Timothy P. Ehlers
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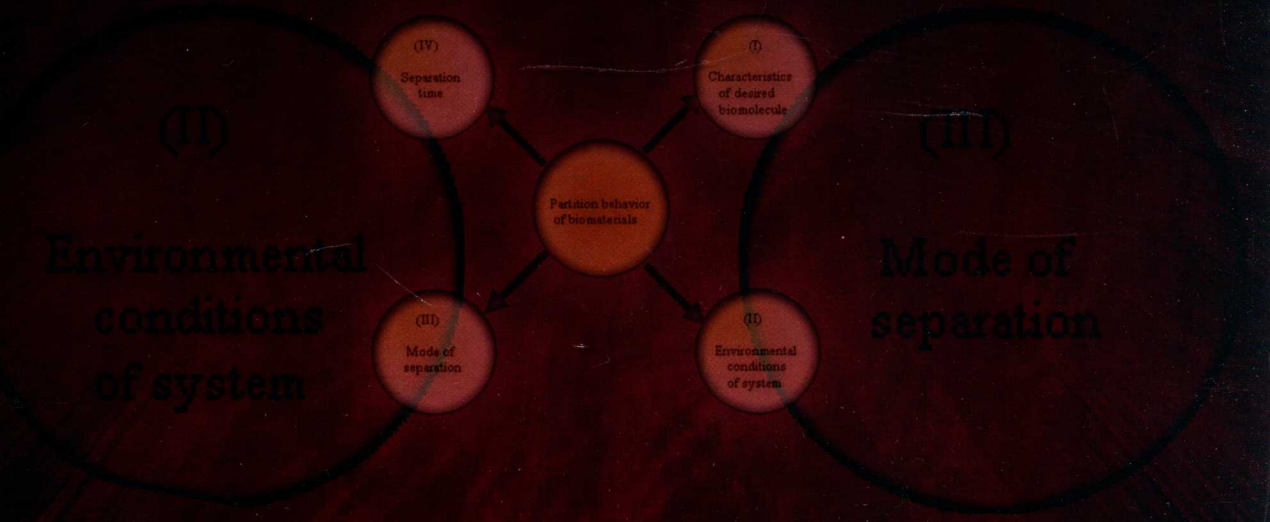
Editors

Polymer Phase Behavior



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POLYMER PHASE BEHAVIOR

TIMOTHY P. EHLERS
AND
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EDITORS

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PREFACE

This book examines the phase behavior of polymers. The authors present topical research in this field. Topics discussed include the phase behavior of PVP as compared with that of poly(N-vinylcaprolactam); the applicability of lattice cluster theory to the calculation of miscibility; Raman study of the pressure and temperature induced transformations in crystalline polymers of C60; polymer phase behavior in nanocomposites; phase inverting polymer systems in drug delivery medicine and the correlation between stereochemistry and phase behavior.

Chapter 1 - Newly developed hyperbranched polymers possess a compact, highly branched, three-dimensional structure, which has a high density of functional end groups and inherently low viscosity. The combination of these two properties, low viscosity and high reactivity, makes them attractive candidates for an overwhelming variety of applications. The experimental and theoretical investigation of the phase behavior of hyperbranched polymer systems is a crucial requirement for a successful introduction of new applications to highly competitive markets. In this context, thermodynamic models, which accurately account for the impact of polymer branching on the phase behavior of polymer systems, play a very important role.

The lattice cluster theory (LCT) is an extension of the well-known Flory-Huggins theory, especially in the calculation of the entropy of the lattice. Whereas the Flory-Huggins theory is limited to linear chains the LCT can be applied to arbitrary chain architecture. This situation permits the incorporation of the architecture in the thermodynamic functions useful for phase equilibrium calculations. The polymer architecture plays an important role in the physical properties of hyperbranched polymers. Additionally, the combination of the LCT with the density gradient theory allows the theoretical investigation of the interfacial properties between the demixed phases.

