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Polymeric micelle improves the bioavailability of low water-soluble phytochemicals

Noora Kadhim Hadi Alyasari[1] Anwar Jasib almzaiel[2]
[1]Department of Soil Science and water resources, College of Agriculture, University of Al-Qadisiyah, Diwaniyah, Iraq. Email: noora.alyasari@qu.edu.iq
[2] Department of Biochemistry, College of Medicine, University of Al-Qadisiyah, Diwaniyah, Iraq.

Abstract

Nanocarriers serve a crucial function in improving the delivery of insoluble and poorly penetrating drugs. Inorganic, lipidic, peptide-based, or virus-like nanocarriers and polymeric nanoparticles are categories of nanoscale materials. In this article, we emphasized on polymeric nanosystems, with micelles as the primary focus. These compounds improve the solubilization, stability, and bioavailability of hydrophobic drugs. Natural or synthetic polymers are utilized to construct polymeric nano-systems. Polymeric Micelles are often composed of amphiphilic di- or tri-block copolymers that contain both hydrophilic and hydrophobic components. They have the ability to self-aggregate. Below a critical micellar concentration, also known as CMC, these polymers persist in solution as free molecules; however, as they exceed CMC, they start to self-assemble into micelles with a hydrophilic shell enclosing a lipophilic core. Shape, size, thermodynamic and kinetic stability, surface qualities, and the capacity to internalize cells are all areas in which they excel. Pluronic F127 is an impressive polymeric micelle used to enhance the delivery of poorly soluble drugs. It enhances the solubility, stability, bioavailability, target selectivity, and bioactivities of a number of phytochemicals, such as berberine, resveratrol, and curcumin, in aqueous settings. Pluronic F-127 is a biocompatible micelle that has shown promise as a drug delivery tool for the research and development of delivery systems for poorly water-soluble therapeutics.

Keywords: Polymeric micelle, Pluronic, nano-carrier, phytochemicals

Introduction

Nanotechnology was Initially coined in 1959 as the study and application of engineering principles to the creation of useful materials, surfaces, and devices with at least dimension on the order of 1–100 nanometers(1) and (2).Because the diameters of biologically important basic components like amino acids, carbohydrates, nucleotides, and proteins are all in the nanoscale range and the majority of biological activities occur at the nanoscale (less than 100 nm), interactions between biological systems and nanomaterials are promoted (1). It is possible to make nanomaterials that make interactions with biological tissues on a similar nanoscale easier by, for example, changing or controlling the topographical features of traditional materials to nanoscale(3).When it comes to enhancing the therapeutic efficacy of a certain medication, nanocarriers play a pivotal role in facilitating the delivery of that chemical. Nanocarriers have a wide variety of applications, but the following are among the most significant:

1- They help pharmaceutical industry create more effective medicines by increasing the solubility of hydrophobic compounds in water (4,5). They has the capacity to improve the stability of compounds that are particularly susceptible to degradation (6,7).

