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Nanomicelles: An Overview

Tapati Mallik*
Assistant Professor, Department of Chemistry, Chandernagore College, Chandernagore, India

***Abstract*: Nanomicelles are around 5 to 100 nm in diameter. They are formed by diphilic surfactant molecules or ions formed spontaneously in their solutions at a definite concentration. The micelles may contain hundred or more ions clumped together with a considerable number of water molecules. Micelles are characteried by the aggregation number i.e. the number of molecules in a micelle and the micellar mass. Interior of these cells are made up of nonpolar groups and the exterior by polar groups. Nanomicelles can be used as hydrophilic and hydrophobic agents. Micelle formation is a spontaneous process. This is entropy controlled .In solvation of individual units, the individual molecules enter inside solvent cages. Once micelle is formed, solvent molecules form a single cage and the forced order is destroyed. They can be used in cancer treatment, several skin diseases and also for eye treatment. In this paper we want to tell about their types, some properties and their important uses which made them important in modern science.**

***Keywords*: Amphiphilic molecules, Drug-delivery system, Membrane proteins, Nanomicelles, Therapeutic interventions.**

1. Introduction

Micelles are the clusters or aggregates formed in solution by colloidal electrolytes. They are generally formed by diphilic molecules in aqueous solution. According to modern concepts, they may be defined as the aggregates of long chain diphilic surfactant molecules or ions formed spontaneously in their solutions at a definite concentration. “Reverse/inverse micelle” is found to be formed in bulk non-polar solvent when the hydrophilic and hydrophobic groups take up just the opposite orientation as is found in micelles.. Micelles can be assembled from a variety of materials. They can be formed from lipid and block copolymers in maximum no of cases. Hydrophobic interactions can be regarded to be the thermodynamic driving force of micelle formation. It is an ordering process of units which is stabilised by greater disorder in the solvent. Micelles are formed, by the cooperative binding of monomers to one another at concentration exceeding a rather narrow region known as critical micelle concentration. The initial concentration at which micelle concentration becomes appreciable and micelle formation takes place is known as the critical micelle concentration (CMC). For most of the functional applications of micelles a lower value of CMC (critical micelle concentration) is always preferred. Nanomicelles are generally spherical in shape. The shapes can be cylinders and ellipsoids in some cases. Which of the shape will be formed is entirely dependent on ionic strength of the solution, concentration of surfactant and to some extent on pH of the solution. Factors that affect formation and development of nanomicelles include : i) chain length of the amphiphiles (especially length of the hydrophobic fraction) – when chain length is long , nanomicelles with lower concentration will form; ii) Presence of dissolved salts in the solution- dissolved salts lower critical micelle concentration value and therefore acts as one of the controlling factor in nanomicelle formation; iii) generally electrostatic force (especially within the hydrophilic fraction); iv) temperature ; v) addition of alcohol to water ; vi)number of surfactants in the solution. Micelles because of their small size are used as solutions for membrane proteins .They are very effective in studying the capabilities of such proteins. They could be used as therapeutic interventions involving protein and peptide delivery.

2. Preparation of Nanomicelles

Nanomicelles are formed from amphiphilic molecules. These molecules assemble themselves in aqueous or in nonaqueous media and forms globular structure with the diameter in the range of 5 to 100 nm .These particles are formed in polar solvent when long hydrocarbon part i.e. hydrophobic part tries to keep away from the solvent This part is called tail and it forms the interior. The other part, which is the hydrophilic polar part, tends to go into the solvent. This part forms the exterior and known as head. Nanomicelles are therefore able to take on both hydrophilic and hydrophobic agents. Different agents are used to create nanomicelles. They are usually made through surfactant molecules which may be non-ionic, ionic and cationic detergents. Anionic surfactants include sodium dodecyl and cationic surfactants include dodecyl trimethyl ammonium bromide [1]. Non-ionic surfactants are neutral such as n-dodecyl tetra (ethylene oxide) whereas zwitterionic surfactants carry both negative and positive charges such as dioctanoyl phosphatidyl choline. Polymeric micelles can be arranged as linear diblock (A-B), triblock (A-B-A), pentablock (A-A-B-A-A), and branched types. Some nanomicelles may also be developed from a mixture of lipids and detergents. The critical micelle concentration and the typical number of detergent molecules are dependent on the amount of lipids and proteins in the micelles.

