

Review

Water Soluble Polymers for Pharmaceutical Applications

Veeran Gowda Kadajji and Guru V. Betageri *

Department of Pharmaceutical Sciences, Western University of Health Sciences, Pomona, CA 91602, USA; E-Mail: vkadajji@westernu.edu

* Author to whom correspondence should be addressed; E-Mail: gbetageri@westernu.edu; Tel.: +1-909-469-5682; Fax: +1-909-469-5600.

Received: 22 September 2011 / Accepted: 10 November 2011 / Published: 11 November 2011

Abstract: Advances in polymer science have led to the development of novel drug delivery systems. Some polymers are obtained from natural resources and then chemically modified for various applications, while others are chemically synthesized and used. A large number of natural and synthetic polymers are available. In the present paper, only water soluble polymers are described. They have been explained in two categories (1) synthetic and (2) natural. Drug polymer conjugates, block copolymers, hydrogels and other water soluble drug polymer complexes have also been explained. The general properties and applications of different water soluble polymers in the formulation of different dosage forms, novel delivery systems and biomedical applications will be discussed.

Keywords: polymers; natural; synthetic; hydrogels; gums; cellulose ethers; povidone; polyethylene glycol; polyacrylamides; polyacrylic acid copolymers

1. Introduction

Advances in polymers sciences have led to the development of novel delivery systems. The introduction of new polymers has resulted in development of polymers with unique properties. Initially polymers were used as solubilisers, stabilizers, mechanical supports for sustained release of drugs. But over a period of time, the functionalities of polymers have changed. The polymers have been synthesized to suit specific needs or rather solve specific problems associated with development of drug delivery systems. So there is need to understand the role of polymers. Polymers can be classified

based on any of the following categories: (1) source (Natural, semi synthetic, synthetic); (2) structure of polymer (Linear, Branched chain, Crosslinked or Network polymers); (3) type of polymerization (Addition, condensation polymers); (4) molecular forces (Elastomers, Fibres, Thermoplastic, Thermosetting); (5) Chain growth polymerization (Free radical governed); (6) degradability (biodegradable, non-biodegradable).

Water soluble polymers have a wide range of industrial applications like food, pharmaceuticals, paint, textiles, paper, constructions, adhesives, coatings, water treatment, *etc.* In this paper, the water soluble polymers have been divided into two categories (1) Synthetic and (2) Natural. This review describes water soluble polymers: their properties and applications in pharmaceutical and biomedical industries.

2. Synthetic Water Soluble Polymers

Synthetic water-soluble polymers are substances that dissolve, disperse or swell in water and, thus, modify the physical properties of aqueous systems in the form of gellation, thickening or emulsification/stabilization. These polymers usually have repeating units or blocks of units; the polymer chains contain hydrophilic groups that are substituents or are incorporated into the backbone. The hydrophilic groups may be nonionic, anionic, cationic or amphoteric [1].

2.1. Poly(ethylene glycol) (PEG)

In general, a low polydispersity index (PDI) is a prerequisite for the polymer to have pharmaceutical applications. A PDI value below 1.1 makes the polymer more homogenous so that it provides reliable residence time in the body [2].

All these prerequisites are fulfilled by PEG, since it has PDI of 1.01. This holds for low molecular weight PEGs. Polyethylene glycol is synthesized by the interaction of ethylene oxide with water, ethylene glycol, or ethylene glycol oligomers. The starting materials used for synthesis of PEG polymers with low polydispersity index (narrow molecular weight distribution) are Ethylene glycol and its oligomers. Reactions catalyzed by anionic polymerization result in PEGs with low PDI.

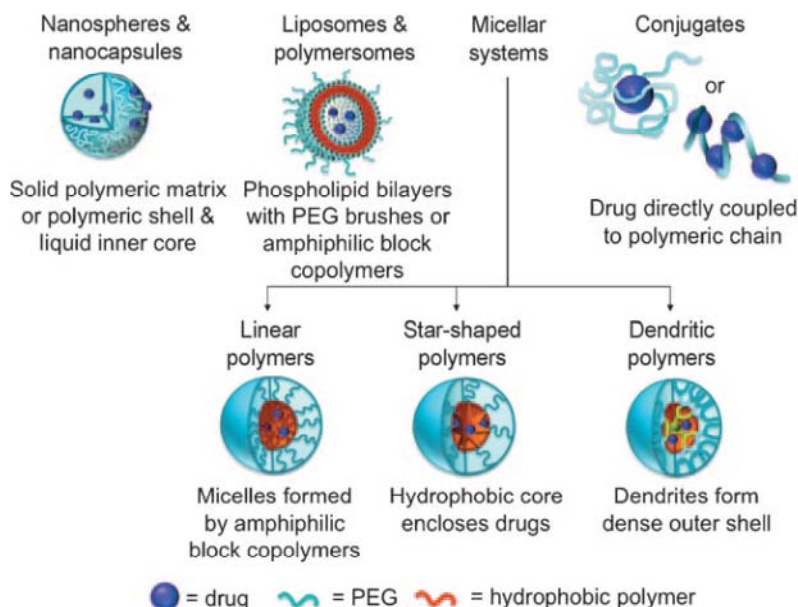
In addition, PEG shows a high solubility in organic solvents and, therefore, end-group modifications are relatively easy. PEG is suitable for biological applications because it is soluble in water and has low intrinsic toxicity. The high hydrophilic nature of PEG enhances the solubility of hydrophobic drugs or carriers when conjugated with them. It enhances the physical and chemical stability of drugs and prevents aggregation of the drugs *in vivo*, as well as during storage, as a result of the steric hindrance and/or masking of charges provided through formation of a conformational cloud [3].

