Review Article

Soluplus-based Polymeric Micelles: A Promising Carrier System for Challenging Drugs

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ABSTRACT

Formulating stable formulations for poorly soluble drugs, particularly those classified as BCS type II and IV presents a significant challenge for scientists and researchers. Among various technological solutions, the inclusion of drug molecules within polymeric micelles, especially polymeric micelles, has emerged as a promising strategy in recent years. Polymeric micelles are nanoscopic core/shell structures created by amphiphilic block copolymers. Their inherent and modifiable properties make them particularly well-suited for drug delivery purposes. Recently, our interest has been drawn to Soluplus®, an amphiphilic polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer known for forming small and stable formulations. This review explores the potential of using Soluplus-based polymeric micelles to enhance the absorption of poorly water-soluble drugs. Through a review of representative literature, the basics of Soluplus-based polymeric micelles are examined. The studies highlighted demonstrate that these polymeric micelles can reduce toxicities, improve delivery to targeted biological sites, and enhance the therapeutic efficacy of active pharmaceutical ingredients. Moreover, the versatility and stability of Soluplus-based micelles make them a highly attractive option for improving drug solubility and bioavailability in pharmaceutical applications.

Keywords: Micelles, Soluplus, Nanonization, Solubility, Bioavailability.

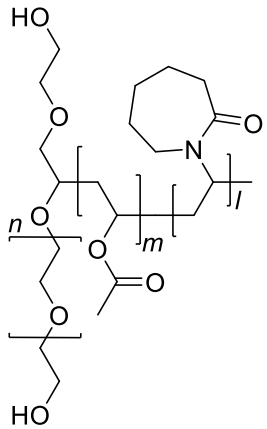
INTRODUCTION

In the pharmaceutical industry, poorly aqueous soluble drug entities often have low bioavailability and inconsistent absorption patterns which pose a significant challenge in developing the desired formulation.[1] The restricted solubility may prevent the intended pharmacological activity from reaching its intended concentration.[2] Numerous approaches to overcome the poor aqueous solubility of drug candidates have been investigated in the research and development of formulations. Examples of these strategies are using pro-drug approaches, in which a polar functional group is inserted into the structure of the drug, and modifying the chemical structure of a drug candidate during the lead optimization process. The most reliable procedure is to increase the rate of dissolution of these poorly water-soluble drug entities, particularly for BCS classes II and IV drugs.[3,4] Upto 50% of all approved medications fall under classes II and IV. Increasing the solubility of compounds in classes II and IV is the primary objective of formulation development.[5,6] The solubility question relates to various therapeutic techniques, including injections, ocular drops, buccal and intranasal solutions, and generally any system that needs stable aqueous formulations. Drug modifications like polymorphs, salts, and co-crystals are sometimes utilized to make these compounds more soluble.[7] The creation of solid dispersions and complexation are two further suggested tactics. Among these, creating micelles with macromolecules that self-assemble into organized structures capable of housing hydrophobic drug molecules in the interior domain is a legitimate method to increase the solubility of APIs. This results in a greater apparent solubility in aqueous fluids.[8,9] Polymeric micelles are gaining significant attention due to their technological attributes: they are highly biocompatible, have straightforward preparation methods that include easy industrial scalability, and can effectively encapsulate poorly soluble and lipophilic compounds, delivering them in the body with a targeting potential.[10,11] A particular class of micelles known as polymeric micelles is made up of copolymers (block copolymers) that contain monomer units that are both hydrophilic and hydrophobic. In aqueous media, the hydrophilic portion forms the corona, or shell, and the hydrophobic portion forms the core.[12] The therapeutic cargo is protected by the shell, which also stops the micelles from aggregating and precipitating. Small molecules that are weakly soluble are solubilized and the micelle is held together by the core.[13] Polymeric micelles can be further classified into four classes: (1) graft copolymers (hydrophilic-hydrophobic), (2) tri-block copolymers (hydrophilic-hydrophobic-hydrophilic), and (3) ionic copolymers (hydrophilic-ionic). The hydrophilic portion of diblock copolymers is typically composed of poly(ethylene glycol) (PEG), which is extremely biocompatible. The hydrophobic portion is more frequently composed of polylactides (PLA), poly(ε-caprolactone), and poly (D, L-lactic-co-glycolic acid), all of which have been given FDA approval for use in human biomedical applications.[14] Despite the numerous advantages of micelles, there have also been significant drawbacks, as seen by the small number of micellar products undergoing clinical testing and even fewer offered for sale.[15] The four primary mechanisms by which polymeric micelles improve drug absorption are: (1) shielding the loaded drug from the harsh GI tract

environment; (2) releasing the loaded drug under controlled conditions at specific sites; (3) prolonging the drug's residence time in the gut through mucoadhesion; and (4) blocking efflux pumps to enhance drug accumulation.[16] High quantities of surfactants, such as Cremophor EL, have been linked to serious neurotoxicity and hematological adverse effects. Tween 80 has a greater critical micelle concentration than micelles, hence after a substantial dilution in various anatomical sites, they no longer stay as stable. More micelle-forming compounds that can create stable micelles with sufficient drug-loading capacity and little toxicity are still being sought.[17]