Chapter 2 - High hydrostatic pressure causes a number of effects in fullerene polymers; the most interesting of them being further pressure-induced polymerization and subsequent structural phase transitions in partially polymerized fullerenes. The behavior of the phonon modes of the polymeric one-dimensional orthorhombic 1D-O phase, the two-dimensional tetragonal 2D-T and rhombohedral 2D-R phases of C_{60} have been studied as a function of pressure, up to ~30 GPa, at room temperature. The 1D-O polymeric phase, even at small pressures, undergoes pressure-enhanced photo-induced transformation to a new polymeric phase characterized by twinned polymeric chains. The photo-transformed 1D-O polymer and two-dimensional 2D-R and 2D-T polymeric phases undergo irreversible structural

transformations at different pressures to new cross-linked three-dimensional polymeric structures. The phonon spectra of the high-pressure phases provide strong indication that the fullerene molecular cage is preserved in the recovered phases. The decomposition of the 2D-R polymer of C_{60} during high temperature treatment leads to the initial face centered cubic structure of the fullerene C_{60} monomer.

Chapter 3 - Polymer phase (polymer matrix) behavior in nanocomposites in many respects defines the behavior of nanocomposite as a whole independently from the used nanofiller type (disperse particles, organoclay, nanotubes and so on). In connection with this it is necessary to account for polymer matrix structure changes at nanofiller introduction in initial matrix polymer. These changes can be realized with the aid of different processes, namely, crystallization, amorphous polymer phase structure change, interfacial regions formation. In its turn, such factors as polymer matrix chain flexibility, interfacial adhesion level, nanofiller particle shape and so on influence on characteristics and realization possibility of the mentioned processes. Hence, at polymer nanocomposites structure formation complex dynamics of polymer phase behavior in them is observed, that defines in the long run a nanocomposite properties. In this aspect particularly important is the role of interfacial regions, which are the same reinforcing element of structure in polymer nanocomposites as actually nanofiller. For semicrystalline polymer matrix nanofiller can play a nucleator role changing in reality the indicated matrices crystallinity degree. In the present review the quantitative relationships of the initial polymer characteristics and their modification at nanofiller introduction and their influence on nanocomposite final structure are considered.

Chapter 4 - Phase inverting polymer systems are primarily utilized in industrial applications such as the microfiltration of bacteria and reverse osmosis, but their use has been rapidly expanding in other areas. In the medical field the predominant role of these systems has been in development of new biomaterial matrixes for drug delivery and tissue engineering. The use of phase inverting systems for the controlled release of therapeutic agents is of interest due to the injectable nature of the implants, which provides a less invasive means of physically placing the implant at or near the site of action. The goals of this chapter are to: provide a basic description of the phase inversion process involved in medical implants, describe factors that affect the phase inversion and drug release processes, overview the techniques used to characterize these systems, and provide insight into the *in vivo* behavior to include biocompatibility and deviations from *in vitro* behavior. *In situ* forming implant systems are an exciting field of study, and have been successfully used to treat diseases that range in severity from prostate cancer to periodontitis. These systems provide a compelling alternative to preformed polymer implants, and may prove to be paramount in overcoming the intrinsic obstacles of the physical targeting of polymer implants for the local delivery of therapeutic agents.

Chapter 5 - Nowadays the urgency for solving plastic waste problems is inducing academic and industrial research to develop novel environmentally friendly polymers, i.e. materials produced from alternative resources, with low energy consumption, non-toxic to the environment, and biodegradable. These biopolymers should have also good physical performances. In the field of aliphatic polyesters, novel (co)polymers, containing 1,4-cyclohexylene units, appear very promising materials, which are obtainable from biomass, potentially biodegradable and characterized by good mechanical properties. Moreover, these polyesters have the interesting peculiarity that their phase behavior is strictly connected to the

ratio of the two possible configurations, *cis* and *trans*, of the cyclic units. Indeed, the *trans* isomer is more rigid and symmetric than the *cis*. Highly symmetrical units tend to improve the chain packing with a consequent increment in crystallinity and crystalline perfection. On the other hand, the *cis* isomer introduces kinks into the main chain, which hinder the formation of stable crystals. Thus, at high *trans* content the polyesters are characterized by relative high degree of crystallinity, whereas at low *trans* content the polymers are amorphous. Therefore, accordingly to the final *cis/trans* ratio, the phase behavior of the homopolymers and copolymers significantly changes and the stereochemistry of the cycloaliphatic units result to be a key factor to tailor the final thermal properties of the material. In this paper the properties of some homopolymers and copolymers, containing the 1,4-cyclohexylene units with different *cis/trans* ratio, are discussed just in terms of the correlations between stereochemistry and phase behavior.

