant amount of solvent may be seen within the micellar core at the CAC (Gao et al., 2010). The micelle formation would encourage at such concentrations as they adopt the shape of their low energy state. As the remaining solvent is released from the hydrophobic core, the micellar size will gradually decrease. Since amphiphiles with high CAC are unstable in aquatic environments and readily dissociate upon dilution, they may not be appropriate for use as drug targeting devices. Physical trapping or chemical conjugation by emulsification or dialysis techniques are two ways that insoluble medications might be incorporated into micelles as shown in figure 3.

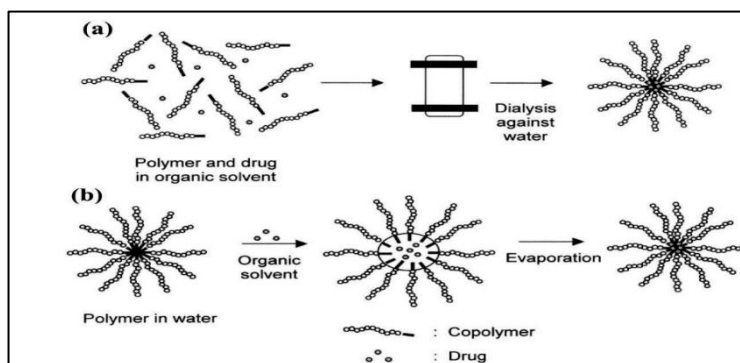


Figure 3: Polymeric micelles Drug loading by the (a) dialysis and (b) oil-in-water methods (Torchilin et al. 1992)

In their respective investigations, once the medication and micelles are simply equilibrated in water, there may not be much drug integrated. The mechanism by which specific groups on the medication and the hydrophobic polymer of the core combine to form a covalent link, like an amide bond, is known as chemical conjugation. Steric hindrance prevents these bonds from being readily hydrolyzed without the addition of spacer groups, making them resistant to enzymatic cleavage. The use of different medical imaging modalities in early cancer diagnosis is essential for cancer treatment. Theranostic agents are used in clinical diagnosis to distinguish diseased structures from surrounding tissues by emitting a specific signal from the designated area of interest. Theranostic agent-loaded polymeric micelles may circulate for a long time, which causes them to accumulate in malignant

tissues more because of the EPR effect. This feature makes it easier to identify the tissues and allows for real-time cancer diagnosis monitoring (Weissleder, 2006). A pH-responsive self-assembled mixed micelle of diethylene tri-amino penta-acetic acid dianhydride-gadolinium chelate (PEG-p(L-LA)-DTPAGd) and methoxy poly(ethylene glycol)-b-poly(L-histidine) (PEG-p(L-His)) amphiphilic block copolymers with a narrow size of ~ 40 nm were created by Kim et al. and as reported, within a few minutes, these micelles show greater T1 MR contrast in the tumor diagnosis of female BALB/c nude mice with CT26 murine tumors (Kim et al., 2014).

### Methodology: Combined Approaches

Various methodology has been employed during the course of existing research by investigators. This has well explored the impact of micellar systems on the solubility, stability and therapeutic efficacy of hydrophobic anticancer drugs. The methodologies employed in the various studies, cited the use of analytical techniques such as dynamic light scattering (DLS), transmission electron microscopy (TEM) and zeta potential analysis for micellar characterization. Drug-loading and release studies commonly utilized quantitative methods like UV-visible spectroscopy and high-performance liquid chromatography (HPLC) to evaluate drug encapsulation efficiency and release kinetics under physiological and tumor-mimicking conditions. Biological evaluations, including in-vitro cytotoxicity assays, cellular uptake studies, and in-vivo animal models, were used to assess therapeutic efficacy, biodistribution, and toxicity profiles of micellar systems compared to free drug formulations. Additionally, experimental approaches to optimize stimuli-responsive micellar systems for tumor-specific drug release accordance to pH, temperature or redox gradients have been utilized by researchers. Preclinical and clinical investigations demonstrated that advanced micellar systems enhanced solubility, pharmacokinetics and therapeutic outcomes while reducing systemic toxicity. By analyzing the methodologies and findings of such studies, it is fascinating to identifies the key trends, challenges, and future directions in micellar drug delivery systems. It also appraises critical limitations, including stability in biological fluids, regulatory hurdles, and clinical translational challenges, and offers a comprehensive perspective on the potential of micellar systems to improve anticancer therapies under the wide domain of methodology.

