General Introduction

1.1 : Amphiphilic Block Copolymers (ABCs)

ABCs are well studied material in research that has a potential function in the further development of macromolecular science, with multiple crucial contributions [1–3]. ABCs spontaneously self-assemble into well-confirmed nanoscale structures and morphologies. They generate a wide range of nanoscalable structures with different applications, particularly in the disciplines of biomedical sciences, in a form of typical self-assembly of block copolymers where distinct covalently bonded blocks are formed chemically [4–6]. Figure 1 depicts the research articles published with the topic "***Amphiphilic block copolymers***" at the *Web of Science (Clarivate Analytics)* up to the present year 2022.

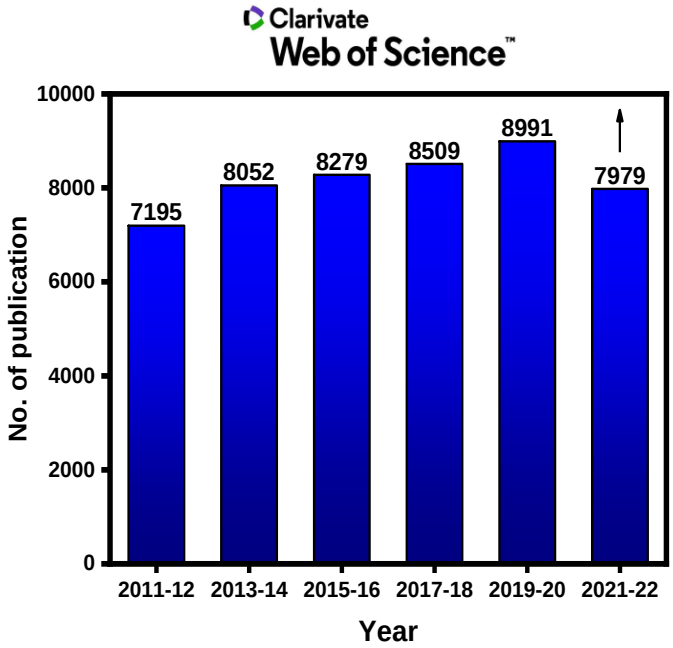

Figure 1.1: Research publications with "*Amphiphilic block copolymers*" as the key word against year.(*Source: WoS*)

ABCs are made up of two or more covalently linked blocks with different chemical properties. In general, polymer blocks in ABCs are immiscible and therefore the focus of a variety of industrial and research problems in the advanced polymer sciences [7,8]. It is widely known that in the solid state, ABCs with chemically incompatible blocks undergo self-assembly into perfectly arranged structures led by contrary mixing enthalpies and small mixing entropies. The covalent bonding between individual blocks precludes apparent phase separation [9,10]. Most of the synthetic block copolymers have been developed using scaffolds like PEG [11], HPMA [12], PLGA [13], PAA [14], and PCL [15].

In addition to the synthetic versatility in the formulations of block copolymers, some of them have interesting biological significance as well.

ABCs are usually linear (di-, tri-, and multi-block), cyclic, miktoarm, and comb-shaped-grafts. The chemical behaviour of the individual blocks, their total molar mass (>1000 Da), and their composition demonstrate diverse solution behavior and excellent characteristics [2,16–18]. The different classes of ABCs are illustrated in Figure 1.2.

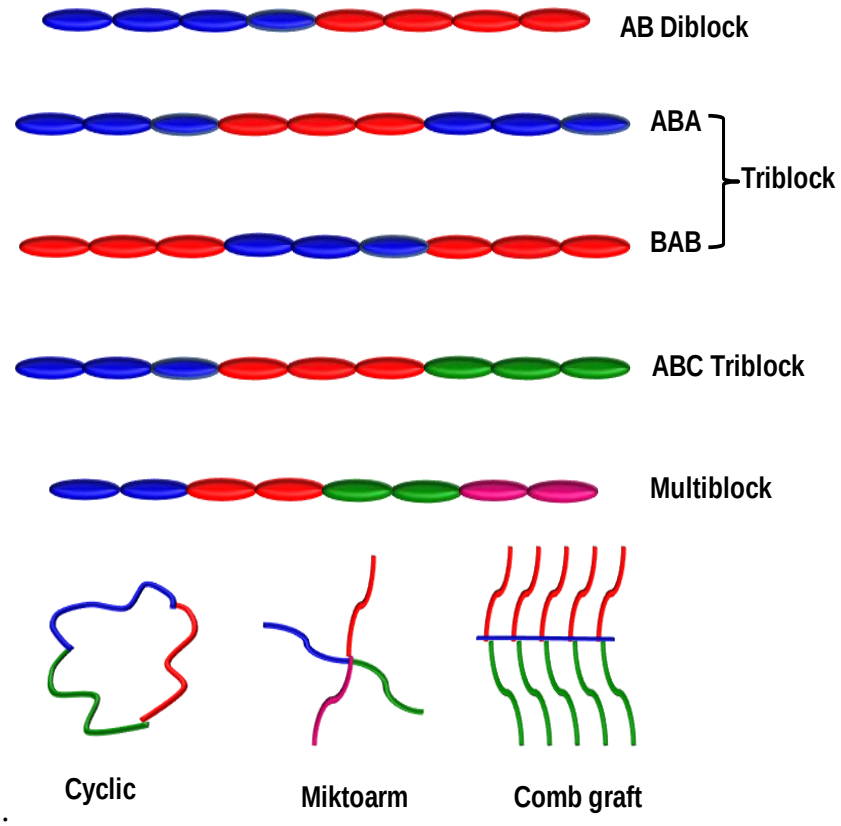

Figure 1.2: Various classes of ABCs.

Commercially available block copolymeric surfactants (surface active agents) offer a variety of structural compositions, molecular weights, and HLBs. Such variations can be made in the size and morphology of the aggregates of block copolymers, making them quite useful for a good range of applications. Figure 1.3 shows how, with different HLB, these block copolymers can be applied in various modes.