Chapter 6 - Partitioning in aqueous two-phase systems (ATPS) is a proved technology for separating and purifying of enzymes. The goal of this study was to evaluate the applicability of polymer-salt ATPS based on polyethylene glycol (PEG)/K_2HPO_4-KH_2PO_4 as a putative method to isolate and recovery of recombinant amino acid dehydrogenases (AADHs). The partition behaviors of three models of AADHs namely phenylalanine dehydrogenase (PheDH), proline dehydrogenase (ProDH) and Leucine dehydrogenase (LeuDH) in two-phase partitioning systems prepared by PEG-4000/K_2HPO_4-KH_2PO_4 were investigated. The influence of different process parameters such as polymer molecular weight, type and concentration of salt, pH, phase volume ratio (V_R), tie-line length (TLL), type and concentration of inorganic salts, temperature, and cell extract loading on system phase behavior and extraction behavior were evaluated. Furthermore, the efficiency of partition behaviors was analyzed by SDS-PAGE method. The best optimal system for model AADHs with regard the partition coefficient (K_E), recovery (R%) and yield (Y%) was: 9.0% (w/w) PEG-4000, 18.0% (w/w) K_2HPO_4-KH_2PO_4, 8% (w/w) NaCl and a TIL of 52.3% (w/w). The partition parameters were as follows; PheDH (K_E=51.4, R=84.7%, Y=92.5) LeuDH (K_E=81.8, R=94.5%, Y=95.34) and ProDH (K_E=73.4, R=91.6%, Y=94.83). Three target enzymes showed to be partitioned in favor of the PEG-4000 rich top-phase. PEG-4000 proved to have a stabilizing effect on the enzymes of interest. K_2HPO_4-KH_2PO_4 was selected as the phase forming salt because of its ability to enhance the hydrophobic difference between the phases. It was found that the partitioning was not affected by V_R, while PEG-4000 concentration and K_2HPO_4-KH_2PO_4 concentration had significant effects on separation behavior. Longer TLL and higher pH resulted in better partitioning into the top phase. Addition of sodium chloride to the ATPS proved to be suitable to increase the recovery of target enzymes. Collectively, the observed partition behaviors of the model AADHs showed that developed ATPS can be a promising system for partitioning and potential recovery of recombinant AADHs.

Chapter 7 - A blend of poly(ε-caprolactone) (PCL) and poly(styrene-co-acrylonitrile) (SAN) containing 27.5 wt% of acrylonitrile having the critical composition (80/20 PCL/SAN) was studied. This PCL/SAN blend having a lower critical solution temperature (LCST) phase boundary at 122°C offered an excellent opportunity to investigate, firstly the kinetics of phase separation above LCST (125-180°C), and secondly the kinetics of phase dissolution below LCST (50-115°C). The blend underwent a temperature-jump above LCST where spinodal decomposition (SD) proceeded, yielding a regularly phase-separated structure (SD structure). Then, it was quenched to the temperatures below LCST when the phase dissolution proceeded. Optical microscopy was used to observe the spinodal decomposition qualitatively

while light scattering was used to characterize the phase separation and phase dissolution quantitatively. It was found that during phase dissolution the peak maximum moved towards a smaller angle (wavelength of concentration fluctuations increases) while the peak intensity decreased. This behavior was explained by a model. Also it was found that the fastest phase dissolution kinetics at 80°C, which was characterized by an apparent diffusion coefficient, was about 10 times slower than the kinetics of phase separation at 180°C. Crystallization after various levels of spinodal decomposition was observed by optical microscopy. Order parameter of the lamellae inside the spherulites was evaluated with the help of H_v light scattering. Transmission electron microscopy revealed interesting lamellar structure after spinodal decomposition.

