The ability of a soapy solution to act as a cleansing agent has been recognized for several centuries. However, it was only at the beginning of the twentieth century that the physical chemistry of soap solutions was studied. Pioneering work in this area was done by J W McBain (founder Director of NCL, Pune) at University of Bristol. As early as 1913 he postulated the existence of “colloidal ions” to explain the good electrolytic conductivity of sodium palmitate solutions [1]. In a lecture at the Royal Society of London, McBain pointed out the idea that unusual solution properties in an aqueous soap solution above a critical concentration could be explained as aggregation of molecules [1]. These highly mobile, spontaneously formed clusters were called micelles, a term borrowed from biology and popularized by G.S. Hartley in his classic book “Aqueous Solutions of Paraffin-Chain Salts; A Study in Micelle Formation”. Later several detergents were developed from petroleum products and were found to be more powerful cleansing agents than soaps and worked in acidic as well as hard water. Soaps and detergent like substances did much more than just cleaning and were later grouped as an important class as Surface active agents.

1.1 Surfactants:

Surface-active-agent (usually referred to as surfactants) are amphipathic molecules that consist of a non-polar hydrophobic portion, usually a straight or branched hydrocarbon or fluorocarbon chain containing 8-18 carbon atoms, which is attached to a polar or ionic portion (hydrophilic). The hydrophilic portion can, therefore, be nonionic, ionic or zwitterionic, and accompanied by counter ions in the last two cases. The hydrocarbon chain interacts weakly with the water molecules in an aqueous environment, whereas the polar or ionic head group interacts strongly with water molecules via dipole or ion-dipole interactions. It is this strong interaction with the water molecules that renders the surfactant soluble in water. However, the cooperative action of dispersion and hydrogen bonding between the water molecules tends to squeeze the hydrocarbon chain out of the water and hence these chains are referred to as hydrophobic. As discussed later, the balance between hydrophobic and hydrophilic parts of the molecule gives these systems their special properties, e.g. accumulation at various interfaces (show adsorption) and association in solution (to form micelles).

Surfactants are one of the multipurpose chemicals which find applications in almost every chemical industry and also at domestic level. The soaps, for washing, the
detergents for cleaning and homes (toiletries), in cosmetics, shampoos, in tanning of leather, in the motor, the medicines (drug delivery), in oil industry e.g. in enhanced and tertiary oil recovery, as flotation agents used in ores purification. Surfactants are extensively used in detergents, paints, dyestuffs, paper coatings, inks, corrosion inhibition, plastics and fibers, personal care and cosmetics, agrochemicals, pharmaceuticals, food processing, etc. as emulsifiers, demulsifiers, dispersants, foaming agents, wetting agents, solubilizers and viscosity modifiers [1, 2]. Apart from this, surfactants are very important for formation of biological membranes and have function in living cells. The study of surfactant solution behaviour is an important facet of colloid and interface science. The main aspects are to explore ability of surfactant molecules to aggregate, and to search surfactant or combination of surfactants or surfactant in presence of different organic/inorganic additives for optimized specific applications.

![Surfactant Monomer](image)

**Figure 1.1** Surfactant in aqueous solution.

1.1.1 Classification of Surfactants:

A simple classification of surfactants based on the nature of the hydrophilic group is commonly used. Thus, surfactants are classified as anionic, cationic, zwitterionic and nonionic. The hydrophobic part of a surfactant may consist of one or several hydrocarbon chains containing from 8 to 20 carbon atoms; the chain may be saturated or unsaturated, linear or branched and may contain hetero (oxygen) atoms, aromatic rings, amides, esters or other functional groups. Based on the charge on the hydrophilic group and its molecular structure, they have been classified as follows,
Classification of surfactants as per their structural features:

- **Anionic**
  - Sodium dodecylsulfate (SDS)
  - Cetylpyridinium bromide (CPB)

- **Zwitterionic**
  - Dipalmitoylphosphatidylcholine (lecithin)

- **Nonionic**
  - Polyoxyethylene(4) lauryl ether (Brij 30)

**Anionic Surfactants**

These are the most widely used class of surfactants in industrial applications [3, 4] due to their relatively low cost of manufacture and they are used in practically every type of detergent. For optimum detergency the hydrophobic chain is a linear alkyl group with a chain length in the region of 12-16 carbon atoms. Linear chains are preferred since they are more effective and more degradable than branched ones. The most commonly used hydrophilic groups are carboxylates, sulphates, sulphonates and phosphates. A general formula may be ascribed to anionic surfactants as follows:

- **Carboxylates:** \( C_n H_{2n+1} \text{COO}^{-} X \)
- **Sulphates:** \( C_n H_{2n+1} \text{SO}_4^{2-} X \)
- **Sulphonates:** \( C_n H_{2n+1} \text{SO}_3^{-} X \)
- **Phosphates:** \( C_n H_{2n+1} \text{OPO(OH)}_2^{-} X \)

with \( n = 8-16 \) atoms and the counter ion \( X \) is a cation usually sodium ion. Several other anionic surfactants are commercially available such as sulpho-succinates,
isethionates and taurates and these are sometimes used for special applications.

