Poloxamine-based nanomaterials for drug delivery

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Poloxamine micelles
   3.1. Self-assembly process
   3.2. Drug solubilization and stabilization
   3.3. In situ gelling systems
4. Polymeric nanoparticles coated with poloxamines
5. Summary and perspectives
6. Acknowledgements
7. References

1. ABSTRACT

Poloxamines (Tetronic®) are X-shaped amphiphilic block copolymers formed by four arms of poly(ethylene oxide)-poly(propylene oxide) (PEO–PPO) blocks bonded to a central ethylenediamine moiety. Such a structure confers multi-responsive behaviour, namely temperature and pH-sensitivity. At relatively low concentrations but above the critical micellar concentration (CMC), poloxamines generate polymeric micelles. Due to the presence of a hydrophobic core, these nanocarriers are useful in the solubilization and stabilization of poorly water-soluble drugs. Moreover, chemical modification of the micellar core is feasible. These remarkable and unique features, compared to the well-known linear poloxamers, have motivated an increasing interest in the study and application of the branched derivatives in different emerging disciplines. The present review concisely overview the most important developments comprising the application of poloxamines in drug delivery, mainly as micellar carriers capable of enhancing drug solubility and stability, and also as surface modifiers in the technology of stealth polymeric nanoparticles. Their potential for the administration of drugs by different routes and the improvement of the drug bioavailability and therapeutic effect are discussed.

2. INTRODUCTION

Amphiphilic copolymers are particularly appealing materials owing to their capability of simultaneously displaying the performance of hydrophilic and hydrophobic polymers. The hydrophilic blocks are responsible of the water solubility of the individualized copolymer molecules and of creating an adequate interface with the aqueous environment when the hydrophobic blocks self-associate or adsorb onto hydrophobic surfaces. Stable colloidal systems based on amphiphilic copolymers can display a broad range of architectures; polymeric micelles, stealth nanoparticles, polymersomes, polyyrotaxane supramolecular structures and self-microemulsifying systems are being all them widely investigated in the design of drug delivery systems (1,2).

Polymeric micelles are the most genuine nanosized carriers based on amphiphilic copolymers that can be custom-designed to fit the physicochemical characteristics of the drug, the physiological constrictions of the administration route and the therapeutic demands of the pathological process (3). It is important to note that most approved drugs as well as the new chemical entities being tested as drug candidates display a low aqueous solubility that notably limits their bioavality (4).
Poloxamine-based nanomaterials

Amphiphilic copolymers that spontaneously aggregate in water lead to supramolecular structures with a hydrophobic core suitable to host poorly-soluble drugs, surrounded by a hydrophilic shell that contributes to physically stabilize the amphiphilic aggregate in the aqueous environment (5-7). Compared to the micelles formed by common low molecular weight surfactants, polymeric micelles have lower critical micellar concentration (CMC), greater thermodynamic and kinetic stability to withstand dilution, and enhanced drug solubilizing and stabilizing capability (8,9). Blood circulation time and control of drug release rate and site can be tuned through an appropriate choice of the copolymer architecture in order to fulfill therapeutic demands (10-13). Passive targeting of drug-loaded micelles to pathological sites with affected and leaky vasculature (tumours, inflammations, and infarcted areas) spontaneously occurs via the enhanced permeability and retention effect (14,15). Active targeting can be achieved anchoring specific ligand molecules, such as antibodies, to the shell in order to direct the micelle to specific cells (e.g., tumour cells) (16,17). Additionally, micelles made of stimuli-responsive amphiphilic block copolymers can specifically release the content in precise sites at rates finely controlled by an external activator (e.g., ultrasounds) or by self-regulation when the microenvironmental conditions change (18-23). Such a gathering of features confer the polymeric micelles the ability to perform as drug carriers capable of modifying drug pharmacokinetics and of increasing the efficacy and the safety of the treatments (24).

Poloxamines present a X-shaped structure made of an ethylenediamine central group bonded to four chains of poly(propylene oxide)-poly(ethylene oxide) (PPO-PEO) blocks. Regular poloxamines are synthesized by the sequential reaction of the acceptor ethylenediamine molecule first with propylene oxide (PO) and then with ethylene oxide (EO) precursors, resulting in a four-arm PEO-terminated molecular structure (Figure 1a). In the case of reverse-sequential poloxamines, the acceptor is primarily reacted with EO and afterwards with PO, leading to tetra-functional block copolymers displaying PPO terminal segments (Figure 1b) (25). In addition to the features displayed by their well-known linear counterparts poloxamer or Pluronic® (PEO-PPO-PEO triblock copolymers) which are common components of pharmaceutical micellar systems owing to their proved biocompatibility and temperature-sensitivity (10,26,27), the unique and more versatile structure of poloxamines provides them with multi-stimuli responsiveness. In this context, the two tertiary amine central groups play an essential role conferring thermodynamical stability and pH sensitivity and enabling further chemical modifications (e.g. methylation of the amine group; Figure 1c) in order to attain additional performances (28).

Poloxamines are commercially available in a wide range of EO/PO ratios and molecular weights under the tradename Tetronic® (Table 1; therein each poloxamine will be noted as T followed by the corresponding identification number). These two features determine their capability to self-assemble and to undergo sol-to-gel transition in physiological environment, and play a decisive role in their performance at interfaces such as adsorption onto nanoparticulated drug carriers.

Figure 1. Structure of a sequential (a), a reverse-sequential (b) and a methylated sequential (c) poloxamine.
Table 1. Currently available poloxamine varieties commercialized by BASF under the trade name Tetronic®