PEG helps in reducing the aggregation of red blood cells and so improves the blood compatibility of PEG copolymers that are implanted as cardiovascular devices such as stents. It is mainly used in storage of blood and organs.

Both temperature-responsive and chemically crosslinked hydrogels have been formed from PEG. Temperature-responsive systems have become increasingly attractive as injectable drug delivery systems [4]. Chemically crosslinked systems have also been studied for *in situ* photo polymerization [5].

The PEGylation technique was first introduced in the late 1970s. However, the applications of this concept to various carrier systems were widely explored in the 1990s (Figure 1) [6,7].

Figure 1. Overview of carrier systems for drug delivery systems (Adapted from [6,7]).



PEG-drug conjugates are being studied for a variety of molecules and drugs including insulin, daunorubicin, camptothecin, peptides and lipids. The main advantages of PEG-drug conjugates are reduced protein immunogenicity, increased residence time in the body, reduced enzymatic degradation. All these features ensure that the drug reaches the site of action and prevents clearance from the body because it is not recognized as the foreign body. Therefore, the majority of conjugated drugs as well as liposomal and micellar formulations on the market or in advanced clinical trials are PEG-containing products [8]. Most of the polymer-based stealth drug-delivery systems that have reached the market are PEGylated products (Table 1) [8-11].

The conjugation of PEG with enzymes looks very promising in antitumoral therapy since several enzymes have proven to be active against various types of cancer by acting through different mechanisms. Enzymes that are able to reduce plasma levels of these tumor target amino acids (*i.e.*, asparaginase, methioninase and arginine deiminase) are studied as therapeutic agents in cancer therapy. The advantage of enzymes is their great specificity.

Since the introduction of PEGylation, several antitumour agents, either proteins, peptides or low molecular weight drugs, have been considered for polymer conjugation but only a few entered clinical phase studies. The majority of the low molecular weight PEG drug conjugates which are in clinical phase are from the camptothecin family, namely camptothecin, SN38 and irinotecan [12]. Other PEG protein conjugation studies investigated include PEG-catalase, PEGuricase, PEG-honeybee venom, PEG-hemoglobin and PEG-modified ragweed pollen extract [13]. Following are some of the PEG conjugates with low molecular weight anti-cancer drugs investigated for different clinical applications.

Table 1. Drug delivery systems stabilized with poly(ethylene glycol) PEG that have received regulatory approval in the USA and EU [8–11].

PEG drug candidate	Company	Indication	Year of approval
Adagen (11–17 × 5 kDa mPEG per adenosine deaminase)	Erzon Inc. (USA & Europe)	Immunodeficiency	1990 (USA)
Oncospar (5 kDa mPEG-L-asparaginase)	Erzon Inc. (USA/Rhone-Poulenc (Europe))	Acute lymphoblastic leukemia	1994 (USA)
Doxil/Cadyx (SSL formulation of doxorubicin)	Alza Corp. (USA)/Schering Plough Corp. (Europe)	ovarian & breast cancer, multiple myeloma	1995 (USA) 1999 (USA) 1996 (EU)
PEG-Intron (2 × 20 kDa mPEG-interferon- α -2a)	Schering Plough Corp. (USA & EU)	Chronic hepatitis C	2000 (EU) 2001 (USA)
(Pegasys) 12 kDa interferon mPEG-interferon- α -2b)	Hoffmann-Laa-Roche (USA & EU)	Chronic hepatitis C	2002 (USA & EU)
Neulasta (20 kDa mPEG-G-CSF)	Amgen Inc. (USA & EU)	Febrile neutropenia	2002 (USA & EU)
Somavert (4–6 × 5 kDa mPEG per structurally modified HG receptor antagonist)	Pfizer (USA & EU)	acromegaly	(2002 (EU) (2003 (USA)
Macugen (2 × 20 kDa mPEG anti-VEGF-aptamer)	Pfizer (EU/OSI Pharm Inc. and Pfizer (USA)	Age related macular degeneration	2004 (USA) 2006 (EU)
Cimzia (2 × 40 kDa MPEG anti TNF α)	CB S.A (USA & EU)	Crohns disease rheumatoid arthritis	2008 (USA) 2009 (USA) 2009 (EU)
Krystexxa (Pegloticase) PEGylated Uric acid	Savient Pharmaceutical Inc. (USA)	Chronic Gout	2010 (USA)