Among all its applications, Soluplus® has been suggested as a secure and adaptable substance for synthesizing micelles in the pharmaceutical industry, either by itself or in conjunction with other polymers.[18] Soluplus is a novel amphiphilic polymeric solubilizer that has been extensively explored recently. Soluplus (SP) is a polyethylene glycol (PEG), polyvinyl caprolactam, and polyvinyl acetate graft copolymer (13% PEG 6000, 57% vinyl caprolactam, and 30% vinyl acetate). It has a PEG 6000 backbone with one or two vinyl acetate sidechains co-polymerized with vinyl caprolactam at random Soluplus molecules include hydrophilic and hydrophobic chains, allowing them to form micelles in aqueous solution even at deficient concentrations. This can significantly increase the solubility of medications that are not very water-soluble. Because of its hydrophobic chains, Soluplus is a viable option for supersaturated solutions and an efficient precipitation inhibitor.[19,20] Its bifunctional nature allows it to act as a matrix polymer for solid solutions on the one hand, and to solubilize poorly soluble drugs in aqueous media on the other. Soluplus has several advantages. Outstanding solubilization properties, particularly for poorly soluble APIs, allow bioavailability enhancement, ideal for hot melt extrusion and all standard granulation techniques, Market tested solutions for specific formulation challenges. The technical detail of soluplus is given in Table 1.

Table 1: Technical details of soluplus

Synonym	Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer
Appearance	white to slightly yellowish granule
Odor	Faint characteristic
Molecular formula	$(C_8H_{13}NO, C_4H_6O_2, C_2H_4O)_x$
Molecular structure	
Molecular weight	90 000 – 140 000 g/mol
Solubility	Purely soluble in water, and also showsolubility in ethanol and dimethylformamide (50%), methanol (45%), ethanol (25%)
Density	1.082 g/cm³
Functions	Bioavailability enhancer, Film former, matrices & fillers, solubility enhancer, surfactant

1. SOLUPLUS-BASED POLYMERIC MICELLES

Soluplus has been shown to improve the solubility and bioavailability of a variety of water-insoluble compounds, including itraconazole, osthole, fenofibrate, and sorafenib[21], and a schematic representation of the formation of micelles solubilising a poorly soluble active pharmaceutical ingredient (API) is shown below in Figure 1. Table 2 presents a compilation of research studies focusing on formulations of polymeric micelles that integrate soluplus. The following paragraph provides descriptions of these studies.

Researchers characterized soluplus® nanomicelles to enhance the apparent solubility of ibuprofen (IBU), idebenone (IDE), and miconazole (MIC). Nanomicelles were prepared using two methods *i.e*. direct dissolution or film hydration method and were found to be around 60–70 nm mean size. The solubility of the tested APIs was shown to increase linearly with the concentration of graft copolymer. The studies indicated that these nano micelles have potential applications where a bioadhesive material is advantageous, such as topical ocular administration.[5]

