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Recent developments in amphiphilic polymers – A review

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ABSTRACT

Amphiphilic polymers are unusual materials having both hydrophobic and hydrophilic parts. They have varied applications, as in drug delivery systems, tissue engineering, as surfactant in polymer synthesis, as compatibilizer in blend incompatible polymers etc. There are various methods used for preparing this novel compounds like general free radical assisted synthesis, group transfer polymerization, graft polymerization, reversible addition fragmentation chain transfer polymerization (RAFT), atom transfer radical polymerization (ATRP) etc. An attempt is made in this review to enlist the recent developments in the above-mentioned methods for the synthesis of amphiphilic polymers.

KEYWORDS

Amphiphilic polymer;
ATRP;
RAFT;
Drug delivery;
Hydrophilic;
Hydrophobic.

INTRODUCTION

Amphiphilic polymers are composed of hydrophilic ("water-loving") and hydrophobic ("water-hating") parts. They are important throughout industry in many applications (e.g. as emulsifiers)[1]. Structure of a typical amphiphilic polymer is given away in Figure 1. Recently, amphiphilic polymers have attracted substantial attention due to their special self-assembly ability to form nano-scale aggregates, which have wide functions such as encapsulation for controlled release of drugs and enzymes, ûllers, pigments, catalysts, adsorption materials etc. Momentous progress is been made in the design and synthesis of variety amphiphilic polymers[2–5]. Since amphiphilic polymers can simultaneously form self-assembled nanostructures, including rod, wire, lamella, sphere, vesicle, and LCM (large compound micelle), they are potentially useful as soft templates for regulating nanometer-sized inorganic materials[6].

Figure 1 : Molecular structure of an amphiphilic polymer having (black) hydrophilic and (white) hydrophobic parts

Amphiphilic copolymers prepared using general polymerization methods

Amphiphilic copolymers approachable to stimuli have emerged as one of the promising nano-carrier systems. In aqueous media, these polymers can self-

Review

assemble into various molecular structures and thus provide interiors able to non-covalently encapsulate the guest molecules[7–9]; moreover, the release of guest molecules can be activated by exterior stimuli, such as pH[10–15], glutathione[16], enzyme[17], temperature[18] and so on. Lu et al. synthesized pH sensitive amphiphilic copolymer using the pH-sensitive hydrophobic monomer 2-phenyl-1, 3-dioxan-5-yl methacrylate and the hydrophilic monomer 2-hydroxyethyl acrylate via free radical polymerization. Amphiphilic block copolymer prepared by them is illustrated in Figure 2. When the amphiphilic nanoparticles solution was adjusted to a pH of 5.5, the size of the nanoparticles increased from 167 nm to about 800 nm within a time interval of 24 h[19].

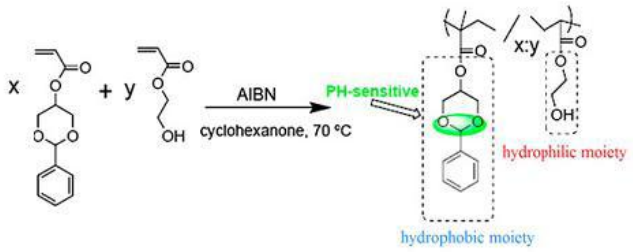

Figure 2 : Amphiphilic block copolymer prepared using 2-phenyl-1, 3-dioxan-5-yl methacrylate and 2-hydroxyethyl acrylate

Injectable materials developed recently have fulûlled many design criteria for diverse clinic applications[20]. Wang et al. synthesized injectable, photo-crosslinking amphiphilic copolymer made of caprolactone fumarate and ethylene glycol fumarate, found to be suitable for tissue engineering. Caprolactone fumarate induces the ability of photo-crosslinking whereas ethylene glycol fumarate increases the biodegradation and bio-compatibility of the copolymer to make it suitable for in-body applications. The structure of the copolymer synthesized is shown in Figure 3[21].

Highly ordered porous polymer films have attracted much attention due to their potential applications in areas such as tissue engineering[22,23], photonic band gap[24], and optoelectronic devices[25]. Porous films with ordered structures have been fabricated by a variety of methods[26,27], including lithography[28] or soft litho-graphy[29,30], the use of colloidal crystals[31,32], emulsions[33], self-assembled rod-coil copolymers[34,35], and microphase-separated block copolymers[36,37]. Kim et al. synthesized a new functional amphiphilic polymer containing ruthenium tris(bipyridyl) photosensitizer to prepare a honey-comb-patterned film. The amphiphilic copolymer was obtained by the radical copolymerization of ruthenium(4-vinyl-4'-methyl-2,2'-bipyridine) bis(2,2'-bipyridine)bis (hexa-flurophosphate) with N-dodecylacrylamide and N-isopropylacrylamide. Scheme for the synthesis of the novel amphiphilic polymer is shown in Figure 4. To prepare the ordered honey-comb structure a solution of the synthesized amphiphilic polymer and polystyrene in chloroform was cast on a glass Petri dish. After complete evaporation of the solution under a humid condition, an opaque film, having honey-comb structure, was obtained. The film is suitable for tissue –engineering application[38].

The self-association of amphiphilic block copolymers in aqueous media is an entropy driven process, which in the majority of cases leads to formation of spherical micelles comprising of hydrophobic core and hydrophilic shell[39,40]. The most extensively studied is the micellization of block copolymers of hydrophilic poly(ethylene oxide) and hydrophobic polyoxiranes such as poly(propylene oxide) or poly(butylenes oxide)[41,42]. In the case of PEO–PPO copolymers, the micellization is a temperature dependent process[43,44], as PPO exhibit the lower critical solution temperature at a relatively low temperature[45,46].

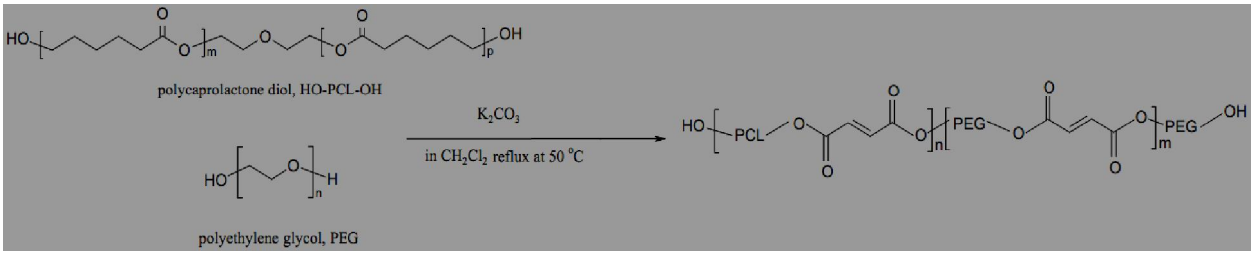

Figure 3 : Amphiphilic copolymer made of caprolactone fumarate and ethylene glycol fumarate