### Micelle Formation and Structure

The critical micelle concentration (CMC) is a parameter, used to characterize the physical properties of a micelle, although it is actually an indication of its stability. The word was initially used to refer to the main thermodynamic parameter of surfactant micelles, but in today's era also prefer to highlight the stability of polymeric micelles. Distinguishingly, one would use the phrase critical association concentration (CAC) to refer to polymeric micelles as against surfactant micelles (Dowling and Thomas, 1990). In minimal concern, the polymers exist only as a mono chain and the polymers chains start combining & forming micelles when the concentration achieve a critical value known as CAC, thereby avoiding the contact of the water phobic part of the copolymer with the aqueous medium in which the polymer is diluted. So, the micelles are loose aggregates that are larger than those produced at higher concentrations, and the micellar core at the CAC contains a significant amount of solvent (Gao et al., 2010). At such concentrations, the similar environment will support the growth of micelles, which will adopt their low energy state structure and gradually release the remaining solvent from the hydrophobic core, resulting in a reduction in micellar size. The high CAC Amphiphiles are not the best drugs targeting compounds since they are unstable when exposed to aquatic conditions and dissolve quickly when diluted. The formation of the micelle requires association between hydrophobic and hydrophilic polymer chains; as mentioned earlier, the micelles of randomly modified polymers are smaller than those of end-modified grafted polymers. Differences in the diameters of random and end-modified copolymers could be explained based on the



1 differences in how these two forces are balanced. The major determining factors of micellar size are  
1 the hydrophobic forces that confine the hydrophobic chains in the core and the excluded volume  
repulsions between chains that limit the size (Chung, et al.1998). Once, terminal hydrophobic groups  
4 form micelles, the water clusters trapped around the hydrophobic segments are prevented from  
entering the core. Moreover, there is no interaction between the core and the hydrophilic shell; rather,  
they stay within the structure as mobile linear chains (Chung et al. 1998). In fact, the micelles  
composed of polymers have a more pronounced stability compared with surfactant micelles with a  
significantly reduced CMC as well as rate of dissociation. Consequently, the released drugs are held  
within the drug-delivery vehicle for a more considerable period, eventually leading to drug  
3 accumulation in the target region over time. In contrast, random modifications of the polymer interact  
in such a way that the hydrophilic and hydrophobic parts of the polymer become entangled, allowing  
possible contact between the core and the aqueous medium. In this case, the chains that makes up the  
shell are fewer mobile.

### 21 **Enhanced Efficacy of Anticancer Agents through Micelles**

22 The use of micelles in anticancer therapy provides several advantages, such as improved drug  
2 solubility, protection of the drug from degradation and enhanced accumulation in tumor tissues  
through the EPR effect. Moreover, micelles can be modified to target specific cancer cells by  
conjugating targeting ligands, such as antibodies or peptides, to their surface. The active pointing  
approach also enhances the selective delivery of anticancer agents, reducing systemic toxicity and  
improving overall therapeutic outcomes. For example, the anticancer drug doxorubicin, when  
delivered via micelles, increased its cytotoxicity against tumor cells while minimizing side effects on  
healthy tissues. Similarly, paclitaxel, a poorly soluble anticancer agent has been successfully  
encapsulated in micelles significantly improving its bioavailability and antitumor activity. (Chen Y,  
et al. 2013)