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3- They can permit the development of highly targeted and localized delivery systems (8).
4- They have the ability to improve permeability and cellular uptake, enhance drug retention in tissues, and protect against proteolytic enzymes as benefits of this strategy (9).
5- It is possible for an internal stimulus (biomarker, pH, or redox) or an exterior stimulus (temperature, light, radiation, or ultrasounds) to initiate and regulate the controlled release of a chemical loaded in a nan carrier (10,11).
6- The most recent use of nanotechnology is in mRNA delivery, as demonstrated by the delivery of an mRNA-based vaccination against SARS-CoV-19 using lipid nanoparticles (12). The use of nanotechnology in this context is cutting edge.
7- Nanocarriers have been the subject of intense research due to their potential as diagnostic agents (13).
More and more nanocarriers are being approved for use or are going through clinical trials(14).Depending on the material employed in their manufacture, nanoscale materials can be categorized as inorganic, lipidic, peptide-based or virus-like nanocarriers, and polymeric nanoparticles (4) . Examples of inorganic nanocarriers that can react to external stimuli are gold nano rods and gold, silver, or metal oxide nanoparticles. Lipid-based formulations such as liposomes, spherical self-assembling colloidal entities with lipid bilayers, and an aqueous center. solid lipid nanoparticles are other examples. Protein structures known as virus-like particles (VLPs) and nanoparticles (NPs) are able to mimic the appearance of wild-type viruses, but they do not possess a viral genome or the ability to cause infection. This makes them, in practice, safer candidates for vaccines(15). Polymeric nano-systems are made from either naturally occurring or synthetic polymers. there are several forms of polymeric nano-systems such as nanocapsules, micelles, and dendrimers each with its own distinct characteristics(4). Typically, polymeric nanoparticles are divided into two kinds: hollow and core shell(16). Drugs are either conjugated with the polymer prior to nanoparticle creation, as is the case with hollow nanoparticles, or they are encapsulated in the very porous polymer matrix of hollow nanoparticles. examples of hollow nanoparticles are poly lactic-co-glycolic acid (PLGA) and chitosan which are both commonly utilized as polymers(17,18). However, the drug loading capacity of these nanoparticles is low, and their nanostructures are relatively unstable. On the other hand, core-shell nanoparticles are comprised of two or more distinct polymer components forming the core and the shell. They have better physicochemical stability and decreased cytotoxicity. Silica-coated chitosan nanoparticles(19) and poly (methyl methacrylate) (PMMA) /chitosan core-shell nanoparticles (20) are examples of core-shell nanoparticles. It is possible to enhance therapeutic agent encapsulation by customizing the nanoparticle's core substance. Polymeric amphiphiles, which may be employed with both hydrophilic and hydrophobic chemicals, have recently seen a rise in popularity as core materials. Pluronic is one of the amphiphilic block copolymers that has been investigated extensively in the context of drug delivery (21).In this part, we focused on polymeric nanosystems, with micelles as the primary topic of interest and Pluronic F127 serving as an example of a notable polymeric micelle.

1-Polymeric micelles:

Approximately half of the approved active compounds have poor solubility in the physiological aqueous environment, resulting in restricted bioavailability and gastrointestinal absorption (22). In addition to being a challenge for the development of injectable and even topical formulations, poor solubility poses a problem. Since increased solubility is predictive of increased bioavailability (23,24),

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Researchers are investigating a variety of nanotechnological approaches to solubilizing drugs in an effective manner (25).One of the nano-oriented tactics studied to increase the solubilization, stability, and bioavailability of medicinal agents is the integration of hydrophobic compounds within polymeric micelles. Polymeric Micelles are usually made of amphiphilic di- or tri-block copolymers with both hydrophilic and hydrophobic parts (26). They are capable of self-aggregation. Below a critical micellar concentration, often known as CMC, these polymers exist in solution as free molecules; however, once they pass CMC, they begin to self-assemble into micelles that have a hydrophilic coating surrounding a lipophilic core (27). These self-assembled micelle structures are capable of preserving insoluble hydrophobic drugs; their structure and function mirror characteristics of biological transport systems (28). As a result, systems are formed with specific attributes relative to other nanocarriers, such as reduced size where they have a size on the nanometer scale, often less than 100 nanometers that enables passive targeting to poorly-permeable targets(27). Interestingly, polymeric micelles, which can be greater than 100 nm, are nevertheless termed micelles(29).Regarding safety, current solubilizing agents, such as polyethoxylated castor oil and polysorbate 80, are believed to be less safe than injections of polymeric micelles(30). Compared to traditional micelles, polymeric micelles dissolve more slowly even at concentrations below the CMC; as a result, they enable more extended periods of time to circulate through the blood (31). Poly (ethylene oxide) structure-containing micelles are sterically stabilized, which means they can stay in the bloodstream for a longer time without becoming opsonized and being taken up by macrophages (32). There are many different kinds of polymeric micelles, like several pluronic derivatives, that block the P-glycoprotein(PGP) at numerous places throughout the body. PGPs are implicated in the mechanisms of multidrug resistance. therefore, they can be utilized to overcome some problems of multidrug resistance(33).Due to their tiny size, ease of synthesis, and high solubility, their hydrophobic cores, are well-suited for solubilizing water-insoluble molecules, protecting unstable compounds from chemical and/or biological degradation, and for providing prolonged release in a variety of compositions. polymeric micelles are attractive carriers for loading drugs. They can increase their bioavailability, prolong circulation durations, and generate a regulated and targeted drug release, which is beneficial for decreasing adverse effects(34, 35) . They can also improve permeability and retention where the internalization within cells is improved, allowing for greater efficiency (36). The intravenous (IV) injection or infusion is the method of administration for micelles for which most study has been conducted (37, 38) Typically, chemotherapy is administered by this method. However, they can be utilized for practically all routes of administration (39). In terms of enhanced drug bioavailability, oral and topical (ocular, nasal, buccal) delivery have also produced extremely intriguing findings(40,41,and42). Polymeric micelles are adaptable, stable, safe, and relatively cost-effective nanovectors thus they are gaining popularity (43).For the first time, a micelle formulation of the chemotherapeutic drug paclitaxel has been approved by the FDA for use in the treatment of breast, ovarian, and lung malignancies (44). In 2018, the FDA gave its approval to a micellar version of cyclosporine intended for topical use in the eyes (27).The lipophilic core enhances the solubility of weakly water-soluble molecules like resveratrol and quercetin, as demonstrated in the literature(45). Whereas, the hydrophilic coating protects the encapsulated drug from the external medium, resulting in increased bioavailability and prolonged circulation (44). Among such