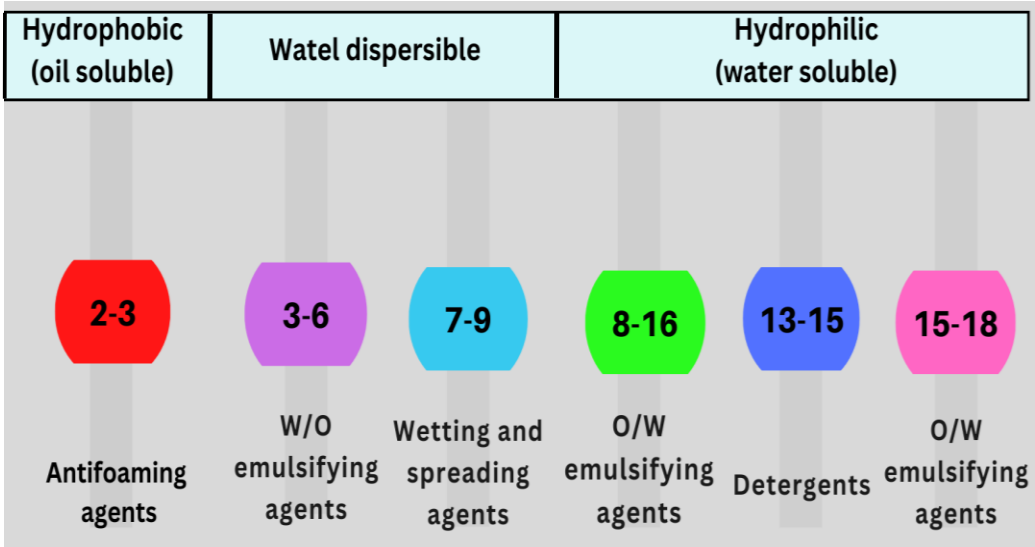

Figure 1.3: Various roles of amphiphiles with their respective HLB ranges

The distinctive structural architecture of ABCs and its surfactant behaviour due to the hydrophilic and hydrophobic blocks have been explored [19,20]. Figure 1.4 presents the uses of ABCs in various fields.

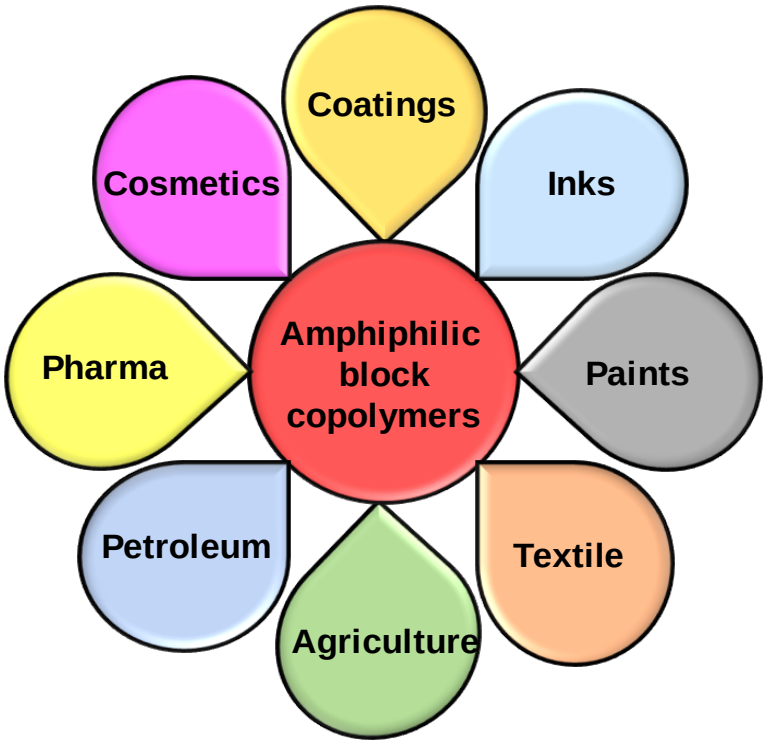

Figure 1.4: Various applications of ABCs.

1.2: Self-assembly of Amphiphilic Block copolymers (ABCs)

Self-assembly is a robust phenomenon for the development of nanostructures, where molecules arrange into well-organized structures in order to minimize energy. For many decades, the self-assembly of surfactant has been studied, and diverse morphologies have been explored in aqueous solutions and bulk media. The morphologies of self-assembled systems are depend on the molecular structure, HLB value, concentration, and temperature. However, by changing the block length, the producing morphology can be altered, resulting in reach polymorphism ranging from spherical-to-rod/wormlike micelles to vesicles [2,17,21,22].

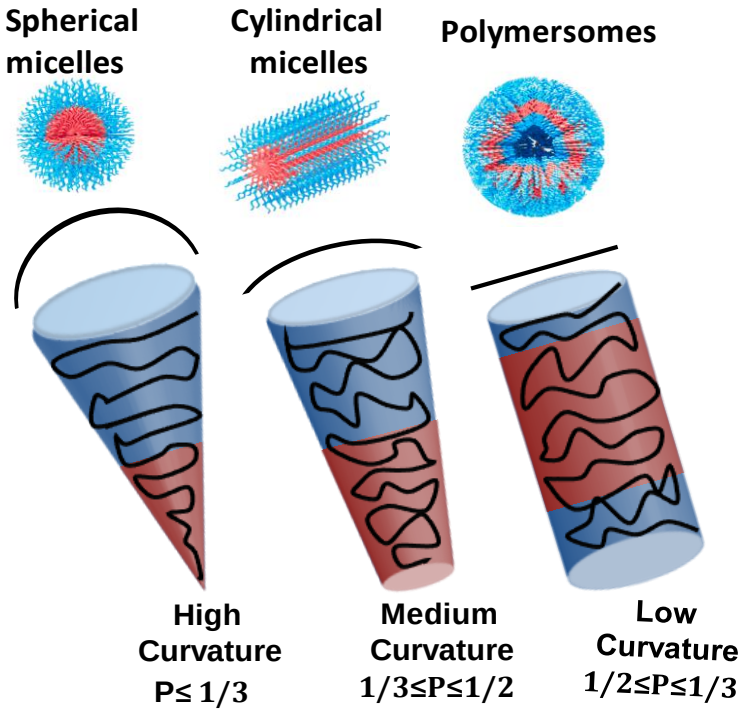

Figure 1.5: Various morphologies resulting in ABCs as a function of P. P denotes a geometrical technique that compares the volume occupied by one amphiphilic molecule to the total micellar volume.*(Refereed from ref 23)*.

ABCs, like conventional surfactants and lipids, spontaneously self-organize in certain solvents above critical parameters, such as CMC and CMT), providing a diverse array of ordered core-shall nanostructures to reduce energetically undesirable hydrophobic block-solvent interactions [23]. Israelachvili and co-workers reported that the critical packing parameter (p) for small molecule amphiphiles determines the canonical equilibrium morphologies for these ABCs [24-27].

$$p_{(\text{critical packing parameter})} = \frac{v_{(\text{volume of the hydrophobic segment})}}{a_{0\left(\begin{smallmatrix}\text{interfacial area of the}\\ \text{hydrophilic segment}\end{smallmatrix}\right)} \times l_{c\left(\begin{smallmatrix}\text{critical length of the}\\ \text{hydrophobic segment}\end{smallmatrix}\right)}}$$

"Empirical results are obtained for spherical micelles (p<1/3), cylindrical micelles (rod-or worm-like micelles, nanofibers, and nanorods) (1/3<p<1/2), vesicles (or lamellae; 1/2<p<1), and inverted nanomorphology (p > 1). Figure 1.5 various morphologies found in ABCs as a function of the critical packing parameter (p) [24]".