<table>
<thead>
<tr>
<th>Tetronic</th>
<th>Mw (Da)</th>
<th>EO units per block (a)</th>
<th>PO units per block (b)</th>
<th>HLB</th>
<th>Solubility in water at 25°C (w/w %)</th>
<th>Cloud point of 1% (ºC)</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>304</td>
<td>1650</td>
<td>3.7</td>
<td>4.3</td>
<td>12-18</td>
<td>&gt; 10</td>
<td>75</td>
<td>4.3, 8.1</td>
</tr>
<tr>
<td>701</td>
<td>3600</td>
<td>2.1</td>
<td>14.0</td>
<td>1-7</td>
<td>Insoluble</td>
<td>18</td>
<td>4.0, 7.9</td>
</tr>
<tr>
<td>901</td>
<td>4700</td>
<td>2.7</td>
<td>18.2</td>
<td>1-7</td>
<td>Insoluble</td>
<td>20</td>
<td>5.1, 7.6</td>
</tr>
<tr>
<td>904</td>
<td>6700</td>
<td>15</td>
<td>17</td>
<td>12-18</td>
<td>&gt; 10</td>
<td>74</td>
<td>4.6, 7.8</td>
</tr>
<tr>
<td>908</td>
<td>25000</td>
<td>114</td>
<td>21</td>
<td>&gt; 24</td>
<td>&gt; 10</td>
<td>&gt; 100</td>
<td>5.2, 7.9</td>
</tr>
<tr>
<td>1107</td>
<td>15000</td>
<td>60</td>
<td>20</td>
<td>18-23</td>
<td>&gt; 10</td>
<td>18</td>
<td>5.6, 7.9</td>
</tr>
<tr>
<td>1301</td>
<td>6800</td>
<td>4</td>
<td>26</td>
<td>1-7</td>
<td>Insoluble</td>
<td>16</td>
<td>4.1, 6.2</td>
</tr>
<tr>
<td>1304</td>
<td>10500</td>
<td>21.4</td>
<td>27.1</td>
<td>12-18</td>
<td>&gt; 10</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1307</td>
<td>18000</td>
<td>72</td>
<td>23</td>
<td>&gt; 24</td>
<td>&gt; 10</td>
<td>&gt; 100</td>
<td>4.6, 7.8</td>
</tr>
<tr>
<td>90R4</td>
<td>6900</td>
<td>16</td>
<td>18</td>
<td>1-7</td>
<td>&gt; 10</td>
<td>43</td>
<td>---</td>
</tr>
<tr>
<td>115R1</td>
<td>8000</td>
<td>5</td>
<td>30</td>
<td>1-7</td>
<td>Insoluble</td>
<td>20</td>
<td>4.8, 7.5</td>
</tr>
</tbody>
</table>

The varieties T707 (12500 Da, 70% EO) and T1508 (27000 Da, 80% EO) are discontinued. Data taken from BASF web page and from (44) and (49).

Figure 2. SciFinder results (up to July 2009) of the search on “poloxamine and micelle” and on “poloxamine and nanoparticle”. The height of the bars indicates the total number of references, the black columns referring only to journal papers.

Commercial applications of poloxamines cover the petroleum industry, where they are used at relatively high concentrations as anti-foaming and demulsifier agents (25,29), and the field of contact lens washing solutions in which poloxamines are incorporated to remove sorbed proteins and to enhance the comfort felling (30,31). Although still few, the studies carried out in the pharmaceutical and biomedical fields have shown the potential of poloxamines as components of transdermal formulations (32), as tissue scaffolds (33-36), and for nanoparticle engineering (37). Figure 2 shows the evolution in last two decades of the number of publications related to polymeric micelles of poloxamines and to poloxamines as components of surface modified nanoparticles for biomedical purposes. The gain in knowledge about toxicological properties and safety (37,38) and on the self-assembly at physiological conditions, together with the development of less time consuming methods for a precise quantification of poloxamines at complex samples (39,40), are expected to increase the interest in poloxamines as components of drug delivery systems. The main two sections below summarize the current state of art of poloxamines as micellar carriers and as stealth coatings of nanoparticles.

3. POLOXAMINE MICELLES

3.1. Self-assembly process
The molecular weight, the EO/PO ratio and the hydrophilic-lipophilic balance (HLB) of poloxamines strongly determine the self-associative behavior and the temperature-sensitiveness and, consequently, their performance as micellar carriers (41-43). Furthermore, the physical-chemical conditions of the medium, particularly the pH and the ionic strength, change the protonation extent of the ethylenediamine central group, perturbing the hydrophobic interactions that govern the self-assembly phenomena. Consequently, both structural parameters and stimuli-sensitiveness have an enormous impact on their performance as drug nanocarriers. According to the HLB
### Table 2. Thermodynamic parameters of micellization of T904 in aqueous solutions of different pH and ionic strength

<table>
<thead>
<tr>
<th>Medium</th>
<th>pH of the T904 solution</th>
<th>X_{cmc} (mole fraction)</th>
<th>ΔH_{mic} (kJ/mol)</th>
<th>ΔG_{mic} (kJ/mol)</th>
<th>ΔS_{mic} (J/molK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>8.5</td>
<td>2.69·10^{-6}</td>
<td>168</td>
<td>-49.56</td>
<td>701</td>
</tr>
<tr>
<td>pH 7.4 buffer</td>
<td>7.4</td>
<td>2.42·10^{-6}</td>
<td>161</td>
<td>-49.97</td>
<td>688</td>
</tr>
<tr>
<td>pH 5.8 buffer</td>
<td>5.8</td>
<td>7.00·10^{-6}</td>
<td>261</td>
<td>-61.15</td>
<td>1039</td>
</tr>
<tr>
<td>HCl 0.01M</td>
<td>6.0</td>
<td>7.00·10^{-6}</td>
<td>167</td>
<td>-61.15</td>
<td>735</td>
</tr>
<tr>
<td>NaCl 0.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCl 0.01M+NaCl 0.9%</td>
<td>6.0</td>
<td>7.00·10^{-6}</td>
<td>255</td>
<td>-61.15</td>
<td>1019</td>
</tr>
<tr>
<td>HCl 0.1M</td>
<td>1.2</td>
<td>1.08·10^{-3}</td>
<td>60</td>
<td>-48.40</td>
<td>478</td>
</tr>
</tbody>
</table>

Standard deviation was in all cases lower than 2%. Reproduced with permission from (42).

### Figure 3. Calorimetric profiles of the demicellization process, at 310 K, of 10% T904 solutions prepared in different media: water (open circles), pH 7.4 buffer (full down triangles), pH 5.8 buffer (full up triangles), HCl 0.1M (full squares), HCl 0.01M (open up triangles), and HCl 0.01M with 0.9% NaCl (open down triangle). Reproduced with permission from (42).

Poloxamine-based nanomaterials

The titration profile of poloxamines shows two inflection points that correspond to dissociation of both protons from the nitrogen atoms on the central ethylene diamine group. The pK_{a1} and the pK_{a2} are in the range 4.0 to 5.6 and 7.5 to 8.1, respectively. At a constant temperature of 25°C, the diprotonated form is the predominant one at pH values below 4, while the monoprotonated one is the predominant form in the pH range between the pK_{a1} and the pK_{a2}. Above pH 8 poloxamines are not protonated. The likelihood of micelles formation depends on the balance between the free energy of micellization and the free energy of protonation. As the pH decreases, the deprotonation-micellization becomes more difficult (44).