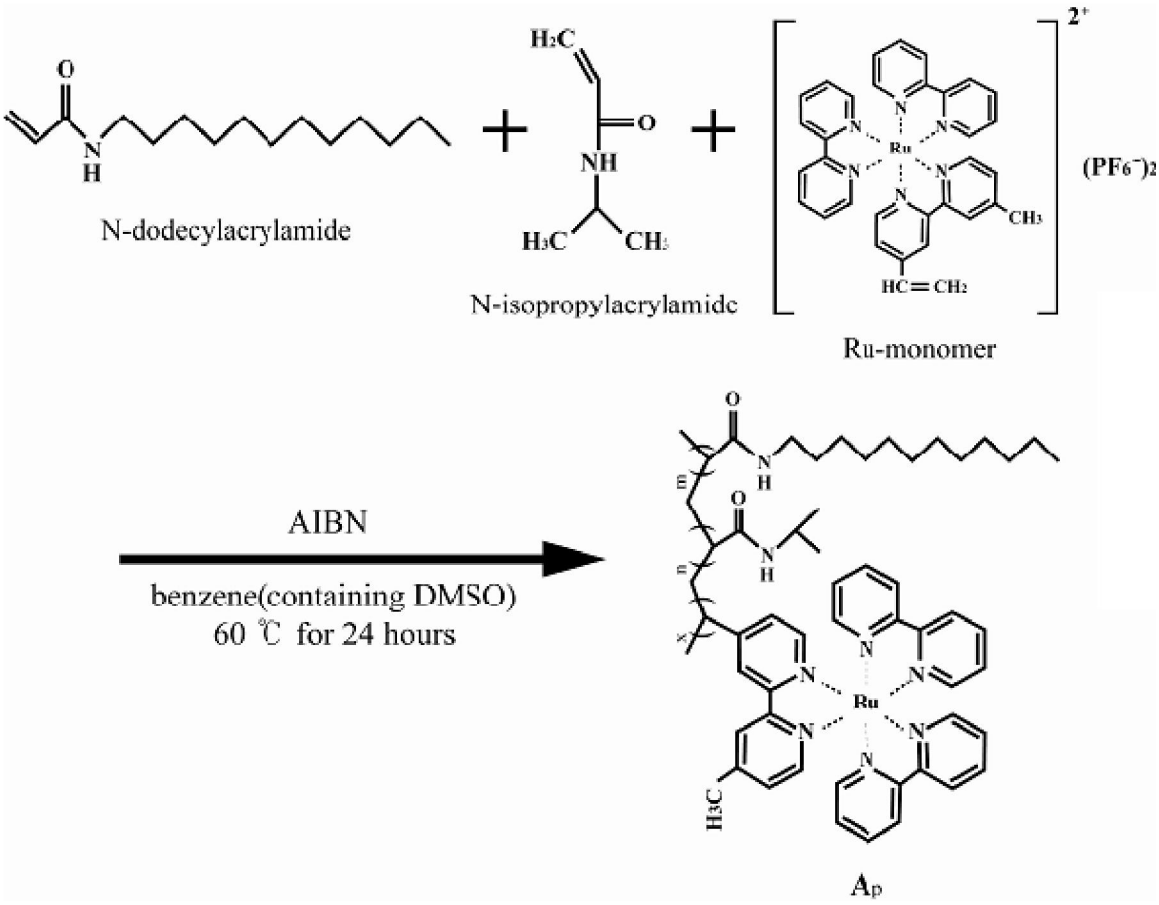

Figure 4 : Scheme for the synthesis of the novel amphiphilic polymer from ruthenium(4-vinyl-4'-methyl-2,2'-bipyridine)bis(2,2'-bipyridine)bis(hexaflurophosphate) with N-dodecylacrylamide and N-isopropylacrylamide

Star polymers and nanospheres obtained by cross-linking the cores of the diblock copolymer micelles. Liu et al. used photochemical reaction to stabilize poly(2-cinnamoylethyl methacrylate) based copolymers in organic medium[47–50]. Poly(ethylene oxide) (PEO) based copolymers bearing polylactide[51], poly (dimethylsiloxane)[52] or poly(1,2-butadiene)[53] as a hydrophobic block were synthesized and cross-linked via thermal, photochemical or g-irradiation initiations. Ishizu et al. reported the synthesis of polystyrene-b-poly(4-vinylpyridine) (PS-b-PVP) nanospheres that can be used as macro-initiator for the living free-radical polymerization[54,55]. Recently, nanoparticles have been built via intramolecular chain collapse of linear copolymers[56]. Cross-linking of the corona has also been developed for the preparation of PS-PVP knedel-like structures[57,58]. Nicol et al. synthesized amphiphilic copolymer using ethylene oxide and alkyl methacrylate and photo cross-linked the obtained nanoparticles of the copolymer in the aqueous medium. Mechanism for the preparation of the copolymer is shown in the Figure5. The cores of the micelles formed by Poly (ethylene oxide-methacrylate) were irreversibly cross-linked by UV irradiation. Star polymers that are stable under dilution in a good solvent were obtained after 1-min irradiation. Star shaped polymer prepared after UV irradiation is shown in Figure 6[59].

Tenkovtsev et al. prepared star-shaped amphiphilic copolymers with calix[8]arene core and amphiphilic alkyloligoethyleneoxide arms using the arm-ûrst approach. The effectiveness of these star-shaped block copolymers as phase-transfer agents was strongly regulated by its supramolecular organization in water. Methodology used for synthesizing the copolymer is shown]in Figure 7[60].

Adsorption of water-soluble amphiphilic block polyelectrolytes could potentially be utilized to modify the wetting properties of the charged surfaces. The polyelectrolyte block can be adsorbed onto the surface from aqueous solution, and the surface wettability could

Review

subsequently be modiûed by the hydrophobic block, given that during the modiûcation process the hydrophobic block ûnally ends on the uppermost layer of the modiûed surface (See Figure 8). Nurmi et al. synthesized ultra-thin ûlms of cationic amphiphilic copolymers and applied on the silica surfaces from aqueous solutions through electrostatic interactions, and the resulting modiûcation in the wettability of the surfaces was studied. The spin-coated surfaces were highly hydrophilic with rapidly dropping contact angles, whereas the surfaces prepared by adsorption had stable water contact angles between 30–60°[61].