Chemical compositions, hydrophilic/hydrophobic block ratios, degree of polymerizations of constituent blocks, molecular weights, and polydispersities of ABCs can all be used to engineer the morphologies and colloidal properties of ABC assemblies [19]. Furthermore, the morphologies of self-assemblies of ABCs can also be influenced by noncovalent interactions with external additives, domain crosslinking, crystallinity of hydrophobic cores, chirality, and polymer architectures [28,29]. Notably, the polymeric nature of hydrophobic blocks confers slow molecular exchange dynamics of ABCs in highly selective solvents (such as water), preventing self-assembled nanostructures from reaching global thermodynamic equilibrium and allowing for the fabrication of a variety of multiple kinetically trapped and hierarchical nanostructures.

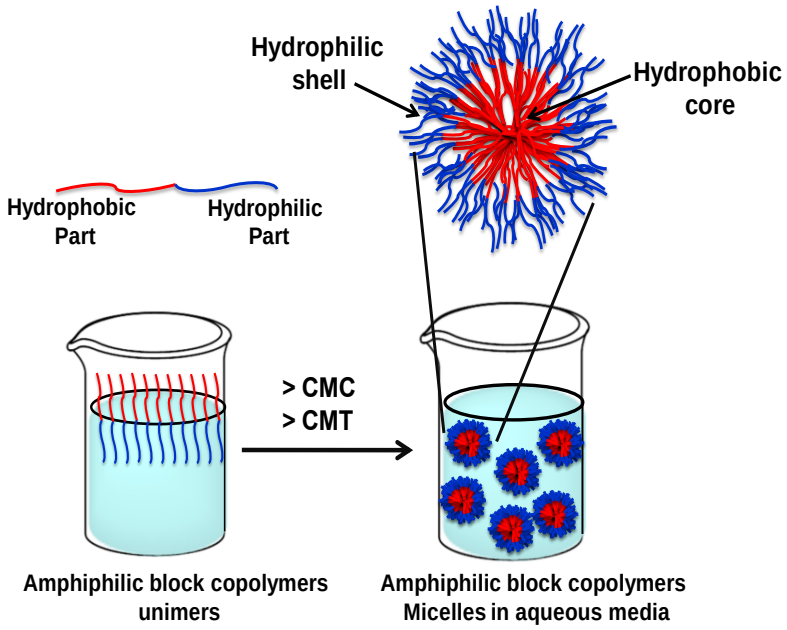

Figure 1.6: Micellization behaviour of ABCs in aqueous medium.

ABCs are composed of hydrophilic (solvophilic) and hydrophobic (solvophobic) polymer blocks. Water is a selective universal solvent for hydrophilic blocks, and beyond CMC, the lipophilic blocks of ABCs self-assembled in an aqueous environment, forming core-shell structures called as micelles (Figure 1.6). The block copolymeric micelle has two parts: the "*core region*", which is made up of hydrophobic polymer chains, and the "*corona-shell region*", which is made up of well-hydrated hydrophilic polymer chains that keep the micelle stable in an aqueous environment.

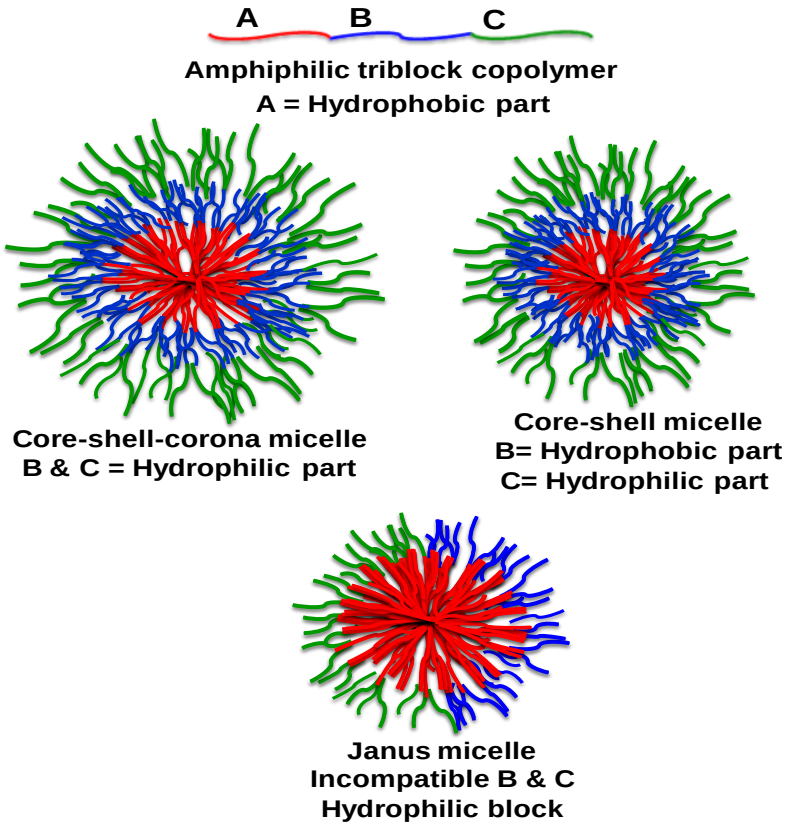

Figure 1.7: Various self-assemblies in ABCs (water as a solvent).

When compared to conventional low molar mass surfactants, ABCs can be constructed to have lower CMC. The CMC indicates the stability of the micelles thermodynamically because it shows the minimum polymer concentration at which the micelles maintain constructed assembly. Many factors influence the CMC of ABCs, including hydrophobicity, glass transition temperature (Tg), crystallinity, and the lipophobic-lipophilic block length ratio. According to the mutual incompatibility of the respective blocks, multiple morphologies for ABCs are feasible above the CMC (shown in Figure 1.7). Although the aggregate form is often spherical and has either a laterally homogenous or

segregated corona, it is also possible to have micelles that resemble rods and worms as well as vesicular structures [30].