Isoperibol microcalorimetry has been used to gain insight into the energy associated to the micellization/demicellization process of poloxamines. Poloxamine micellization is an endothermic entropy-driven process owing to hydrophobic interactions between the PPO blocks. Experiments carried out with T904 revealed remarkable differences in enthalpy and CMC, depending on the composition of the medium (Figure 3) (42). The exothermic demicellization process of poloxamines resembles that of poloxamers, which takes place through hydrogen-bonding formation between the PEO blocks and water after breakage of water-water and copolymer-copolymer hydrogen-bonds (45-47). The thermodynamic parameters of T904 micellization in different aqueous media are summarized in Table 1. As the pH of the T904 solutions decreases, the CMC rises. The decrease in ΔH observed at pH 1.2 is related to an apparent reduction in the entropy-driven force for micellization (Table 2), which is due to the disturbance of the microenvironment around the PPO blocks in the diprotonated species and, hence, to the weaker hydrophobic associations generated. At acid pH, an increase in ionic strength results in a greater micellization enthalpy, which can be attributed to the shields of the ionic repulsions among the protonated ethylenediamine groups and to a salting-out effect on the PEO blocks that promotes hydrogen bonding (48). Transmission electron microscopy (TEM) micrographs of T904 30% systems, prepared and visualized at 20°C, clearly showed the influence of pH and ionic strength on the micellar size. 2-nm micelles were observed in HCl 0.1M, while in water and NaOH 0.02M the diameter was 10-20 nm. In phosphate buffers, the micelles presented a wider size distribution. Dynamic light scattering (DLS) experiments carried out at 37°C showed unimodal distributions with micellar radius increasing from 0.9 nm to 4 nm as pH increases (42). When comparing T904 with T304 and T1307, the micellization enthalpy ranked in the order T1307 ≥ T904 >> T304. The small T304 requires a remarkably greater concentration to induce the self-associative process and, once the micelles are formed, they are easily broken by dilution, which is related to their shorter PPO and PEO chains. The other hand, the length of both blocks has been also shown to exert a remarkable effect on the states of water in the poloxamine dispersions. Only free and bound water were evidenced, by differential scanning calorimetry (DSC) and FTIR, in 10 to 40% T304 and T904 aqueous dispersions. Bound water corresponded to 3 water molecules per EO repeating unit. T1307 aqueous dispersions also evidenced the presence of water at a third type of state: a monomolecular layer of interfacial water onto the EO units (1 water molecule per EO unit) (43).

A comparative study carried out in HCl 10 mM with almost all available poloxamines and a methylated
Table 3. CMC values estimated from surface tension measurements, pyrene fluorescence and solubilization of simvastatin in HCl 10 mM at 25°C

<table>
<thead>
<tr>
<th>Poloxamine</th>
<th>Self-aggregation concentrations (mM)</th>
<th>Surface tension</th>
<th>I₁/I₃</th>
<th>Minimum solubilizing concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>T304</td>
<td>12.1</td>
<td>6.06</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>T901</td>
<td>2.12</td>
<td>1.48</td>
<td>1.49</td>
<td></td>
</tr>
<tr>
<td>T904</td>
<td>0.29</td>
<td>1.04</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>T908</td>
<td>0.28</td>
<td>0.40</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>T1107</td>
<td>0.67</td>
<td>0.46</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Met-T1107</td>
<td>0.67</td>
<td>0.67</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>T1301</td>
<td>1.47</td>
<td>0.15</td>
<td>1.47</td>
<td></td>
</tr>
<tr>
<td>T1307</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>T150R1</td>
<td>0.88</td>
<td>0.09</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>

Reproduced with permission from (49)

Figure 4. Surface tension plots of poloxamines in HCl 10 mM at 25°C. Reproduced with permission from (49).

Three well-differentiated groups can be established according to the surface tension profiles (Figure 4) and the evolution of pyrene fluorescence as a function of poloxamine concentration [49]:

1. T304 shows the lowest surface activity and requires a high concentration to form micelles. Between 0.5 mM and 12 mM the surface tension rapidly decreases and then a plateau is reached.

2. T1107, met-T1107, T908 and T1307 present an almost constant slope in the semi-log plot. These varieties possess the lowest PO/EO ratio and, thus, the highest HLB. The I₁/I₃ ratio of pyrene fluorescence slowly decreases as the concentration of these poloxamines raises, showing a marked difference between the concentration at which the first changes in the I₁/I₃ ratio were observed and the concentration at which the plateau was reached. Compared to T1107, the methylated derivative (met-T1107) show a nearly superimposable profile, which means that methylation does not significantly alter the self-association of the poloxamine at acid pH.

3. T901, T904, T1301 and T150R1 are highly surface-active. These poloxamines have the highest PO/EO ratio and a low-to-medium HLB. The surface tension plots of these copolymers had an initial sharp slope up to 10⁻³ mM, followed by a second region of much lower slope. T1301 and T150R1 plots evidence a marked increase in the hydrophobicity of the environment when the unimers associate as micelles.

The CMC of the poloxamines (estimated applying different methods, Table 3) are in the same order of magnitude of those of related diblock and triblock PO-EO copolymers (including poloxamers). The longer the hydrophobic chains, the lower the CMC is. Nevertheless, the slope of the logCMC (proportional to the Gibbs energy of micellization, Figure 5) and the total hydrophobe chain length (0.019) was smaller than that previously found for diblock and triblock amphiphilic copolymers (0.041-0.056). Thus, the particular X-shape of poloxamines with the PO blocks separated in four arms notably influences the self-assembly process; the incidence of PO units on CMC being less marked [49]. SLS and DLS experiments indicated that micelles of water-soluble poloxamines are mainly formed by 3 to 14 unimers and posses a core with a radius of 2.5-3.5 nm and a total hydrodynamic radius of 5-12 nm. The greater the PO/EO ratio, the larger the micelles are as confirmed by TEM micrographs. The hydrophobic poloxamines T901 and T150R1 evidenced the coexistence of aggregates of varied sizes. Such behavior was also seen for T1301 systems although less markedly. It is interesting to note that the methylated derivative of T1107, which posses a permanent positive charge at the ethylenediamine central group, leads to micelles of markedly lower size. This means that although met-T1107 can self-assemble, a lesser number of unimers are gathered together in each single micelle. This behavior could rely on a stronger repulsion between the positively-charged central blocks and the steric hindrance of the bulky methyl group.