### **Challenges and Future Perspectives**

20 Various investigating studies based on micellar drug delivery systems show the possibility, but still  
various obstacles are yet to overcome. In vogue, early release of medications from micelles is one of  
the main issues as it can reduce therapeutic efficacy and increase toxicity. Moreover, further research  
in the respective area will enable to determine the long-term stability of micelles in biological  
contexts. Developing stimuli-responsive micelles that only release their payload within the tumor  
microenvironment may be the main goal of future micellar nanotechnology advancements. Also,  
real-time tracking of medication distribution and therapeutic benefits may be possible by fabricating  
multifunctional micelles that combine drug delivery and imaging capabilities, improving  
personalized cancer treatment.

### 9 **Barriers in Oral delivery of Anticancer Drugs**

6 Many variables influence the oral bioavailability of a drug, including the water solubility of drug,  
stability in the gastrointestinal tract, intestinal epithelial accessibility, stability of intestinal and liver  
cytochrome P450 (CYP) metabolic proteins and stability to the P-glycoproteins (P-gp) efflux pump.  
On the basis of the above, one can categorize the primary obstacles to oral administration as either  
the physiological limitations imposed by the body or the physicochemical characteristics of the  
medications themselves. (Thanki, et al. 2013). In general, the medications are categorized into four  
15 groups, Class I to Class IV, according to the Biopharmaceutical Classification System (BCS), the  
primary physicochemical qualities that impact the oral bioavailability of the pharmaceuticals are their  
23 solubility and permeability. The majority of anticancer drugs cannot be taken orally because they  
12 belong to one or two classes i.e. class II, with high permeability and poor solubility or class IV,  
which has low permeability but low solubility. Proteotaxel, docetaxel, methotrexate (MTX) and



etoposide are examples of class IV drugs, while resveratrol, tamoxifen, and serofenib are examples of class II pharmaceuticals (Banna, et al., 2010). There are some parameters that the investigators took into account during the study:

**Solubility:** As one of the established parameters, the solubility is a fundamental component of cancer chemotherapy. The medication that is given orally or intravenously needs to have a better oral absorption rate or be soluble in blood. Because most anticancer medications are hydrophobic, their solubility is low, leading to a poor therapeutic effect. Anticancer medications such as resveratrol, tamoxifen, gefitinib, and others require improved solubility to avoid low bioavailability (Mohanty, et al. 2014 & Negut, et al. 2023). The therapeutic applications of flutamide and resveratrol anticancer drugs from BCS class II are limited because of their less aqueous solubility, which makes it difficult to formulate them as oral dosage forms (Banna, et al. 2010).

**Permeability:** In order for anticancer drugs used in oral cancer treatment to reach systemic drug concentration, they must have high intestinal epithelial permeability and be stable. For drugs to be absorbed via the epithelium, two important characteristics are how well they dissolve in water and how ease they percolate through cell membranes. Oral distribution of BCS class IV anticancer medicines like Paclitaxel has been challenging due to their limited solubility and permeability. Doxorubicin, an anticancer medication of BCS class III, has limited oral administration due to its low permeability. Golla K., et al. 2013 developed doxorubicin-loaded protein nanoparticles to treat hepatocellular carcinoma in order to get around this permeability problem. Doxorubicin's permeability was increased in order to maximize its oral bioavailability.

