REVIEW ARTICLE

Polymeric Micelle as a New Carrier in Oral Drug Delivery Systems

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Abstract

Almost half of the orally administered drugs are poorly soluble in water; therefore they have low absorption in the gastrointestinal (GI) tract. In addition, drugs which are administered orally must remain stable during passing the GI tract, despite different physiologic challenges such as pH changes, and dilution effect. Hence, new methods are needed to increase the solubility of these drugs while making them more stable in the physiologic environment. Polymeric micelles are one of the new nanocarriers which are able to increase the solubility of these drugs while protecting them from pH changes, dilution effect, and biological barriers such as filtration in the spleen or scavenging by the phagocytic system. This article provides some important and basic information including polymeric micelles characteristics, structure, and preparation.

Key words: Characteristics, oral, polymer, micelle, structure, preparation

INTRODUCTION

Modern drug delivery systems are only about 60 years old, and this period is divided into three distinct generations. The first generation (1950–1980) was very productive compared to the second. In this generation, the scientist and pharmacist regulated physicochemical properties of drugs and they achieved many oral and transdermal formulations. On the other hand, the second generation (1980–2010) was not as prolific as the first. In this generation, scientists had more difficulties with biological barriers (biological membranes, filtration by the spleen, phagocytic system, etc.). Today, in the third generation, it is known that achieving more effective formulations would not be possible unless physicochemical properties of drugs are regulated and biological barriers are overcome.

Most drug products on the global pharmaceutical market are administered orally. Therefore, the oral route of administration is one of the most important routes of administration. The procedure of oral drug absorption is very complicated and it undergoes changes by so many factors. The drug which is orally administered travels through gastrointestinal (GI) tract, but it will not be able to penetrate the GI membrane unless it dissolves in GI fluids.[1] GI fluids are hydrophilic. As drug solubility in GI fluids increases, the dissolution rate and therefore bioavailability of drug increases as well.[2] In conclusion, one of the most important characteristics of drugs which affect oral drug absorption procedure and oral drug bioavailability is solubility of the drug in hydrophilic liquids which is a physicochemical barrier. According to previous research, about 70% of new chemical entities are poorly soluble in water and 40% of oral drugs in immediate release formulations, are considered practically insoluble in water.[3] On the other hand, drugs which are administered orally are exposed to different physiologic challenges such as pH changes and dilution effect and physiologic barriers such as filtration by the spleen or scavenging by the phagocytic system as biological barriers. Polymeric micelles are novel nanocarriers which are able to increase the solubility of a drug while protecting it from physiologic challenges, hence polymeric micelles make drug able to overcome both physicochemical and biological barriers.

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POLYMERIC MICELLE

Micelle formation mechanism

Reduction in particle size is one of the oldest methods which are used to increase the solubility of any substances. Nanonization of hydrophobic drugs is usually done by two distinct approaches, including chemical precipitation and disintegration.[4] These nanocrystal formulations have shown 1.7–60-folds enhancement in maximum concentration (C_{max}) and 2–30-folds enhancement in the area under the curve (AUC) in comparison to microcrystalline formulations.[5] However, the problem is that these hydrophobic nanoparticles would accumulate together to form a larger particle, when being exposed to hydrophilic fluids in the GI tract, to decrease the free surface energy. In this situation, no nanoparticles would be remnant. Therefore, some methods are needed to stabilize these hydrophobic nanoparticles.

These nanoparticles may stabilize by adding some surfactants or hydrophilic polymer.[6] Surfactant molecule contains a hydrophilic and a hydrophobic part. As it is added to a hydrophilic liquid, amphiphilic monomers start to locate on the surface of the liquid and decrease the surface tension.[7] A threshold at which surface tension remains constant while the surfactant concentration is increasing is called critical micelle concentration (CMC). At CMC, surfactant monomers self-assemble and form a micelle. If hydrophilic polymers are used instead of surfactant, the micelle which would be formed is called polymeric micelle [Figure 1].