3.2. Drug solubilization and stabilization

The capability of poloxamine micelles to host relatively hydrophobic drugs and to increase their apparent solubility and/or to protect them against chemical or biological degradation has been already demonstrated for
medium. To overcome this problem, triclosan was
concentrations achieved by this drug in surfactant-free
(VREF), is limited due to the low
Enterococcus faecalis
(MRSA) and vancomycin-resistant
Staphylococcus aureus
relevant pathogens, including methicillin-resistant
(51). The antibacterial activity of triclosan against clinically
aromatic –OH moiety of the drug and the polyether chains
ability of generating hydrogen bonding between the
more complex behaviour due to the ionization of the drug
observed for triclosan in T1107 medium, although with a
5.6 when the temperature of the poloxamine solution rose
solubility of phenanthrene and pyrene were observed at pH
dependence of CMC values obtained from
pyrene fluorescence measurements on the total hydrophobe
length (i.e. four times the PO values of Table 1) of the
poloxamines. Reproduced with permission from (49).

relevant therapeutic agents, such as antifungal,
hypolipidemic, or antiviral drugs (50). The pH-
sensitiveness of T904 micellization was clearly reflected in
the amount of griseofulvin solubilized in 10% copolymer
solutions prepared in different media. Solubility of
griseofulvin in water is low and pH-independent (4 mg/100
ml). T904 micelles increased drug solubility 3-fold in HCl
0.1M and 6-fold under alkaline pH conditions (42). The
fraction of drug hosted by the micelles as well as the
amount of drug that was incorporated per gram of PPO
block clearly raised as the pH increased. These findings are
related to the influence of pH on the protonation and
hydrophobicity of the unimers and, consequently, on the
concentration and properties of the micelles. The lower the
pH is, the lower the number of micelles in the medium. As
reported for T803, protonation of the central diamine group
results in a shift in the CMC towards greater concentration
and in a decrease in the solubilizing ability in the post-
CMC region. A raise in pH from 4 to 10.3 increased the
apparent solubility of naphthalene, phenanthrene and
pyrene by one, two and three orders of magnitude,
respectively, in 5 mM T803. Similar increments in
solubility of phenanthrene and pyrene were observed at pH
5.6 when the temperature of the poloxamine solution rose
from 25 to 40°C (41).

pH-dependent solubilization has been also
observed for triclosan in T1107 medium, although with a
more complex behaviour due to the ionization of the drug
at extremely high pH-values (>10) and a more limited
ability of generating hydrogen bonding between the
aromatic –OH moiety of the drug and the polyether chains
(51). The antibacterial activity of triclosan against clinically
relevant pathogens, including methicillin-resistant
Staphylococcus aureus (MRSA) and vancomycin-resistant
Enterococcus faecalis (VREF), is limited due to the low
concentrations achieved by this drug in surfactant-free
medium. To overcome this problem, triclosan was
solubilized in T1107 dispersions at various pH values. As
expected, a decrease in CMC values occurred as pH
increased: from 0.61% at pH 2.0 to 0.16% at pH 12, as
determined by surface tension. Triclosan solubility rose
from 0.002 mg/ml in poloxamine-free medium to 0.62, 0.73
and 0.75 mg/ml in 0.5% solutions of T1107 prepared at pH
2.0, 5.8 and 7.4, respectively. An increase in the
poloxamine concentration up to 3% enabled the
solubilization of 17 mg of triclosan per ml at pH 7.4, owing
to an increase in the number of micelles in the medium.
Further increases in poloxamine concentration led to a less
pronounced solubility increase; 10% T1107 systems
solubilized ~30 mg/ml. This behavior is explained by the
incorporation of more unimers to the micelles, increasing
the size of the preexistent micelles but not significantly
their number. A similar finding has been reported for
solubilization of polyaromatic hydrocarbons by poloxamine
803 (41). In the case of a 10% T1107 solution, a sharp
growth in the size of micellar aggregates (from 190 to 500
nm) was observed by DLS when triclosan was incorporated
into the micelles up to saturation. Simultaneously, the
system became opalescent (51). Stability studies were
carried out to elucidate changes in the hosting performance
of the micelles as a function of time, under the regular
room temperature fluctuations of a formulation intended for
topical application. A sharp decrease in triclosan solubility
(below 30% and 10% of the initial level after one and two
months, respectively) was only observed for 1%
poloxamine concentrations. Greater poloxamine
concentration was capable to effectively maintain the drug
solubilized for three months. The failure of the 1%
poloxamine system was attributed to that the closeness to
the CMC (0.5%) may enable that small temperature
fluctuations result in the disassembly of the micelles,
releasing the drug to the unfavourable medium. Triclosan-
poloxamine systems can be freeze-dried and redispersed in
water maintaining the initial solubility performance. It is
worth to note that, despite the affinity of the drug for the
micellar core, triclosan-poloxamine systems showed an
antibacterial activity far better than triclosan alone
solubilization. This means that triclosan can be efficiently
delivered to the bacteria growth medium reaching a higher
concentration level. Inclusion of triclosan into poloxamine
micelles led to a more effective inhibition of MRSA and
VREF growth and to a very relevant antibacterial activity
against Staphylococcus epideridis biofilm (Figure 6) (51).

Triclocarban is an extremely poorly-water
soluble microbicide (~50 ng/ml) that displays a molecular
structure similar to that of triclosan, though without the
phenol group. Ionization of a ureide functional group at
pH-values above the pKa (~ 12) is supported by the
increase in the intrinsic solubility of the drug above this pH
from 50 to 300 ng/ml. When the solubility in T1107 and
T1307 polymeric micelles was investigated, solubility
gradually increased between pH 2 and 7.4 (up to 4 orders of
magnitude) and decreased slightly above pH 12 due to the
ionization and a more limited H-bonding interaction
(Figure 7) (52). In addition, the solubilization ability of
T1307 polymeric micelles was substantially higher than
that of T1107. T1307 possesses higher molecular weight and
Poloxamine-based nanomaterials

Table 4. Micellar size and size distribution (% intensity) of triclocarban-loaded 3, 5 and 7% T1107 and T1307 systems (polydispersity index 0.419-0.530)

<table>
<thead>
<tr>
<th>Poloxamine</th>
<th>Poloxamine concentration (%)</th>
<th>Peak 1</th>
<th>Peak 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Size (nm)</td>
<td>%</td>
<td>Size (nm)</td>
</tr>
<tr>
<td>T1107</td>
<td>8.03</td>
<td>82.9</td>
<td>89.81</td>
</tr>
<tr>
<td>3</td>
<td>8.89</td>
<td>68.8</td>
<td>64.11</td>
</tr>
<tr>
<td>7</td>
<td>6.51</td>
<td>56.5</td>
<td>112.7</td>
</tr>
<tr>
<td>T1307</td>
<td>8.05</td>
<td>52.2</td>
<td>76.4</td>
</tr>
<tr>
<td>5</td>
<td>8.97</td>
<td>53.3</td>
<td>54.3</td>
</tr>
<tr>
<td>7</td>
<td>6.03</td>
<td>37.0</td>
<td>50.3</td>
</tr>
</tbody>
</table>

Reproduced with permission from (52)

Figure 6. *Staphylococcus epidermidis* CFUs (Log10) in a biofilm assay after 30 and 90 minutes. The Log10(CFU) value at time = 0 was 6.65 ± 0.44 (n=3). Reproduced with permission from (51).