**Macrophages uptake:** When monocytes split, macrophages i.e. white blood cells are created, which are present in tissues. The width of a human macrophage is roughly 21 micrometers. The crucial function of macrophages is to locate foreign substances that enter into the bloodstream, swallowing and assimilating them. It serves also as a protective barrier to prevent infections from entering the bloodstream and attacking the body. Chemotherapy may be hampered by this since the anticancer medications may be interpreted as foreign objects by the macrophages, resulting in incredibly subpar treatment. (Deepak, et al. 2011). The tumor cells that have developed resistance to the cytostatic or cytotoxic effects of various drugs commonly used in cancer chemotherapy are known as multidrug-resistant organisms (MDRs). The most accepted explanation for multidrug resistance (MDR) is the over expression of ATP-binding cassette (ABC) transporters, which cause tumor cells to reject a series of chemotherapy drugs. Three notable ABC transporters which interacts with MDR are MDR-associated proteins, ABC-G2 protein, and P-gp. P-gps are large glycosylated membrane proteins that are primarily limited to the cell's plasma membrane. They are thought to be the most important transporters that reduce the anticancer effect of medications. By dynamically ATP-dependently expelling cytotoxic drugs from the cell, they confer drug resistance and reduce drug aggregation in cancer cells. The majority of significant anticancer medications, such as vinca alkaloids, taxanes, epipodophyllotoxins and anthracyclines are impacted by MDR.

### **Futuristic Trends in Oral Delivery of Anticancer Drugs**

Despite the problems encountered in the practice of cancer therapy, oral administration of a few anticancer drugs has been explored with their therapeutic efficiency and safety. This predominantly practiced by delivering simultaneously an active agent, a functional excipient, a metabolism inhibitor, and/or an anticancer drug. It either makes easier the passing through the GIT for the anticancer drug or defeats the biological obstacles that stand as obstacles against this process. It has been possible to provide many anticancer medications that otherwise could not be given orally with great success using several methods. Figure 4 depicts several methods that may be used to boost the oral bioavailability of anticancer medications.

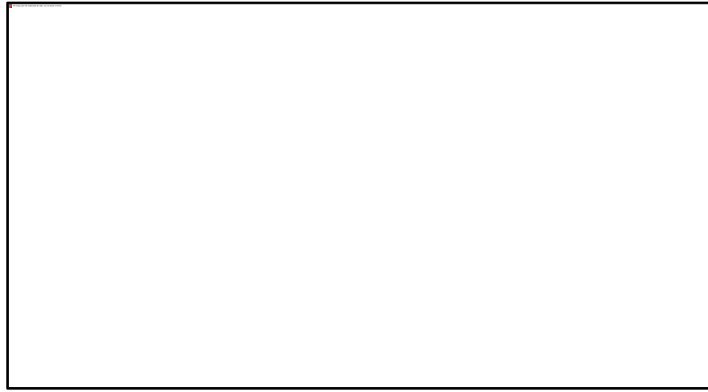


Figure 4: Different techniques to enhance the oral bioavailability of anticancer drugs (Thanki, et al 2013)

## Conclusion

In the review, we comprehensively investigate the significant role of micellar characteristics including size, surface charge, shape and stability-in optimizing the dissolution and therapeutic efficacy of hydrophobic anticancer agents based on the findings of the investigators. The key findings highlight that micellar systems address the inherent challenges of poor solubility and bioavailability associated with many anticancer drugs. The smaller micellar sizes enhance the solubility and tumor penetration of the drug, while non-spherical morphologies improve cellular uptake and prolong circulation time. The surface charge significantly influences micelle-cell interactions with cationic surfaces that often promote cellular internalization, although neutral or slightly negative charges may reduce non-specific interactions in systemic circulation. The stability, governed by factors such as critical micelle concentration (CMC) and polymer composition, ensures controlled drug release, preventing premature leakage and enhancing accumulation at tumor sites via the EPR effect. Despite these advantages, challenges continue, including premature drug release during systemic circulation, long-term stability in biological environments and scalability for clinical translation. Future advancements should be focused on stimuli-responsive micelles that release payloads selectively in the tumor micro-environments (pH or redox-sensitive systems) and focus on multifunctional designs integrating imaging agents for real-time therapeutic monitoring. Additionally, optimizing ligand-conjugated micelles for actively targeting can further reduce off-target toxicity and improve therapeutic precision. In conclusion, tailoring micellar properties presents a transformative strategy to enhance anticancer drug delivery. By addressing the current limitations and leveraging emerging technologies, micellar systems have immense potential to advance personalized, effective and safer cancer therapies.

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