When biodegradability is needed in the amphiphilic polymer, the hydrophobic block is generally the degradable one, and is usually a polyester, for example poly(lactic acid)[62], poly(lactic-co-glycolic acid)[63,64], poly(3-caprolactone)[65,66]. In particular, biodegradable AB[65], ABA[67–69], and multiarm[70,71] block copolymers containing Polyethyleneglycol and Polycaprolactone segments have been developed. Amphiphilic block copolymers of malic acid and malic acid esters have also been reported to self assemble in water[72]. Signori et al. prepared a new biodegradable–biocompatible amphiphilic block copolymers by $SnOct_2$ catalyzed ring

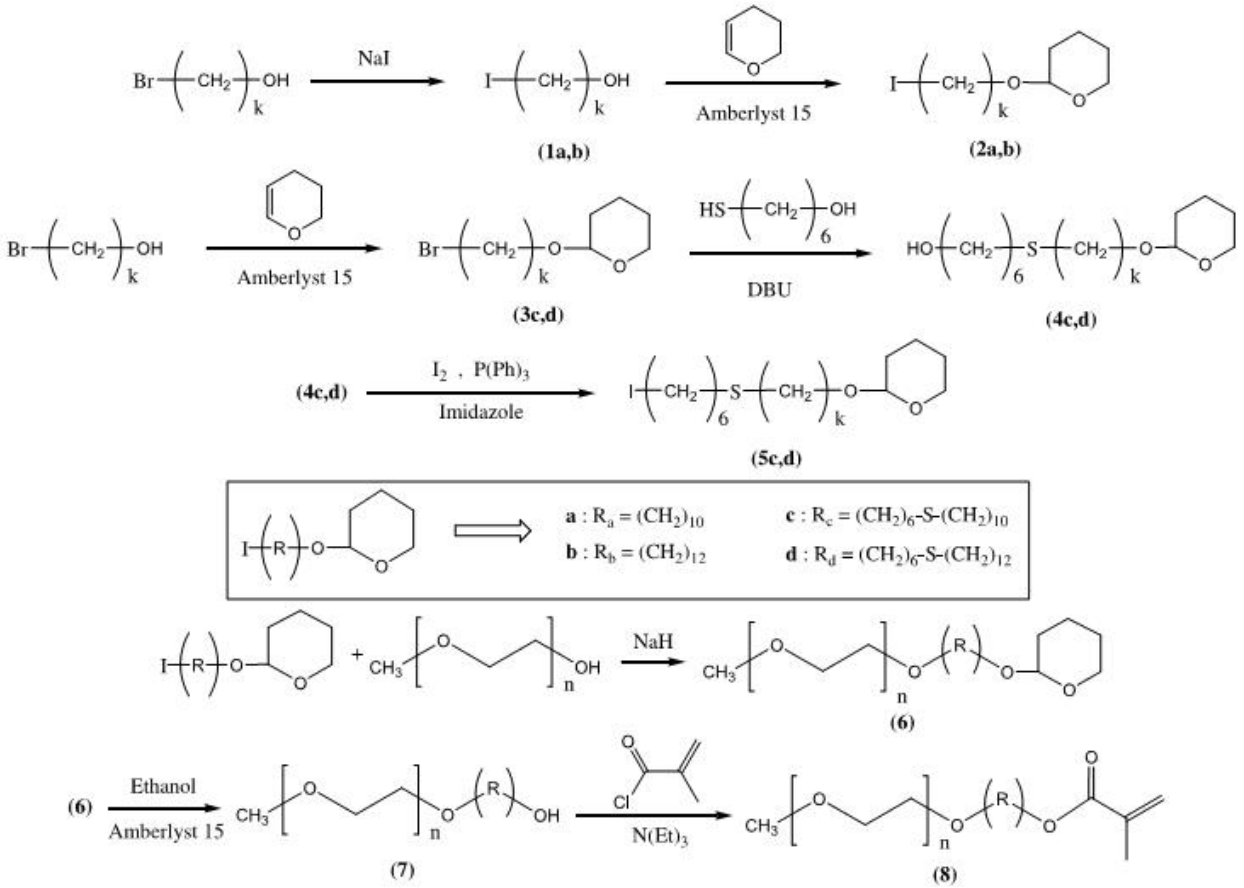

Figure 5 : Scheme for preparing diblock poly(ethylene oxide)-b-alkylmethacrylate amphiphilic copolymer

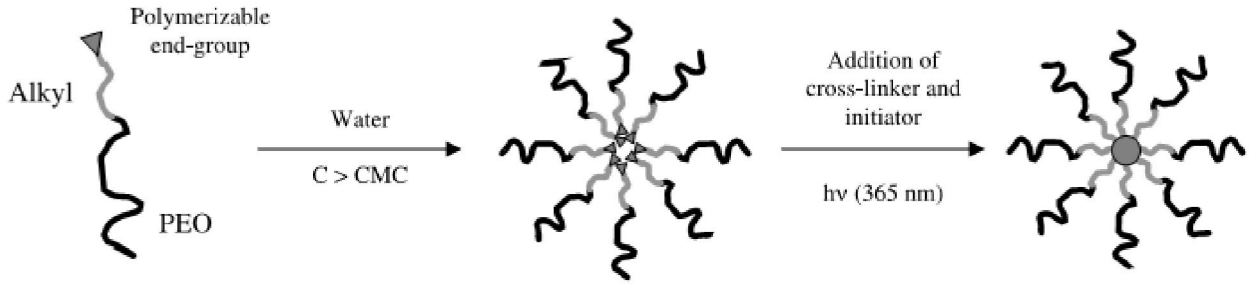

Figure 6 : Star shaped copolymer formed on UV irradiation

opening polymerization of 3-caprolactone initiated by monomethoxy-terminated poly(ethylene glycol). The lack of in vitro toxicity (indicated by cytocompatibility tests), and the hydrophilic–lipophilic balance supports the potential of the prepared polymer in the biomedical applications. Scheme of the preparation of the block copolymer is shown in he Figure 9[73].

Triftaridou et al. synthesized a amphiphilic ABC triblock copolymer from methylmethacrylate 2-(dimethylamino)ethyl mecthacrylate and hexa(ethylene glycol) methacrylate by group transfer polymerization. The presence of three different monomers placed in three different blocks unites three different functions into the polymer[74]. ABC triblock copolymer has sufficiently