ABC self-assembly has been used in a wide range of nanomedicines, including pH-sensitive micelles [31,32], self-assembled organic-inorganic nanomaterials blended block copolymers and functionalized metal nanoparticles [33,34], lipid nanovehicles [35,36], and polymersomes (vesicles) [37,38]. ABCs-based drug formulations can be designed with care to achieve optimal drug solubilization, proper structural size, administration, and transport stability.

1.3: Pluronic® Polymers: Versatile Amphiphilic Block Copolymers

Poloxamer polymers (also known as Pluronics) are gaining popularity in the fields of pharma [39,40], agro [41,42], food [43,44], detergent [45,46], oil extraction [47,48], cosmetics [49,50], paints [51,52], and others [53,54] due to their potential as promising nanomicelles in various systems. They were introduced by Baden Aniline and Soda Factory (BASF, NJ, USA) in the 1950s. Figure 1.8 depicts the number of research articles published on the topic "*Pluronic*" at the *Web of Science (Clarivate Analytics)* since 2011. Such an assessment proves the significance of these versatile polymers in recent and future research perspectives.

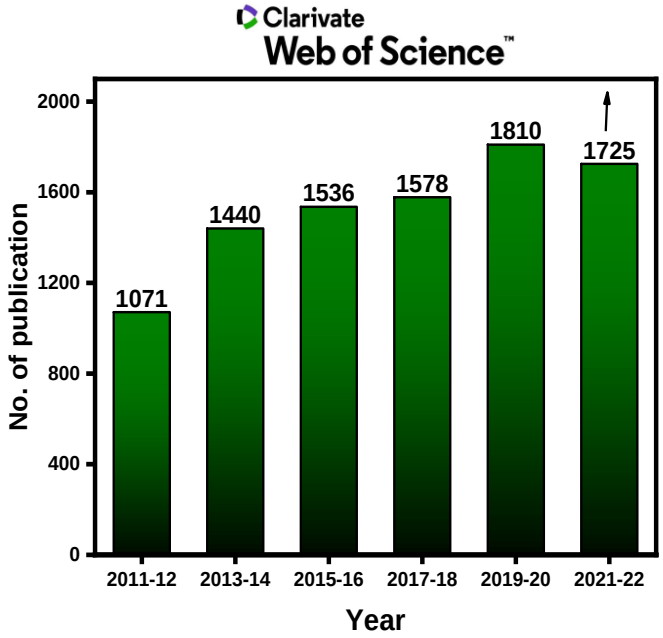

Figure 1.8: Research articles with "*Pluronic*" as the key word against year.

1.4 Chemistry of Pluronics

Pluronics are a class of synthetic triblock copolymers made of hydrophilic PEO and hydrophobic PPO, which are also commercially available under the trade names of *Lutrol*®(BASF), *Kolliphor*®(BASF), *Synperonic*®(Croda), and *Antarox*®(Rhodia) [16,55]. The general molecular structure of Pluronics is shown in Figure 1.9.

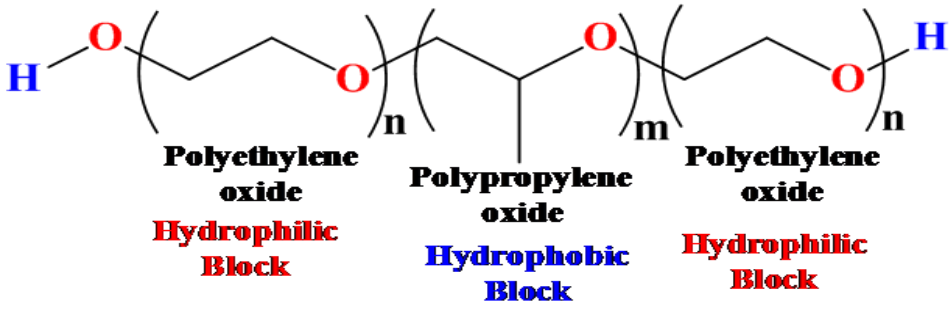

Figure 1.9: Molecular structure of Pluronic

As discovered several years ago by Szwarc, the anionic chain polymerization pathway has been employed in general to synthesize a variety of block copolymers. The anionic polymerization leads to well-defined polymers with low polydispersity. Pluronic was synthesized by sequential anionic ring opening polymerization of EO (ethylene oxide) and PO (propylene oxide) in the presence of either potassium hydroxide or sodium hydroxide as an activator. PPO segments are produced initially, and then PEO is polymerized to the chain [56,57]. Many synthesized Pluronics have been found to show impurities of PPO and diblock(PEO-PPO) polymers, but there is still not found their considerable effects on the properties of Pluronics in studies [58].

The Pluronic nomenclature was introduced by BASF and is graded into different types. Figure 1.10 shows the nomenclature for Pluronic grades. The capital letter mentioned before the digit in the Pluronic denotes the physical state of the polymer at room temperature: F=Flake , P=Paste, or L=Liquid. For example, P65 and L61 denote the paste and liquid types, respectively. The molecular weight of PPO can be estimated by multiplying the first one or two digit by 300, and the last digit corresponds to one-tenth of the wt% of PEO in the copolymer [59,60]. The three physical states of Pluronic polymers at RT can be determined by their molecular weight, which ranges from 1100 to 14,000. They are comprised of a collection of over 50 amphiphilic, water-soluble molecules [61].