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micelles is the pluronic polymeric micelles which are a type of smart material that exhibits micelle-formation capabilities (46).

2-General properties of polymeric micelles:

Shape: Micelles are typically shown as spherical structures; however, it is possible to observe rod-like, worm-like, and even disk-like shapes(47)and (48). The changes in micellar shape are mostly attributable to the polymer structure and to the temperature, pH, and chemical content of the surrounding environment(49).

Size: Polymeric micelles can have a size that is greater than 100 nm while still being considered to be micelles (29). It has been demonstrated that micelles in the size range of 30 to 100 nm can readily aggregate in highly permeability tumors. The smaller the size, the greater the ability to penetrate. For example, micelles with a size of 30 nm can penetrate less permeable tumors in an efficient way, demonstrating the importance of size(29).

Thermodynamic and kinetic stability:

Micelles must have both good kinetic and thermodynamic stability (50). Therefore, numerous physicochemical approaches have been proposed to prevent the rapid disaggregation of the structure or to stabilize the substance entrapped within the micellar core. As it is general knowledge that the CMC can be decreased by increasing the length of the hydrophobic section of the unimer , this is an example of an approach that can be employed to achieve this objective (49).Other ways to improve micelle stability include Block copolymers coupled to lipid molecules. Functionalizing the hydrophobic block, and crosslinking polymer and drug to observe drug release upon bond breakdown are further techniques (51).

Interestingly, recent research on stimuli-responsive polymeric micelles can tune micelles disintegration and drug release in response to biological (pH, redox potential, enzymes) and artificial (like magnetic field, temperature change) impulses(52).

Micellar Surface properties:

Surface properties affect micelle behavior. Hydrophilic and neutral surfaces diminish interacting of serum proteins with micellar corona and increase intravenous circulation time. They also improve the micellar ability to penetrate mucus (53). However, positively charged nanocarriers are mucoadhesive, meaning that they interact favorably with epithelia(54).

It has been reported that micelles with a positive zeta potential have a very low stability in body fluid as a result of non-specific protein complex formation and an enhanced tendency to aggregate in vivo (55).

Ability to internalize cells:

A micelle is an extremely important component in the process of delivering drugs to their intended subcellular destination. Micelles often enter cells by a process known as endocytosis. This process begins when a micelle binds to the cellular membrane and continues with uptake and translocation through endosomes to the cytoplasm of the cell that is receiving it (56). Micelles have the ability to be taken into cells in their original state, but they also have the potential to release the drug outside of cells or to be carried into cells as deconstructed unimers and lysed in lysosomes (57). Producing drug accumulation in plasma membrane or cellular compartments (58). Because micelles are able to easily bypass the energy-dependent efflux pumps that are a contributing factor in drug resistance and multidrug resistance, endocytosis-mediated uptake has proven to be a viable technique for addressing these issues (59).