**Cationic Surfactants**

These are usually quaternary ammonium compounds where alkyl group R contains 8-18 C atoms \([5, 6]\). They dissociate in water into an amphiphilic cation and an anion, most often of the halogen type. Cationic surfactants first became important when the commercial potential of their bacteriostatic properties was recognized by Domagk in 1935. A very large proportion of this class corresponds to nitrogen compounds such as fatty amine salts and quaternary ammoniums, with one or several long chain of the alkyl type, often coming from natural fatty acids. These surfactants are in general more expensive than anionics, because of the high pressure hydrogenation reaction to be carried out during their synthesis and account for only 5-6% of the total surfactant production. They are generally water soluble when there is only one long alkyl group. They are generally compatible with most inorganic ions and hard water, but they are incompatible with metasilicates, highly condensed phosphates and with protein like materials. Cationics are generally stable to pH changes, both acid and alkaline. They are incompatible with most anionic surfactants but are compatible with nonionics.

Their *positive charge* allows them to adsorb on negatively charged substrates, as most solid surfaces are at neutral pH. This capacity confers to them an antistatic behavior and a softening action for fabric and hair rinsing. The positive charge also enables them to operate as floatation collectors, corrosion inhibitors as well as solid particle dispersant and as emulsifiers. Many cationic surfactants are *bactericides*. They are used to clean surgery hardware, to formulate heavy duty disinfectants for domestic and hospital use, to sterilize food bottle or containers, particularly in the dairy and beverage industries. They are also used as anticorrosive agents for steel, flotation collectors for mineral ores, dispersants for inorganic pigments, fabric softeners, hair conditioners, anticaking agent for fertilizers.

➢ **Zwitterionic surfactants (amphoteric)**

They are those for which the charge on the polar head group can be either positive or negative depending upon the pH of the solution. An example of zwitterionic surfactants is N-dodecyl-N, N-dimethyl betaine, \(\text{C}_{12}\text{H}_{25}\text{N}^+\text{(CH}_3\text{)}_2\text{CH}_2\text{COO}^-\). Phospholipids that constitute biomembranes are zwitterionic amphiphiles.
Nonionic Surfactants

The most common nonionic surfactants are those based on ethylene oxide, referred to as ethoxylated surfactants [7, 8]. Several classes can be distinguished: alcohol ethoxylates, alkyl phenol ethoxylates, fatty acid ethoxylates, monoalkaolamide ethoxylates, sorbitan ester ethoxylates, fatty amine ethoxylates and ethylene oxide-propylene oxide copolymers (sometimes referred to as polymeric surfactants). Another important class of nonionics is the multihydroxy products such as glycol esters, glycerol (and polyglycerol) esters, glucosides (and polyglucosides) and sucrose esters. Amine oxides and sulphinyl surfactants represent nonionics with a small head group.

New class of Surfactants

With the continuous search for improving surfactant properties, new structures have recently emerged that exhibit interesting synergistic interactions or enhanced surface and aggregation properties. Table 1 illustrate such novel surfactants which have attracted much interest, and include the Catanionics, Bolaform, Gemini (or dimeric), Polymeric and Polymerisable surfactants [9, 10].
Moreover, surfactants are characterized by the hydrophilic-lipophilic balance (HLB): a relative ratio of polar and nonpolar groups in the surfactant.

HLB ca. 1 to 3.5 : Antifoams
HLB ca. 3.5 to 8 : Water-in-Oil Emulsifiers
HLB ca. 7 to 9 : Wetting and Spreading Agents
HLB ca. 8 to 16 : Oil-in-Water Emulsifiers
HLB ca. 13 to 16 : Detergents
HLB ca. 15 to 40 : Solubilizers

The concentration at which a surfactant starts aggregation in solution is known as its **critical micelle concentration** (CMC). Surface active agent at a particular temperature and electrolyte concentration has a characteristic CMC value. As a result, there is considerable interest in the determination of CMC because in practice, it is the lowest concentration of the surfactant offering the optimum benefits.

---

### Table 1.1 Structural features and examples of new class of Surfactants.

<table>
<thead>
<tr>
<th>Classes</th>
<th>Structural characteristics</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catanionic</td>
<td>Equimolar mixture of cationic and anionic surfactants (no inorganic counterion)</td>
<td>( n )-dodecyltrimethylammonium ( n )-dodecyl sulfate (DTADS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \text{C}<em>{12}\text{H}</em>{25}\text{(CH}<em>{3}\text{)}\text{3NN}^+\text{O}<em>4\text{S C}</em>{12}\text{H}</em>{25} )</td>
</tr>
<tr>
<td>Bolaform</td>
<td>Two charged headgroups connected by a long linear polymethylene chain</td>
<td>Hexadecanediyl-1,16-bis(trimethyl ammonium bromide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \text{Br}^-\text{(CH}<em>{3}\text{)}\text{3N}^-\text{(CH}</em>{2}\text{)}\text{16}^-\text{N}^+(\text{CH}_{3}\text{)}\text{3Br}^- )</td>
</tr>
<tr>
<td>Gemini (or dimeric)</td>
<td>Two identical surfactants connected by a spacer close to or at the level of the headgroup</td>
<td>Propane-1,3-bis(dodecylmethyl ammonium bromide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \text{C}<em>{3}\text{H}</em>{6}\text{-1,3-bis[(CH}<em>{3}\text{)}\text{2N}^+(\text{CH}</em>{3}\text{)}\text{2Br} )</td>
</tr>
<tr>
<td>Polymeric</td>
<td>Polymer with surface active properties</td>
<td>Copolymer of isobutylene and succinic anhydride</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Copolymer structure" /></td>
</tr>
<tr>
<td>Polymerisable</td>
<td>Surfactant that can undergo homopolymerisation or copolymerisation with other components of the system</td>
<td>11-(acryloyloxy)undecyltrimethyl ammonium bromide</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Surfactant structure" /></td>
</tr>
</tbody>
</table>
Due to their characteristic aggregation behavior in solutions, a study of bulk properties of these materials such as surface tension, electrical conductivity, sound velocity, dye solubilization and light scattering etc. show dramatic changes over very small concentration ranges. These properties when measured as a function of concentration of the surfactant show curves with sharp inflections at the CMCs.