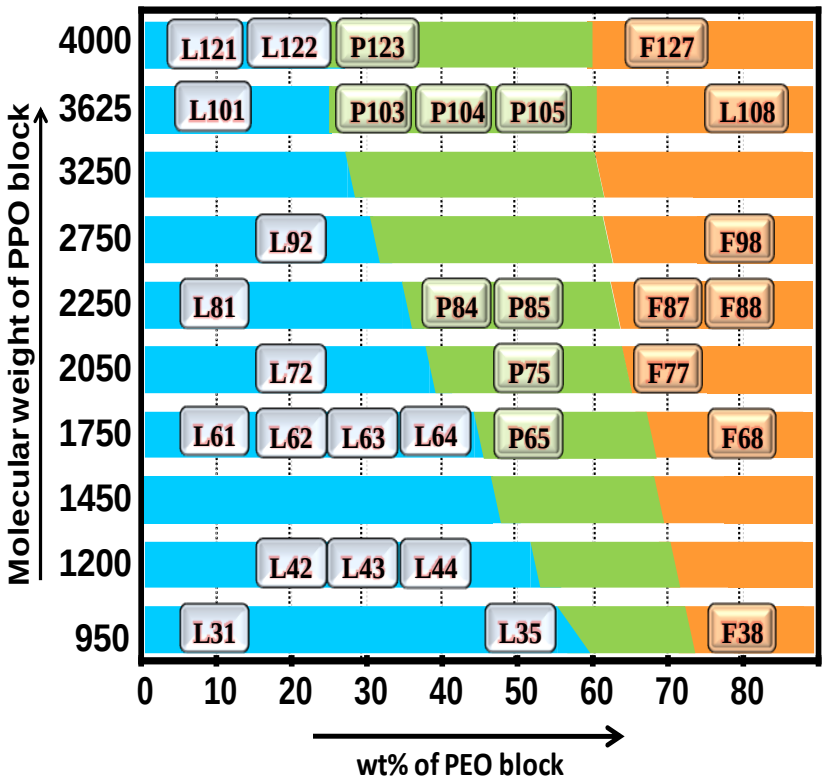

Figure. 1.10: Pluronic Grid system

The composition ratios of the hydrophilic PEO block and the hydrophobic PPO block have a large influence on the water solubility of Pluronics [62]. Based on its segmental weight, Pluronic can be used in a variety of applications, ranging from surfactants to drug delivery carriers. Due to a high solubility of PEO in aqueous medium and a low solubility of PPO in aqueous medium, Pluronics structures act as amphiphilic structures with surface-active properties [63,64]. Many Pluronics have already been approved by the FDA and EPA for various applications in different field [65,66].

1.5: Self-assemblies of Pluronic polymers

Pluronics exist as unimers in water below the CMC and self-assemble to form micelles above the CMC in water in equilibrium with unassociated unimers. Pluronics forms core-shell-type polymeric assemblies in sizes ranging from 10 nm to 200 nm as polymeric micelles. A number of triblock copolymers have been shown to aggregate in the form of micelles, which possess a two-phase structure with an inner core dominated by hydrophobic PPO blocks, and an outer shell dominated by hydrophilic PEO blocks. They are self-assembled into nano-sized structures, normally ranging from 10 nm to 200 nm [67–69].

At room temperature, more hydrophilic Pluronics do not aggregate to form micelles. Moreover, the CMC decreases when the number of PPO units increases at a certain temperature. At a fixed PPO/PEO ratio, CMC and CMT decrease with the increasing molecular mass of Pluronics. Pluronic copolymers self-assemble in solution and adsorb onto interfaces. In a selective solvent, these polymers form stable micelles with a variety of morphologies. Consequently, in the series of Pluronics with constant PPO chain length, the Pluronic with only 10% PEO blocks forms enormous lamellar structures rather than spherical micelles. Temperature-dependent micellization is one of the most significant characteristics of Pluronic in an aqueous medium [70,71]. Once the micellar structure is formed, the micellar molecular weight increases with temperature, and the minimal micelle radius changes. However, as concentration increases, micelle size increases, resulting in polydispersity, implying numerous association pathways showing concentration-dependent micellization [72–74].

Pluronic exhibits structures such as cylindrical, hexagonal rod-like, and lamellar phases that can be investigated in a phase diagram as temperature, concentration, and composition change. Figure 1.11 represents the various micellar morphologies given by Pluronic with increasing concentration and/or temperature. The system's cylindrical, rod-like, and lamellar structures are formed by the continuous growth of small spherical micelles. Such structural changes of Pluronic micelles can also be happened in the presence of additives like hydrotropes, inorganic salts, small organic compounds, etc. It is widely proven that additives highly impacted on micellar behaviour of Pluronics. Pluronics' ability to self-assemble with the various morphologies discussed above has been investigated as an appealing strategy for addressing the problem of poor aqueous solubility of many APIs and lipophilic molecules [26,75–77].

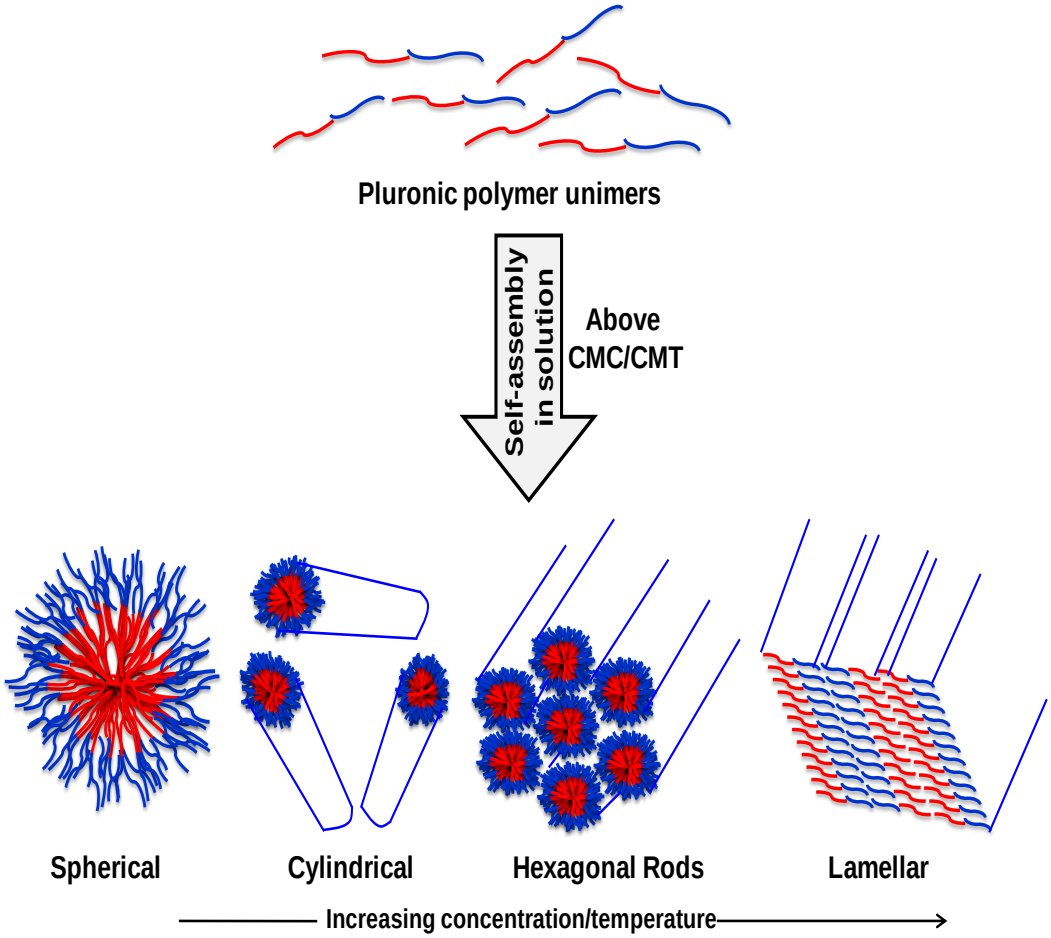

Figure 1.11: Schematic presentation of micellar phases formed by Pluronic with increasing concentration/temperature

Despite the complexity of Pluronics micellar behaviour, complete information can be obtained through a variety of conventional and advanced techniques. The main techniques applied for micellar characterization are scattering (DLS, SLS, SANS, SAXS), spectroscopic (UV-Vis, FT-IR, NMR, fluroscence spectroscopy), microscopic (TEM, cryo-TEM, SEM, AFM), calorimetric (ITC, DSC), rheological strategies (viscoelastic behaviour), and other (solublization measurements, zeta-potential, CPT, surface tension) methods. Such micellar characterization, along with many biological investigations, provides knowledge not only on the Pluronic micellar structure but also on their ability to solubilize and sustainably release of relevant drug. Figure 1.12 summarize information about micellar characterization techniques.