Chapter 8 - In recent years, a number of polymers that undergo phase separation in water solutions on temperature rising are studied. These polymers are characterized by lower critical solution temperatures (LCST). Poly(*N*-vinylpyrrolidone) (PVP) is not thermo- or pH - sensitive under usual conditions. However, since this polymer is widely used, especially in medicine, several studies are dedicated to the problem of making this polymer stimuli-responsive, too. In the review, the phase behavior of PVP in water solutions under various conditions is covered. The phase behavior of PVP-containing copolymers and hydrogels are described. The effect of the addition of salts, including transition metal ones, on the PVP phase separation temperature is considered, the attention being paid to the different influence of anions and cations on this value. It is known that PVP readily forms complexes with many organic and inorganic compounds. Examples of such complex formation effects on cloud points of the polymer solutions are given. The phase behavior of PVP is compared with that of poly(*N*-vinylcaprolactam), a PVP close analog, which is a well-known thermosensitive polymer.

CONTENTS

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Chapter 1

APPLICATION OF LATTICE CLUSTER THEORY TO THE CALCULATION OF MISCIBILITY AND INTERFACIAL BEHAVIOR OF HYPERBRANCHED POLYMER CONTAINING SYSTEMS

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ABSTRACT

Newly developed hyperbranched polymers possess a compact, highly branched, three-dimensional structure, which has a high density of functional end groups and inherently low viscosity. The combination of these two properties, low viscosity and high reactivity, makes them attractive candidates for an overwhelming variety of applications. The experimental and theoretical investigation of the phase behavior of hyperbranched polymer systems is a crucial requirement for a successful introduction of new applications to highly competitive markets. In this context, thermodynamic models, which accurately account for the impact of polymer branching on the phase behavior of polymer systems, play a very important role.

The lattice cluster theory (LCT) is an extension of the well-known Flory-Huggins theory, especially in the calculation of the entropy of the lattice. Whereas the Flory-Huggins theory is limited to linear chains the LCT can be applied to arbitrary chain architecture. This situation permits the incorporation of the architecture in the thermodynamic functions useful for phase equilibrium calculations. The polymer architecture plays an important role in the physical properties of hyperbranched polymers. Additionally, the combination of the LCT with the density gradient theory

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allows the theoretical investigation of the interfacial properties between the demixed phases.

INTRODUCTION

The development of linear polymers and their impact on all aspects of modern life is one of the major achievements of the last century. As this field has matured it is increasing apparent that further developments will likely arise, not from the synthesis of totally new linear polymers, but from more accurately controlling the architecture of polymers from currently available monomers. The production and processing of polymers are influenced by the presence of phase separation and segregation, which may be either necessary or highly undesirable. For example, proper orientation and crystallization conditions are needed to secure useful fibers and films; on the other hand, segregation of highly viscous phases during a polymerization process may lead to catastrophic consequences like plugged lines or overheated reactors [1, 2]. Partial miscibility also plays important roles in biology and medicine, as for example in the formation of cataracts in eye lenses [3], protein separations [4], and fibril formation related to Alzheimer's disease [3]. Polymer solutions, which are mixtures of high-molecular weight compounds (solutes) and low-molecular weight solvents, have been examined experimentally, since the early 1930s. These studies revealed some abnormalities when the results were compared with those for low-molecular weight solutions e.g. an unexpectedly small vapor depression, small boiling point elevation, small osmotic pressure and extremely high solution viscosities. These abnormalities became a strong motivating force in the search for a thermodynamic theory for polymer solutions. For polymer solutions, where the difference in molecular size of the components is very large, miscibility gaps become highly asymmetric. A useful approximate model describing the thermodynamic properties, including the phase behavior, in polymer systems is the well-known Flory-Huggins lattice theory [5]. In the lattice model the mixture is represented by a number of regularly arranged lattice sites, each of the same size. The lattice is thought to have a definite coordination number z, which however; does not remain as a relevant variable in the simplest version of the theory. Each polymer molecule is considered to be composed of a number of segments, and the entropy of mixing is evaluated by counting the number of distinguishable ways of placing the molecules on the lattice. Flory and Huggins [5] in their initial works were mainly concerned with the effects of varying molecular size on the thermodynamic properties. In the framework of this theoretical approach no information about the architecture of the monomers and the resulting polymers are involved. The architecture of the polymer is often determined by the functionality of the monomers from which it is formed. This property of a monomer is defined as the number of reaction sites at which may form chemical covalent bonds. The basic functionality required for forming even a linear chain is two bonding sites. Higher functionality yields branched or even crosslinked or networked polymer chains. Modern polymerization strategies such as dendritic macromolecular chemistry involve the formation of large multiples of covalent bonds between homogeneous monomers to produce large molecules or infinite networks with a broad range of structure control [6].