There are several textbooks and monographs published describing the aqueous solution behavior of surfactants [11-36]. Since most work in this thesis concerns with block copolymers, a brief discussion on these polymeric surfactants is provided below.

### 1.2 Polymeric Surfactants Block Copolymers in Solution:

Block copolymers are a special type of polymers in which each molecule consists of two or more segments of simple polymers (blocks) joined in certain arrangements. These copolymers are classified by the number of blocks each molecule contains; block copolymers with two, three, and more blocks are called diblock, triblock, and multiblock copolymers respectively. Some arrangements are linear, in which the blocks are connected end-to-end and some are in star arrangement, in which all of the blocks are connected via one of their ends at a single junction. Of course, more complicated arrangements are also possible. The number of
monomer types in a block copolymer may be less than or equal to the number of blocks. Thus, an ABC linear triblock copolymer (also called terpolymer) consists of three different monomers, whereas an ABA linear triblock copolymer consists of two monomer types. The different structures from block copolymers are schematically shown below.

Block copolymers self-assemble in solution in a selective solvent, i.e., good for one block and poor for the other and form stable micelles and a variety of structures [37-39]. A block copolymer has structural similarity to surface active agents and thus shows adsorption and aggregation.

**Figure 1.3** Amphiphilic block copolymers self-assemble into a supramolecular core-shell nanostructures in water called polymeric micelles.
Depending upon molecular characteristics of copolymers, solvant conditions and external factors like pH, temperature, pressure etc. different other morphologies are possible (as shown below).

Before CMT/CMC
- Molecules
  - Spherical
Above CMT/CMC
- Cylindrical
- Hexagonal Rods
- Lamellar

However, earlier studies on block copolymers were mostly carried out in nonaqueous solvents [37]. Formation and morphologies (spherical, cylindrical, lamellar, etc.) of such copolymer micelles in selective solvents have been investigated using different techniques. Similar morphological structures were observed from the microdomain formation in block copolymers with varying composition in solid state [40, 41]. The aggregation of block copolymers in selective solvents and microdomain formation in solid state seem to have important technological applications with several new emerging areas of applications, most notably in nanotechnology and controlled release of bioactive molecules [42-44]. Water-soluble block copolymers may have hydrophilic and hydrophobic moieties and in analogy to a conventional surfactant form micelles/aggregates. Aggregation of amphiphilic block copolymers in aqueous solutions has also been examined in details and the most extensively studied copolymers are the ethylene oxide-propylene oxide (EO-PO) based triblock copolymers [45-49]. Also, diblock copolymers with both hydrophilic blocks are important; they dissolve in water to form molecularly dissolved solutions but also form potentially useful micelle-like aggregates through polyion complex formation. In recent years, interest has developed in water-soluble ABC triblock copolymers [50] which form core-shell-corona micelles that can be pH or temperature-sensitive and thus act as good vehicles for controlled drug release [51]. Different techniques have been used to monitor the formation and microdomains (spherical, cylindrical, lamellar, etc.) of copolymers in solids and in selective solvents [Figure 1.4].
Figure 1.4 The possible structural changes in Self-assembled nanostructures for block copolymers.

1.2.1 PEO-PPO-PEO (Pluronic®) block copolymers:

A number of triblock poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) (Figure 1.5) copolymers have been commercially available since 1950’s under the generic name Poloxamers and the trademarks Pluronic® (BASF, Mount Olive, NJ, USA) and Synperonic® (ICI, Cleveland, UK). The triblock architecture is the result of the polymerization process where first a PPO homopolymer is synthesized (constituting the middle block of the copolymer) by the addition of propylene oxide to the hydroxyl groups of propylene oxide to the hydroxyl groups of propylene glycol, and then ethylene oxide is added at both ends of the PPO block to form the PEO end-blocks. Triblock copolymers PPO-PEO-PPO types are also available (and known as Meroxapols and Pluronic® R), as are tetra-functional block copolymers (known as Poloxamines or Tetronics®) formed by the addition of (first) propylene oxide and (then) ethylene oxide to ethylene diamine. Whereas typical surfactants afford a rather limited variation of their hydrophobic (tail) and hydrophilic (head) parts, PEO/PPO copolymers allow alteration of the hydrophobe/hydrophile composition and total molecular weight, as well as block
sequence. Such a flexibility in molecular architecture results in a wide range of amphiphilic properties, which can be controlled in small increments.

![Figure 1.5](image)

**Figure 1.5** The representative formula for Pluronic® copolymer.

A Pluronic® grid (Figure 1.6) was developed to provide graphic representation of the relationship between copolymer structure, physical form, and surfactant characteristics [52]. The possibilities of large variation in total molecular weight and block composition have led to a large number of products. Information on the molecular weight and composition of the PEO/PPO copolymers currently available from BASF. The molecular weights of the commercially available copolymers are typically in the 2000-20000 Da range and their PEO contents in the 10-80 wt% ranges.
Figure 1.6 Pluronic® and Pluronic® R grids showing physical state of block copolymers.

Pluronics® available in different molecular weights can be used for different applications. Figures 1.7 and 1.8 shown next illustrate the molecular characteristics of Pluronic® block copolymers which can be employed to explore certain role for an application. The marked shaded area in the figure provides a possible architecture for Pluronics® for certain use.