*Corresponding author: tapatimallik123@gmail.com

3. Classification of Nanomicelles

- *Nano micelles:* Diphilic molecules like liposomes, micelles and nanomicelles are very common subunits of supramolecular assembly.They contain both hydrophilic/lypophilic (polar) and hydrophobic/lyophobic (non-polar) groups. These molecules combine together to form the assembly and this can be attributed to orientation of the groups to a suitable environment such as a solvent. In a polar solvent, the hydrophilic portion of the molecules tends to move towards the outer surface and hydrophobic parts tends to move towards the centre [2-4]. This type of supramolecular assembly formed is known as normal nanomicelles. The supramolecular assembly formed in non-polar solvent is known as reverse nanomicelles. The property to change orientation depends upon the nature of the solvent and this property is responsible for loading different types of drugs in the nanomicelles. Nonsoluble drugs can be loaded into normal micelles while soluble drugs can be loaded in reverse nanomicelles [5]. Nanomicelles act as protective shell .The reason lies in reducing the direct contact of drugs with the in vivo environment. They improve drug bioavailability and reduce adverse side effects [6-8].
- *Surfactant Nanomicelles*: Surfactant is one type of amphiphilic molecules and contain hydrophilic heads and hydrophobic tails. Surfactant tends to form a supramolecular assembly of diameter 5 to 100 nm [9]. They are known as colloidal dispersion. The characteristics of the head group and the variation of the alkyl chain length is the controlling factor of the size of the nanomicelle [10-11].Head groups are classified in different categories such as charged (anionic or cationic), dipolar (zwitterionic) and noncharged (non-ionic) [12].In aqueous solution, surfactant orients with head to the solvent and first accumulates on the air-liquid interfaces. By increasing the amount of surfactant, we induce the self-assembly of surfactants into micelles. The hydrophobic core is formed by van der waals bond recognition [9]. The micelles formed, set up a hydrogen bond crosslink between the head group and water molecules from aqueous solution.
- *Polymeric micelles:* Polymeric micelles have gained much attention in drug delivery. They have the ability to solubilize hydrophobic molecules. They have small particle size, good thermodynamic solution stability, extended release of various drugs, and prevention of rapid clearance by the reticulo endothelial system. For formation of polymeric micelles CMC value must lie in lower region. These are all important parameter for pharmaceutical applications. A micelle with a high CMC values may associate into unimers if we dilute it with a large volume of blood. The dilution release the entrapped drug molecules.

Polymeric micelles with a core-shell morphology is formed from block polymers. They are hydrophobic polymer chains that are linked to hydrophilic polymer chains [13]. When the hydrophobic parts of the block copolymers assemble, they form the inner micelle core in water medium. The interaction responsible for such assemblance is hydrophobic interactions. The outer hydrophilic parts surround the inner core as a hydrated shell .They are very advantageous because of their unique core shell structure. The core compartment of the polymeric micelles indicate high loading capacity, controlled release profile for the incorporated drug. The micelle corona provides an effective steric protection for the micelles .It determines the micelle hydrophilicity, charge and the length and surface density of hydrophilic blocks [14].These properties control important biological characteristics of a micellar carrier, such as its pharmacokinetics, biodistribution, biocompatibility, longevity, surface adsorption of biomacromolecules, adhesion to bio surfaces and targetability. The use of polymeric micelles often allows for achieving extended circulation time, favourable biodistribution and lower toxicity of drug. By use of suitable anionic complexing agent, anticancer drugs such as doxorubicin can be encapsulated in pluronic block copolymer micelles [15].

- *Mixed micelles*: Mixed micelles are generally mixtures of amphiphilic systems (including surfactants, polymers and copolymers). They form micellar aggregates. They exhibit characteristic properties different from individual amphiphile. They are fascinating from a scientific as well as from industrial standpoint. The properties of mixed micelles can be turned to the desired requirements through simple composition variations rather than through synthesis of new materials. They have been widely used in pharmaceutical industries for solubilisation of hydrophobic drugs. This solubilisation improve their therapeutic efficacy. The mixed micelles stabilized drugs have been successfully administered by various ways such as parental, oral and dermal routes.