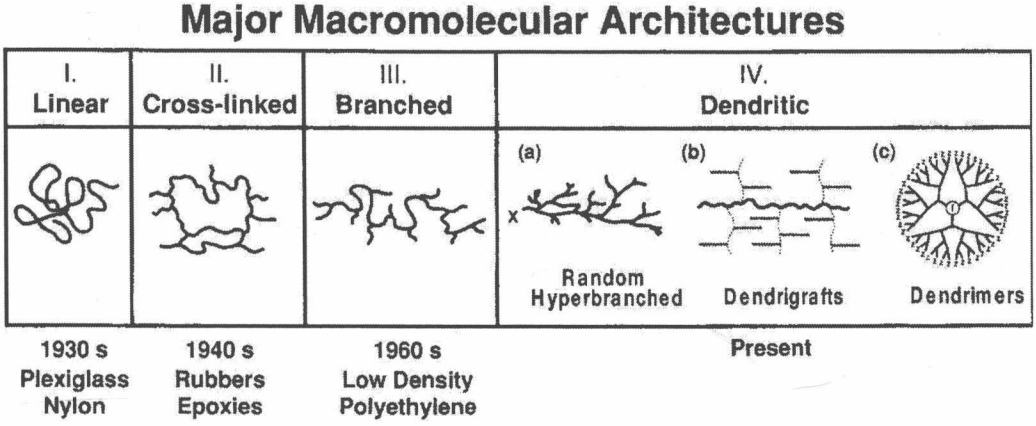

Figure 1. Representation of the four major classes of macromolecular architectures [6].

Historically, each of the three macromolecular architectural classes, i.e. (I) linear, (II) crosslinked, and (III) branched, has spawned rich polymer science (Figure 1). These architectural discoveries have been characterized by the emergence of new syntheses, structures, phenomena, properties, and products that have dramatically improved the human condition. Nanotechnology initiatives have focused on new synthesis strategies, structures, phenomena, and properties associated with length scales of 1-100 nm. These dimensions encompass biological building blocks (protein, DNA, RNA, etc.) and abiotic application areas (nanophotonics and nanoelectronics) [7]. Dendritic polymers are recognized as the fourth major class of polymeric architecture consisting of three subsets that are based on degree of structural control, namely: a) random hyperbranched polymer, b) dendricraft polymers and c) dendrimers [6, 7].

The outstanding polymer chemist Flory [8] was the first to hypothesize concepts, which are now recognized to apply to statistical, or 'random hyperbranched' polymers. However; the first synthesis of hyperbranched polymer could be realized 35 years later [9]. Webster and Kim [10] coined the popular term 'hyperbranched polymer' that has been widely used to describe this type of dendritic macromolecules. In theory, all polymer-forming reactions can be utilized for the synthesis of hyperbranched polymers, however; in practice some reactions are more suitable than others [6]. Hyperbranched polymers are typically prepared by polymerization of AB_X monomers, where x is two or more. They are produced by the one-pot polymerization of AB_X monomers or macromonomers involving polycondensation [11, 12, 13, 14, 15], ring opening [9, 16, 17, 18], or polyaddition [19, 20] reactions hence the product usually consist of broad statistical molecular weight distribution [21, 22, 23, 24]. Frechet et al. [25] presented the first example of a hyperbranched vinyl polymerization initiating the birth of a 'second generation' of hyperbranched polymers. Frechet and Chang [26] reported proton-transfer polymerization as a versatile route to hyperbranched polymers. Remarkable progresses have been made in recent years in the exploration of metal-mediated and metal-free click polymerization [27, 28] systems and in the syntheses of linear and hyperbranched polytriazoles with regioregular molecular structures and advanced functional properties [29]. Hyperbranched polymers are often modified to tailor their properties for a specialized purpose. Five modification methods have been developed: 1) end-capping with short chains or organic molecules; 2) terminal grafting via living polymerization; 3) growing

hyperbranched polymers on the surface, or grafting from/onto the surface; 4) hypergrafting to obtain hyperbranched polymers with a linear macromolecular core; 5) blending or crosslinking.