The influence of triclocarban loading on the micellar size was studied by DLS and compared to the size of drug-free nanocarriers. Two main populations were observed (Table 4). Small size aggregates (~6-8 nm) were in agreement with the presence of regular drug-loaded micelles; this size population decreased in intensity as the polymer concentration (and the drug loading) increased. In addition, larger aggregates in the ~65-110 nm range indicated the enlargement of the micelles due to the incorporation of triclocarban into the micellar core. It is worth mentioning that triclocarban/poloxamine systems were completely transparent, which means that micellar fusion was not involved in the aggregates enlargement process [51]. The solubility improvement achieved with the incorporation of triclocarban to the micelles led to a slightly broadening of the inhibition area of Gram positive *Staphylococcus aureus* and MRSA in plate assays.

Since the oral route is the most patient friendly and of first choice for most systemic long-term treatments, solubilization studies carried out with the hypolipidemic drug simvastatin were focused on the capability of poloxamines to effectively host and protect this drug in an acidic environment. As explained above low pH environments as of the gastric medium are the less favourable for micellization. Additionally, the stability of simvastatin lactone form can be compromised. Simvastatin exhibits a quite limited oral bioavailability because the drug predominantly exists in the poorly water soluble lactonic form at intermediate pH values (53,54). The drug undergoes reversible hydrolysis to the hydroxy acid form at both very low and alkaline pH values. Similarly to other polymeric micelles capable of stabilizing sensitive molecules (55), some poloxamines were able to protect simvastatin lactone from a gastric-mimicked environment, preventing hydrolysis to the open form. Simvastatin solubility was remarkably enhanced in micellar medium of poloxamines 1301 and 150R1, which posses the highest surface activity and provide micellar cores with a more hydrophobic environment (Figure 8). In quantitative terms, micellar solutions of 10% T901, T904, T908, T1107, met-T1107, T1301, T1307 and T150R1 raised the apparent solubility of simvastatin by a factor of 3.7, 8.5, 2.4, 4.7, 8.3, 391, 21, and 152, respectively. Furthermore, the lactone form predominates in the micellar systems constituted by T1301, T1307 or T150R1, which posses the longest PPO blocks. The apparent partition coefficients of lactone and hydroxy acid forms at pH 5 have been estimated as 53800 and 4200, respectively (53). The hydrophobic cores of T1301, T1307 and T150R1 are able to host the lactone species, which are the most hydrophobic ones, and to protect them efficiently against the hydrolysis caused by the surrounding acid aqueous environment. The relatively larger radius of the micellar core of T1301 explains the highest capability to load and to protect lactone molecules compared to the micelles formed by the other poloxamines. The unexpected relatively high solubilization observed in the hardly micellizable T304 solutions was explained by the raise in the pH of the medium caused by this poloxamine (>7), which prompted the lactone form of simvastatin to transform into a salt of the hydroxy acid form. On the other hand, the positive effect of the methylation of poloxamine 1107 suggests a higher drug/micellar core affinity.

Another relevant aspect related to the in vivo performance of polymeric micelles refers to their kinetic stability, which enables the micelles to remain assembled for long time after dilution (56). Recording the absorbance of simvastatin-loaded micelles (10% poloxamine in HCl 10 mM) when subjected to a sudden 26-fold dilution, three differentiated responses were evidenced: a) one fastly disintegrating group (T901, T904, T908 and T1107), b) one intermediate group (T304, T1301 and T150R1) that still maintain solubilized nearly 60% drug after one hour, and c) one very stable group formed by poloxamine 1307 and met-T1107. These two latter varieties combine a relatively good efficiency for protecting the lactone form and a high stability against dilution, owing the stabilizing effect of its larger PEO shell.

3.3. In situ gelling systems

The viscoelastic behaviour of poloxamines as a function of their concentration as well as the effect of several stimuli such as pH and temperature has attracted some attention (57). At room temperature, 10% poloxamine solutions show a mainly viscous behaviour (only loss modulus G’’ is quantifiable) with negligible storage
Poloxamine-based nanomaterials

![Graph showing TCC solubility vs T1307 concentration](image)

Figure 7. Dependence of triclocarban (TCC) solubility on T1307 concentration in media of different pH, expressed as ratio between the solubility in T1307 solution and in water. Reproduced with permission from (52).

![Graph showing molar solubilization capacity](image)

Figure 8. Molar solubilization capacity, i.e., the number of moles of simvastatin that can be solubilized by one mol of poloxamine at micellar state (white bars) and ratio of lactone to hydroxy acid forms of simvastatin in drug-saturated 10% poloxamine solutions in HCl 10 mM (circles connected with a line to serve as a guide to the eyes). Reproduced with permission from (49).

modulus (G’). When the solutions are heated, a sharp raise of G’ is often apparent; the sol-gel transition temperature being 35.7ºC for T1307 and 62.4ºC for T304 and T904 (Figure 9) (58). Similarly to other PPO-PEO block copolymers, poloxamines become less hydrophilic as the temperature rises owing to the progressive dehydration of the polyether blocks. This process promotes the formation of more micelles and, eventually, their packing into body centred cubic phase gels (59). The highest values of both G’ and G’’ occur at the temperature with the highest micellar volume fraction. At greater temperatures, the dehydration of PPO chains, and even of PEO blocks, causes the polymer to phase separate, and G’ and G’’ to decrease. For example, 50% solutions of T704 exhibited two transitions: the first (sol-to-gel) at 26ºC and the second (melting of the gel) at 53ºC (57). The differences in the gel temperature among poloxamines are explained by the length of PPO and PEO blocks. Compared to T304 and T904, T1307 has a greater ability to bind water to its structure because T1307 has sufficient EO groups per block for adopting a helicoidal conformation in which interfacial (freezing bound) water may exist. Interfacial water is easily lost during the heating process. Additionally, the hydrophobic association requires a minimum number of PO units per block. It was shown that for a given content in EO groups, the longer the PO block of Pluronics, the lower the gel temperature (60). These reasons explain the low gel temperature of T1307 compared to T904 and T304.