3-Pluronics:

Pluronics® is a brand name for a category of water-soluble nonionic triblock copolymers known as poloxamers that were first produced by BASF (60). Currently, they are utilized extensively in a multitude of fields, including

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the fabrication of nanoparticles as well as drug delivery(61).The copolymer blocks are composed of chemically different monomers (polar and non-polar) include the polyethylene oxide (PEO) monomers which are water-soluble and the polypropylene oxide (PPO) monomers which are water-insoluble. As a result, the PEO blocks are hydrophilic whereas the PPO blocks are hydrophobic; hence, the block copolymers are amphiphilic, resulting in surface-active characteristics(60). Pluronics are available in a number of forms, each of which has a unique molecular weight and ratio of hydrophobic to hydrophilic building blocks (62).BASF's nomenclature for Pluronics® consists of a letter representing the physical state (P for Paste, F for Flake, and L for Liquid), one or two digits representing the molecular weight, and a final number representing the weight of the PEO block (63).Mainly, low bioavailability and water insolubility impede the clinical use of many effective medications thus pharmaceutical biotechnology improves medication absorption and stability, therapeutic effectiveness, and bioavailability by creating optimal polymers such as the development of micellar block copolymer-drug complexes(64). PF127, also known as Poloxamer 407, is one example of tri-block amphiphilic synthetic copolymers. These copolymers are made up of a chain of PPO that is surrounded by two chains of PEO (65). It has a molecular weight of 12,600 kDa, and its PPO and PEO units come in at 65 and 200 respectively. Its critical micellar concentrations change depending on the temperature of the solvent; at 25, 30, and 35 degrees Celsius, they are respectively 0.7, 0.1, and 0.025 W/V (60). PF127 improves the pharmacokinetics and pharmacodynamics of poorly water-soluble medications by increasing their oral bioavailability and stability and circulation time (66). The capacity of F127 to dissolve hydrophobic solutes has sparked a great amount of interest in controlled-release medication administration and other application areas(67).The Food and Drug Administration has given its approval for the use of pluronic F127 as an excipient in oral, ophthalmic, and topical pharmaceutical formulations (68). It was found that pluronic F127 had an acute cutaneous toxicity in rats that was greater than 2000 mg/kg, and that its oral toxicity was larger than 15000 mg/kg (69). In mice that were given pluronic F127 via intraperitoneal injection for a period of four days at a dose of one gram per kilogram, there was no discernible difference in the mortality or morbidity rates (70). Protein excretion by the kidneys was not affected by Pluronic F127 (71). Due to its low immunogenicity and toxicity, Pluronic F-127 (PF) has been the most commonly employed member of this family of copolymers for uses in controlled release systems(72).

4-Micellization of pluronic F-127 and chemicals loading:

Micellization process of Pluronic F-127 can be begin when the concentration of PEO-PPO block copolymer in solution exceeds the critical micellization concentration (CMC) (73). Below the CMC and at room temperature, the copolymer is existing in form of unimers. Unimers are block copolymer that are not linked, as opposed to supramolecular chains (74). Reduced solubility induces microphase separation of PPO blocks from the aqueous environment into the micelle core. PEO and PPO blocks are covalently connected to a copolymer chain, allowing for the self-assembly. Two stages create micelles that are thermodynamically stable: initially, unimers rapidly combine into metastable aggregates (less than millisecond) then, after 1–100 ms, aggregates relax into thermodynamically stable micelles(75).In an aqueous solution, poloxamer micelles are generally spherical and core-shell . The micelle core is hydrophobic and composed of PPO blocks, while the corona is hydrated PEO(76).Self-assembly of pluronic copolymer is promoted by solubility; hence, solvent type and temperature as well as e, presence of