Star polymers are three-dimensional hyperbranched structures in which linear arms of the same or different molecular weights emanate from a central core. The existence of numerous functional groups in a small volume makes these polymers important for use in biological and pharmaceutical applications. Biologically active molecules can be immobilized on the surface of the polymer gel or incorporated into the network.

Unique architecturally driven properties that may be expected from hyperbranched polymers will be largely derived from their a) amplified number of terminal functional groups, b) new rheological properties based on less chain entanglement, c) new architectural arrangements that may modulate crystallinity, flow characteristics and glass transition properties in designed systems and d) the formation of micelles.

The degree of branching is one of the most important molecular parameters of hyperbranched polymers since it determines many physical properties including the phase behavior of these polymers. This contribution focuses on the incorporation of the architecture of the polymers in the thermodynamic equations necessary for phase equilibrium calculations.

PROPERTIES AND APPLICATIONS OF HYPERBRANCHED POLYMERS

The unique properties of hyperbranched polymers are mainly manifested by their intrinsic globular structure and large number of terminal functional groups. Unlike dendrimers, however; hyperbranched polymers have elements of conventional polymers, namely molecular weight dispersity, isomerism, and geometrical shapes. Because the addition of each monomer takes place randomly, a large number of geometrical isomers can be formed even for a given molecular weight and branching degree. The polydispersity of the hyperbranched polymers is expected to increase to infinity at infinite polymer molecular weight. Besides the complex structure, also molar mass determination for hyperbranched polymers is far from trivial. It is obvious that molar mass determination by GPC lacks the fact that linear standards are not suitable for calibration. The application of light scattering and viscosity detector in the GPC as mostly done for branched polymers improves the results but still the broad molar mass distribution and the large number of polar end groups might cause problems [30, 31].

Some of these polymers exist as unusual colloid-like aggregates and form unimolecular micelles. Unimolecular micelles are defined as a class of macromolecules, wherein an interior hydrophobic core is surrounded by a hydrophilic surface layer. These structures closely resemble the shape of classical micelles except that they are static, in contrast to the dynamic nature of micelles, with all end-groups attached to the central core. The ability of guest molecules to penetrate the lipophilic interior can be used as drug or gene nano-carriers [10, 32, 33, 34, 35, 36]. In addition dendrimers can be surface engineered to release the drug at desired site, that is, as targeted drug delivery. This property along with the solubilisation behavior could improve the bioavailability of drugs. Hyperbranched polymers should be an attractive candidate for a gene- or drug-delivery system in aqueous media and could provide

the phase-transfer carriers between water and organic media. Recently [34, 37, 38], biodegradable unimolecular reversed micelle consisting of a hyperbranched hydrophilic core and hydrophobic shell, were introduced. Liang et al. [39] demonstrate the possibility that a unimolecular micelle can simultaneously deliver both polar and apolar guests. In a biphasic water/chloroform mixture, the nanocapsule can transfer anionic, water-soluble guest from an aqueous phase to the chloroform phase; while when dissolved in water, the nanocapsule can efficiently capture both ionic and apolar solutes. Release of the guest can occur under the stimulus of pH or the switch of medium.

Above their glass transition temperature, these hyperbranched polymers are considered to minimize their free energy by lowering their free volume via a conventional nematic mesophase which is generated by a conformational change of their structural units from gauche to anti [40]. Percec et al. [41] were the first to report on flexible, non-spherical polymers with AB_2 mesogens in the branches that exhibit nematic and smectic behavior. On the other hand, aromatic polyamides exhibit polymer aggregation in the absence of a complexing salt resulting in a mesomorphic phase [42].

