International Journal of Pharmaceutics 532 (2017) 249–268

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Polymeric micelles: Basic research to clinical practice

Anand S. Deshmukh, Pratik N. Chauhan, Malleshappa N. Noolvi, Kiran Chaturvedi, Kuntal Ganguly, Shyam S. Shukla[1], Mallikarjuna N. Nadagouda, Tejraj M. Aminabhavi[*,1]

Department of Pharmaceutical Research, Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat 394 110, India

ARTICLE INFO

Keywords:
Amphiphilic micelle
Polymeric micelle
Drug delivery
Block copolymer
Clinical application
Drug targeting

ABSTRACT

Rapidly developing polymeric micelles as potential targeting carriers has intensified the need for better understanding of the underlying principles related to the selection of suitable delivery materials for designing, characterizing, drug loading, improving stability, targetability, biosafety and efficacy. The emergence of advanced analytical tools such as fluorescence resonance energy transfer and dissipative particle dynamics has identified new dimensions of these nanostructures and their behavior in much greater details. This review summarizes recent efforts in the development of polymeric micelles with respect to their architecture, formulation strategy and targeting possibilities along with their preclinical and clinical aspects. Literature of the past decade is discussed critically with special reference to the chemistry involved in the formation and clinical applications of these versatile materials. Thus, our main objective is to provide a timely update on the current status of polymeric micelles highlighting their applications and the important parameters that have led to successful delivery of drugs to the site of action.

1. Introduction

The versatility of micelles produced from amphiphilic copolymers as self-assembled nanostructures (≈10 to 200 nm) has signalled significant advances in biomedical area due to their varying functions and clinical success (Kataoka et al., 2001). The enormous progress in polymer science has enabled the design of these colloidal systems that can selectively accumulate in solid tumors, have improved loading capability, better therapeutic efficacy and superior targeting ability by surface modification with tumor homing ligands and aptamers. Polymeric micelles that can form above the critical micellar concentration (CMC) are composed of solvophilic and solvophobic portions. In aqueous media, solvophobic portion forms the core, while solvophillic portion forms the shell, also called corona. Both these portions are covalently attached to each other as blocks (block copolymers) or grafts (graft or brush type copolymers) (Tuzar and Kratochvil, 1976). The core of polymeric micelles acts as a reservoir for hydrophobic bioactives, while the shell provides required colloidal stability. The shell plays an important role in preventing opsonization, protein adsorption and together with the small size of polymeric micelles when accumulated in tissues with leaky vasculature through enhanced permeation and retention effect (EPR). Long circulation of these carriers can be prevented by glomerular filtration (Kang et al., 2005).

Although a number of polymeric micelles are in clinical trials, process scalability still remains a serious challenge and demands more judicial approach at the very early stages of research in order to transfer basic research to clinical practice. Further, limited understanding of preclinical and clinical aspects (Yokoyama, 2011) of these materials has caused a serious downfall to realize their full potential in clinical practice. To address these issues, a thorough understanding of biodistribution, pharmacokinetics, pharmacodynamics, accelerated blood clearance (i.e., immunogenic response) and *in vivo* degradation profiles is necessary (Chung et al., 2014; Koide et al., 2008).

Over the past decade, synthetic and natural polymers have been investigated as biodegradable building blocks of amphiphilic copolymer. Even though a majority of work focused on synthetic polymers, natural polysaccharides have also been used especially as the hydrophilic portion of amphiphilic copolymers either directly or in their modified forms. Micelles based on polysaccharides have shown promising results in cancer therapies (Ganguly et al., 2014) due to their unique structural features. However, available data on essential parameters like acute, sub-acute and chronic toxicity are insufficient to establish any meaningful scientific insight to explore their possibilities, which otherwise hinder the probability of transformation of these materials for commercial success. In view of these issues, we have addressed the critical issues related to design and development of

* Corresponding author at: Department of Pharmaceutics Shree Dhanvantary Pharmacy College Near Kim Railway Station, Kim (E), Kudsad Road, Surat, Gujarat, 394 110, India.
E-mail addresses: dranandsdeshmukh@gmail.com (A.S. Deshmukh), aminabhavit@gmail.com (T.M. Aminabhavi).
[1] Department of Chemistry and Biochemistry, Lamar University, Beaumont, Texas 77710, USA.

http://dx.doi.org/10.1016/j.ijpharm.2017.09.005
Received 23 May 2017; Received in revised form 2 September 2017; Accepted 2 September 2017
Available online 05 September 2017
0378-5173/