mPEG: Mmethoxypoly(ethylene glycol); SSL: Sterically Stabilized Liposome; G-CSF: Granulocyte-Colony Stimulating Factor; HG: Human Growth; VEGF: Vascular Endothelial Growth Factor; TNF: Tumor Necrosis Factor.

2.1.1. PEG-Irinotecan (NKTR-102)

In a mouse model, the conjugate showed prolonged pharmacokinetic profiles with a half-life of 15 days when compared to 4 h with free irinotecan [14]. Currently the drug conjugates is being tested for its efficacy in breast cancer patients which is in phase 3 stage. Also phase 2 studies in ovarian and cervical cancer patients are in progress. Some of these studies have shown significant antitumor activity (reduction in tumor size) [15].

2.1.2. PEG-Docetaxel (NKTR-105)

NKTR-105 is a novel form of the anti-mitotic agent, docetaxel, and was designed using Nektar's advanced polymer conjugate technology. NKTR-105 is in a Phase 1 clinical trial in patients with

certain types of solid tumors including hormone-refractory prostate cancer. It is also being explored as a therapy for breast, non-small cell lung, gastric, head and neck cancers [16].

2.1.3. PEG-Camptothecin (PROTHECAN or Pegamotecan)

Pegamotecan (Enzon Pharmaceuticals, Inc.) is a prodrug obtained by coupling two molecules of camptothecin to a diol PEG of 40 kDa. The drug is linked through an ester bond involving the C-20 hydroxyl group and a carboxylic group of PEG. This PEGylation technique helped increasing the half-life of the drug in blood and stabilized camptothecin by acylation [17]. A phase II clinical study done in patients with gastric or gastro-esophageal adenocarcinoma is also documented [18].

2.1.4. PEG-SN38 (EZN-2208)

This is another advanced PEG conjugate which is in phase I clinical trials. This was synthesized by coupling a 4armPEG of 40 kDa with the camptothecin derivative SN38, through a glycine spacer. PEGSN38 showed an increase in drug loading with respect to Pegamotecan, reaching a value of 3.7 wt %. This conjugation resulted in a 1,000 fold increase in the solubility of SN38. The conjugated derivative acts as a prodrug and showed some antitumour activity when studied using *in vitro* and *in vivo* techniques. When this conjugate was administered either as a single dose or multiple injections in mice, it showed better results than irinotecan [19].

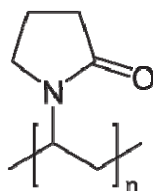
Block copolymers containing PEG have also become very popular in recent years. Copolymers with poly(propylene oxide), poly(ethylene butylene), poly(caprolactone) are just a few examples. Copolymers containing PEG have been formed into thermo-sensitive gels, interconnected micelles, nanospheres, and films [20]. While the advantages of PEG in biomedical applications are lengthy, the primary disadvantage for its use in biomedical applications is its non-degradable structure.

Jeong *et al.* [20] have studied the thermo-reversible gelation of PEG-PLGA-PEG triblock copolymers. They have shown that an aqueous solution of PEG-PLGA-PEG triblock copolymers with a specific composition is a free flowing solution at room temperature but becomes a transparent gel at body temperature. The primary focus of this research was to use this thermo-reversible behavior as a long-term, injectable drug delivery device.

2.2. Polyvinyl pyrrolidone (PVP)

Polyvinyl pyrrolidone is a water soluble polymer having molecular weight ranging from 40,000 to 360,000. It is synthesized by polymerization of vinylpyrrolidone in water or isopropanol. The structure of PVP is given in Figure 2.

Figure 2. Structure of polyvinyl pyrrolidone.



PVP is available in different grades based on molecular weights. It is mainly used as a binder in tablet formulations. When compared to other binders, wet granulation with PVP having a molecular weight of 25,000 to 90,000 generally gives harder granulates with good flowability, higher binding and low friability [21,22]. In addition to enhancing the above properties, PVP also increases the dissolution of the active ingredient. Acetaminophen (paracetamol) tablets formulated with 4% PVP 90,000 as binder released the drug more quickly than tablets with gelatin or hydroxypropylcellulose as binder, even though the povidone tablets were harder [23]. Similar results were obtained with 0.6 or 1.0% of PVP 90,000 or hydroxypropylcellulose [24].