In general, hyperbranched polymers and dendrimers are more soluble in the same solvents than their linear analogous [43]. For higher generation dendritic polymers, solubility characteristics depend predominantly on the properties of their functional endgroups. As an example, dendrimers with hydrophobic interiors such as polyethers and polycarbosilanes can be made water soluble by introducing hydrophilic groups. Oppositely, water soluble dendrimers can be generated to be hydrophobic by converting their functional groups into hydrophobic units [44]. Furthermore, end group modification allows ideally to optimize their properties for special applications and to fine tune e.g. miscibility, melt rheology, surface and optical properties as well as biocompatibility.

Numerous applications in the field of coatings and blends, nanoscience, microelectronics, information technology, optics, lithography, organic light-emitting diodes, solid electrolytes, photoresponsive materials, chemical- and biosensors, and medicine (drug delivery systems, tissue engineering, magnet resonance contrast agents) have been suggested for hyperbranched polymers but only a few have yet reached full commercial exploitation. Several reviews [6, 7, 15, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54] about this issue were publicized in the past. In this contribution only a few of them will be highlighted.

Application in Medicine

After drug administration, the drug may pass through different physiologic barriers and/or pathways, decreasing the actual amount of drug that reaches the site. Tissue specificity, product stability and solubility all desirable characteristics of drug, but are not always attained. Therefore, the need of develop a drug carrier system with such characteristics is of great importance. In the last 25 years [55], there have been numerous efforts focused on the development of the drug carrier systems. Investigators have made attempts to develop a specific drug carrier system, which can maintain continuous drug levels in a desired range, reduce side effects by improved tissue or organ specificity.

Many polymeric carriers have been investigated for therapeutic applications [55]. However; only a few polymers such as linear poly (lactide-co-glycolide), polyethylene glycol, and acrylic-based polymeric carriers have been introduced at commercial scale for controlled-

release applications. Müller et al. [56] indicated that most polymeric drug delivery systems suffer from two major drawbacks, i.e., the cytotoxicity of polymers and the lack of processability. Hence, the successful formulation of a polymeric drug delivery system requires a system solution, i.e. a) a carrier with a narrow molecular mass distribution that fulfils nontoxicity and controlled-release criteria, b) sufficient loading capacity for the desired applications and c) processability by means of a commercial encapsulation technique. Even after considering the aforementioned system solution, factor such as the bioavailability, biodegradability, biodistribution, and drug efficacy can still limit the effectiveness of a polymeric drug delivery system. The processing of many therapeutic formulations has been suggested with commercial encapsulation techniques employ volatile organic compounds for the processing of polymeric carriers, where the residuals leading to the major health concern. However; most polymeric carriers such as polyesters and polyamides are very difficult to process in the absence of volatile organic compounds, because of high melting points, limited solubilities in supercritical gases, or high solution and melt viscosities are nonprocessable in most encapsulation techniques. Furthermore, harsh operating conditions and the cost effectiveness of the encapsulation technique may also limit the commercialization of the polymeric drug delivery system.

In the search for an ideal carrier system, the hyperbranched polymers may have significant potential. Hyperbranched polymers and their substitutes can be used as nanomaterials for host-guest encapsulation for several molecules such as dyes, pharmaceuticals, cosmetics, fragrances, catalysts and pollutants as well as the fabrication of organic – inorganic hybrids, and even directly as nanoreactor [37] for some reactions. As carriers, hyperbranched macromolecules can offer their interior or peripheral functional groups to covalently fix bioobjects, or depending on their core-shell architecture, to sequester guest molecules. The information stored at a molecular level plays a key role in this process. For a controlled release application, a change in pH, temperature, pressure, or a bacterial, enzymatic, or catalytic activity disintegrates the carrier system, leading to the release of the encapsulated active substance. The loading capacity and the release kinetics of carriers based on hyperbranched polymers are dependent on the polymer backbone, the number and type of functional groups, the molar mass, the polydispersity, and the amphiphilicity of the macromolecule. In controlled-release applications, hyperbranched polymers are functionalized in such a way that the shell of the hyperbranched carrier not only protects the encapsulated guest molecules, but also responds to the target environment via specific physiological change such as temperature, pH, chemical, and/or enzymatic reactions [57, 58].