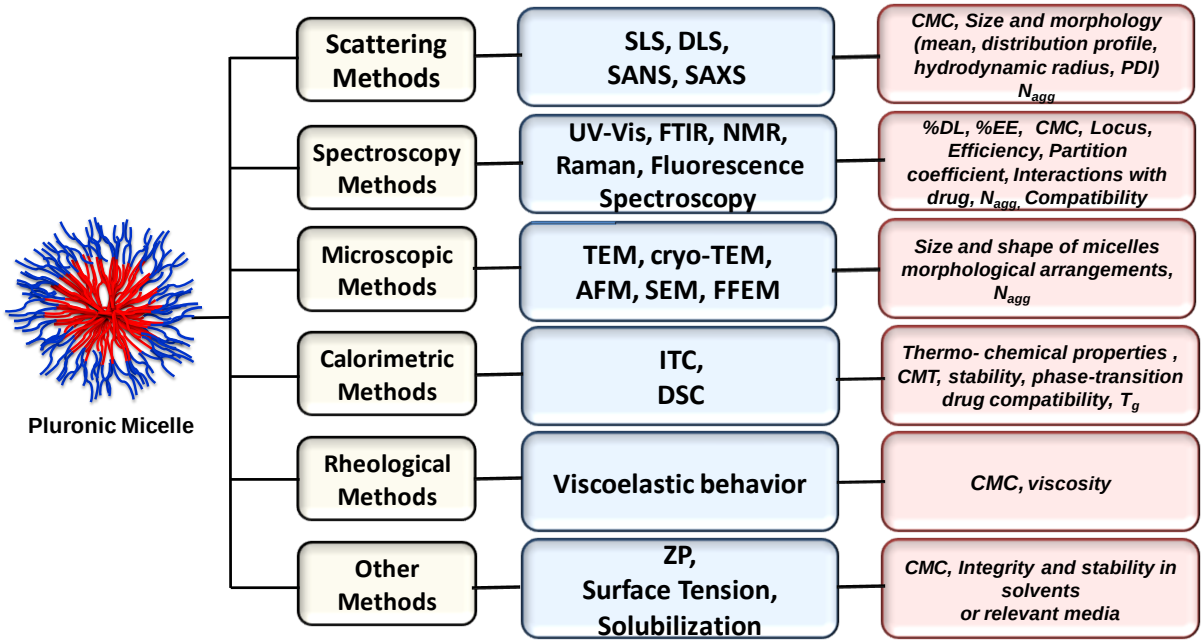

Figure 1.12: Techniques applied for the characterization of Pluronic micelles

Pluronic micelles have a core-shell structure that provides significant benefits, such as drug targeting, ease of production, and long circulation. Single Pluronic micelles are quite often failing because of their own drawbacks, which include their inability to encapsulate significant amounts of lipophilic drugs and their high CMC values, which result in low micelle stability and dissociation while diluted by blood throughout intravenous or oral administration [78]. However, the poor stability of single Pluronic micelles in the cardiovascular system or GI fluids, as well as the eventual drug precipitation, prohibits their application in the delivery of drugs. Because of this, a lot of research is being done on Pluronics mixed micelles to improve the oral bioavailability of lipophilic drugs. Pluronic mixed micelles made of thermally stable hydrophobic Pluronic and kinetically stable hydrophilic Pluronic performed exceptionally well in drug solubilization and stability, paving the way for much more effective pharmaceutical applications [79–82]. Pluronic mixed micelles increase the volume of the PPO core of respective micelle by combining extra materials with hydrophobicity, furnishing a larger solubilization site for water-insoluble drugs. It also retains all the benefits of single Pluronic micelles while enhancing the solubilization capacity for hydrophobic drugs [83–85].

To evaluate these benefits, several research groups have developed mixed Pluronic micellar systems, which have notably increased the compatibility and bioavailability of

various lipophilic drugs. For example, mixed F127/P123 micellar systems have been confirmed to have enhanced compatibility and bioavailability of paclitaxel [86], nevirapine [87] nicosamide [88], lacidipine [89], and isoliquritigenin [90] with significantly high solubilization capacities of the drugs, greater drug loading efficiency, and small micellar size with low polydispersity.

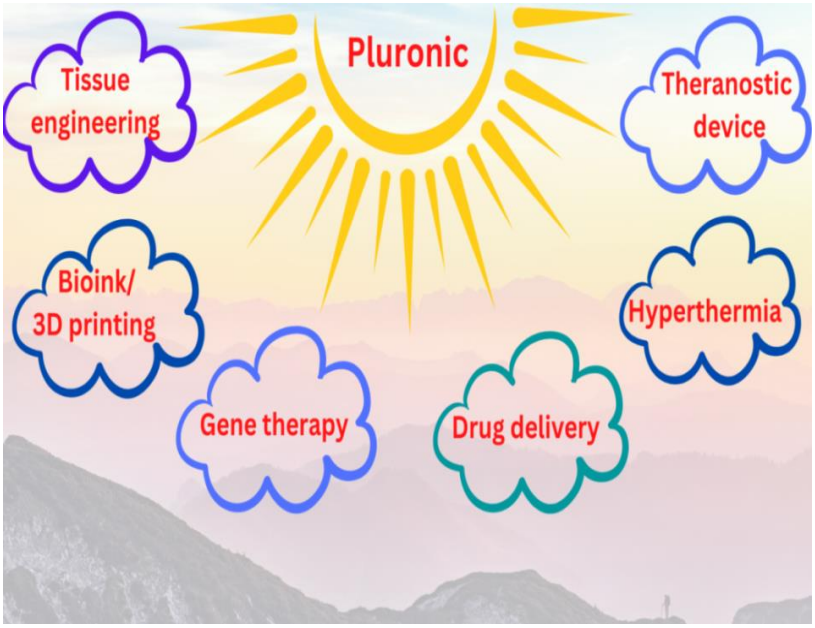

Figure 1.13: Biomedical applications of Pluronic polymers

Furthermore, their adaptable mechanical and small size morphological characteristic of Pluronic mixed micelles obtained through functionalization or combining with other biocompatible compounds imbues them with a broad range of biomedical application (Figure 1.13). Pluronics have been extensively functionalized to produce drug delivery nanovehicles that have active targeting, stimuli responsiveness, and high drug loading capacity. To develop a more potent Pluronic mixed micellar system for drug delivery, many biocompatible compounds are combined. The combination of highly biocompatible compounds with Pluronic mixed micelles plays a crucial role in drug delivery. These Pluronics mixed micellar systems with biocompatible compounds offer various advantages for improving therapeutic efficacy in addition to drug solubilization [91–94].