Table 2: Various polymeric micelles incorporating soluplus

Drug	Route	Method of preparation	Inferences	Ref
Ibuprofen (IBU), idebenone (IDE), and miconazole (MIC)	Topical- ocular administration	Direct dissolution or film hydration method	Enhanced solubility	5
Lornoxicam	Oral	Thin film hydration method	Enhanced solubility	15
Silybin	Oral	Solvent shift method	Enhanced bioavailability	19
Ibuprofen	-	Hot-melt extrusion coupled hydration method	Enhanced solubility and bioavailability	22
Tamoxifen	Oral	-	The formulation is effective for cancer drug delivery	23
Paclitaxel	-	-	The formulation is effective in clinical nanoformulations	24
Curcumin	-	Spray drying	The formulation showed better release profiles than traditional hydrophobic adsorbents	25
Fenbendazole	IV route	Freeze-drying method	Superior bioavailability was achieved	26
Icaritin	Oral	Acid-base shift method	It showed oral bioavailability of icaritin	27
Docetaxel and piperine	-	-	The formulation could be a promising strategy for the treatment of liver cancer	28
Usnic acid	-	Freeze drying process	The formulation showed inhibitory action on neuroblastoma cell migration	29
Acetaminophen	Oral	-	The study showed enhanced biological activity for protection and therapeutic of liver injury	30
Scopoletin	Oral	-	The formulation represents a potential oral strategy for the treatment of hyperuricemia	31
Thymoquinone	-	-	The formulation is effective in inhibiting human SH-SY5Y neuroblastoma cell migration.	32
Quercetin	-	-	The polymeric mixed micelle (PMMs) enhanced the therapeutic effect of quercetin and could be considered an effective therapeutic strategy to treat Glioma.	33
Nobiletin	Oral	Hot melt extrusion technology	The formulation is a promising hepatoprotective nano-drug delivery system for acute liver injury with superior bioavailability	34
Thymoquinone	Oral and parenteral administration	-	The carrier enhances the permeability of thymoquinone in the intestine	35
Meloxicam	Nasal administration	-	The formed polymeric micelle formulation provides higher meloxicam transport to the central nervous system	36
Mannose-coated rifampicin-curcumin	Nasal administration	-	The prepared formulation is potential for active drug delivery in pulmonary tuberculosis therapy	37
Glycyrrhizic acid	Oral	Thin-film hydration method	The formulation showed improved bioavailability, anti-hyperuricemic activity, and anti-inflammation	38
Paclitaxel	-	Solvent-diffusion technique	The formulation is a potential approach for nano-drug delivery systems for cancer chemotherapy	39
Betulinic acid	-	Thin film- hydration method	The formulation is effective for anti-breast cancer drug delivery system	40
Tamoxifen citrate	Oral	-	The formulation enhanced tamoxifen bioavailability and tolerability associated with dose reduction and decreased side effects	41

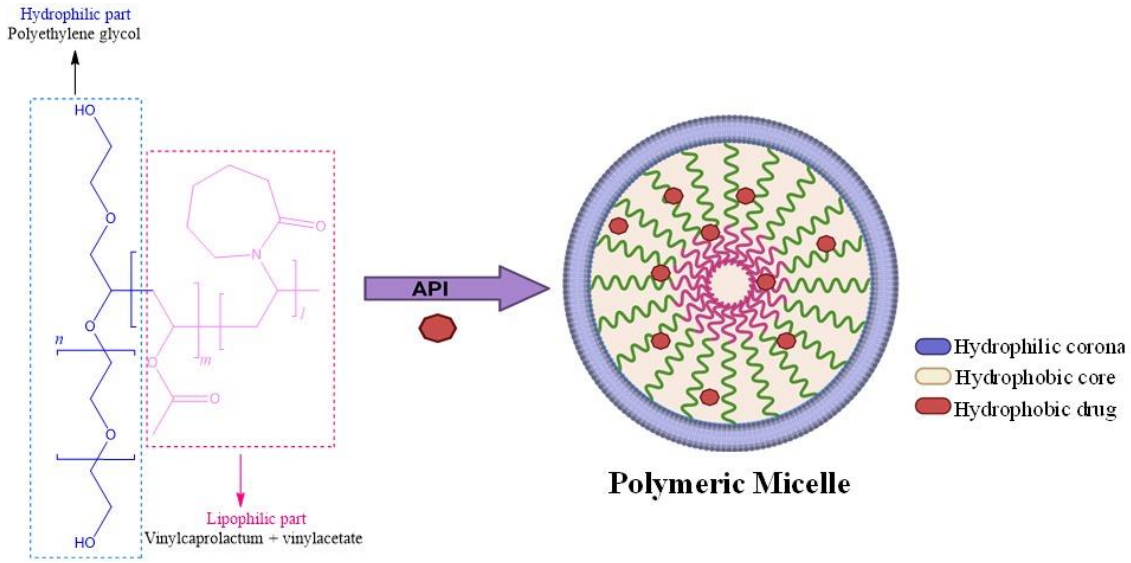


Figure 1: Schematic representation of the preparation of polymeric micelles

In another study, researchers investigated the potential of soluplus to form lornoxicam (LNX) loaded micelles and its ability to improve solubility and therapeutic efficacy using the thin film hydration method. Soluplus has demonstrated the capability to create stable micellar systems, showing promising potential for enhancing the solubility of LNX, a BCS class II drug. In vivo studies in rats have indicated improved therapeutic efficacy and reduced adverse effects as a result.[15]