(a) Best detergency  (b) Best wetting
(c) Best defoaming   (d) Best foaming
(e) Best gels       (f) Best emulsions (w/o and o/w)
Chapter 1

General Overview

Figure 1.7 Pluronic® grids showing application of block copolymers for certain use.
These EO-PO based block copolymers are available in varieties of molecular configurations. The HLB values of these block copolymers play an important role in deciding their area of application.
Table 1.2 Molecular characteristics of different Pluronic® block copolymers
(Compiled from BASF datasheet 1998).

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>EO\textsubscript{11}PO\textsubscript{16}EO\textsubscript{11}</td>
<td>L35</td>
<td>1900</td>
<td>50</td>
<td>48.8</td>
<td>73</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{43}PO\textsubscript{16}EO\textsubscript{43}</td>
<td>F38</td>
<td>4700</td>
<td>80</td>
<td>52.2</td>
<td>&gt;100</td>
<td>31</td>
<td>&gt;70</td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{4}PO\textsubscript{22}EO\textsubscript{4}</td>
<td>L42</td>
<td>1630</td>
<td>20</td>
<td>46.5</td>
<td>37</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{6}PO\textsubscript{22}EO\textsubscript{6}</td>
<td>L43</td>
<td>1850</td>
<td>30</td>
<td>47.3</td>
<td>42</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{10}PO\textsubscript{23}EO\textsubscript{10}</td>
<td>L44</td>
<td>2200</td>
<td>40</td>
<td>45.3</td>
<td>65</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{6}PO\textsubscript{34}EO\textsubscript{6}</td>
<td>L62</td>
<td>2500</td>
<td>20</td>
<td>42.8</td>
<td>32</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{6}PO\textsubscript{32}EO\textsubscript{9}</td>
<td>L63</td>
<td>2650</td>
<td>30</td>
<td>43.3</td>
<td>34</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{3}PO\textsubscript{30}EO\textsubscript{3}</td>
<td>L64</td>
<td>2900</td>
<td>40</td>
<td>43.2</td>
<td>58</td>
<td>15</td>
<td>31.5</td>
<td>1.5</td>
</tr>
<tr>
<td>EO\textsubscript{19}PO\textsubscript{29}EO\textsubscript{19}</td>
<td>P65</td>
<td>3400</td>
<td>50</td>
<td>46.3</td>
<td>82</td>
<td>17</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>EO\textsubscript{76}PO\textsubscript{29}EO\textsubscript{76}</td>
<td>F68</td>
<td>8400</td>
<td>80</td>
<td>50.3</td>
<td>&gt;100</td>
<td>29</td>
<td>50</td>
<td>---</td>
</tr>
<tr>
<td>EO\textsubscript{6}PO\textsubscript{38}EO\textsubscript{6}</td>
<td>L72</td>
<td>2750</td>
<td>20</td>
<td>39.0</td>
<td>25</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{24}PO\textsubscript{36}EO\textsubscript{24}</td>
<td>P75</td>
<td>4150</td>
<td>50</td>
<td>42.8</td>
<td>82</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{53}PO\textsubscript{34}EO\textsubscript{53}</td>
<td>F77</td>
<td>6600</td>
<td>70</td>
<td>47.0</td>
<td>&gt;100</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{19}PO\textsubscript{43}EO\textsubscript{19}</td>
<td>P84</td>
<td>4200</td>
<td>40</td>
<td>42.0</td>
<td>74</td>
<td>14</td>
<td>28.5</td>
<td>0.6</td>
</tr>
<tr>
<td>EO\textsubscript{26}PO\textsubscript{40}EO\textsubscript{26}</td>
<td>P85</td>
<td>4600</td>
<td>50</td>
<td>42.5</td>
<td>85</td>
<td>16</td>
<td>29.5</td>
<td>0.9</td>
</tr>
<tr>
<td>EO\textsubscript{61}PO\textsubscript{40}EO\textsubscript{61}</td>
<td>F87</td>
<td>7700</td>
<td>70</td>
<td>44.0</td>
<td>&gt;100</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{104}PO\textsubscript{39}EO\textsubscript{104}</td>
<td>F88</td>
<td>11400</td>
<td>80</td>
<td>48.5</td>
<td>&gt;100</td>
<td>28</td>
<td>38</td>
<td>---</td>
</tr>
<tr>
<td>EO\textsubscript{113}PO\textsubscript{45}EO\textsubscript{118}</td>
<td>F98</td>
<td>13000</td>
<td>80</td>
<td>43.0</td>
<td>&gt;100</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{17}PO\textsubscript{60}EO\textsubscript{17}</td>
<td>P103</td>
<td>4950</td>
<td>30</td>
<td>34.4</td>
<td>86</td>
<td>9</td>
<td>19.5</td>
<td>0.01</td>
</tr>
<tr>
<td>EO\textsubscript{27}PO\textsubscript{61}EO\textsubscript{27}</td>
<td>P104</td>
<td>5900</td>
<td>40</td>
<td>33.1</td>
<td>81</td>
<td>13</td>
<td>21.5</td>
<td>0.04</td>
</tr>
<tr>
<td>EO\textsubscript{37}PO\textsubscript{56}EO\textsubscript{37}</td>
<td>P105</td>
<td>6500</td>
<td>50</td>
<td>39.1</td>
<td>91</td>
<td>15</td>
<td>21.7</td>
<td>0.025</td>
</tr>
<tr>
<td>EO\textsubscript{133}PO\textsubscript{50}EO\textsubscript{133}</td>
<td>F108</td>
<td>14600</td>
<td>80</td>
<td>41.2</td>
<td>&gt;100</td>
<td>27</td>
<td>29.5</td>
<td>0.8</td>
</tr>
<tr>
<td>EO\textsubscript{13}PO\textsubscript{69}EO\textsubscript{13}</td>
<td>L122</td>
<td>5000</td>
<td>20</td>
<td>33.0</td>
<td>19</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO\textsubscript{20}PO\textsubscript{69}EO\textsubscript{20}</td>
<td>P123</td>
<td>5750</td>
<td>30</td>
<td>34.1</td>
<td>90</td>
<td>8</td>
<td>16</td>
<td>0.005</td>
</tr>
<tr>
<td>EO\textsubscript{106}PO\textsubscript{63}EO\textsubscript{100}</td>
<td>F127</td>
<td>12600</td>
<td>70</td>
<td>40.6</td>
<td>&gt;100</td>
<td>22</td>
<td>24</td>
<td>0.1</td>
</tr>
</tbody>
</table>