CMC level determines so many characteristics of the polymeric micelle; micelle resistance to dilution effect is one of these important characteristics. Whatever the CMC is achieved in lower concentration of hydrophilic polymer (<135 mg/ml), the formed polymeric micelle would be more resistant to dilution effect.[9] Lower CMC conferred by two different strategies: (1) Increasing the chain length of the core-forming polymer.[10] (2) Decreasing the chain length of hydrophilic shell-forming polymer.[11]

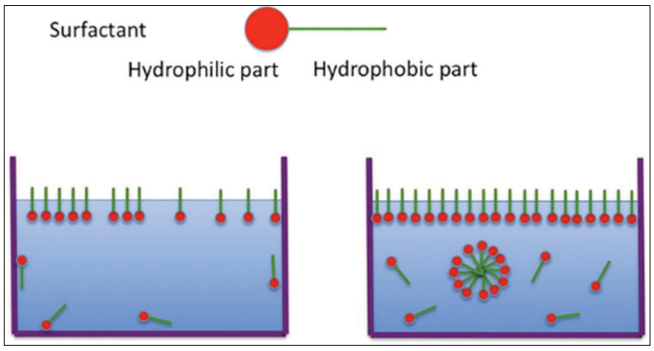

Figure 1: Below critical micelle concentration (CMC): The surfactant molecules are separated (left). Above CMC: Surfactant molecules are assembled and formed a micelle (right)[8]

STRUCTURE AND COMPOSITION

Polymeric micelles are formed by self-assembly of amphiphilic polymers in an aqueous environment. These nanosize carriers contain a hydrophilic shell and a hydrophobic core that may serve as a reservoir for hydrophobic drugs.[12]

SIZE

The size of these micelles varies from 10 to 200 nm.[12] This small size offers many advantages, such as evading scavenging by the phagocytic system in the liver and bypassing filtration of the interendothelial cells in the spleen. These two advantages result in longer circulation time and accumulation of the micelles at tissue site with the vascular abnormality (might be useful in delivering anticancer drugs).[12]

There are some different methods which are used to study micelle dimensions including dynamic light scattering, static light scattering, atomic force microscopy (AFM), and transmission electron microscopy (TEM). AFM and TEM give direct images and insight into shape.

Shell of polymeric micelles

The hydrophilic shell provides some protection in limiting opsonin adsorption and results in longer blood circulation time and increases the solubility of the micelle in the GI fluids.[13] In addition, the hydrophilic shell has the ability to load a distinct component from the core in itself; therefore, it is possible to load different components in shell and core simultaneously in a single micelle.[14] Several important characteristics make polyethylene glycol (PEG) invariably, one of the shells forming polymer of choice. It is non-toxic and FDA approved.[15] It forms dense and brush like shell which limits the polymeric micelle interactions and reduces protein adsorption[16] resulting in longer blood circulation time and high blood compatibility.[17] It can be easily functionalized to tether ligands for targeted drug delivery.[18] However, there are still some drawbacks in use of PEG including immunologic response, non-biodegradability of PEG, relatively easy degradation on exposure to oxygen, and unexpected changes in pharmacokinetics of pegylated nanocarriers, it is still one of the most important ingredients which are used in producing nanocarriers.[19] Since PEG is easily oxidized, the lower molecular weight of PEG is preferable and generally use as a solvent and higher molecular weight is used as a component in the micelle, possibly due to the fact that oxidative degradation significantly decreases with increasing molar mass.[12]

There are some other polymers which are used as hydrophilic shell-forming polymer including:

a. Poly (N-vinyl-2-pyrrolidone)[20]

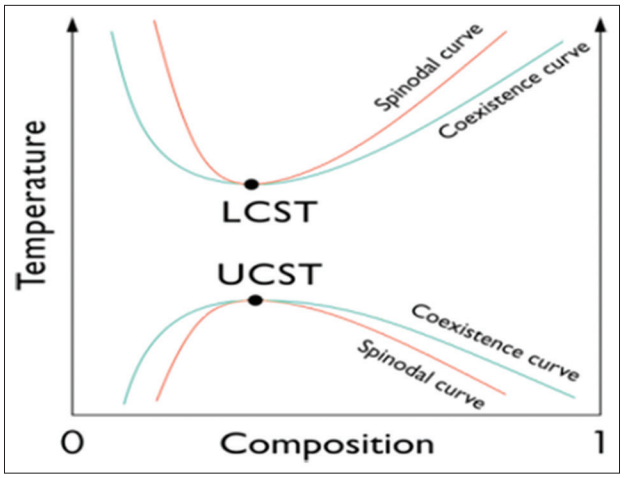

Figure 2: Thermosensitive polymers are soluble between lower critical solution temperature and upper critical solution temperature[23]

b. Poly(N-(2-hydroxypropyl) methacrylamide): It is a non-immunologic polymer which is multifunctional and several ligands can be attached to, to use in targeting drug delivery.[21,22]
c. Poly(N-isopropylacrylamide): It is a thermosensitive polymer which is used in producing thermosensitive polymeric micelles. Its low critical solution temperature is 33°C and therefore it is insoluble in water in above temperature and it is soluble in water below 33°C [Figure 2].