Researchers reported on a complex system involving Soluplus and Copovidone (Soluplus-PVPVA) loaded with silybin (SLB), a model drug. This system maintained the stability of a supersaturated solution and effectively enhanced oral absorption. A pharmacokinetic study conducted in rats demonstrated the advantages of the Soluplus-PVPVA complex. The findings revealed that PVPVA adsorbed onto the hydrophilic-hydrophobic interface of Soluplus micelles, spontaneously forming complexes in aqueous solution. Importantly, the Soluplus-PVPVA complex significantly improved the absorption of SLB. In conclusion, the Soluplus-PVPVA complex represents a promising strategy for enhancing the bioavailability of hydrophobic drugs.[19] Investigators developed and assessed various polymeric mixed micelles using a hot-melt extrusion coupled hydration method to enhance the solubility and prolong the release of ibuprofen. The physicochemical characteristics of the prepared formulations were evaluated, including particle size, polydispersity index, zeta potential, surface morphology, crystallinity, encapsulation efficiency, drug content, in vitro drug release, dilution stability, and storage stability. The formulation exhibited average particle sizes of 86.2 ± 2.8 nm, 89.6 ± 4.2 nm, and 102.5 ± 3.13 nm, respectively, with encapsulation efficiencies ranging from 80% to 92%. *In vitro* release studies exhibited extended-release characteristics compared to the free drug. Furthermore, the developed polymeric mixed micelles-maintained stability upon dilution and storage for one month. The findings suggested that this could be a promising, efficient, and environmentally friendly approach for scaling up the production of polymeric mixed micelles for delivering poorly soluble drugs.[22] A dual stimuli-responsive nanocarrier was created using biocompatible chitosan and soluplus graft copolymers. These optimized chitosan-soluplus nanoparticles (CS-SP NPs) were used to encapsulate tamoxifen citrate (TC), a poorly water-soluble anticancer drug. The nanoparticles increased in size upon reaching the soluplus lower critical solution temperature and released 70% of the drug at acidic pH and 40°C within the first hour. They also showed a 3.5-fold increase in cytotoxicity against MCF7 cells at 40°C. Cellular uptake studies indicated successful drug delivery to MCF7 and MDA-MB-231 cells. Overall, these CS-SP NPs offer a promising platform for effective cancer drug delivery.[23] Researchers developed a scalable, size-tunable paclitaxel polymeric micelle formulation using Soluplus and a microfluidic platform. By adjusting the drug-to-polymer ratio, they created micelles of approximately 90 nm and 180 nm. The smaller micelles demonstrated superior encapsulation efficiency, controlled drug release, and increased cytotoxicity in both 2D and 3D models. Cellular uptake studies showed higher internalization for the smaller micelles. In 3D spheroids, the smaller micelles achieved nearly complete penetration within 24 hours, while the larger micelles had minimal penetration. This method shows potential for developing effective clinical nanoformulations.[24] In another study, researchers aimed to enhance the oral delivery of poorly water-soluble drugs using self-assembled hybrid nanoparticles (SHNPs) of sodium taurocholate (STC) and Soluplus. Felodipine (FLDP) was used as a model drug. Results indicated that STC and Soluplus formed SHNPs through hydrophobic interactions. FLDP permeability in the ileum was dependent on STC and was inhibited by higher STC concentrations and an ASBT inhibitor. STC/Soluplus (1:9) SHNPs significantly improved FLDP drug loading, achieved the highest permeability, and increased the area under the curve (AUC) by 1.6 times compared to Soluplus SNPs. Therefore, STC/Soluplus