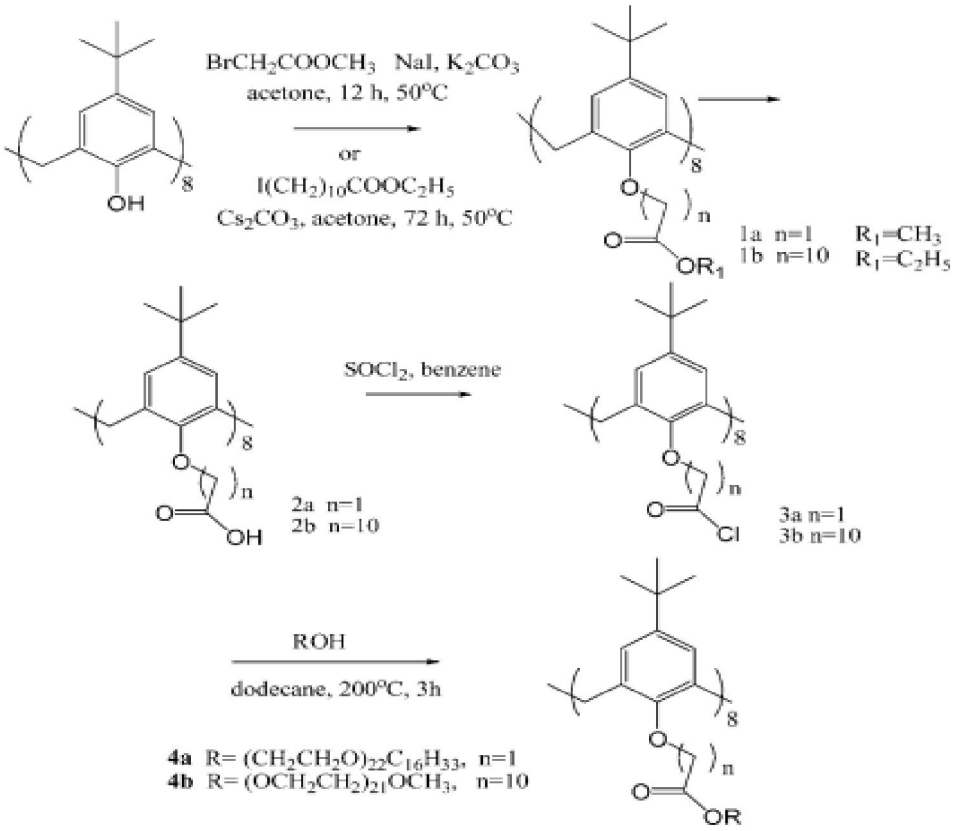

Figure 7 : The synthetic route to the star polymers

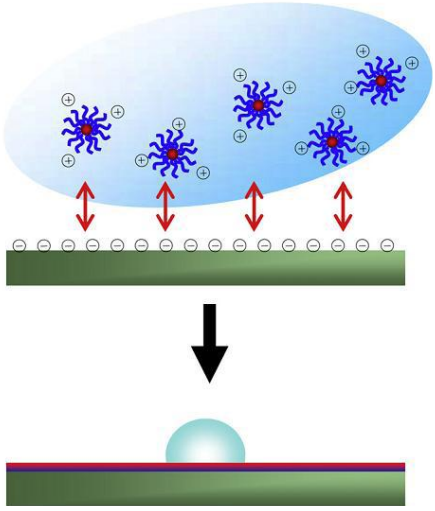

Figure 8 : Mode of working of amphiphilic copolymers in modification of surface properties of the substrate

high molecular weight and have three microphases in bulk. Figure 10 illustrates the micellar structure formed by the ABC triblock amphiphilic copolymer in the aqueous medium[75].

Use of atom transfer radical polymerization in the synthesis of amphiphilic copolymers

Atom transfer radical polymerization (ATRP) is a controlled polymerization method based on radical polymerization to prepare polymer. The Matyjaszewski research group developed a controlled polymerization, which was a simple and inexpensive polymerization system. It is capable of polymerizing a wide variety of monomers, is tolerant of trace impurities (water, oxygen, inhibitor), and is readily applicable to industrial processes. The system that was developed was termed

Review

Atom Transfer Radical Polymerization (ATRP). The control of the polymerization afforded by ATRP is a result of the formation of radicals that can grow, but are reversibly deactivated to form dormant species. Reactivation of the dormant species allows for the polymer chains to grow again, only to be deactivated later. Such a process results in a polymer chain that slowly, but steadily, grows and has a well-defined end group. ATRP remains the most powerful, versatile, simple, and inexpensive. ATRP mechanism is shown in Figure 11[76].

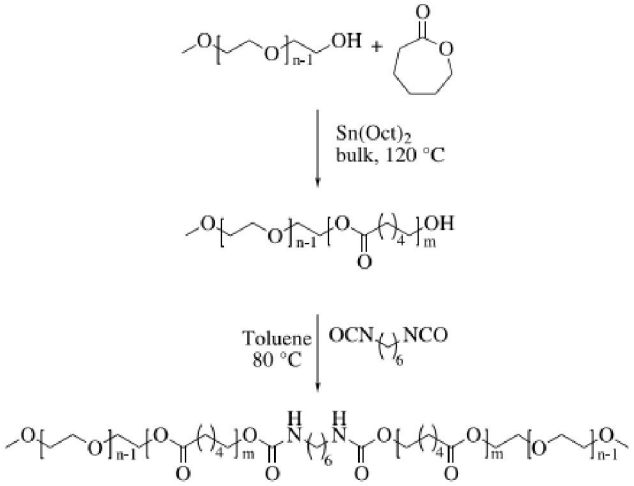

Figure 9 : Scheme for the preparation of 3-caprolactone and ethylene glycol

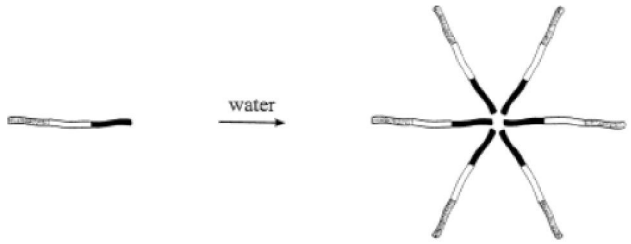

Figure 10 : Micellar structure formed by the prepared ABC triblock amphiphilic copolymer in water

$CaCO_3$ is the most important mineral in nature and is found in biominerals mainly as exoskeleton in shells or cell walls or as mechanical support in spicules and spines. Calcium carbonate has three anhydrous crystalline polymorphs: vaterite (polycrystalline sphere), aragonite (needle), and calcite (rhombohedra)[77]. Yang et al. synthesized a new class of amphiphilic triblock copolymers of poly(ethylene glycol)-block-poly(acrylic acid)-block-poly(n-butyl acrylate) was synthesized by atom-transfer radical polymerization, which tend to form a globular micelles in water solution. The single hydrophobic block formed the core and two ûanking hydrophilic blocks formed the corona. The micelle morphology of the amphiphilic triblock copolymer was efficient for controlling the crystallization behavior of calcium carbonate. Mechanism for formation of the triblock copolymer is shown in Figure 12[78].

Rigid macroporous polymer monoliths surfaced in the early 1990s and were found useful in separation, catalysis, sensors, and solid-phase extraction[79,80]. They should have uniform interconnected repeating macropores or cells. High separation efficiency can be realized with well-controlled skeletal structures. But, it is difficult to control the porous morphology of polymer monoliths prepared by traditional free radical polymerization because of the fast phase separation between the growing polymer chains and the porogenic solvents[81], giving aggregated microglobules at micrometre scale. Xin et al prepared a novel amphiphilic diblock copolymer using butyl methacrylate block and glycidyl methacrylate blocks via atom transfer radical polymerization (ATRP) and then utilized as a phase separator to control the porous structure of poly (butyl methacrylate-co-ethylene dimethacrylate) monoliths. The prepared porous structure had a well-definied skeletal structure as shown in Figure 13[82].