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additives influence system features (77).Differential scanning calorimetry, static and dynamic light scattering, small-angle neutron scattering, and surface tension measurements are among of the methods utilized to analyze the micellization behavior of pluronic solutions(78).In order for hydrophobic drug molecules to become encapsulated in hydrophobic PPO cores, it is necessary to raise the temperature of the reaction and combine hydrophobic drug molecules with the quantities needed for pluronic molecules. The nontoxic hydrated PEO coronas prevent the loaded substance from being removed from the core of the micelles. enabling Hydrophobic medicines to be more soluble in water, increasing their bioavailability(79).The passive accumulation of pharmaceuticals loaded in Pluronic micelles is more effective than the free drugs .This is due to the prolonged circulation duration and progressive dissociation of drug-encapsulated micelles in the blood (80). Pluronic F127 micelles can facilitate the transport of drugs through the blood-brain and intestinal barriers (77). The pharmacological properties of pluronic F127 micelles make them an important drug carrier improving their pharmacokinetics and pharmacodynamics (81).

5-Pluronic F127 improves delivery of low soluble phytochemicals:

Because of their poor water solubility, low lipophilicity, unsuitable molecular size, structural instability in the biological environment, rapid clearance, and high metabolic rate, natural products present significant difficulties when applied to therapeutic settings. In addition, some natural products are inactivated by gastric contents or undergo substantial first-pass action and pre-systemic metabolism in the liver after oral administration before they reach the systemic circulation. Moreover, Reduced bioavailability is also linked to the accumulation of some natural products in non-targeted tissues, which raises undesired side effects and severely diminishes therapeutic efficacy (44).Pluronic F127 is frequently utilized because of its ability to increase natural products solubility and stability, it improves their therapeutic bioavailability as well as distribution. Resveratrol is a plant-based phytoalexin with significant biological action, however, it is insoluble in water, reducing its therapeutic use. Emulsion synthesis created stably loaded nanoparticles from Pluronic F127 block copolymer and D-alpha-tocopheryl polyethylene glycol 1000 succinate (Vitamin E-TPGS). Forming a highly soluble formulation. The formed nanoparticle successfully targeted aggressive breast cancer cell lines and reduced cell viability (82). In addition, Pluronic F127 micelles were developed to incorporate resveratrol. Its ability to kill bacteria was tested on E. coli, S. aureus, and Candida albicans. The cytotoxicity was tested on a bladder cancer cell line. The results showed that pluronic f127 micellar nanostructures significantly improve resveratrol's cytotoxic and antibacterial properties of resveratrol (83). The loading of curcumin into Pluronic F127 micelles led to improvements in the solubility, stability, permeability, and controllability of curcumin's release (84).The use of Pluronic F127 to encapsulate quercetin, a phytochemical with limited water solubility, increased quercetin's solubility behavior in simulated stomach and intestinal fluids (85). Also, the pluronic f127 encapsulated quercetin was effective in suppressing congenital cytomegalovirus, the most common virus responsible for birth defects(86). It is important to note that the concurrent treatment of both resveratrol and quercetin loaded in pluronic f127 provides a promising method to attenuate acute cardiotoxicity generated by doxorubicin in cardiomyocytes. On the other hand, co-delivery of resveratrol and curcumin included in pluronic F127 micelles also gives considerable effects in lowering the cardiotoxicity generated by doxorubicin in vitro. Interesting,

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combinations of resveratrol and quercetin or curcumin in pluronic F127 micellar not only reduce the cardiotoxicity caused by doxorubicin but also proved to be chemo-sensitizing combinations (87). Moreover, an increase in oral bioavailability of the genistein, poorly water-soluble phytoestrogen, was observed in rats when the chemical was provided as a loaded substance within Pluronic F127 micelles(88).

Conclusion: Collectively, encapsulating bioactive compounds, such as phytochemicals, can be done effectively with the use of the nano-carrier polymer known as pluronic F-127. It improves the solubility of several phytochemicals in aqueous environments, as well as their stability, bioavailability, target selectivity, and bioactivities. The Pluronic F-127 micelle is an interesting candidate for use as a medication delivery tool in the research and development of delivery systems for less soluble phytochemicals.

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