4. Different Properties Exhibited by Nanomicelles

Stability of nanomicelles can be explained both from thermodynamic and kinetic point of view. The stability can be explained on the basis of entanglement of polymer chains present in the inner core of the micelle. A nanomicelle becomes thermodynamicallyally stable when its copolymer concentration exceeds its CMC (Critical Micelle Concentration).CMC value is influenced by the hydrophilic-lipophilic balance (HLB) of the copolymer [16]. Nanomicelles generally show very low CMC values ranging from 10−6 to 10−7 M. The values are smaller than that of micelles formed from low-molecular weight surfactants. It helps to retain its micellar structure on series of dilution [17]. We can tell of kinetic stability when the conditions for drug delivery are not at equilibrium and copolymeric concentration goes below its

CMC. Nanomicelles disassemble much slowly .This can be explained in terms of their kinetic stability when the concentration is less than that of CMC. This slow dissociation allows nanomicelles to retain the integrity and maintain its drug content until it reaches its target site.This enhance bioavailability of the drug [18].

1) Ability to solubilise hydrophobic drug

Nanomicelles are considered to be the best pharmaceutical carriers. They are very helpful in solubilising hydrophobic drugs. Hydrophobicity is one of the major limiting factors which helps nanomicelles in attaining therapeutic levels. They also have the capability to solubilise hydrophobic drugs by entrapping the drugs within a mixed micellar hydrophobic core, while the shell is composed of hydrophilic chains extending outwards [19].

2) Physicochemical properties

Nanomicelles are amphiphilic copolymers and they are usually block copolymers [20]. Block copolymers can be diblock or triblock copolymers. In general, diblock copolymers are mainly A-B type, where A represents hydrophilic part and B represents hydrophobic part. Triblock polymers are of two types – ABA type and ABC type. AB and ABA type is widely used to make nanomicelles [8, 21]. These arrangements in these two types enhance drug solubility and increases loading efficiency. The inner core made up of hydrophobic blocks.They are stabilised by hydrophobic interaction, or by electrostatic interaction. Besides these, it can be formed by metal-ligand binding and also by hydrogen ion bonding [22-24]. The outer hydrophilic shell has steric stability that plays an important role in in vivo condition due to interaction with the cells [25]. Nanomicelles can therefore self-assemble in water, enhances drug solubility, and remains stable in the gastro-intestinal tract because of its structure.

3) pH sensitivity

Micelles, polybases and polyacids are the building blocks that impart pH sensitivity in releasing drug [26]. Drug releasing capacity depends upon intracellular signals which is highly dependent on pH. Amine is the basic core and it is uncharged .It becomes hydrophobic at high pH and becomes hydrophilic upon protonation at low pH. Carboxylic acid is the acidic core. It is uncharged at low pH and upon being protonated becomes negatively charged at high pH. Micelles are therefore destabilised because of protonation. pH of the solution ,therefore, must be above pKa of the protonable group for the formation of the nanomicelle. But, as soon as the pH falls below the pKa value, hydrophilicity and electrostatic repulsion are increased because of the ionisation of the polymers.It leads to the destabilisation of the micelle which in turn leads to controlled drug release [27]. Absorption of drug in the intestine can be promoted by making use of this pH gradient [28].

4) Light sensitivity

Studies indicate that hydrophilicity and hydrophobicity can be altered on exposure to light. Thus, light can trigger disintegration of nanomicelles and thus leads to release of drug [29-30].

5. Application of Nano micelles

Nanomicelles are used to improve cancer treatment by overcoming drug resistance, improving anti-cancer drug efficacy and reducing drug toxicity.They are formed by self-assembly of amphiphilic dendrimers.They work by removing drug resistance among cancer cells and have the ability to generate supramolecular nanomicelles with large void space in core. In this way it helps to encalsulate anti-cancer drugs with high loading capacity.This process helps to decrease efflux of the drug and at the same time helps cellular uptake.

They can be used in the early stage of cancer treatment. Near-infrared triggered polymeric nanomicelles have been found useful in photoactive delivery and imaging at the early stage.under NIR light irradiation, nanomicelles could be spatially and temporarily released.