Hence, it can be used as hydrophilic polymer below 33°C as shell-forming polymer, while, it can be used as core-forming polymer above 33°C which is at, insoluble in water and hydrophobic.[24]

Core of polymeric micelles

The core is a dense region which may be solid or fluid dependent on the structure of the surfactant. It contains the hydrophobic part of the amphiphilic polymer and it serves as a reservoir for the hydrophobic drug, therefore, it has hydrophobic interactions with the drug and determines the micelle capacity.[25] Core capacity is affected by three different factors: Compatibility,[13] hydrophilic-lipophilic balance (HLB),[26] and the polymer-drug ratio (P/D ratio).[12]

1. Compatibility: Since each drug has its own unique chemical and physical properties, no delivery vehicle prepared from a particular polymer will assist as a universal carrier for all drugs. The degree of compatibility between polymer and drug has been shown to be of importance in the design of a wide range of delivery systems including block copolymer micelles.[27,28] The similarity in polarity and structure, between drug and hydrophobic part or hydrophobic side chain of the core-forming polymer, increase compatibility and therefore core capacity.[13] To determine the compatibility by means of polarity, Flory-Huggins interaction parameter can be used as equation below:

$$\chi_{SP} = \frac{(\delta_s - \delta_p)^2 v_s}{KT}$$

Where V_S is molar volume of drug, δ_s and δ_p are solubility parameters of drug and core-forming polymer, respectively, k is Boltzmann constant and T is the temperature in kelvin. The lower value of χ_{SP} will result in more compatibility and better drug loading, theoretically.

2. HLB: While the micelle is designed to increase the solubility of hydrophobic drugs, as the hydrophobic part of the micelle increases, the core capacity increases as well, and better drug loading capacity is achieved.
3. P/D ratio: Choosing lower or higher ratio of polymer to drug depends on compatibility between drug and polymer. (1) When the drug and the polymer are compatible, they tend to stay together and as drug release is needed, the polymer to drug ratio must decrease. (2) On the other hand, when the drug and the polymer are incompatible and tend to separate, the polymer to drug ratio must increase, as solubilization of drug in the polymer is needed for drug loading.[29]

Common hydrophobic polymers which are used in drug delivery can be classified as below:

a. Poly(propylene oxide) pluronics®[30]
b. Polyesters like poly(lactic acid) (PLA)[31]
c. Poly(ε-caprolactone)[32]
d. Poly(L-amino acid) such as poly(L-lysine)[33]
e. Phospholipids and lipidic derivatives such as phosphatidylethanolamine [Table 1].[34]

STABILITY

Micelles are facing dissimilar environmental and physiological factors such as significant dilution, pH changes in GI tract, exposing bile salts, and distinct proteins and cells. To use polymeric micelles as drug carriers, they must remain intact during formulation and administration. Polymeric micelles stability is studied from two aspects.

Thermodynamic stability

Thermodynamic stability describes the system function since micelle formation till equilibration point. The principal factor in determination of thermodynamic stability is CMC. CMC value is related to thermal energy, K_BT, and effective interaction between polymers and bulk solution, ε_h. lower CMC value, result in higher thermodynamic stability.

$$CMC=\exp(-n\varepsilon_h/K_BT)$$

CMC value also has direct relation with micelle formation standard free energy.

Table 1: Polymeric micelle different compositions

Polymeric micelle components	
Shell-forming polymers	**Core**
Poly (N-vinyl-2-pyrrolidone)	Poly (propylene oxide)
Poly (N-(2-hydroxypropyl) methacrylamide)	Polyesters like poly (lactic acid)
Poly (N-isopropylacrylamide)	Poly(ε-caprolactone)

ΔG_{mic}=RT ln (CMC)

Polymeric solutions have diverse behaviors above and below CMC. This value is usually in micromolar range for polymeric micelles.[35,36] In addition, hydrophobic part height has a direct relation with micelle stability.[37,38] Micelle tendency to decomposition depends on the components and adhesion of hydrophobic core.[39] Interactions between polymeric chains in the shell and interaction of these chains with the bulk solution are other factors which affect thermodynamic stability. As it is said noticed before, PEG is usually used as hydrophilic shell-forming polymer. PEG chains interact with each other by Van der Waals force and interact with water molecules in bulk solution by hydrogen and dipole-dipole bonds.[40] Longer PEG chain, results in higher surface density, which makes the surface harder and brush-like. While decreasing in PEG density, result in the lower surface covering and hence, hydrophobic part of the micelle will face to bulk solution, which causes micelle instability. Therefore, PEG high density and adequate surface covering by the hydrophilic polymer, lead to micelle fluid movements and prevent hydrophobic part exposure to the environment.[41]

Measuring the surface tension is one of the methods to determine the CMC value. The surface tension of the solution is measured by Du Nouy ring in the distinct concentration of polymer. CMC is indicated by the noteworthy decrease in surface tension as a function of concentration and demonstrates the surface satiation between air and liquid or aqueous and organic solution of polymer.[42]

Kinetic stability

The system behavior during the time, details of the polymeric chains exchange rate between micelles and disassembly are described by kinetic stability.