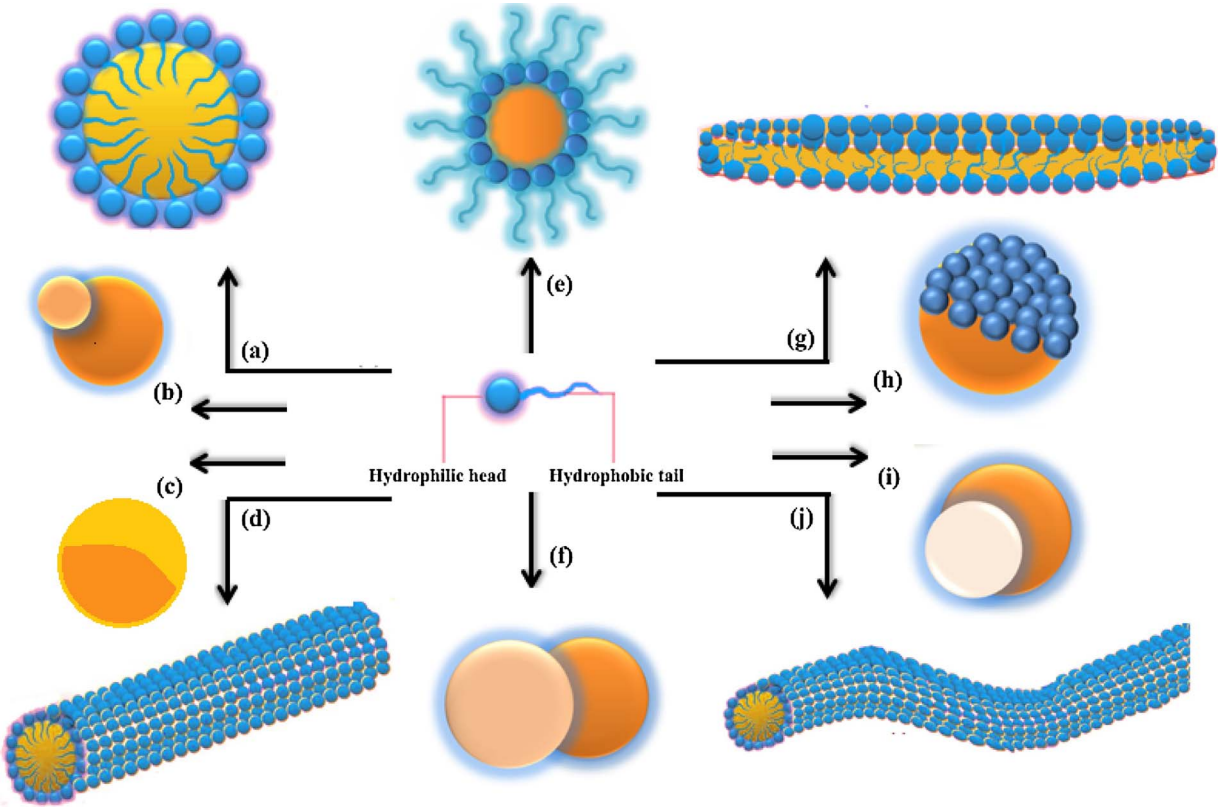

Fig. 1. Different micellar structures: (a) regular, (b) snow man, (c) two hemispheres, (d) cylindrical, (e) reverse shape, (f) dumbbell shape, (g) disc shape, (h) half cut view of raspberry shapes, (i) corn shape and (j) worm shape.

polymeric micelles including those prepared using polysaccharides right from starting stage to the execution level along with their technological and pharmaceutical aspects as well as future prospects.

The micelle-based delivery systems have unique versatility to deliver a variety of pay loads including, but not limited to drugs, proteins, peptides, DNA, SiRNA etc. These nano or submicron delivery systems have mostly a spherical structure, thereby giving the most physical stability due to lowest surface energy. Block copolymers have been tailor-made based on their physic-chemical properties of the drug, thereby achieving cellular, tissue, or organ level targeting. In this review, we have described how a micelle can be prepared and how its properties can be manipulated to offer better bioavailability or localized delivery. Modification of micelle components can be done to achieve biological target specificity, leading to better safety due to dose reduction of drugs. Stimuli responsiveness of the micelle determines the target specificity and thereby multiple targeting approaches are possible.

The design and refinement of drug-polymeric micelle solubility parameters, biocompatibility, drug disposition in various tissues and release profile with localized delivery option have been identified as the critical parameters for successful micelle-based delivery. In this regard, we have discussed the micelles in achieving desired characteristics required in clinical and preclinical testing. The preclinical and clinical findings of such micellar systems would reach the market. In these aspects, this review gives a clear understanding of the overall scenario of these micellar systems.

2. Micellar architecture

Polymeric micelles have unique features such as high molecular weight, substantially low CMC, greater stability, slower rate of dissociation, better retention of encapsulated drugs and higher site specific accumulation of a drug at the target site (Kataoka et al., 1993). This is in comparison to other polymeric carriers such as drug-polymer conjugates, which show low water solubility, precipitation and problems in injecting into blood stream due to hydrophobic nature of most of the drugs. These features are atributed to architectural composition of micelles leading to an array of desired performance. Additionally, micellar composition, its size and characteristics are important in meeting their crucial design criteria. Ideally, micelles have small size (≈10–200 nm) for an effective penetration into the tissue, provide stealth against mononuclear phagocyte system (MPS) for sufficient longer circulation and better accumulation in the target tissue, biodegradability for easy elimination from the body, targetability for therapeutic efficacy, tuneable stability, improved pharmacokinetics (PK) and pharmacodynamic (PD) profiles, high drug loading capacity, and reproducibility along with facile and inexpensive method of synthesis (Torchilin, 2011; Aliabadi and Lavasanifar, 2006).

Most of the polymeric micelles studied for drug delivery are composed of either diblock or triblock copolymers or graft polymers with a hydrophobic and a hydrophilic segment or ionic copolymers with a hydrophilic segment and an ionic segment. Block copolymer micelles can be categorised based on the type of intermolecular forces governing the segregation of the core segment from the aqueous environment viz., amphiphilic micelles (hydrophobic interactions), polyion complex micelles (PICM; electrostatic interactions), and micelles formed by metal complexation (Kang et al., 2005). However, the usage of poly(ethylene glycol) (PEG) with a molecular weight of 2–15 kDa to form the hydrophilic shell in a majority of polymeric micellesis widely studied. PEG is an FDA approved inactive excipient for oral consumption. It has low toxicity, reduces micelle aggregation and prevents interaction with serum proteins while in systemic circulation. It increases the circulation time of the micelle in blood and causes efficient accumulation at the tumor site. PEG also imparts stealth property and protects the biomacromolecules from steric hindrance. Other polymers studied for hydrophilic segment are poly(vinyl alcohol) (PVA) (Munk and