Basalious et al. [80] demonstrate the feasibility of mixed Pluronic F127/P123 micellar systems containing the biocompatible compound PC. They found that mixed Pluronic F127/P123 micelles with PC were more thermodynamically and kinetically stable even after

high dilution, which increased the solubilization capacity and absorption rate of lipophilic drugs compared to their own single or mixed micelles. Many research groups have demonstrated mixed micellar systems with biocompatible materials like TPGS [95,96], Soluplus [97,98], phospholipids [99,100], and Solutol HS15 [101,102], which have remarkably increased the thermodynamically and kinetically stable properties as well as excellent compatibility and bioavailability of lipophilic drugs in biological medium [103].

As a result, self-assemblies of Pluronics in the form of individual micelles, mixed micelles with Pluronic mixtures, or mixed micelles with Pluronics and other biocompatible materials are highly influenced and are very useful for the development of bio-applications. So it is always important to understand and investigate how Pluronic micelles and their structure are employed in drug delivery applications.

1.6: Pluronic Micelles in Drug Delivery

Pluronic micelles-based drug delivery systems are faster growing and are one of the most appealing fields in pharmaceutical research. The micellar size, adsorption characteristics, and various morphologies of Pluronics make them appropriate for use in a wide range of drug delivery applications. The wide availability of hydrophilic and hydrophobic blocks permits scientists to explore various Pluronic combinations for maximum loading, stability, systemic circulation, and targeted delivery at the site.

Numerous publications have shown that Pluronics can be used as drug carriers due to their inherent ability to solubilize drugs in both the core of PPO and the shell of PEO, as well as resist the rapid degradation of drugs in aqueous medium. Moreover, PEO regions increase the circulation time in the body by providing steric stability. Recent studies have shown that Pluronic can act as a biological response modifier, increasing drug transport across intestinal barriers and BBB, as well as into cells and tissues. For example, they have sensitized MDR cells by inhibiting proteins [104] and avoiding sequestration by the RES organs. Pluronics have sparked interest in the realm of cancer therapy because they exhibit desirable properties for constructing stable systems capable of encapsulating and delivering drugs efficiently.

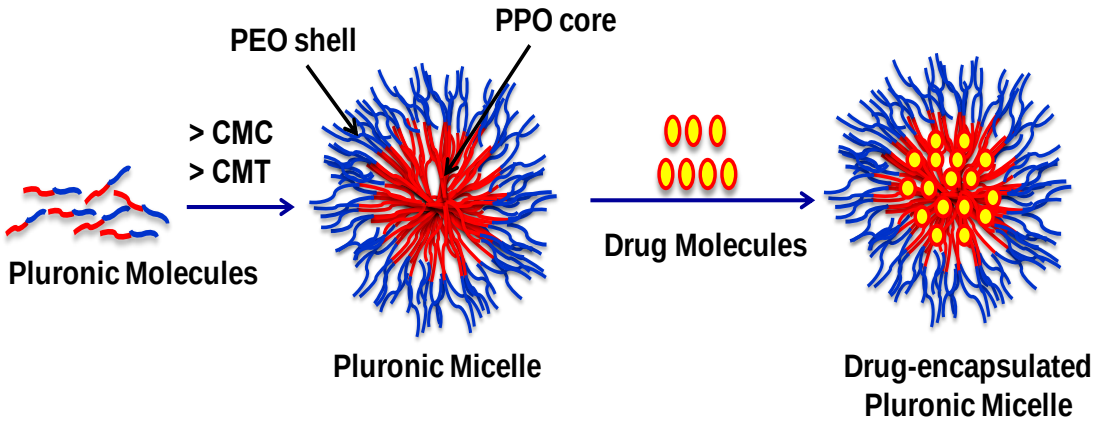

Figure 1.14: Representation of Pluronic micelle as nanovehicles for drug solubilization.

Several Pluronics mixed micelles, made by the combination of Pluronics or with other biocompaitable materials, have been used as surfactants [105,106] or to solubilize and stabilize various lipophilic drug in the past five years, including APIs like clinically used docetaxel [107], pemetrexed [108], and 5-fluorouracil [109], and. Plant-derived metabolites [110] that attracted attention because of interesting anticancer activity like quercetin [111], myricetin [112], topotecan [113], gossypol [114], and curcumin [115,116] were also successfully delivered by Pluronic-based systems. Delivery of organometallic complexes [117], nanodots [118], bioimaging agents [119] and other classes of drugs [120–127].

Pluronic nanomicelles gather at the tumour tissues at the tumour site (pH<6.8) through the leaky vasculature and hold on in the microenvironment because of the poor lymphatic drainage. Such happening is generally known as the EPR effect. After this fact, various Pluronic micelles and mixed micelles have been studied to deliver hydrophobic chemotherapeutic agents in cancer [128–130]. Unlike conventional drug molecules that enter the cells by diffusion, Pluronic nanomicelles get internalized through receptor-mediated endocytosis. The procedure allows Pluronic nanovehicles to go inside and liberate the drug in the lysosomal compartments. The availability of drugs in the cellular core activates apoptotic signals for cell killing and makes the drugs less available in the peripheral cytoplasm to induce efflux mechanisms. Therefore, by utilising micelles' cellular internalisation mechanisms, Pluronic nano-micellar systems are less influential on MDR than free drugs. Figure 1.15 shows the Pluronic micelles pathways to the tumour site and impact cancer cells for improved therapeutic activity.