Many of the active substances have poor aqueous solubility due to which they have limited bioavailability. An easy way of enhancing the bioavailability of an active substance is to improve its dissolution by adding solubilizing agents, such as the soluble PVP grades. These form water-soluble complexes with many active substances and increase the bioavailability. The bioavailability of per oral gidaepam was increased by the addition of povidone.

The soluble PVP grades are also useful for preparing solid solutions and dispersions because of their good hydrophilization properties, universal solubility and ability to form water soluble complexes. More than 140 papers between 1960 and 1990 describe the preparation of drugs in solid solution, dispersions using PVP [25].

Soluble grades of PVP and polyvinyl pyrrolidone-vinyl acetate (PVP-VA) copolymer have been used to improve the bioavailability of many poorly water soluble drugs like indomethacin, tolbutamide, nifedipine [26]. These amorphous polymers can be used to formulate these drugs as glass solutions by hot melt extrusion (HME). The extrudates obtained by this process showed high dissolution of the drug depending on the chemical stability and temperature employed for the process. The use of PVP-VA as a polymer in improving the dissolution and bioavailability of these drugs by hot melt extrusion has been cited in other papers as well [27-29].

Povidone provides excellent stability to the tablet formulations (Ex; Phenytoin tablets) [30]. Lyophilisates are produced for parenteral and for oral preparations. Povidone is used to bind the lyophilisate together during freeze drying and to improve the solubility, stability and even the absorption of the active ingredient by virtue of its hydrophilic and complexing properties. Povidone and triesters of citric acid can be combined to obtain clear soft gelatin capsules of insoluble drug substances [31].

Table 2. The main applications of Povidone [32].

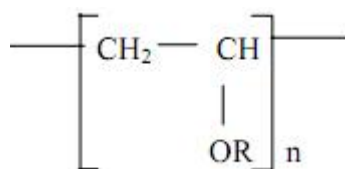
Function	Pharmaceutical form
Binder	Tablets, capsules, granules
Improved Bioavailability	Tablets, capsules, granules, pellets, suppositories, transdermal systems
Film forming agent	Tablets, ophthalmic solutions
Solubilising agent	Oral, parenteral and topical solutions
Taste masking	Oral solutions, chewing tablets
Lyophilizing agent	Injectables, oral lyophilisates
Stabiliser	Suspensions, dry syrups
Hydrophiliser	Sustained release forms of suspensions
Adhesive	Transdermal systems, adhesive gels
Stabilizer	Enzymes in diagnostics, different forms
Toxicity reducer	Injectables, oral preparations, <i>etc.</i>

All grades of povidone can be used as hydrophilic polymers to physically stabilize suspensions. Their most important and primary function in all suspensions is as protective colloids, which hydrophilize the individual solid particles and sterically separate them. This increases the volume of any sediment and makes it easier to redisperse by shaking. Kollidon also prevents the dissolved portion of the active substance from crystallizing out by forming soluble complexes with it. Table 2 lists the pharmaceutical applications of povidone [32].

2.3. Polyvinyl alcohol (PVA)

Polyvinyl alcohol (PVA) has a hydroxyl group in its structure. It is synthesized by the polymerization of vinyl acetate to polyvinyl acetate (PVAc) which is then hydrolysed to get PVA. The structure of PVA is given in Figure 3. The extent of hydrolysis and content of acetate groups in PVA affect the crystallizability and solubility of PVA [33].

Figure 3. Structure of polyvinyl alcohol.



Where R = H or COCH₃.

PVA is soluble in highly polar and hydrophilic solvents, such as water, Dimethyl Sulfoxide (DMSO), Ethylene Glycol (EG), and N-Methyl Pyrrolidone (NMP) [34]. Water is the most important solvent for PVA. The solubility of PVA in water depends on the degree of polymerization (DP), hydrolysis, and solution temperature. Any change in these three factors affects the degree and character of hydrogen bonding in the aqueous solutions, and hence the solubility of PVA.

It has been reported that PVA grades with high degrees of hydrolysis have low solubility in water. The solubility, viscosity, and surface tension of PVA depend on temperature, concentration, % hydrolysis and molecular weight of the material [35].

PVA hydrogels have been used for various biomedical and pharmaceutical applications [36]. PVA hydrogels have certain advantages which make them ideal candidates for biomaterials. Advantages of PVA hydrogels are that they are non-toxic, non-carcinogenic, and bioadhesive in nature. PVA also shows a high degree of swelling in water (or biological fluids) and a rubbery and elastic nature and therefore closely simulates natural tissue and can be readily accepted into the body. PVA gels have been used for contact lenses, the lining for artificial hearts, and drug- delivery applications.