A: Molecular Formula, B: Name of copolymer, C: Average molecular weight, D: wt% PEO, E: Surface tension of 0.1% copolymer at 25 °C (dyne/cm), F: Cloud points (CP), G: HLB (Hydrophilic lipophilic balance), H: CMT (Critical micellization temperature, °C), I: CMC (Critical micelle concentration in % w/v at 30 °C)
Chapter 1

General Overview

The Pluronic® block copolymers give rise to wide application possibilities. They gain advantage over conventional block copolymers due to some of their distinct characteristics such as biocompatibility, low toxicity (oral, skin & eye irritation, fish toxicity) and low immunogenicity. Pluronics® are commercially available in different molecular characteristics (total mol wt., % block).

The Pluronics® have been an interesting class of block copolymers and have been used extensively as dispersant/emulsifier/solubilizer/ and for rheology controller in different industries. In Biology they are used in surface modification of biocolloids. Preparation of mesoporous silica and nanoparticles, controlled release of bioactive molecules and synthesis of artificial blood are some of the areas where the Pluronics® play an important role.

1.2.2 Tetronics® block copolymer:

Ethylene oxide-propylene oxide block copolymers commercially available as linear (Pluronics®) and star shaped (Tetronics®) amphiphiles are well-known for their strong temperature dependant micelle formation and reversible thermo-rheological behavior. Pluronics® have been extensively investigated for their surface activity and micelle formation. However, the related X-shaped Tetronics® (Figure 1.9) were practically ignored until recently investigation as efficient pharmaceutical excipient [53-58]. These pH sensitive and thermodynamically stable Tetronics® are synthesized by the sequential reaction of the acceptor ethylenediamine molecule, initially with propylene oxide (PO) and then later with ethylene oxide (EO) precursors, resulting in a four branched arms, each one individually consisting of two -EO and -PO blocks (4 x 15 -EO units; 4 x 17 -PO units) attached to the central ethylenediamine core as shown in Scheme 1

![Representative formula for Tetronic® copolymers](image)

**Figure 1.9** Representative formula for Tetronic® copolymers
Chapter 1

General Overview

Figure 1.10 *X-shaped EO-PO based amphiphilic block copolymers self-assemble into a spherical supramolecular core-shell nanostructure (micelle) in water.*

Table 1.3 *Molecular characteristics of different Tetronic® block copolymers (Compiled from BASF datasheet 1998).*

<table>
<thead>
<tr>
<th>Copolymer</th>
<th>Mw</th>
<th>Total PO units</th>
<th>Total EO Units</th>
<th>HLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>T304</td>
<td>1650</td>
<td>16</td>
<td>12</td>
<td>12-18</td>
</tr>
<tr>
<td>T701</td>
<td>3600</td>
<td>56</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>T704</td>
<td>5500</td>
<td>56</td>
<td>48</td>
<td>N/A</td>
</tr>
<tr>
<td>T803</td>
<td>5500</td>
<td>60</td>
<td>44</td>
<td>N/A</td>
</tr>
<tr>
<td>T901</td>
<td>4700</td>
<td>72</td>
<td>12</td>
<td>1-7</td>
</tr>
<tr>
<td>T904</td>
<td>6700</td>
<td>68</td>
<td>60</td>
<td>12-18</td>
</tr>
<tr>
<td>T908</td>
<td>25000</td>
<td>84</td>
<td>456</td>
<td>31</td>
</tr>
<tr>
<td>T1107</td>
<td>15000</td>
<td>80</td>
<td>240</td>
<td>18-23</td>
</tr>
<tr>
<td>T1301</td>
<td>6800</td>
<td>104</td>
<td>16</td>
<td>1-7</td>
</tr>
<tr>
<td>T1307</td>
<td>18000</td>
<td>92</td>
<td>288</td>
<td>24-30</td>
</tr>
</tbody>
</table>

In this context, the two tertiary amine central groups play an essential role in conferring thermodynamical stability and pH sensitivity and enabling further chemical modifications in order to attain additional abilities. The molecular weight, EO/PO ratio, and hydrophile-lipophile balance (HLB) of poloxamine and the degree of protonation of the amine moieties strongly determine the self-associative behavior and temperature sensitiveness and, consequently, the performance as micellar carriers [58, 59-62]. Furthermore, the physicochemical conditions of the medium, particularly
the pH and ionic strength, can alter the extent of protonation of the ethylenediamine central group, perturbing the hydrophobic interactions that govern the self-assembly process.