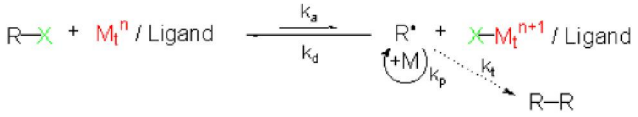

Figure 11 : Mechanism of working of ATRP

Star shape amphiphilic block copolymers generally contain linear arms. The block copolymers containing arms with globular structures by the incorporation of dendrons or hyperbranched structures are rarely synthesized. Frechet et al.[83-85] reported the synthesis of amphiphilic star block copolymers containing dendrons. These block copolymers contained 2- or 4-arm Polyethyleneglycol in core as a hydrophilic block and polyether dendrons in shell as hydrophobic block. An et al synthsized amphiphilic star block copolymers containing tetra-armed Polyethylene glycol core (hydrophilic part) and polystyrene having controlled number of branches and chain lengths as the shell (hydrophobic part). The number of branches per initiator functional group was controlled by the adjustment of the mole ratio of chloromethylstyrene to macroinitiator,

and the average chain length or branch length was controlled via adjustment of the mole ratio of styrene to chloromethylstyrene. Steps involved in the synthesis of the star copolymer is illustrated in Figure 14[86].

be accomplished through one of the three routes: 'grafting from' reactions (utilizing polymerization of grafts from a macroinitiator with pendant functionality), 'grafting through' processes (operating by homo- or

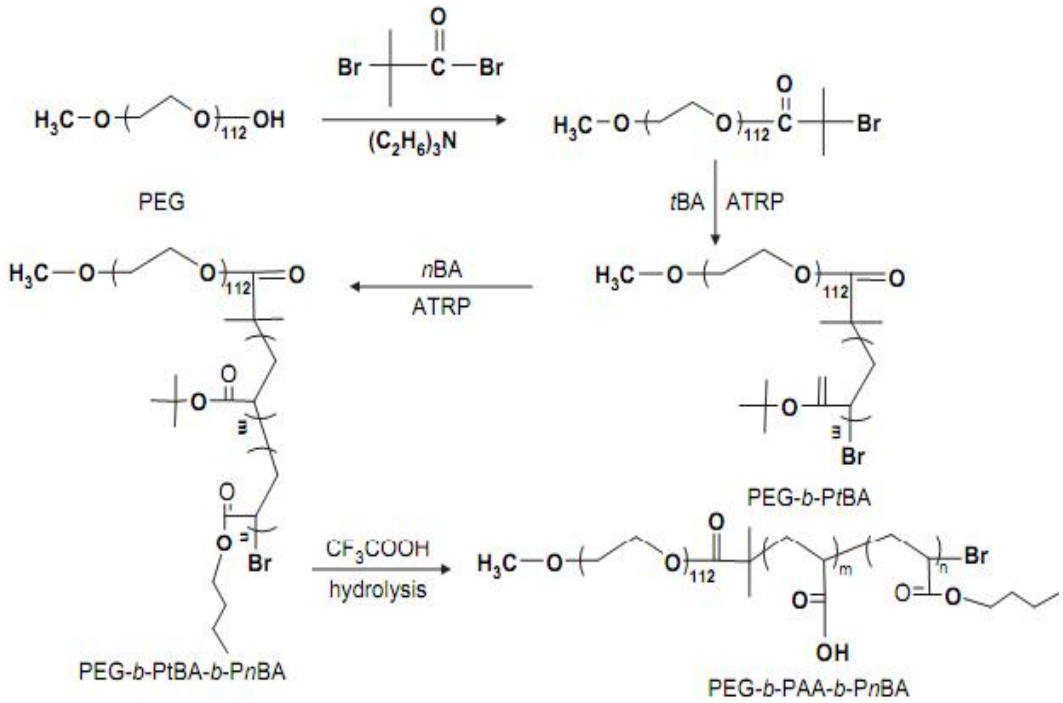

Figure 12 : Mechanism for formation of poly(ethylene glycol)-block-poly(acrylic acid)-block-poly(n-butyl acrylate)

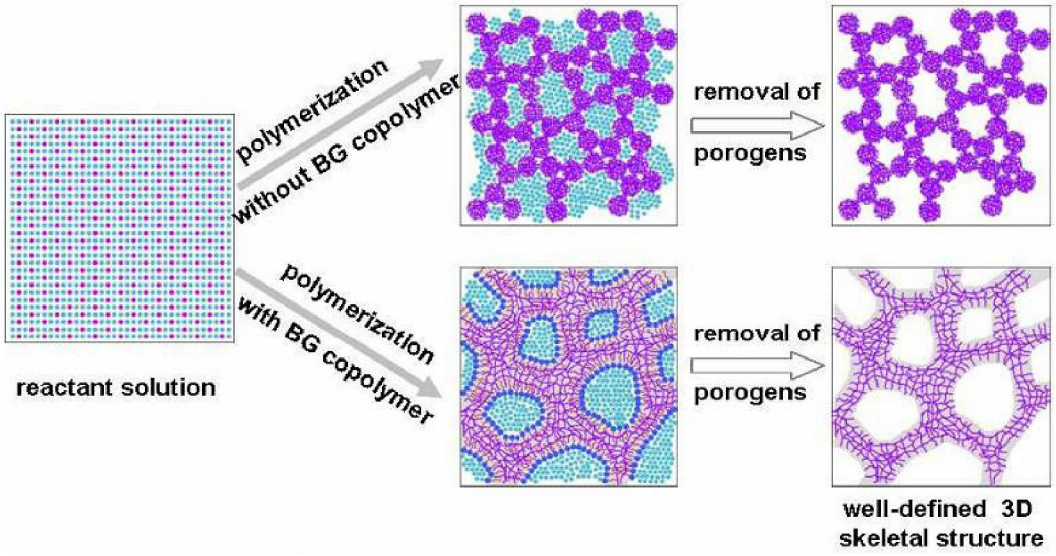

Figure 13 : Skeletal structure formed when using and using butyl methacrylate (B) – glycidyl methacrylate (G) copolymer

Brush-type copolymers have recently attracted considerable attention in a broad range of applications like drug carriers for targeted drug delivery, new class of elastomeric materials, sensitive to environment materials[87-89]. The synthesis of graft copolymers can

copolymerization of a macromonomer) and 'grafting onto' (occurring when the growing chain is attached to a polymer backbone)[90]. Hu et al. synthesized a series of polystyrene with different molecular weights and narrow molecular weight distributions via ATRP, and

then functionalized it by chloromethylation. Subsequently, the brush-type copolymers, Polystyrene-g-Poly (2-(dimethylamino)ethyl methacrylate) were prepared using chloromethylated polystyrene as the macroinitiator via ATRP. Mechanism for the synthesis is shown in Figure 15.] (46) [Chatterjee et al. synthesized amphiphilic block copolymers of 2-(dimethylamino)ethyl methacrylate and methyl methacrylate via atom transfer radical polymerization at ambient temperature (35 °C)[91].

polymerization. RAFT is one of the most versatile CRP techniques as it exhibits:

1. Good tolerance to a diverse range of functional groups in monomers,
2. Good tolerance to solvents and initiators, and
3. Offers control over a wide range of monomers through the use of different classes of chain transfer agents (CTAs).

Benefits of RAFT are:

1. It can be used to form narrow polydispersity polymers and copolymers, and
2. It is often possible to take the polymerisations to high conversion
3. RAFT polymerisation has been used to synthesise complex architectures such as block copolymers, stars, hyperbranched polymers and higher order supramolecular structures.