PVA is mainly used in topical pharmaceutical and ophthalmic formulations (Table 3) [37,38]. It is used as a stabilizer in emulsions. PVA is used as a viscosity increasing agent for viscous formulations such as ophthalmic products. It is used as a lubricant for contact lens solutions, in sustained release oral formulations and transdermal patches [39].

Table 3. Uses of polyvinyl alcohol [37,38].

Use	Concentration (%)
Emulsions	0.5
Ophthalmic formulations	0.25–3.00
Topical lotions	2.5

2.4. Polyacrylic acid (PAA)

Polyacrylic acid is a biodegradable water soluble polymer with various industrial applications, including as a super adsorbent (e.g., in disposable nappies), in water treatment, *etc.* [40]. Poly(acrylic acid) (PAA) copolymers modified with block-copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) have a wide range of medicinal applications as their components are considered pharmaceutically safe [41].

The unique property of Polyacrylic acid is that it exists as a liquid at pH 5 and a gel at pH 7. Permeation of cations into the gelled polymer converts the gel back to a liquid [42]. It is ideal for ocular delivery of ribozymes to the corneal epithelium as a drug delivery vehicle. Carbopol 974 and Pemulen TR1 have been used for ocular delivery of Ribosomes [43].

Hydrophobically modified poly(acrylic acid) (HMPAA) shows some interesting rheological properties in semidilute aqueous solutions, such as interchain aggregation followed by an increase in the apparent molecular weight and enhanced viscosity as well as shear sensitivity [44]. HMPAA is prepared by modification of PAA in its acidic form by alkylamines in an aprotic solvent in the presence of N,N'-dicyclohexylcarbodiimide (DCCD) [45].

Polyacrylic acid based polymers are mainly used for oral and mucosal contact applications such as controlled release tablets, oral suspensions and bioadhesives. It is also used as a thickening, suspending and emulsion stabilizing agent in low viscosity systems for topical applications. Carbopol[®] 71G NF polymer is a granular form of Carbopol[®] 971P NF polymer which is suitable for use in direct compression of tablets. For bioadhesive applications, high molecular weight acrylic acid polymer crosslinked with divinyl glycol are extensively formulated in a variety of drug delivery systems for mucosal applications. Buccal, intestinal, nasal, vaginal and rectal bioadhesive products can all be formulated with such polymers [46].

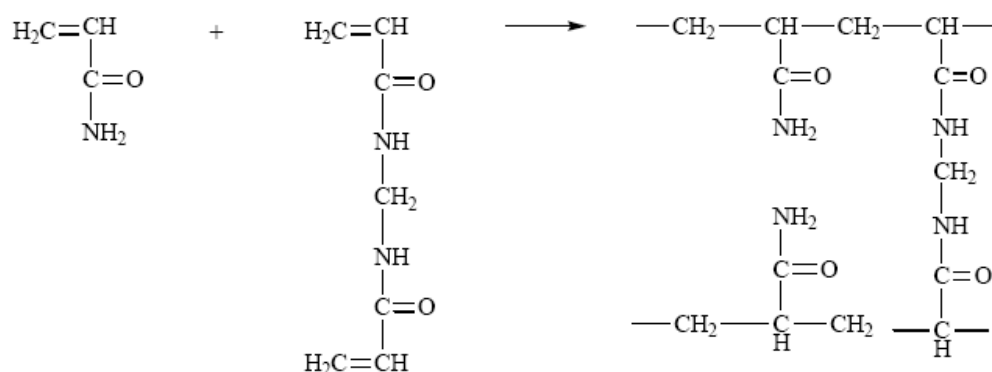
2.5. Polyacrylamides

Polyacrylamide, is a synthetic polymer derived from acrylamide monomer which was originally introduced for use as a support matrix for electrophoresis in 1959 [47]. Polyacrylamide gels result from polymerization of acrylamide with a suitable bifunctional crosslinking agent, most commonly, N,N'-methylenebisacrylamide (bisacrylamide) (Figure 4).

Gel polymerization is carried out using ammonium persulfate and the reaction rate is catalyzed by addition of N,N,N',N'-tetramethylethylenediamine (TEMED). Polyacrylamide gels with a range of pore size can be made to suite size fractionation of a variety of proteins for practical purposes by adjusting the total acrylamide concentration (% T), Polyacrylamide is stable over wide pH intervals (pH 3–11), as well as simple and economical. It has been widely used for a range of applications ranging

from microanalysis to macro-fractionation for proteins, nucleic acid, and other biomolecules, and is nowadays the medium of choice in all electrophoretic techniques [48,49]. In addition to electrophoresis, polyacrylamides have also been used as carriers for delivery of drugs and bioactive molecules.

Figure 4. Representative segment of crosslinked polyacrylamide.



N,N'-Methylenebisacrylamide representative segment of cross-linked polyacrylamide.