In the case of T904 and T908, a concentration of 30% is needed to observe gelation at 30-36ºC due to the transformation of the aqueous micellar solution into a crystalline phase (42,60). At room temperature, 30% T904 solutions behave as Newtonian viscous fluids disregarding the pH of the medium. The sol-to-gel transition was observed around 30ºC for solutions prepared in neutral pH. By contrast, in HCl 0.1M a negligible storage modulus was recorded, which clearly indicates that the copolymer chains cannot entangle when they are strongly protonated (42). Therefore, in highly acidic physiological environment it is not expected that T904 systems become gel-like. Such a dependence of the rheological properties on the pH of the medium notably determines drug diffusion rate at physiological temperature. Griseofulvin release profiles from 30% T904 solutions revealed that the diffusion coefficients obtained in HCl 0.1M (1.46·10^{-4}; s.d. 8.5·10^{-6} cm²/min) were almost twice those recorded at pH 7.4 phosphate buffer (0.89·10^{-4}; s.d. 8.7·10^{-6} cm²/min).

The sol-gel transitions of 20-25% w/w T1508 in water take place at 25-27ºC with a 4-fold increase in the apparent viscosity of the medium. Such an increase in viscosity did not decrease the degradation rate of aspirin as much as expected, which was attributed to the existence of a low viscosity microenvironment (1-10 mPa·s) within the network (10⁰ mPa·s). The existence of enough content in free water may explain the low viscosity at the microscopic level. The findings suggest that the sol-gel transition did not decrease the proportion of free water (61). In this sense, it was even observed a decrease in microviscosity as the temperature of poloxamine 704 increases above the critical micellar temperature, from 65 mPa·s at 35ºC to 35 mPa·s at 50ºC. This effect is explained by the increasing packing of the micellar cores as temperature increases (62).

Combination of the surface activity with the in situ gelling features has been used for the design of solid self-(micro)emulsifying delivery systems, S(M)EDDS, for poorly-soluble drugs, based on mixtures of poloxamines and polyglycolyzed glycerides (e.g., Labrasol®, Labrafac®, and Labrafil®) (58). Under the temperature and waving conditions of the gastrointestinal tract, S(M)EDDS can lead to microemulsions in situ with enhanced drug solubility and improved oral absorption (63,64). Mixtures of T304 and T904 with any glyceride led to homogeneous microemulsions once diluted in water. By contrast, T1307 was only miscible with Labrasol®, the most hydrophilic...
than in the glyceride-free poloxamine solution. To prepare the dispersions the solubility of griseofulvin was markedly greater in some glyceride evaluated. In some glyceride-poloxamine aqueous solutions. Reproduced with permission from (58).

**Figure 9.** Effect of temperature on the storage ($G'$, solid symbols) and loss ($G''$, open symbols) moduli of 10% Tetronic solutions. Reproduced with permission from (58).

4. POLYMERIC NANOPARTICLES COATED WITH POLOXAMINES

Nanoparticles are interesting delivery systems for intravenous administration of drugs, hormones, enzymes or contrast agents. Encapsulation in the nanoparticles offers protection over prolonged periods of time and enables systemic or targeted release (66-68). Nevertheless, the first generation of non-coated nanoparticles failed due to short vascular circulation lifetimes (69,70). In general, particles in the blood stream are rapidly recognized and captured by the reticuloendothelial system (RES) and thus cleared within short periods after their injection (71,72). Coating of nanoparticles with copolymers containing poly(ethylene oxide) (PEO) blocks (PEGylation) has attracted much attention in the last two decades in order to overcome these limitations (73). The hydrophobic blocks of the copolymer serve as anchorage points to the nanoparticle surface, while the PEO blocks make the particle surface non-charged and less hydrophobic, providing a mobile stealthy shell that hinders the recognition by RES (74,75). In the particular case of poloxamine copolymers, electrostatic interactions between their tertiary amine groups and certain anionic groups on the surface of the nanoparticles also contributes to a more efficient coating, but makes the thickness of the coating sensitive to the conditions of the medium (76). Immobilization of poloxamines on particle surface remarkably modifies the circulation time and the biodistribution when the length of the PEO chains exceeds a minimum. Interestingly, it has been shown that such a coating has not necessarily to occur before administration, but it may also happen in vivo if poloxamine solution is injected some time before the nanoparticles.

*In vitro* coating of the nanoparticles can be easily achieved by preincubation in 1.0% w/v solutions of selected poloxamines at room temperature. This concentration is well above the plateau of the adsorption isotherms (0.005 to 0.1%w/v) found for these copolymers and other structurally related polymers on polystyrene latex (77). The stealth effect of the coating layer is mainly determined by the length of the PEO chains and the EO/PO ratio. In general, the longer the PEO, the thicker the coating is. For example, T304 (4 EO per block), T904 (19 EO per block), T707 (50 EO per block), T1508 (60 EO per block), and T908 (114 EO per block) provide coating layers onto polystyrene with a thickness of 2.1, 4.6, 9.1, 11.7 and 15.5 nm, respectively. A thickness of 4 nm has been established as the critical threshold for steric stabilization against phagocytic uptake of large particles (78,79). On the other hand, a long PPO block promotes a better anchoring on the surface, but simultaneously renders a flatter adsorption of the poloxamine; i.e. less poloxamine molecules per area. Therefore, an adequate balance between EO and PO groups is required. The most promising results have been obtained with T904 and T908.