In equilibration, individual polymeric chains concentration to micelle concentration ratio can be shown as below:

$$K_m = \frac{[A]^n}{[micelle]}$$

Which, K_m is dissociation constant which has the unit of the concentration and n is the aggregation number of the micelle.[41]

Three distinct mechanisms are involved in dynamic equilibration in polymeric chains exchange between micelles:

1. Chain insertion/expulsion: Polymeric chain expelled by a micelle and enters to bulk solution and then it captures by another micelle.
2. Micellar merger/splitting: While two micelles merge temporarily and micellar cores are in contact, polymeric chains can exchange.
3. Micellar spanning: In this mechanism, a bridge is made by a polymeric chain between the exteriors of two micelles and the micellar chain migrate to another micelle without becoming a free chain in bulk solution and even contacting the core of the micelles.

Inspecting the kinetic of the micelles can be done by labeling a chain and tracing it.[43]

ADVANTAGES

Small particle size

Small particle size of the polymeric micelle (10–200 nm) helps it to evade scavenging by phagocytic system and filtration by the spleen that results in longer blood circulation time.[12]

High structural stability

Polymeric micelles have much lower CMC (1–10μg/ml) in comparison to micelles formed by low molecular weight surfactants, therefore, as it is explained in stability of polymeric micelles, these nanocarriers are much more thermodynamically stable in comparison to typical micelles.[36] In addition, decomposition rate of polymeric micelles is low which demonstrate its kinetically stability.[41]

High drug loading

By regulating compatibility, HLB and P/D factors, core capacity can be modified.

High water solubility

Hydrophilic shell increases the solubility, despite the high amount of hydrophobic drug in the core. In addition, hydrophilic shell prevents aggregation of micelles from forming larger particle and impedes decreasing the solubility.[44]

Low toxicity

Polymeric micelles cause lower toxicity in comparison to low molecular weight surfactants, generally. Polymeric micelles evade filtration in the kidney due to their much larger particle

size than critical molecular weight for filtration in the kidney. In addition, if the polymeric chain designed to have smaller particle size than critical molecular weight for filtration in the kidney, then they will be able to excrete by kidney entirely due to absolute decomposition of polymeric chains by the time.[44]

Different components can be loaded

Shell chemical characteristics, size and micelle stability are the determinants factor of pharmacokinetic behavior of the micelles, therefore, drug delivery control by polymeric micelles is drug independent. Hence, loading different compounds or drugs in polymeric micelle are possible, by regulating bounded drug quantity to correct the hydrophobic-hydrophilic balance for micelle formation [Table 2].[45]

POLYMERIC MICELLE PREPARATION METHODS

Polymeric micelles can be prepared by three common methods including direct dissolution, solvent evaporation, and dialysis.

Direct dissolution of the amphiphilic copolymer and drug in water, at or above CMC, results in self-assembling of the drug and copolymer to form polymeric micelles. This is the simplest approach to polymeric micelle preparation, although it is usually associated with low drug loading. In solvent evaporation technique, drug and amphiphilic copolymer are dissolved in a volatile organic solvent and a thin layer film of the copolymer and drug forms by evaporating the solvent. The polymeric micelles are obtained by reconstitution of film with water.[46] Dialysis technique is suitable for the situation which the core-forming polymer is long and more hydrophobic. In this condition by choosing the correct method of preparation, better drug loading can be accomplished. In this method, solutions of the drug and the polymer in an organic solvent are placed in the dialysis bag and the solvent is exchanged with water by immersing the bag into the water, inducing micelle assembly.[47,48] This technique often requires more than 36 h for efficient loading which is a drawback in use of this approach.

Table 2: Advantages and disadvantages of polymeric micelles[12]

Polymeric micelles	
Advantages	**Disadvantages**
Small particle size	Lack of suitable method for large scale production
High structural stability	Long processing time
High drug loading	-
High water solubility	-
Low toxicity	-

Several oral polymeric micelle formulations of distinct drugs are designed which need to be evaluated by clinical studies. Unfortunately, no oral polymeric micelle formulation is available on the market to product in large scale yet.