SHNPs via ASBT offer a promising strategy to improve the oral bioavailability of poorly water-soluble drugs.[25] Researchers designed and developed low-toxicity Soluplus® polymeric micelles encapsulating Fenbendazole and conducted both *in vitro* and *in vivo* toxicity assays. These FEN-loaded Soluplus® micelles had nano size having a zeta potential of -2.3 mV, a drug loading of 0.8 %, and an encapsulation efficiency of 85.3 ± 2.9%. Pharmacokinetic studies indicated that the micelles had lower total clearance, lower volume of distribution, higher area under the curve, and higher plasma concentration at time zero compared to the FEN solution. The *in vivo* toxicity assay demonstrated that FEN-loaded Soluplus® micelles did not cause severe toxicity.[26] One more study aimed to enhance the oral bioavailability of icaritin by developing mixed polymeric micelles with high drug loading capacity using Soluplus® and Poloxamer 407, employing an innovative acid-base shift (ABS) method. The resulting IPMs were spherical, with an average size of 72.74 ± 0.51 nm and a drug loading content of 13.18%. *In vitro* release tests demonstrated that icaritin was released more rapidly from IPMs compared to an oil suspension. These findings suggest that the mixed micelles of Soluplus® and Poloxamer 407 could effectively improve the oral bioavailability of icaritin. Additionally, the ABS method shows promise for preparing polymeric micelles to encapsulate poorly water-soluble weakly acidic, and alkaline drugs.[27] The study developed mixed micelles using Soluplus® and TPGS for the co-administration of docetaxel (DTX) and piperine (PIP), aiming to enhance synergistic effects, increase cytotoxicity, and improve anti-cancer activity in HepG2 cell lines compared to free DTX. In vitro (MTT assay, intracellular uptake) and in vivo (pharmacokinetic study, immunostaining, TUNEL analysis) studies demonstrated the benefits of co-delivering anticancer drugs with Soluplus®/TPGS mixed micelles. The findings suggest that co-delivery of DTX and PIP via these mixed micelles is a promising approach for liver cancer treatment.[28] Soluplus, Solutol HS15, and D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) were used to create polymeric micelles (UA-PM). This study shows that these polymeric micelles are highly effective in inhibiting neuroblastoma cell migration.[29] PTE-loaded Soluplus/Poloxamer 188 mixed micelles (PTE-MMs) were prepared and their protective mechanism against APAP-induced liver injury was examined. The results indicated that PTE-MMs effectively mitigated APAP-induced acute liver injury. In summary, this study demonstrates that the Soluplus/Poloxamer 188 MM system can enhance the therapeutic and protective effects of PTE against liver injury.[30] Researchers aimed to compare the biodistribution and antihyperuricemic efficacy of Sco and Sco-Ms, as well as to investigate their therapeutic mechanisms. The findings suggest that Sco-Ms could be a promising oral treatment strategy for hyperuricemia.[31] Soluplus® and Solutol® HS15 were used as amphiphilic polymers to create polymeric micelles (SSM). The formulation of TQ into SSM enhances its anti-migration activity, indicating that TQ-SSM is more effective than unformulated TQ in inhibiting the migration of human SH-SY5Y neuroblastoma cells.[32] This study evaluates quercetin-loaded polymeric mixed micelles (Qu-PMMs) against C6 and U87MG glioma cell lines. Qu-PMMs exhibited superior cellular uptake, inhibited migration, and induced apoptosis in C6 and U87MG cells compared to pure quercetin. Therefore, Qu-PMMs enhance the therapeutic efficacy of quercetin and represent a promising treatment strategy for glioma.[33] The optimized NOB/SD system was developed using Soluplus and PVP/VA 64 amphiphilic copolymers via hot melt extrusion technology (HME). This study indicates that NOB/SD holds promise as a nano-drug delivery system for hepatoprotection, effectively mitigating APAP-induced acute liver injury with improved bioavailability and efficient hepatoprotective effects. This approach offers a potential strategy for both preventing and treating APAP-induced acute liver injury.[34] Soluplus® and Solutol® HS15 polymeric micelles (TQ-MP) were developed to enhance the permeability of TQ, targeting both the intestinal and blood-brain barriers for potential oral and parenteral administration. Toxicity was assessed using three lines of Zebrafish: wild type, a transgenic line Tg(Myl7) where cardiomyocytes are marked with green fluorescent protein, and Tg(flk1-GFP) which expresses GFP controlled by the vascular endothelial growth factor receptor 2 (vegfr2) promoter.[35] Scientists explored the nasal applicability of a previously developed polymeric micelle formulation of Soluplus® and meloxicam. Our findings indicate that this formulation enhances meloxicam transport to the central nervous system, leading to a slow elimination compared to traditional physical particle size reduction methods. Based on these results, we propose this nanocarrier as a promising solution for effectively transporting acidic non-steroidal anti-inflammatory drugs to the brain.[36] Researchers developed a mannose-decorated micellar nanoformulation using Soluplus® to co-encapsulate rifampicin and curcumin. The inclusion of mannose resulted in a significant 5.2- fold enhancement in microbicidal efficacy against *Mycobacterium tuberculosis* H37Rv compared to micelles without mannose. This innovative inhaled nanoformulation shows promise for delivering drugs actively in the treatment of pulmonary tuberculosis.[37] Researchers developed an enhanced drug delivery system using Soluplus® (a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) and glycyrrhizic acid to enhance the solubility, bioavailability, and anti-hyperuricemic activity of aloe emodin (AE). AE-loaded mixed micelles (AE-M) were prepared using the thin-film hydration method. The AE-M showed potential in improving the bioavailability, anti-hyperuricemic activity, and anti-inflammatory effects of AE.[38] Researchers designed and characterized novel nanomicellar polymeric formulations using the biocompatible copolymer Soluplus® (S), surface-decorated with glucose (GS), and co-loaded with either histamine (HA, 5 mg/mL) and/or PTX (4 mg/mL). Our findings indicate that all loaded micellar systems effectively reduced tumor volume, while both HA and HA-PTX-loaded SG micelles significantly decreased tumor weight and neovascularization compared to empty