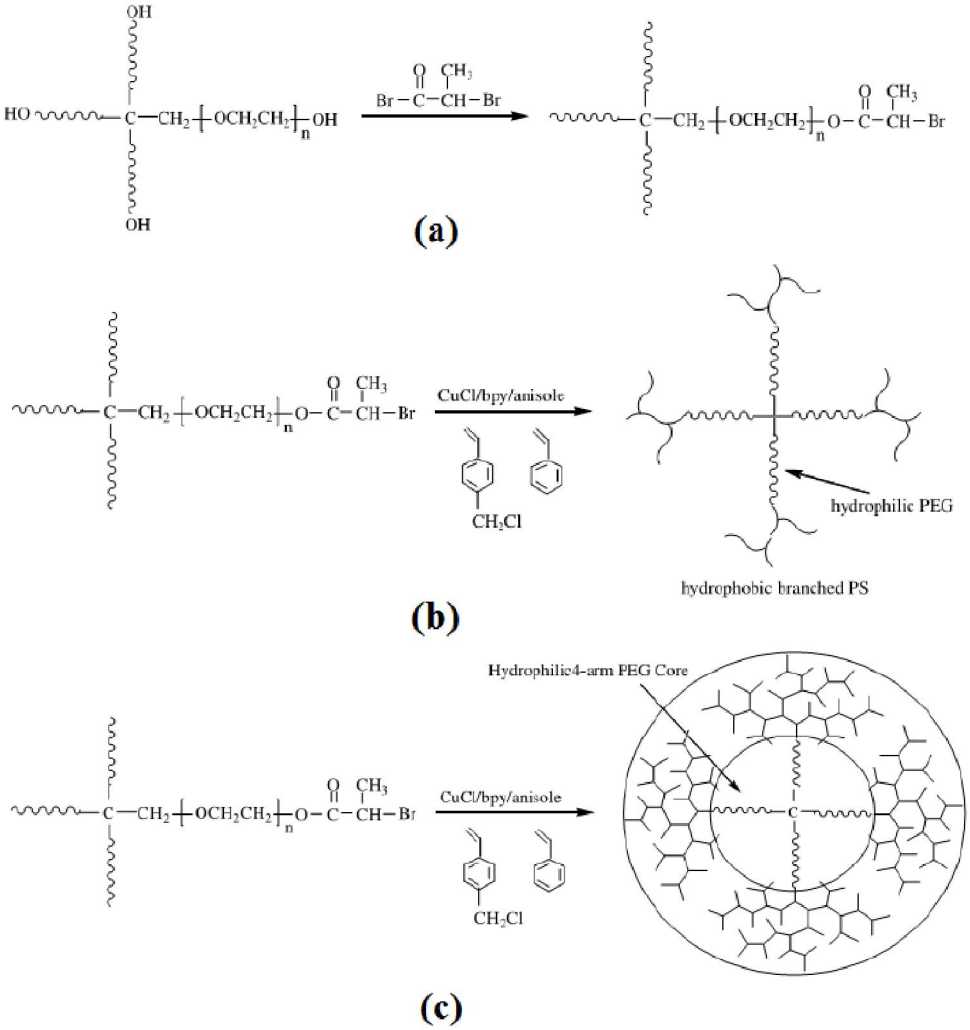

Figure 14 : Steps involved in the synthesis of the star copolymer from polyethylene glycol and polystyrene

Use of reversible addition–fragmentation chain transfer polymerization in the synthesis of amphiphilic copolymers

There has been great interest in the use of controlled radical polymerization (CRP) techniques, especially in reversible addition–fragmentation chain transfer (RAFT)

4. Compared with ATRP, RAFT is a metal-free process and therefore could avoid the contamination of the product by transition metal catalyst, which is vitally important for biomedical applications

Wong et al synthesized amphiphilic block copolymer, polystyrene-block-poly(N,N-di-methyl-acrylamide) (PS-b-PDMA), focusing on the inûuence of the sizes of the ûrst polymer block used in the chain

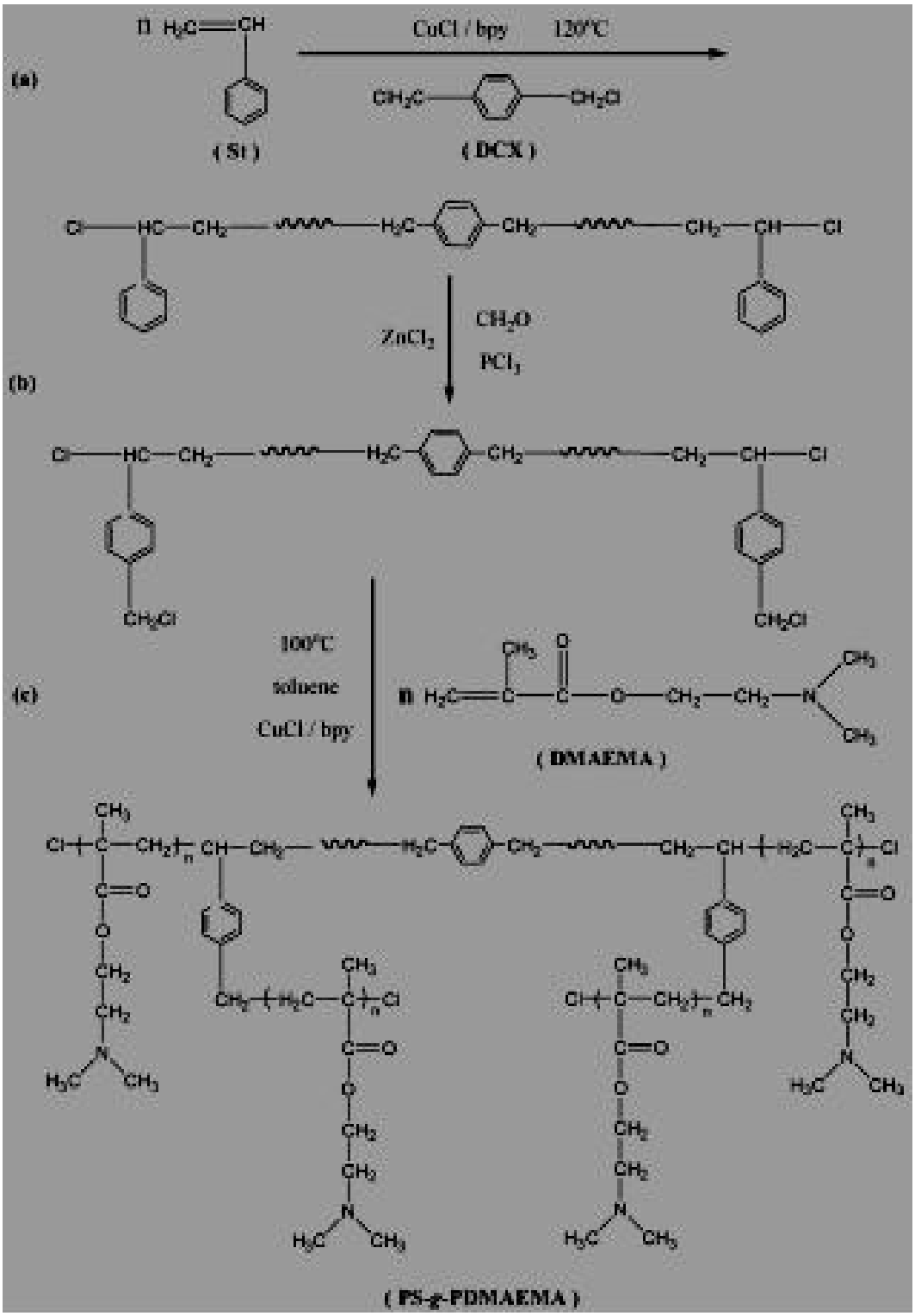

Figure 15 : Mechanism for preparation of Polystyrene-g-Poly (2-(dimethylamino)ethyl methacrylate) via ATR