Unlike Pluronic®, which undergo a transition from unimers to loose aggregates interpenetrated with water to dense micelles that almost entirely exclude water, Tetronic® do not form the same compact micellar structure as observed with Pluronic® [63, 64]. This may be due to presence of the X-shaped junction at the center of the polymer chain introduces extra free volume in the micelle and hinders the polymer chains from forming a more compact structure. It may also be possible that the tertiary amines are protonated (at neutral or lower pH) and thus entrain water into the core. Nivaggioli et al. found that the diameter of the micelle formed with Tetronic® T704 (Mw 5,500) is approximately 11.5 nm (in the 40-50°C temperature range), which is significantly smaller than that of the 16.2 nm micelle formed with Pluronic® P104 (Mw 5,900) [63]. This relatively small size and aggregation number of T704 micelles is another indication of the hindrance encountered by the copolymer chains to form a larger, more compact micelle structure. Spancake et al. reported that Tetronic® 1508 undergoes sol-gel transition at about 25~27°C when the concentration was 20~25% w/w [65]. Various grades of Tetronic® vary in small increments of hydrophilic-hydrophobic balance (HLB) depending on the length of the poly(propylene oxide) and poly(ethylene oxide) chains; this determines their solubility characteristics. It was reported that the CMC of Tetronic® 908 in water at 25°C is 0.06% w/w, while the CMC of Tetronic® 707 at same temperature is 0.005% w/w [66]. This because Tetronic® 908 has longer PEO blocks than Tetronic® 707, which makes the former one more soluble in water than the latter one.

1.3 Solubilization:

Solubilization represents one of the major challenges in formulation development nowadays since approximately 40% of the new compounds in drug discovery are poorly water-soluble [67]. This is of particular concern in the parenteral delivery field because the number of approved excipients is limited. Furthermore, currently used solubilizers such as Cremophor have been implicated in clinically important adverse effects and unfavourable alterations of the pharmacokinetics of drugs as shown for paclitaxel [68].
Several PEO-PPO block copolymers were approved by FDA and EPA as thermo-viscosifying materials and find application as direct and indirect food additives, pharmaceutical ingredients and agricultural products. The efficacy of cancer chemotherapy is limited by toxic side effects of anticancer drugs. The ideal scenario would be to sequester the drug in a package that would have minimal interaction with healthy cells, then at the appropriate time, release the drug from the sequestering container at the tumor site. To achieve this goal, various long-circulating colloid drug delivery systems have been designed in the last three decades. A common structural motif of all these long circulating systems, whether they be nanoparticles, liposomes, or micelles, is the presence of poly(ethylene oxide) at their surfaces. The dynamic PEO chains prevent particle opsonization and render them ‘unrecognizable’ by reticulo-endothelial system (RES). This invaluable advantage has promoted extensive research to develop new techniques to coat particles with PEO, techniques ranging from physical adsorption to chemical conjugation. From the technological perspective, the most attractive drug carriers are polymeric micelles formed by hydrophobic-hydrophilic block copolymers, with the hydrophilic blocks comprised of PEO chains. These micelles have a spherical, core-shell structure, with the hydrophobic block forming the core of the micelle, while the hydrophilic PEO block (or blocks) forms the shell. Block copolymer micelles have promising properties as drug carriers in terms of their size and architecture. The advantages of polymeric micellar drug delivery systems over other types of drug carriers include:
1. long circulation time in blood;
2. appropriate size (10-30 nm) to escape renal excretion but to allow for the extravasation at the tumor site;
3. simplicity in drug incorporation, compared to covalent bonding of the drug to the polymeric carrier; and
4. drug delivery independent of drug character [69].

The ability of PEO-coated particles to prohibit adsorption of proteins and cells depends on the surface density of PEO chains, their length and dynamics [70, 71]. However, only a few known block copolymers form micelles in aqueous solutions. Among them, AB-type block copolymers, e.g. poly(L-amino acid)-block-poly(ethylene oxide) [72-81] and ABA-type triblock copolymers, e.g. Pluronic® [82-89] have deserved special attention. Pluronic® is a triblock PEO-PPO-PEO copolymer, where PPO stands for poly(propylene oxide); the hydrophobic central PPO blocks form micelle cores, whereas the flanking PEO blocks form the shell, or corona which protects micelles from the recognition by RES. Pluronic® structure in aqueous solutions has been extensively investigated by many authors and was recently reviewed by Alexandridis and Hatton [90]. The phase state of Pluronic® micelles can be controlled by choosing members of the Pluronic® family with appropriate molecular weight, PPO-PEO block length ratio, and concentration. The hydrodynamic radii of Pluronic® micelles at physiological temperatures range between 10 and 20 nm, which makes them potential drug carriers. The incorporation of drugs into block copolymer micelles may be achieved through chemical and physical routes. Chemical routes involve covalent coupling of the drug to the hydrophobic block of the copolymer leading to micelle-forming, block copolymer-drug conjugates. Physical entrapment is a better way of loading drugs into micellar systems.

1.4 Instrumental techniques used for characterization of block co-polymer micelles:

In recent studies on aqueous solution behaviour of PEO-PPO-PEO block copolymers, several instrumental techniques (Table 1.3) have been employed to investigate the self-assemblies formed. These include static and dynamic light scattering [91-94], SANS [94-96], static and time resolved fluorescence [97, 98], FTIR [99], PGSE-NMR [100], microcalorimetry [101, 102], GPC [102, 103], surface
tension [104, 105], viscometry [106], oscillatory shear measurements [107-109] and sound velocity/ultrasonic absorption method [110, 111], etc.