micelles. These results suggest that HA-PTX co-loaded micelles, along with HA-loaded formulations, show promising potential as nano-drug delivery systems for cancer chemotherapy.[39] To enhance the anticancer efficacy of betulinic acid (BA), researchers developed micelles encapsulating BA using a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (PVCL-PVA-PEG) graft copolymer (Soluplus) (Soluplus-BA). Our in vivo study confirmed that Soluplus-BA significantly improved the anti-tumor effect and inhibited angiogenesis, suggesting that Soluplus-BA could serve as a potent drug delivery system for treating breast cancer effectively.[40] In this study, poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) triblock copolymer, FDA-approved for oral use, was utilized for its micellar solubilization properties. Self-assembled micelles were prepared to deliver tamoxifen (TMX), enhancing TMX solubility by approximately 60 times. The encapsulation of TMX in PEG-PPG-PEG micelles significantly improved cellular uptake, increasing cytotoxicity in MCF-7 cancer cells. A tablet formulation containing lyophilized TMX-loaded micelles exhibited better dissolution compared to the commercial TMX tablet (Tamoxifen® TEVA). These findings suggest that the enhanced drug dissolution rate and increased cytotoxicity to tumor cells will likely improve TMX bioavailability and tolerability, allowing for dose reduction and fewer side effects.[41]

2. FORMULATION DESIGNS OF POLYMERIC MICELLES

In the formulation of polymeric micellar delivery systems, the design is crucial. Micelle-forming polymer-drug conjugates, polymeric micellar nano-containers, and polyion complex micelles are three different types of polymeric micellar carriers that have been studied for drug delivery.[42]

a) **Micelle-forming polymer-drug conjugates:** The integration and stabilization of the drug enclosed in the micellar carrier are achieved in this design by forming hydrolyzable chemical bonds between the polymeric backbone's functional group(s) and the drug. Polyethylene oxide is used to make a variety of micelle-forming drug conjugates. Several studies have been conducted on -b-polyester and poly(ethylene oxide)-b-poly(amino acid) block copolymers.[43] Covalent bonds are formed between the activated terminal hydroxyl group of the poly(ester) segment and reactive groups on the drug molecule during drug conjugation to polyethylene oxide-b-polyesters.[44] The poly amino acid block has several benefits over the polyester block regarding drug conjugation. To begin with, the poly amino acid segments support many functional groups, allowing a variety of drug molecules to be conjugated to a polymeric chain. This may result in a lower dose of the polymeric drug being administered. Instead, the poly amino acid chain's diversity of functional groups (hydroxyl, amino, and carboxyl groups) allows for the conjugation of various chemical entities to the polymeric backbone.[45]

b) **Polymeric micellar nano-containers:** The formation of hydrophobic interactions or hydrogen bonds between the micelle-forming block copolymer and the drug provides the foundation for drug stabilization and solubilization in the polymeric micelles in this design. Direct addition and incubation of the drug with block copolymers in an aqueous environment will produce polymeric micellar nano-containers, but only if the block copolymer and the drug are both water-soluble.[46] Although inefficient in terms of drug loading speeds, the method is not feasible for most block copolymer/drug structures. On the other hand, the physical integration of drugs into polymeric micelles is normally accomplished using one of the following encapsulation methods.[47]

c) **Dialysis method:** Dialysis entails dissolving the drug and blocking copolymer in a water-miscible organic solvent, then dialysis against water. The self-association of block copolymers and the entrapment of drugs in the assembled structures are triggered by the slow replacement of organic solvent with water in this process. The semi-permeable membrane maintains the micelles in the dialysis bag thus allowing unloaded free drug to be removed from polymeric micelles.[48] This method has been commonly used in clinical settings to prepare polymeric micellar formulations, but it may not be suitable for large-scale manufacturing. Another disadvantage of this approach is that the free drug is not fully removed from the polymeric micellar formulation.[49]

(i) **Oil/water emulsion method:** The oil/water (o/w) emulsion process involves dissolving the substance in a water-insoluble organic solvent (such as chloroform or methylene chloride), then vigorously stirring the organic phase into the aqueous phase. In either an organic or aqueous form, the polymer may be dissolved. Evaporation is used to extract the organic solvent.[50]

(ii) **Solvent evaporation method:** The solvent evaporation method involves dissolving the drug and polymer in a volatile organic solvent and allowing the organic solvent to evaporate fully, resulting in the creation of a polymer/drug film. After intense shaking, the film is reconstituted in an aqueous process. While the solvent evaporation method of drug loading has scale-up advantages over dialysis, it can only be used for micelle-forming block copolymers with high hydrophilic lipophilic balance values and polymer films that can be easily reconstituted in aqueous media.[51]