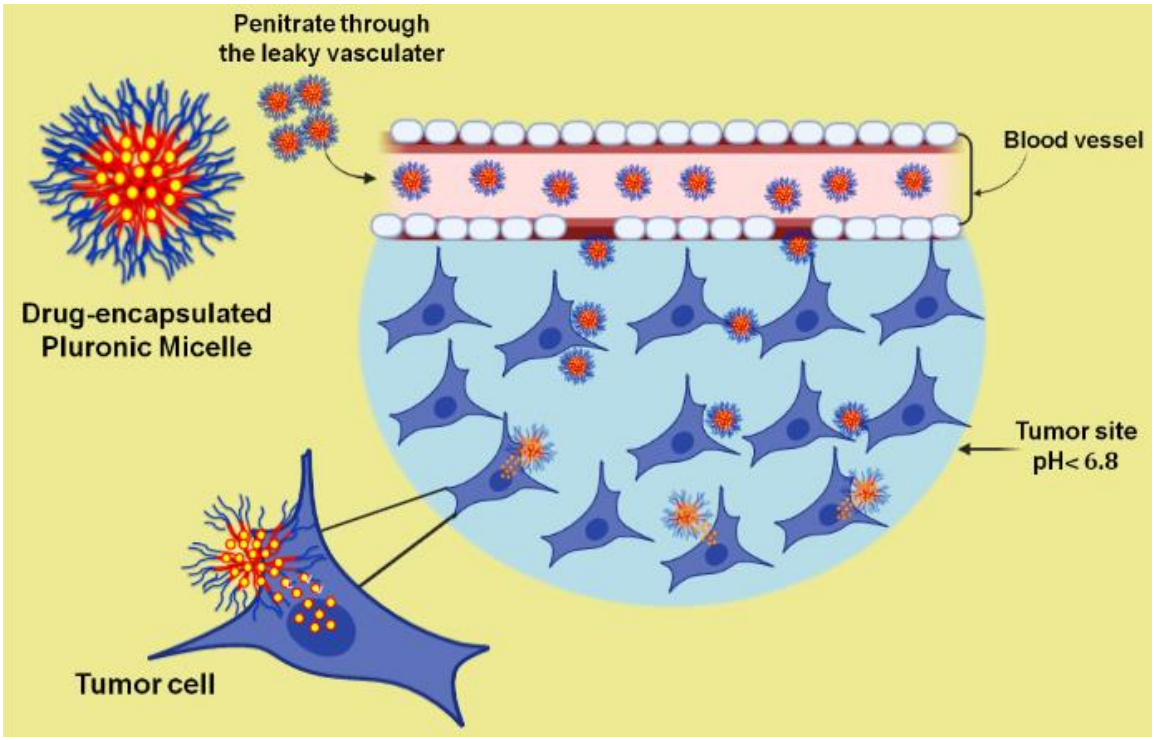

Figure 1.15: Schemetic representation of EPR effect for cancer treatment.

In this context and given the micellization behaviour of Pluronic polymers, Pluronic F127, which has a longer hydrophilic PEO block and a higher molecular weight, stopped Pluronic L61 from clumping together in water by stabilizing the self-assembly of Pluronic L61, which has a longer hydrophobic PPO block. This Pluronic mixture of F127 and L61 is as effective as SPC1049C in delivering the anticarcinogenic drug doxorubicin (DOX). This DOX-loaded mixed F127/L61 micelle formulation (SPC1049C) was approved for use in clinical trials and given to patients through an intravenous route for the treatment of cancer [131–133]. Other docetaxel (DTX), an anticancer drug, is also formulated Tween 80 and clinically used. This formulation is known as Texotere®, which was FDA approved in 2004. However, the usual side effects of Taxotere® were found, including neurotoxicity, nephrotoxicity, hypersensitivity, and incompatibility. Fang et al. [134] investigated in 2013 that DTX encapsulated in the Pluronic F127/P105 mixed micellar system had greater anti-cancer activity against A549 taxol-resistant cells than Taxotere® while having fewer side effects. These kinds of effective outcomes encourage the use of Pluronic micelles as drug delivery agents in the development of pharmaceutical formulations.

The inclusion of other surfactants may also improve the Pluronic mixed micelle stability and drug incorporation efficiency. Nambam et al. analyzed the Pluronic F108 micellar systems with ionic surfactants and concluding that SDS promotes the formation of a strong electrostatic barrier which minimizes the micellar growth [135]. Gao et al. reported that mixed micelles of Pluronic P105 with TPGS (at mol ratio 3:7) give low CMC, hence creating more stable systems and it was due to the presence of an aromatic cycle of TPGS which enhances the hydrophobic interactions in the core of Pluronic mixed micelle [136]. Mixed micelles of Pluronic F127 and cremophor were designed [137] and the interactions between the F127 and cremophor was investigated using β parameter given by Rubingh [137]. The β parameter is (-) negative if synergism is there, working to the micelle formation at a lower concentration than the surfactants alone. Here, a moderate synergistic effect was found, lowering the CMC (from 80 µM to 28 µM). In addition to the potency of Pluronics to form micellar nanovehicles, these polymers have been utilized in the modification of a wide variety of other nanoparticles (NPs), making hybrid structures with blended properties. Some of the NPs that have been modified with Pluronics include metal NPs, nano-suspensions, nanogels, liposomes, dendrimers, polymeric micelles, and solid-lipid NPs. [138]. Not only that, they have also been functionalized with variety of other moieties such as pH-sensitive, biological-responsive moieties, antibodies, aptamers, vitamin, or drugs [139]. Therefore, Pluronic-based nanotechnology is one of the fast-growing research fields in pharma research. However, very few Pluronic formulations are employed in clinical research because of some distinguish limitations, mainly their complex characterization, instability under physiological environment and low-encapsulating efficacy.

Due to the versatility and importance of micelles and mixed micelles of Pluronics in the area of drug delivery and other bioapplications, we aimed to study the self-assemblies of Pluronic mixed micelles as nanosized drug delivery vehicles for very useful lipophilic drugs like quercetin, curcumin, and glipizide. The mixed Pluronic micellar systems, as well as highly potent biocompatible additives such as PC and TPGS, are being studied. Pluronic functionalization with SA is also being investigated for its potential applications as nanovehicles for drug solubilization and delivery.

In this context, the present thesis research work includes the design, characterization, and evaluation of Pluronic mixed micelles as the nanovehicles for drug delivery applications

for quercetin, curcumin, and glipizide drugs. Various conventional and modern methods such as UV-Vis, DLS, SANS, TEM, SEM, FTIR, NMR, XRD, and DSC are employed to characterise the drug-loaded mixed Pluronic micelles and their interactions with drugs. In-vitro, ex-vivo, and in-vivo studies of cumulative drug release, DPPH scavenging antioxidant activity, cell proliferation, and cell viability have also been performed to study the biological activities of drug-loaded mixed Pluronic micelles.

1.7. References

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