extension polymerization process. These amphiphilic block copolymers were used to fabricate honeycomb structured porous ûlms using the breath ûgure technique. The regularity of the ûlm was considerably inûuenced by the humidity of the environment, which could be controlled by the rate of the airûow or the humidity in the casting chamber. The interaction between the hydrophilic block copolymer and the humidity was found responsible for the delicate equilibrium during the casting process, which prevented high pores regularity at very low (below 50%) and at elevated (above 80%) humidity. The interactions of the hydrophilic block with the humidity were observed to superimpose an additional nano-scaled order onto the hexagonal micron-sized porous array. Pores, which are created by encapsulation of water droplets, were found to be more hydrophilic than the surface. Scanning electron microscopy images of the prepared films at different humidity as shown in Figure 16[92].

effect on their pH-induced micellization behaviors. The Dynamic Light Scattering results showed that the mean size of the micelles was smaller than 60 nm with narrow and near-monodispersed size distributions. These pH-sensitive micelles might be useful for the targeted delivery of anticancer drugs[94].

Amphiphilic copolymers prepared using grafting

[Jeong et al. reported the synthesis of a new amphiphilic graft copolymer using poly(asparagine) as the backbone and poly(caprolactone), a semi-crystalline biodegradable polymer[95-99] as the graft (hydrophobic chains). Poly(asparagine) has an amide linkage, which is fully biodegradable, water soluble polymer and can be used as drug carrier. Scheme for the synthesis of the graft copolymer is shown in the Figure 17 and the schematic view is shown in Figure 18[100].

Peng et al. synthesized an amphiphilic copolymer with poly(acrylic acid) as the backbone and having

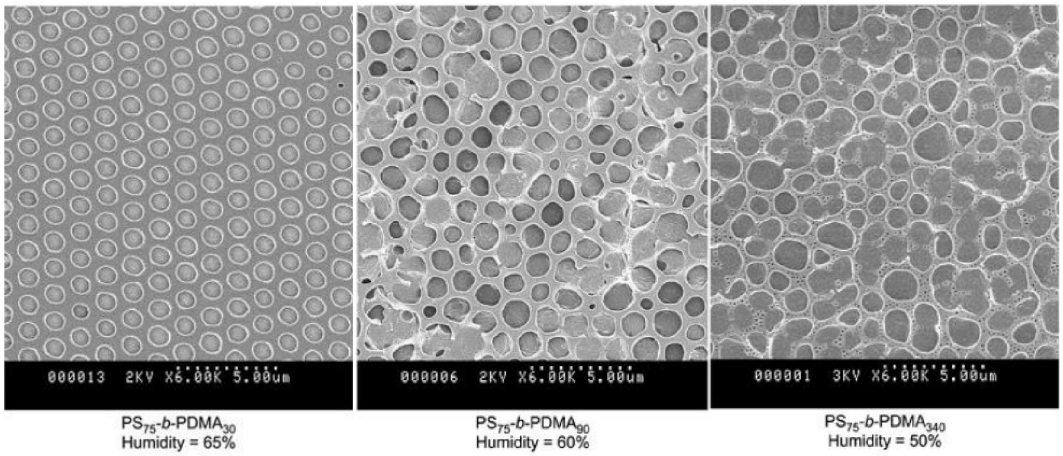

Figure 16 : Scanning electron micrographs of the films prepared

Lambert et al. prepared Poly(N-tert-butyl acrylamide-b-N-acryloylmorpholine) amphiphilic block copolymers via RAFT polymerization. Conversion reached 90% with a linear increase of the MW up to 60-70% conversion. Poly(N-acryloylmorpholine) chains of 10 000-90 000 g mol^{-1} could be grown from a poly(N-tert-butyl acrylamide) ûrst block of 14 000 g mol^{-1}[93].

Hu et al. investigated synthesis and pH dependent micellization of 2-(diisopropylamino)ethyl methacrylate based amphiphilic diblock copolymers via RAFT polymerization using 1,4-dioxane. The hydrophilic/ hydrophobic balance of the copolymer had no apparent

polystyrene side chains. Scheme for the synthesis of the copolymer is shown in Figure 19.

These amphiphilic graft copolymers can form stable micelles in water. Preliminary studies showed that they have a low cmc values of about 10^{-7}g/mL. The shapes and sizes of micelles were found to be related with the micellar preparation methods. The sizes of micelles increased with the addition of NaCl to water and decreased at high pH values[101].

Chiu et al. investigated the synthesis of amphiphilic graft copolymer from stearyl methacrylate and poly(ethylene glycol). Encapsulation of pyrene (as a drug model) into the micelles was found to be dependent on

their stearyl methacrylate content. These copolymers also exhibited a sustained release pattern for pyrene in aqueous solutions and might indicate their future applications as potential drug delivery systems[102].

compositions. These copolymers have proven to eûciently improve the interfacial adhesion and accordingly the mechanical properties of the compatibilized composites, leading to stiûer and tougher composite materials.