Polyacrylamide is a polymer that is formed from units of acrylamide, a known neurotoxin. However, polyacrylamide itself is non-toxic, but is a controversial ingredient because of its potential ability to secrete Acrylamide. Polyacrylamide is used in wide range of cosmetic products (moisturizers, lotions, creams, self-tanning products, *etc.*). The Food and Drug Administration (FDA) allows Polyacrylamide (with less than 0.2% acrylamide monomer) to be used as a film former in the imprinting of soft-shell gelatin capsules. The Cosmetics Ingredient Review (CIR) Expert Panel allows the use of 5 ppm acrylamide residues in cosmetic products.

Polyacrylamides were first used as an implantable carrier for sustained delivery of insulin to lengthen the life of diabetic rats [50]. Since then, various drug delivery systems based on polyacrylamide have been developed [51,52]. It is also used as a carrier for other bioactive macromolecules and cells to produce the desired effects [53,54]. Polyacrylamide-chitosan hydrogels are biocompatible and are used for sustained antibiotic release [55].

Recently Tsung-Hua Yang [56] has reviewed several patents describing the use of polyacrylamide for drug delivery, biomedical and other applications. U.S. 5874095 patent describes pharmaceutical compositions comprising certain specific non-ionic polymers for topical application to the skin which increased transdermal penetration of the drugs through the skin.

The nonionic polymers used in the above invention are polyacrylamides and substituted polyacrylamides, branched or unbranched. These polymers are non-ionic water dispersible polymers which can be formed from a variety of monomers including acrylamide and methacrylamide which are unsubstituted or substituted with one or two alkyl groups (preferably C1–C5).

For example, polyacrylamide microgels derivatized by saponification of the $-\text{CONH}_2$ group to the $-\text{COOH}$ group are responsive to pH and ionic strength of the external medium [57]. Polyacrylamide that contains rationally designed single-strand DNA (ssDNA) as the cross-linker can shrink and swell in response to ssDNA samples and recognize a single base difference in the sample [58]. Among these polymers that can respond to external stimuli, poly-N-isopropylacrylamide (PNIPAA) has been widely

examined as a smart drug delivery material because of its unique phase separation behavior upon external temperature change.

A device which is placed outside the body where total or partial blood diverted from the heart or arterial system is processed to remove unwanted toxic substances and subsequently returned to the circulation is called as extracorporeal toxin removal device. These devices are considered to be simple, efficient and economical to the patients. They have become popular because of their easy accessibility, lower infection and immune rejection probability, avoidance of a major surgical procedure [59]. The function of polyacrylamide in an extracorporeal toxin removal modality is to provide a support matrix for immobilization of the functional parts or ligands.

Because polyacrylamide is chemically inert and stable over various conditions, polyacrylamide has been employed, whether clinically or under development, to serve as a useful matrix for several types of extracorporeal toxin removal devices and has been described in the following patents: WO 02081006 [60], U.S. 7066900 [61].

2.6. *N*-(2-Hydroxypropyl) methacrylamide (HPMA)

The polymeric systems that have been very successfully used for passive drug targeting purposes are copolymers based on *N*-(2-hydroxypropyl) methacrylamide (HPMA). HPMA copolymers were initially developed as plasma expanders, they are highly hydrophilic, non-immunogenic and non-toxic, and reside in the circulation well.

Jindrich Kopecek and colleagues at the Czech (-oslovak) Academy of Sciences in Prague in the mid-1970s started using these long circulating synthetic macromolecules as carriers for low molecular weight drugs [62]. Rationale for using HPMA drug conjugates has been explained by Jindřich Kopeček & Pavla Kopečková [63] in one of their recent papers. HPMA copolymer-drug conjugates are nanosized (5–20 nm) water-soluble constructs. Their unique structural, physicochemical, and biological properties offer several advantages when compared to low molecular weight drugs. The concept of targeted polymer-drug conjugates was developed to address the lack of specificity of low molecular weight drugs for cancer cells. This approach was based on the work of DeDuve, who realized that the endocytic pathway is suitable for lysosomotropic drug delivery [64].

The characteristic features needed to design an ideal conjugate are: a polymer-drug linker that is stable during transport and able to release the drug in the lysosomal compartment of the target cell at a controlled rate, solubility of the conjugate in the biological environment and the ability to target the diseased cell or tissue by an active (receptor ligand) or a passive (pathophysiological) mechanism. The first passively tumor-targeted polymeric prodrug to enter clinical trials was pHPMA-GFLG-doxorubicin [65,66]. The conjugate was named as PK1, *i.e.*, Prague-Keele 1, Its average molecular weight is ~28 kDa and it contains on average 8% wt of doxorubicin [67]. The initial half-life time of PK1 was found to be 2.7 h, as compared to less than 10 min for free doxorubicin. Several other HPMA drug conjugates which are in various clinical phases are listed in Table 4.