(iii) **Freeze-drying method:** A freeze-dryable organic solvent such as tert-butanol is used to dissolve the polymer and medication. After that, the solution is mixed with water, freeze-dried, and reconstituted with isotonic aqueous media. While this method is pharmaceutically feasible for large-

scale manufacturing, it is limited to block copolymers and drug structures that can be dissolved in *tert*-butanol. This method cannot be used for PEO-containing block copolymers due to PEO's insolubility in *tert*-butanol.[52]

(iv) Polyion complex micelles: Polymeric micelles are formed by electrostatic interactions between two oppositely charged moieties, such as polyelectrolytes. When oppositely charged polymers are mixed with water, they can join the micelle's corona and form polyionic micelles.[53] Polyion complex micelles are the name given to such micelles (PICMs). The structure and size of the charged micelle coronas are regulated by electrostatic forces and the vander Waals force of interaction. PICMs have a number of unique characteristics, including a simple synthetic path, easy self-assembly in aqueous medium, structural stability, high drug loading capability, and prolonged blood circulation.[54] Micelles are prepared in an aqueous medium without the use of any organic solvents, which eliminates the related side effects caused by residual organic solvents. Via electrostatic, hydrophobic, hydrogen bonding interactions, the centre of the PICMs will entrap and release a variety of therapeutic agents, including hydrophobic compounds, hydrophilic compounds, metal complexes, and charged macromolecules. Because of these factors, PICMs have a lot of potential for drug delivery, particularly when it comes to charged drugs.[55]

(v) Drug releasefrom polymeric micelles: Drugs must be released slowly from polymeric micelles for drug targeting. Dose dumping, or the rapid release of drugs from polymeric micelles, may result in the precipitation of hydrophobic drugs in the vascular system. In addition, there isn't enough time for polymeric micelles to accumulate at target sites.[56] Slow drug release from polymeric micelles, or the depot effect, on the other hand, allows for polymeric micelle aggregation at target sites with limited drug loss and localized drug release. Chemically conjugated polymeric micelles are believed to be affected in this way. Polymeric micelles are ideal for achieving controlled drug rates. For doxorubicin, the value of slow drug release from long-circulating liposomes was discussed.[57]

3. CHARACTERIZATION OFPOLYMERIC MICELLES

1. **Critical micelle concentration:** Amphiphilic polymers may form micelles in aqueous media at concentrations greater than Critical micelle concentration (CMC), but when diluted below this concentration, the micelles can collapse. As a result, CMC is an important factor in the formation and static stability of polymeric micelles. Surface tension tests, chromatography, light scattering, small angle neutron scattering, small angle X-ray scattering, differential scanning calorimetry, and the use of fluorescent probes are some of the techniques used to determine CMC in aqueous dispersions of micelles.[58] CMC is calculated from plots of surface tension as a function of the logarithm of the concentration for practical purposes. The CMC is said to have been reached when the surface tension stops decreasing and reaches a plateau. For estimating CMC, the majority of researchers have relied on the use of pyrene as a fluorescent probe.[59]

2. **Size and shape determination:**By analysing the micellar solution with a quasielastic light scattering technique after the micelles have been prepared, useful information about the polydispersity index of the prepared structures can be obtained. In contrast to the white colour shown by aggregates, monodisperse micelles emit blue colour from light scattering, indicating good micellar preparation.[60] Polymeric micelles are normally in the colloidal range in size. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques have been commonly used for determining the size and shape of block copolymer micelles for many years. Cryo-TEM, a relatively new technique for characterization of block copolymer micelles in aqueous medium, is becoming increasingly common.[55,61] When chemically attached micelles to surfaces are exposed to SEM or atomic force microscopy (AFM), knowledge about size distribution is revealed. AFM allows for direct visualisation of block copolymer micelles in the dried state or directly "in situ" inside a liquid cell.[62] Photon correlation spectroscopy is used to assess the hydrodynamic diameters and polydispersity indices of micelles. Recently, asymmetrical flow field-flow fractionation was used to characterise the size of drug-loaded polymeric micelles, and small angle neutron scattering was used to determine the structure of assemblies.[63]

3. ***In vitro* drug release behaviour:** Placing the micellar solution in a dialysis tube allows researchers to study in-vitro drug release behaviour from micelles. The dialysis bag is submerged in a flask of release medium, which is held at a constant temperature. Aliquots of the release medium are taken and replaced with fresh medium at fixed time intervals. Spectroscopic or other appropriate methods may be used to determine the amount of drug released in the medium.[64]

4. APPLICATIONS OF POLYMERIC MICELLES

Polymeric micelles have several uses. Anticancer drug delivery, stimuli-responsive nanocarriers for drug and gene delivery, and immunomicelles, which are made by covalently attaching monoclonal antibody molecules to a surfactant or polymeric micelles, all demonstrate high binding specificity and target capacity.[65]