Genexol-PM® is a preferred intravenous formulation of paclitaxel, and first Food and Drug Administration approved polymeric micelle formulation, that is made by direct dissolution method with considering some special regulations in this method.[49] NK105,[50] SP1049C,[51] DTXL-TNP,[52] NC6004,[53] NK012,[54] and NK911[55] are other polymeric micelle-based formulations which have evaluated in clinical studies.

In addition, in researches conducted by Makhmalzadeh *et al.* and Salimi *et al*., polymeric micelles loaded by griseofulvin and celecoxib, respectively, have shown increased aqueous solubility and permeability trough rat intestine, in comparison to control.[56,57]

Cinacurcumin® is an oral polymeric micelle formulation containing curcumin, with the indications including kidney function improvement, repairing of the damaged tissues, decreasing the chemical therapy adverse effects.

IN VIVO STUDIES

While several clinical studies have evaluated polymeric micelle formulations efficacy by intravenous route of administration, only few studies have worked on oral administration of these formulations. In this section, some of the *in vivo* studies are reviewed.

US597 loaded polymeric micelles

In a research conducted by Chen *et al.* 2017[58] PLGA-PEG-PLGA triblock copolymer micelles were designed as US597 carriers for oral administration. US597 is an anticancer agent.[59] The micelles were prepared by double emulsion solvent evaporation method. *In vivo* pharmacokinetic study demonstrated significant improvement in the absorption and elimination characters of US597 loaded polymeric micelles in comparison to free US597.

Curcumin loaded mixed micelles

In a study, methoxy poly(ethylene glycol)-PLA/D-α-tocopherol PEG 1000 succinate (TPGS) mixed micelles loaded by curcumin were designed and improvement in aqueous solubility and intestinal absorption of curcumin were evaluated. The relative bioavailability of curcumin

loaded (TPGS) mixed micelles to curcumin suspension were reported 927.3% which demonstrate the great potential of polymeric micelles in improving oral bioavailability of curcumin.[60]

Baicalin loaded mixed micelles

Baicalin is a flavone glucuronide with extensive pharmacological effects including antibacterial,[61] anti-allergic,[62] and anti-inflammatory[63] effects. Despite all these pharmacological effects, its low aqueous solubility limited its clinical application.[64] In a recent research conducted by Zhang *et al*. mixed micelles were designed, which contain Pluronic P123 copolymer (P123) and sodium taurocholate as carrier materials for oral delivery of baicalin. After oral administration, the results demonstrated significant difference between C_{max}, AUC and blood retention time of the baicalin loaded mixed micelles and baicalin suspension and the mixed micelles were suggested by the researchers as promising oral vehicle for administration of baicalin.[65]

CONCLUSION

Polymeric micelles are nanosize carriers which are able to enhance the bioavailability of hydrophobic drugs in the oral route of administration, by increasing the solubility of these drugs and protecting them from environmental factors. The polymeric micelles are able to evade scavenging by the phagocytic system in blood circulation system and filtration in the spleen due to their small size and this result in longer blood circulation time. They also evade from filtration in the kidney due to their larger particle size than critical molecular weight for filtration which result in longer half-life time [Figure 3].

These carriers can be loaded by different compounds in different part of their structure concurrently and use in drug targeting. In a research, intestinal absorption of polymeric micelles loaded by cyclosporine A was compared with cyclosporine A loaded polymeric micelles which were designed by Vitamin B12 on their surface and the results demonstrate the significant increase in intestinal absorption of designed polymeric micelles.[66,67] Despite all these advantages, there are still some drawbacks in using these nanocarriers including polymer synthesis difficulties, slow extravasation and possible liver chronic toxicity due to slow metabolism. Therefore, more research and clinical studies are required to evaluate the polymeric micelles pharmacokinetic and pharmacodynamics.

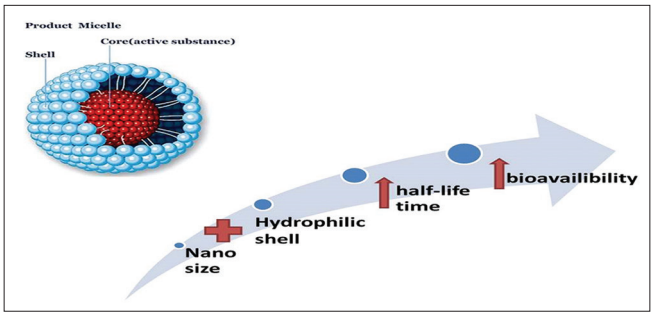

Figure 3: In conclusion, the polymeric micelle increases the solubility of hydrophobic drug by its nanosize and hydrophilic shell outside. In addition, it will increase drug half-life time since it is able to evade scavenging system in blood circulation system; therefore, it might increases oral bioavailability of hydrophobic drugs

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