Table 1.3 Instrumental techniques for characterization of block copolymer micelles.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Measurement</th>
<th>Information obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scattering:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Static Light Scattering (SLS)</td>
<td>Rayleigh scattering or light intensity</td>
<td>• Weight average molar mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radius of gyration</td>
</tr>
<tr>
<td>Dynamic Light Scattering (DLS)</td>
<td>Intensity-intensity autocorrelation function.</td>
<td>• Diffusion coefficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hydrodynamic radius</td>
</tr>
<tr>
<td>Small Angle X-ray Scattering (SAXS) &amp; Small Angle Neutron Scattering (SANS)</td>
<td>Scattering intensity $I(Q)$ vs. scattering vector($Q$)</td>
<td>• Weight average molar mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radius of gyration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Core radius</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Macro lattice structure</td>
</tr>
<tr>
<td><strong>Calorimetry:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isothermal titration calorimetry (ITC)</td>
<td>Enthalpy change($\Delta H$)</td>
<td>• Enthalpy of association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CMC</td>
</tr>
<tr>
<td>High-sensitivity differential scanning calorimetry (HSDSC)</td>
<td>Heat flow</td>
<td>• Enthalpy of association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cloud point(CP)</td>
</tr>
<tr>
<td><strong>Spectral:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuruclear magnetic resonance (NMR)</td>
<td>Chemical shift</td>
<td>• Dynamics on segmental level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CMT</td>
</tr>
<tr>
<td>Infrared Spectroscopy (IR) &amp; Fourier transfer infrared (FTIR)</td>
<td>Stretching vibrational frequency</td>
<td>• Dynamics on segmental level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CMT</td>
</tr>
<tr>
<td>Steady state &amp; Time resolved fluorescence</td>
<td>Decay curves and quenching rate</td>
<td>• Micellar equilibrium dynamics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aggregation number</td>
</tr>
<tr>
<td>Ultra-violet (UV-visible)</td>
<td>Optical density</td>
<td>• Drug/dye solubilization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CMC</td>
</tr>
<tr>
<td><strong>Tensiometry:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surface Tensiometry</td>
<td>Surface tension</td>
<td>• CMC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Area per molecule</td>
</tr>
<tr>
<td><strong>Microscopy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryo transmission electron microscopy (Cryo TEM)</td>
<td>Nanoparticulate image</td>
<td>• Size and shape</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Morphological features</td>
</tr>
</tbody>
</table>
Chapter 1  General Overview

Work plan:

The present thesis concerns with the aggregation and solubilization behavior of Pluronics® and Tetronics®. Studies on the effect of different kind of additives and even surfactants on block copolymers have been carried out. Several block copolymers with different molecular characteristics have been examined using physical methods like cloud points, viscometry and instrumental techniques like spectral (FTIR, NMR, Fluorescence) and scattering (DLS and SANS). The entire experimental work has been grouped into chapters 2-7; each chapter constitutes one manuscript. Of these 3 have already been published and 3 communicated (Please see the reprints attached in the end).

The experimental studied done are briefly discussed below:

**Chapter 2:** The solubilization of four phenolic antioxidants, namely p-hydroxybenzoic acid (PHBA), syringic acid, sinapic acid, and quercetin in micelles of an ethylene oxide (EO)-propylene oxide (PO) triblock copolymer Pluronic® P104 (EO_{27}-PO_{61}-EO_{27}, PPO mol wt =3540, % PEO=40) was examined at different temperatures, pHs, and in the presence of sodium chloride. The nano-size core-shell micelles of P104 characterized by dynamic light scattering had hydrodynamic diameter of about 18-20 nm with low polydispersity. Antioxidants induced micellization and micellar growth was observed. The critical micellar concentration (CMC), critical micellar temperature (CMT), cloud point (CP) of P104 decreased due to solubilization and interactions of antioxidants. The solubilization was favoured at higher temperature, pH and in the presence of salt and follows the order PHBA > syringic acid > sinapic acid > quercetin which corresponds to the trend in their aqueous solubility. The location of antioxidant in micelles observed from NOESY spectra. Structure and hydrophobicity of antioxidants were found to be governing factors for their interaction and location in the micelles.

**Chapter 3:** The commercially available polyethylene oxide (PEO)-polypropylene oxide (PPO)- polyethylene oxide (PEO) symmetrical triblock copolymers (Pluronics®) have been recognized as pharmaceutical excipients and used in a variety of applications. This paper reports studies on micellar and solubilization behavior of three PEO-PPO-PEO block copolymers viz. P103, P104 and P105 (same PPO mol. wt. = 3250 but different % PEO= 30, 40 and 50%, respectively) in aqueous solutions. Critical micellization concentration (CMCs), Critical micellization temperature
(CMTs), micelle size/polydispersity for copolymers with and without the drug nimesulide (NIM) are reported. The solubilization of NIM is significantly raised with increase in hydrophobicity (P103>P104>P105), concentration, temperature and in the presence of added salt. The copolymer hydrophobicity, temperature and the drug loading strongly affect micelle behavior. The micelle-water partition coefficient (P) and thermodynamic parameters of solubilization viz. Gibbs free energy (ΔG\text{so}), enthalpy (ΔH\text{so}) and entropy (TΔS\text{so}) were calculated. The solubilization site of the drug in different micellar solutions and its release from P103, P104 and P105 micelles in phosphate buffer saline (PBS) solution at 37 °C were examined. The kinetics of NIM exhibits burst release characteristics, which are believed to be controlled by degradation of copolymers. These studies were carried out to investigate the feasibility of Pluronics® as a release vehicle of nimesulide in vitro. From the results, it was concluded that Pluronic® based formulation might be practical for drug delivery.