1. **Chemotherapy of cancer:** Four main related methods were used to improve chemotherapy of tumours using polymer micelles: 1) passive targeting of polymer micelles to tumours due to the EPR effect; 2) targeting of polymer micelles to particular antigens overexpressed on the surface of tumour cells; 3) enhanced drug release at low pH tumour sites; and 4) sensitization of drug-resistant tumours using block copolymers.[66]
2. **Drug delivery to brain:** The blood brain barrier (BBB) provides a troubling impediment to the treatment of neurodegenerative diseases such as HIV-associated dementia, stroke, Parkinson's and Alzheimer's diseases, and brain tumours by reducing drug transport to the brain. To improve the delivery of biologically active agents to the brain, two scenarios using polymer micelles were tested. The first scenario involves modifying polymer micelles with ligand molecules or antibodies capable of transcytosis through the blood-brain barrier's endothelial cells in brain microvessels. In the second example, Pluronic block copolymers are used to inhibit drug efflux systems, specifically P-glycoprotein, and increase BBB permeability to P-glycoprotein substrates selectively.[67,68]
3. **Formulations of Antifungal Agents**: The demand for safe and efficient chemotherapeutic delivery modalities to treat systemic fungal infections in immunocompromised patients with Acquired Immune Deficiency Syndrome, surgery, transplant, and cancer patients is extremely high. Low solubility and, in some cases, high toxicity of antifungal agents are barriers to their delivery. Amphotericin B, for example, has a low compatibility with the hydrophobic cores of polymer micelles formed by several block copolymers.[69,70]
4. **Delivery of imaging agents:** The delivery of imaging agents to the site of disease in the body will help with early cancer and other disease detection. Torchilinm's group pioneered research in this field, using polymer micelles as carriers for imaging agents.[71] Micelles of amphiphilic Poly (ethylene oxide)-lipid conjugates, for example, were filled with gadolinium diethylenetriamine pentaacetic acidphosphatidylethanolamine (Gd-DTPA-PE) and used to predict the local lymphatic chain following subcutaneous injection into the rabbit's paw. A gamma camera and a magnetic resonance (MR) imager were used to capture photographs of local lymphatics. The micelles were inserted into the lymph fluid and remained there, acting as lymphangiographic agents for indirect MR or gamma lymphography.[72,73]
5. **Gene delivery:** There are three main types of polymeric micelles for gene delivery 1) polyion complex micelles for plasmid DNA delivery, 2) polyion complex micelles for small interfering RNA delivery and 3) Novel gene carriers enveloped in dendritic photosensitizer for light-induced gene transfer.[74] Gene therapy is a promising approach for the treatment of genetic and intractable diseases, and its success relies on the capacities of gene vectors.Compared with viral vectors, non-viral gene carriers have many advantages, such as safety for clinical use, simplicity of preparation, and easy large-scale production.[75]

FUTURE PERSPECTIVE AND CONCLUSION

A variety of drugs have been successfully used to prepare micelles to transport drugs used in a variety of diseases including cancer, HIV, tuberculosis and other bacterial infections. However, not all of these medications have the same probability of making it to the clinical stage. Many that have been licensed by regulatory authorities for example, have the best chance of reaching these levels. Furthermore, to obtain clearance, the latter must be able to bypass time-consuming and costly toxicity studies relevant to their biodegradability and biocompatibility. Along with effectiveness and pharmacokinetic evaluations, it should be one of the primary concern of researchers dealing with these types of "nano" vehicles. Finally, based on the findings of the aforementioned studies, it is clear that these drug delivery systems represent a flexible, versatile, and well-studied nanotechnology platform and that there are a large number of polymers approved by the Food and Drug Administration (FDA) or the European Medicine Agency (EMA), and that the application of polymeric micelles to clinical stages of diseases other than cancer appears to be promising in coming future. After getting to the reviews of representative literature and recent clinical trial advances, this manuscript attempted to clarify the basics of soluplus dependent polymeric micelles.The benefits of soluplus-based polymeric micelles have been illustrated, as well as how to tackle possible drawbacks. Finally, other potential particle size reduction methods for solubilising poorly water-soluble drugs were discussed. Poorly soluble compounds have been studied in polymeric micelles for oral and intravenous administration. While oral drug delivery *via* polymeric micelles is appealing, few *in vivo* studies have been conducted. More fundamental research promoting a deeper understanding of amphiphilic copolymer degradation mechanisms and micelle stability characterization *in vivo* is still required to fully realize the potential of polymeric micelles as a solubilization strategy for poorly water-soluble drugs.

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