Microcalorimetric titration experiments revealed that, in general, the adsorption process of ethoxylated amphiphilic copolymers on polystyrene nanoparticles takes place in three sequential steps: a) an exothermic phase due to hydrophobic interaction of the copolymer and the particle surface; b) an endothermic phase due to interfacial micelle formation, which is the most relevant event and indicates that the adsorption is a mainly entropy-driven process; and c) an exothermic phase due to molecular rearrangements in the adsorption layer. This third step was
Poloxamine-based nanomaterials

Figure 10. Schematic view of the changes in the conformation of PEO and PPO blocks onto the nanoparticle surface when the poloxamine concentration in the medium raises.

only observed for high molecular weight copolymers (80). Recently, fine construction of sorption isotherms evidenced that adsorption of T908 onto polystyrene nanoparticles (232 nm) follows a bimodal pattern and that physiologically relevant changes in the conformation of the PEO chains occur as the adsorption progresses (81). At low concentrations, the isotherm follows the Langmuir profile up to a plateau observable at an equilibrium poloxamine concentration of 0.004-0.007% (3712 poloxamine molecules/nanosphere), which corresponds to a coating of 4.6 nm thickness. Then, the sorption increases again and a final plateau is reached at concentrations above 0.015% (12000 poloxamine molecules/nanosphere = 0.112 µmol/m²), which corresponds to a thickness of 9.5 nm. Since the radius of gyration of a PEO chain of T908 is 3.1 nm, the thickness at the final plateau should be 6.2 nm and not 9.5 nm. Such a discrepancy reveals that the PPO block also contributes to the thickness of the coating adopting loops and trails conformations. Furthermore, the increase in the thickness from the first plateau to the second one also reveals rearrangements in the conformation of the PEO chains at the nanoparticle surface (Figure 10). The first plateau may correspond to a mushroom-like conformation, in which the PEO chains are not completely extended towards the outer medium but some portions are in close contact with the surface of the particle. As poloxamine concentration in the outer solution increases, the surface of the nanoparticle becomes crowded with the copolymer. This causes a lateral compression of the PEO blocks and makes them to arrange in a direction perpendicular to the plane of the particle surface (brush conformation). Poloxamine adsorption remarkably increased (up to 15-fold) the viscosity of the colloidal systems, due to interactions and entanglements among the PEO chains of adjacent nanoparticles. Another difference with uncoated nanoparticles was that poloxamine adsorption beyond the second plateau prevented the activation of the complement system when placed in human serum. Therefore, nanoparticles coated with T908 at the saturation level are resistant to blood opsonization. At least 90% surface coverage is necessary in order to minimize the initiation of untoward immunological reactions (81).

Pioneering studies by the group of Illum and Davis demonstrated that the coating process enhances the hydrophilic character of polystyrene particles and dramatically reduces their interaction with peritoneal macrophages. The incidence of surface characteristics on the interaction of colloidal particles with mouse peritoneal macrophages (82) and liver cells has been studied both in vitro and in vivo (83). For example, the hepatic uptake of uncoated particles was 38.6% of the injected dose while those coated with T904, T908 or T1508 were only uptaken to 5.5, 4.9 and 2.3% extents, respectively. Similar results were reported by the group of Müller, who observed that T1508 was able to increase the nanoparticle levels in blood for up to 6 hours by a factor between 19 and 268 in comparison to untreated control nanoparticles. The levels in RES organs decreased while in non-RES organs (mainly kidneys, heart, brain and ovaries) remarkably increased (78). These findings have been explained by steric repulsive barriers imposed by the hydrophilic PEO blocks of poloxamines to particle-cell adhesion; the longer the hydrophilic chain, the greater the steric stabilization effect. The interaction with liver cells was further reduced in the presence of either autologous plasma or serum. A heat-stable (60°C for 15 min) serum component of molecular mass above 100 kDa was found to mediate this suppressive effect. Studies carried out with T908-coated gold nanoparticles confirmed that the coating modulates particle clearance by effectively blocking opsonization but still allowing for dysopsonization (i.e., preferential adsorption of albumin and apolipoproteins) (84). The prolonged circulation time enables particles coated with T908 to reach sites of induced inflammation in tight muscles (85).

Poloxamine-coated particles become splenotropic, making the spleen the primary site of clearance (86). After intravenous administration to rats, T908-coated particles mostly remained in blood up to 3 hours but the fraction accumulated in the rat spleen by a factor between 19 and 268 in comparison to untreated control nanoparticles. The levels in RES organs decreased while in non-RES organs (mainly kidneys, heart, brain and ovaries) remarkably increased (82). For example, the hepatic uptake of poloxamine-coated microspheres did not saturate splenic and phagocytic functions, but promoted a rapid and dominant uptake by the liver that resulted in a low blood concentration of microspheres. These results suggested an enhanced opsonic activity of serum and hemorul response following repeated administration of the coated microspheres. Further studies revealed that a single injection of T908-coated particles also dramatically affects the circulation half-life and the biodistribution of a second dose administered between 3 and 13 days latter. The second dose is rapidly recognized by the macrophages of liver and spleen and cleared from the body faster. This behavior can be reverted to the situation observed for the first injection when free T908 is injected as a bolus (30 mg per 150 g body weight) 1-3 hours before the second dose of coated nanoparticles (88). It was suggested that the poloxamine, as well as some poloxamers, can adhere to the hydrophobic domains or penetrate the lipid bilayer of macrophage plasmalemma through the PPO chain, creating a steric hindrance to the
Poloxamine-based nanomaterials

Table 5. Poloxamines used to coat nanoparticles with a stealth shell in order to enhance blood circulation time and to modify the biodistribution

<table>
<thead>
<tr>
<th>Nanoparticles</th>
<th>Poloxamine</th>
<th>Reference</th>
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<tr>
<td>Polystyrene</td>
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<td>43, 79, 81, 88, 92, 107</td>
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<tr>
<td>poly(methyl acrylate)</td>
<td>908</td>
<td>93, 94, 108</td>
</tr>
<tr>
<td>poly(butyl 2-cyanoacrylate)</td>
<td>908</td>
<td>95</td>
</tr>
<tr>
<td>poly(lactic acid)</td>
<td>908</td>
<td>95</td>
</tr>
<tr>
<td>poly(lactic-co-glicolic acid)</td>
<td>904, 908</td>
<td>96, 97, 99, 100, 101</td>
</tr>
<tr>
<td>poly(methyl methacrylate)</td>
<td>908, 1508</td>
<td>95, 97, 109, 110, 111</td>
</tr>
<tr>
<td>(Poly(beta-malic acid-co-benzyl malate)</td>
<td>304, 304, 704, 904, 908, 1504</td>
<td>76</td>
</tr>
</tbody>
</table>

interaction with the second nanoparticles. Alternatively, the free poloxamine can also cover the coated nanoparticles with a stealthier layer prolonging the circulation time. When the interval between the two injections was 2 weeks, poloxamine-coated particles again exhibited long circulation half-life (89). The guaranty that every successive administration of coated particles yields a similar circulation half-life is very relevant in the case of treatments that require several doses, such as cancer therapy. Overall, intravenous injection of poloxamine prior to particle injection has been shown as a successful approach to increase the blood circulation time of nanoparticles without altering macrophage phagocytic activity, but efficiently acting as stealth coats of the nanoparticles (90, 91).