Well-characterized, hyperbranched polymers were subjected to functionalization for preparing drug delivery systems of low toxicity, high loading capacity, ability to target specific cells and transport through their membranes [57]. They open new routes for the development of controlled-drug delivery systems with the potential to inhibit microbial adhesion to host tissues. In past years, the scope of encapsulation has expanded from pharmaceutical applications to cosmetics and agrochemical products [51]. The common goal for these applications is a high degree of control over the release mechanism for the encapsulated active substances.

As hydrophobic drug substances are difficult to introduce in the human body, many studies focus on increasing the solubility of drugs in the aqueous phase. As an example, tamoxifen, which is a hydrophobic breast anticancer drug, was encapsulated by Tziveleka et al. [59] in hyperbranched polyglycerols modified with polyethylene glycol. The results

demonstrate that molecular encapsulation, based on hyperbranched nanocarriers, allows transporting 12 times more tamoxifen into an aqueous phase, compared to the solubility of the pure drug. The release of tamoxifen observed upon addition of sodium chloride is, in most of the cases, significant only at concentrations exceeding the physiological extracellular concentration [59].

Hyperbranched polymers such as polyesters, polyethyleneimine, polyglycerol, poly(ethylene glycol) and different copolymers have been investigated as potential polymeric vehicles for drug delivery applications and have proven to be highly biocompatible, thermally and chemically stable [57]. Moreover, although most dendritic polymers show cytotoxicity, low-molecular mass hyperbranched polyglycerols have proven to be nontoxic. The encapsulation of therapeutic agents such as ibuprofen [60, 61, 62, 63, 64], acetaminophen [65], tamoxifen [59, 66], ketoprofen [63], diflunisal [63], naproxen [63], paclitaxel [67, 68, 69, 70, 71, 72, 73], docetaxel [73], glimepiride [74], doxorubicin hydrochloride [75, 76], methotrexate [75], sodium ibandronate [75], cisplatin [77], chlorambucil [78], cytochrome c [79], amphotericin B [80], nimodipine [81], indomethacin [82], doxorubicin [76, 83], and docetaxel [70] were studied. The in vitro release of ibuprofen from drug-dendrimer complex is appreciably slower compared to pure ibuprofen. The complex drug enters A549 cells much more rapidly than pure drug suggesting that dendrimers may be able to carry the complex drug inside cells efficiently [64]. Hyperbranched Polyol with 128 OH end groups appears to encapsulate approximately 24 drug molecules [60].

The use of oral antidiabetic drugs for management of type 2 diabetes increases rapidly caused by the discovery and approval of several new types of oral antidiabetic drugs with different mechanism of pharmacological action [74]. Many of these drugs show poor solubility, slow dissolution rate in water, pH-dependent solubility and high permeability. Several approaches to improve water solubility include prodrugs, complexation, cosolvency, solid state modifications, surfactants were investigated. Among these the addition of cosolvents, the formation of cyclodextrins or micellar inclusions and the preparation of solid dispersions are the most commonly used. Many of these solubilisation techniques have their own limitations, toxicity, nephrotoxicity. The transformation of the drug to its amorphous form is often desirable since the solubility increases from a few to many-fold. The presence of hydrophilic compounds in close contact with the drug molecules increases the solubility by maintaining the drug in a molecular state and maximizing the surface area of the compound. The polymeric molecules also act as crystallization inhibitors and preserve the drug in its amorphous state [74].

Polymeric biomaterials are also of particular interest for the parenteral administration of peptides and proteins [84]. In an initial phase, release occurs predominantly by pore diffusion through an interconnecting network formed by the dissolving drug substance itself. The second release phase is governed by polymer degradation. Polyphasic drug release profiles can be overcome either by formulation approaches or by modification of the biodegradable polymers. While the release properties of biodegradable microspheres can be modified only in a limited sense, polymer modifications provide a broader spectrum of possibilities. Hydrophilic multi-arm polyethylene oxides seem to be promising candidates for parenteral protein delivery systems, allowing a synchronization of both pore diffusion and polymer erosion for the controlled release [84].

Boltorn hyperbranched dendritic polymers functionalized with mannose have been used to inhibit DC-SIGN-mediated infection in an Ebola-pseudotyped viral model [85]. Their