Table 4. Selected List of N-(2-hydroxypropyl) Methacrylamide HPMa copolymer based formulations in various phases of clinical trials (Adapted from [68]).

Acronym	Description	Phase	Ref.
PK1	HPMA copolymer-bound doxorubicin; Prague-Keele-1; GFLG-spacer	II	[65-67]
PK2	Galactosamine-modified PK1; GFLG-spacer; for liver targeting	I	[69-71]
PK3	Tyrosinamide-modified PK1; for imaging purposes	I	[66]
AP5280	Polymer-bound cisplatin-derivative; GFLG-spacer; well-tolerated; moderately active	I	[72,73]
AP5346	Polymer-bound oxaliplatin; GGG-spacer; well-tolerated; moderately active	II	[74-76]

2.7. Divinyl Ether-Maleic Anhydride (DIVEMA)

Divinyl ether-maleic anhydride (DIVEMA) is a water soluble polymer which has shown antitumor activity against various tumors [77]. The preparation of 1:2 divinyl ether-maleic anhydride copolymer was first reported by Butler. The biological activities of DIVEMA are due to its ability to activate immunocompetent cells, particularly macrophages and natural killer cells [78,79]. DIVEMA has been used as a drug carrier to superoxide dismutase [80] and anticancer agents such as Adriamycin and methotrexate.

Tumour necrosis factor (TNF- α) cause necrotic effect and has been shown to be effective against tumours induced in mice. The antitumor effect of TNF- α has been studied for murine tumors transplanted into mice and for human tumors transplanted into nude mice. However the clinical applications of TNF- α are limited because of the adverse effects. So water soluble polymer like DIVEMA was conjugated with TNF- α in order to increase the antitumor activity *in vivo* with reduced side effects.

The conjugate DIVEMA-TNF- α (+) showed a significant hemorrhagic necrotic effect on the tumor when compared to native TNF- α 24 h after i.v. injection into mice bearing Sarcoma-180 solid tumors. The antitumor effect was approximately 100 times greater than native TNF- α . The study proved that, upon administration of conjugated DIVEMA-TNF- α , the antitumor activity improved remarkably as compared to the activity observed when DIVEMA and TNF- α was given separately [81].

2.8. Polyoxazoline

Poly(2-alkyl-2-oxazolines) are gaining high interest in biomedical research as they are structurally similar to peptides. Their physico chemical properties can be modulated by varying the alkyl substituent [82,83]. Their properties range from high hydrophilicity which enables synthesis of hydrophilic water soluble biocompatible polymers with good antibiofouling properties (alkyl = methyl or ethyl) through thermal sensitivity of thermoresponsive polymers (alkyl = isopropyl) to hydrophobicity typical for hydrophobic aromatic or aliphatic polymers (substituent = phenyl, butyl, nonyl, etc.) [82,84].

They act as versatile polymers and, as they have the ability to form nanostructures, they are being extensively investigated.

Poly(2-oxazolines) are used as adhesive and in coating formulations, and in various drug in delivery applications [85]. Despite this, their commercial application is limited as the batch polymerisations times range from several hours to several days [86-89]. However, delayed polymerization reactions can be overcome by use of modern technology like microwave reactors. Commercially, however, only 2-methyl, 2-ethyl, 2-isopropyl and 2-phenyl oxazoline are currently available.

Woodle *et al.* reported the use of these polymers for the synthesis of lipo-polyoxazolines-poly(2-methyl-2-oxazoline) and poly(2-ethyl-2-oxazoline)-based lipid conjugates as an alternative to PEG-based materials [90]. The lipopolymers were used to prepare 67 Ga-labelled liposomes, which were subsequently injected into the bloodstream of rats. They behaved similar to the PEG based liposomes with long circulation time in blood, uptake by liver and spleen [91]. This similarity was attributed to their high mobility of chains and water binding ability both in turn contributing to the steric stabilization in polymer-lipid liposomes.

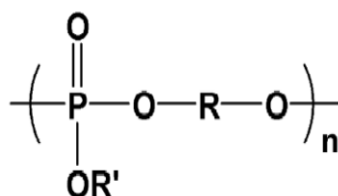
Apart from these, a number of other applications of polyoxazoline in preparation of nanoscale systems, thermoresponsive systems, gene delivery applications have been reviewed by Nico Adams *et al.* [82].

2.9. Polyphosphates

Biodegradable polyphosphoesters (PPE) like polyphosphates, polyphosphonates have been studied for their use in drug delivery, gene delivery and tissue engineering. These polymers have a backbone consisting of phosphorous atoms attached to either carbon or oxygen. The uniqueness of this class of polymer lies in the chemical reactivity of phosphorous, which enables attachment of side chains to alter the biodegradation rates and molecular weight of the polymer [92].