Coating with poloxamines has been also explored as a way of promoting the lymphatic distribution of subcutaneously administered 60 nm-polystyrene nanospheres. Delivery of therapeutic agents to the regional lymph nodes requires a good spread from the injection site and a good uptake in the regional nodes. 70% of uncoated nanoparticles remained at the interstitial site even at 24 hours post-administration. By contrast, poloxamine-coated nanospheres could move easily through the interstitium owing to minimization of the interaction with the components of the gel-like matrix. This requires that the dimensions of the PEO chains exceed the range of the van der Waals attraction force. Poloxamines with less than 15 EO units (e.g., T901 and T904) are too short to prevent opsonization and, thus, the particles are sequestered by the macrophages of the regional lymph nodes. In particular, T904 notably enhances lymphatic absorption of the nanoparticles without altering macrophage phagocytic activity, but efficiently acting as stealth coats of the nanoparticles (90, 91).

Since the adsorption of poloxamines on polyester nanoparticles (PLA, PLGA and PHB) is in general less efficient than that on polystyrene nanoparticles (95), the possibilities of incorporating poloxamines to PLGA nanoparticles as structural components have been explored. Blends of PLGA:poloxamine (T904 or T908) have been used to obtain nanoparticles by an emulsification-solvent diffusion technique. The blend nanoparticles exhibit the copolymer at both the matrix and the outer face of the nanoparticles, notably modifying their electrophoretic mobility and enhancing physical stability through steric mechanisms without a significant increase in the nanoparticle size (99). In this regard, PLGA:poloxamine nanoparticles behave quite similar to PLGA:poloxamer F68 nanoparticles. Furthermore, the presence of poloxamine helps to maintain the stability of DNA during the biodegradation of the nanoparticles, rendering these colloidal carriers as promising gene vectors both for systemic and mucosal routes (100, 101). Poloxamines have been shown to self-assemble with DNA, through electrostatic, hydrogen bonding and hydrophobic interactions, resulting in negatively charged nanostructured materials with a conformation clearly different from that of lipoplexes and polypeplexes (102, 103). DNA-poloxamine 304 supramolecular assemblies were capable to deliver reporter and therapeutic genes to skeletal and heart muscle cells in vivo.

Similarly, solid lipid nanoparticles prepared with T908 have shown a modified protein adsorption pattern, compared to other nanoparticles, with a prevalence of adsorption of albumin and fibrinogen over immunoglobulin and complement activating proteins (which are not adsorbed) (104). Such a protein adsorption pattern explains the reduced uptake by the cells of the mononuclear phagocytic system and, thus, the prolonged circulation in blood. Furthermore, T908 prevented cytokine production by RAW 264.7 macrophages (105). Although the information regarding other poloxamines is scarce, poloxamines may show a trend similar to that observed for poloxamer: the shorter the PEO block, the greater the sorption of ApoE and ApoA-IV on solid lipid nanoparticles, which facilitate the targeting to the brain.

Chemically modified poloxamines have been also explored as coatings of nanoparticles. Introducing a terminal amine group at the end of each PEO block renders tetramine poloxamine that showed a greater stability of the adsorbed copolymer layer on polystyrene nanospheres but lower on PLGA nanospheres once incubated with serum in vitro (106). Compared to unmodified T908 which provided the polystyrene nanospheres with a 8.9 nm layer and
resulted in negatively charged nanoparticles (-12.5 mV), tetratermine poloxamines led to positive (+9.6 mV) 10.0 nm coatings. The free amino groups caused an increase in the phagocytosis in experiments carried out with non-parenchymal liver cells. When the amine groups were capped (acetylated), the coating was 10.2 nm, the surface recovered the anionic character (-10.6 mV) and the uptake by the cells was reduced, although it was still higher than for the unmodified nanoparticles. Minor differences were observed regarding biodistribution: tetratermine poloxamine enhances splenic uptake, while the capped poloxamine derivative reverts this effect and slightly enhances the fraction of nanoparticles at blood 3 hours after injection (97).

5. SUMMARY AND PERSPECTIVES

Poloxamines possess unique features compared to other PEO-PPO block copolymers, being responsive to changes in temperature, pH and ionic strength of the medium in the range of physiological values. The stimuli-sensitive conformation and hydrophilicity of the poloxamine unimers and micelles greatly affects the CMC, the in situ gelling phenomena, and the capability of the micelles to solubilize and stabilize the drug. On the other hand, poloxamine adsorption onto polymeric nanoparticles strongly determine mucosal uptake, blood circulation time, capture by the reticuloendothelial system, biodistribution, drug release kinetics and clearance. Therefore, poloxamines are revealed as versatile copolymers that may enable the preparation of drug delivery systems with customized performance.

6. ACKNOWLEDGEMENTS

This work was financed by MICINN (SAF2008-01679), FEDER and Xunta de Galicia (PGIDT07CSA002203P R), Spain. The authors express their gratitude to BASF Corporation for providing samples of Tetronic® varieties. The Agencia Española de Cooperación Internacional is also acknowledged for a PCI-Iberoamerica grant (MAE, A/016343/08).

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Poloxamine-based nanomaterials


Poloxamine-based nanomaterials


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**Abbreviations:** ApoE: apolipoprotein E; ApoA-IV: apolipoprotein A-IV; CMC: critical micellar concentration; DLS: dynamic light scattering; DNA: deoxyribonucleic acid; DSC: differential scanning calorimetry; EO: ethylene oxide; FTIR: Fourier transform infrared spectroscopy; MRSA: Methicillin-resistant *Staphylococcus aureus*; PEO: poly(ethylene oxide); PHB: poly(betahydroxybutyrate); PLA: poly(lactic acid); PLGA: poly(lactic-co-glycolic acid); PO: propylene oxide; PMMA: poly(methyl methacrylate); PPO: poly(propylene oxide); RES: reticuloendotelial system; SLS: static light scattering; S(M)EDDS: solid (micro)emulsifying drug delivery systems; T: Tetronic; TEM: transmission electron microscopy; USP: United States Phamacopeia; VREF: vancomycin-resistant *Enterococcus faecalis*.

**Key Words:** Amphiphilic copolymers, Drug solubilization, Drug stability, PEO-PPO block copolymers, Polymeric micelles, Poloxamines, Stealth nanoparticles, Tetronics, Review

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