Chapter 4: Solubilization of quercetin (QN), a hypolipidemic drug in aqueous micellar solution of a star-like octablock ethylene oxide-propylene oxide copolymer Tetronic® T904 covering different salt concentration, pH and temperature is investigated. The change in pH modulates the charge of the copolymer which alters the dibasic nature of the centrally located ethylenediamine moiety and makes T904 to undergo the deprotonation favouring self assembly. At low pH, the columbic repulsion among the positively charged amine groups of Tetronic® hinders the micellization while presence of salt facilitates it. The drug solubility data in micelles in aqueous/salt solutions determined by UV-Visible spectroscopy and micellar size with loaded drug from dynamic light scattering (DLS) are reported. Hydrophobic/anionic QN, deprotonates T904 and induces the micellization in acidic pH thus assists solubilization. The expected locus (site) of the QN in T904 micelles was successfully correlated by the significant and positive cross peaks obtained from two-dimensional nuclear Overhauser effect spectroscopy (2D-NOESY). The evaluated in vitro release profile employing different kinetic models explain the controlled release rate of drug from T904 micelles.

Chapter 5: The aqueous solution behavior of PEO-PPO-PEO block copolymer F88 (EO\textsubscript{103}PO\textsubscript{39}EO\textsubscript{103}), is investigated in the presence of aliphatic alkanols (C\textsubscript{2}, C\textsubscript{4}, C\textsubscript{6} and C\textsubscript{8}). The nonassociated polymer chains remain extremely hydrated in water, but aggregation in form of spherical micelles was evidenced, triggered by the interaction
Chapter 1: General Overview

of polymer chains with hydrophobic alkanol. We assume that hydrophobic interaction between PPO block of the copolymer and Alkanol promotes micellization, which increases further with introduction of higher chain length species. The critical micellization temperature (CMT), as measured by UV-Visible spectroscopy, indicates interaction of polymer chains with the alkanol bearing higher chain length, which triggers aggregation. The micelles were characterized by small angle neutron scattering (SANS) to elucidate the size and related micellar parameters. The gradual increase in the alkanol content increases the aggregation number, though the micelles were spherical in shape. We conclude that ethanol, due to its preferential solubility in aqueous phase, does not affect the aggregation. The alkanol with chainlength of C₄ to C₈ chain, interact with PPO block through hydrophobic interaction and shift the CMTs to lower values. The combined effect of inorganic salt (NaCl) and alkanols show enhanced micellar properties.

Chapter 6: Moderately hydrophobic poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) block copolymers [Pluronics® with 20 >% PEO< 80] form micelles in water with hydrodynamic diameter ca 20nm. The aqueous mixed systems of Pluronics® P103, P104 and P105 [Pluronics® with mol.wt. of PPO = 3250, % of PEO 30, 40 and 50 respectively] with cationic surfactants of the type alkyltrimethylammonium bromide (CₙTAB, n = 10, 12, 14 and 16) were studied in water and salt solution. It is apparent that presence of trace amount of cationic surfactant induces charge on nonionic Pluronics® micelles and leads to decrease in their size. The efficiency of surfactants to decrease micellar size depends on alkylchain length of surfactants. A representative system, P103-C₁₄TAB was chosen to investigate and compare the feasibility of Pluronic®-surfactants system with pure Pluronic® micelle as an in vitro release vehicle for hydrochlorothiazide (HCT); a hydrophobic diuretic drug with poor aqueous solubility. Pluronic®-surfactant systems were found to be more efficient for HCT loading; their loading capacity can be tuned by changing surfactant concentration and pH. P103 and P103- C₁₄TAB mixed micelles and the release profiles were established.

Chapter 7: The effect of three ionic liquids (ILs) 1-alkyl 3-methyl imidazolium tetrafluoroborates (Cₙmim BF₄ n= 4, 6, 8) on micellar solutions of an ethylene oxide-propylene oxide block copolymer (PEO-PPO-PEO), Pluronic® P103 was examined from scattering and NMR techniques. The ILs alter the cloud point and micelle size
dependant on their alkyl chain length and the results are discussed in terms of their behavior as cosolvent/cosurfactant. Cloud point data support the hydrogen bonding between the imidazolium cation and P103 while dynamic light scattering (DLS) and small angle neutron scattering (SANS) reveal that presence of ionic liquid is not conducive to the micelle formation of P103. The selective nuclear Overhauser effect (NOESY) indicates that the PPO block of the P103 interacts with the alkyl group of the C\textsubscript{n}mim\textsuperscript{+} cation by hydrophobic interaction. Through this kind of interactions, C\textsubscript{n}mim BF\textsubscript{4} and P103 can form mixed micelles. This result indicates that the presence of ILs hinders the micelle formation of P103 in solution and promotes P103 to orient at air/water interface.

Each chapter forms a manuscript (published/communicated/under communication). Therefore, some text in the introduction and experimental part of different chapter may look similar.

References


Chapter 1

General Overview


[75] M. Yokoyama, T. Okano, Y. Sakurai, H. Ekimoto, C. Shibazaki, K. Kataoka,


Chapter 1  General Overview