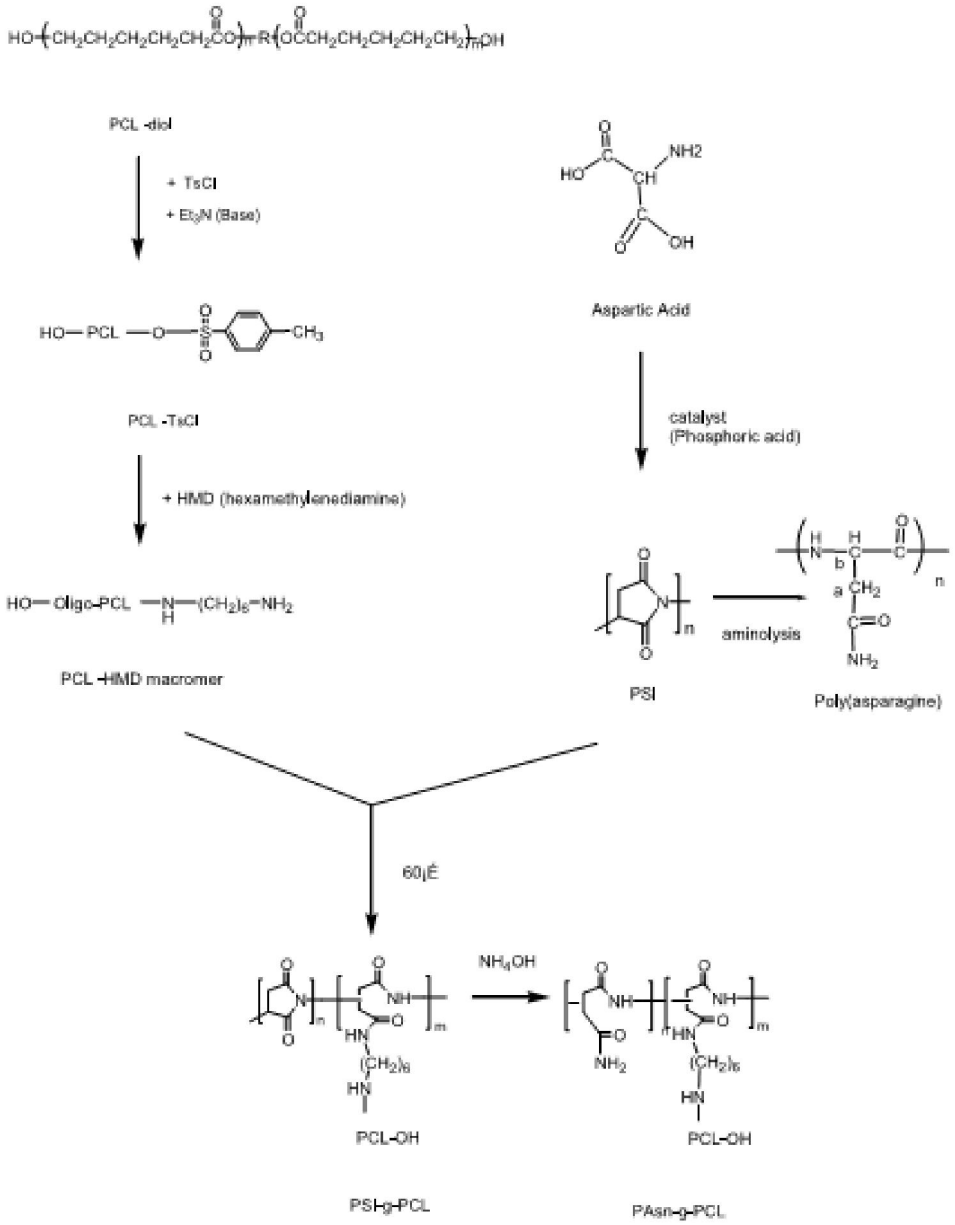

Figure 17 : Scheme for the synthesis of the graft copolymer poly(asparagine)-g-poly(caprolactone)

Considerable effort has gone to the development of biodegradable polymers initially with the purpose of designing resorbable biomaterials in surgery and chemotherapy, and more recently for developing plastics that degrade more rapidly in the environment when discarded. Rutot et al. reported the controlled synthesis of poly(ε-caprolactone)-grafted dextran copolymers and their eûciency as compatibilizers in PCL/granular starch

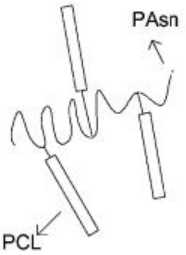

Figure 18 : Schematic view of the prepared graft copolymer

Review

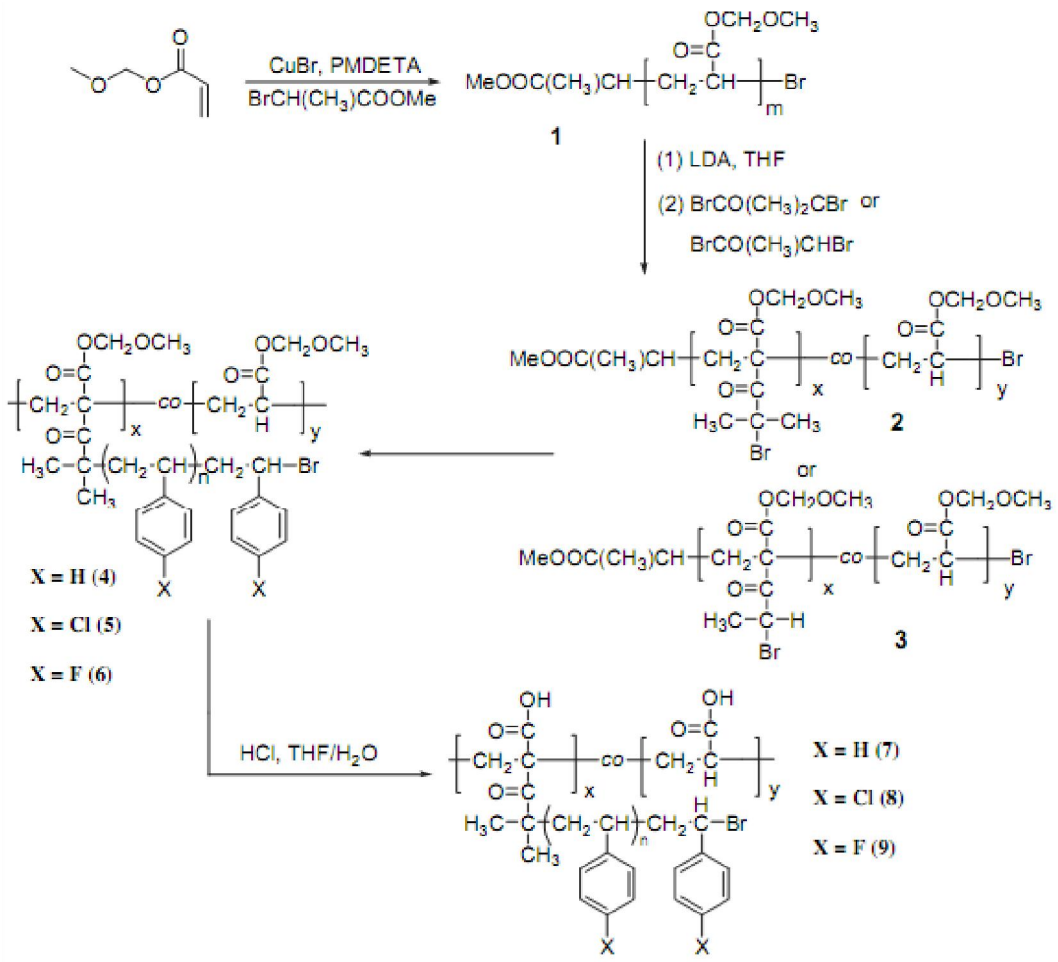

Figure 19 : Scheme for preparation of amphiphilic graft copolymer using poly(acrylic acid) and polystyrene

CONCLUSION

Amphiphilic polymers are novel polymers having both hydrophilic and hydrophobic parts. They are very useful compound in medical as well as polymer composite applications. Various methods are available for synthesizing this compounds and an effort was made in this review for giving an idea of the research happening in this amazing field.

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