Chemptherapy ia an important part of treatment for different type of cancers. But application of it is not so effective because of poor water solubility, non-specificity and toxicity.Polymeric micelles, dendrimers , liposomes and nanoparticles are under investigation to reduce these limitations of chemotherapy and improve the potential of anticancer drugs.For targeted cancer have gained great interests. This can be attributed to their several physicochemical as well as biochemical advantages over other nanocarriers. The small size is responsible for a hydrophobic core for efficient drug loading for poorly water-soluble drugs and a hydrophilic shell to provide colloidal stability [31-32]. Biodegradable polymeric micelles are ideal for targeted and controlled drug delivery of hydrophobic anti-cancer drugs which include paclitaxel (PTX) and doxorubicin (DOX) [17, 33]. These nanocarriers (i) enhance water solubility of the anti-cancer drugs (ii) can enhance drug circulation time (iii) are able to passively target tumour tissues via the EPR effect [34] (iv) improve bioavailability and (v) possess great biocompatibility and are also degraded into non-toxic products in vivo. It can be absorbed and excreted from the human body and patient can get rid of toxic effects.Polymeric micelles have proved to be an efficient drug carrier. It helps to indiscriminate biodistribution to both normal and tumour tissues because of having low molecular weight [35].

1) In the treatment of eye

There are various vision threatening ocular diseases. These include age related macular degeneration, diabetic retinopathy, glaucoma, proliferative vitreoretinopathy. Ocular drug delivery is still difficult because of certain physiological barriers.Nanomicelles because of their amphiphilic nature, small diameter, highly modified surface properties and increased bioavailability plays a significant role in the ocular tissues [36]. Fordexamethasone-loaded nanomicelles were developed by employing copolymers of poly hydroxyl ethyl aspartamide [PHEAC (16)] and PEGylated PHEAC (16) for the delivery of the anterior segment of the eye [37]. This method of drug delivery is very helpful as potential pharmaceutical carrier for the topical administration of hydrophobic drugs. This technology is very much patient compliant and highly efficient for the treatment of age related ocular diseases such as mascular degeneration, diabetic retinopathy, diabetic macular oedema, and posterior uveitis [38].

2) In the treatment of skin diseases

One of the approaches for local drug therapy is dermal application because of easy accessibility of skin.Effectiveness of such approach is dependent bon skin barrier properties, physicochemical properties of drug and vehicle, and interaction between drug and its vehicle with the skin layers. The new strategy for skin penetration of drugs is by the use of nano-sized carriers [39]. Nanocarriers encapsulate pharmaceutical ingredients to perform activities such as penetrate the hair follicles, interacting with skin's lipid to transport. There is high permeation through all routes including intracellular, intercellular and the hair follicle shafts in trans-appendage pathway due to their high surface to volume ratio [40]. Several non-toxic and biodegradable synthetic or semi-synthetic polymers such as poly lactic acid (PLA), poly (lactic-co-glycolic acid) (PLGA), poly (e-caprolactone), chitosan have shown great results in topical drug delivery. The polymeric nano carriers have shown merits in controlled release. This can be done through modification of the polymer composition and reducing irritation due to direct contact of drug with skin [41-43].

6. Conclusion

Nanomicelles possess the advantages of having a small diameter, exhibiting low toxicity, increasing the solubility of hydrophobic drugs and achieving therapeutic concentrations. They have gained great advantage because is its core-shell structure.The hydrophobic portion within the nanomicelle shell facilitates the solubilization of hydrophobic drugs in water. The hydrophilic shell itself acts as a protector for the drug by eliminating the MPS that enables prolonged circulation. The nanomicellar drug delivery platform appears to be a potential pharmaceutical carrier for topical administration of hydrophobic drugs. Another advantage of nanomicelles are their quality as an efficient pharmaceutical content. This is because of their low toxicity, ability to minimize drug degradation. But the structures have inefficient drug-loading capabilities (smaller than liposomes), poor physical stability in vivo, and insufficient cellular interactions with neutral micelles. Substantial progress still needs to be made in this field to achieve sustained drug release from the micelles relative to other larger particulate systems such as nanoparticles, microparticles and liposomes.

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