Penczek and others thought that these polymers, which are analogs of nucleic acid and teichoic acids, would represent a large number of bio-macromolecules. They have reported the synthesis of many of these polymers by various methods [93-96]. The general structure of polyphosphoesters is given in Figure 5.

Figure 5. General structure of polyphosphoesters where R = divalent organic groups.



Water-soluble positively charged polymers are useful for gene delivery [97-101]. Positively charged polymer interacts with negatively charged DNA by electrostatic interactions resulting in the formation of complexes and thus providing protection to DNA from enzymatic attack. This also enables greater cellular uptake of DNA. The commonly used cationic polymers for gene delivery are the ones having amide bond like poly(L-lysine) and vinyl bonds like in polyethyleneimine (PEI) because they show excellent stability in aqueous solutions. Among a large number of cationic polymers reported in the literature, the most extensively studied polymeric gene carriers have either amide bonds (e.g.,

poly(L-lysine) and cationic PAMAM dendrimers) or vinyl bonds (e.g., poly-ethyleneimine, PEI). These bonds are very stable in aqueous solution and there is no direct evidence of their degradation in body fluid.

Wang *et al.* have reported the development of biodegradable polyphosphoesters including polyphosphates (PPEs) and polyphosphoramidates (PPAs) as gene carriers [102-104]. They reported that these systems can show sustained release behavior both inside and outside the cell thus increasing the bioavailability of DNA in the cells. Further they showed that the controlled release behavior of these polymers can be controlled by changing the ratio of polycationic polymer to DNA ratio.

2.10. Polyphosphazenes

Polyphosphazene belongs to a class of polymers with inorganic moiety as the main chain and two active chloride groups on each repeat unit. Substitution of these chloride groups gives multifunctional polyphosphazenes with tunable physicochemical and biological properties [105]. These polymers have been used to formulate nano-fibers [106] and hydrogels [107]. Zhang *et al.* have synthesized and developed thermally sensitive amphiphilic phosphazenes for sustained local delivery [108,109]. They also synthesized methoxypoly(ethylene glycol) and ethyl-p-aminobenzoate side groups (PEG/EAB-PPPs) polyphosphazenes for delivery of water soluble anticancer agent like Doxorubicin HCl [110].

Some of the most important water-soluble polyphosphazenes such as poly[di(carboxylatophenoxy)phosphazene] (PCPP), poly[di(methoxyethoxyethoxy) phosphazene] (MEEP), and a number of others have been studied in pioneering works of H. Allcock and his coworkers [111,112]. Andrianov has reviewed about the advances in the synthesis of water-soluble polyphosphazene and their degradation pathways [113].

Some water-soluble polyphosphazenes containing ionic groups can be used to formulate hydrogel microspheres or nanospheres for controlled release and drug delivery applications. These methods are ideal for protein encapsulation as they do not use organic solutions or heat. Polymers include polyphosphazene immune adjuvants, which have been also formulated in microspheres and studied for mucosal immunization [114-117]. Water-soluble polyphosphazene containing amino aryloxy and methyl amino side groups has been synthesized and investigated as an inert polymeric carrier for the covalent attachment of biologically active agents.

3. Natural Water Soluble Polymers

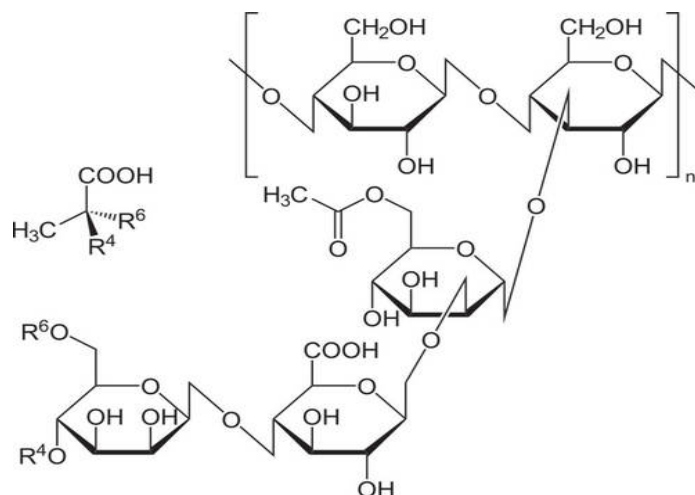
3.1. Xanthan Gum

The primary structure of xanthan (Figure 6) consists of repeating pentasaccharide units consisting of two D-glucopyranosyl units, two D-mannopyranosyl units and one D-glucopyranosyluronic unit [118].

Xanthan is a free flowing powder soluble in both hot and cold water to give viscous solutions at low concentrations. Its industrial importance is based upon its ability to control the rheology of water based systems. It is a very effective thickener and stabilizer because it gives highly viscous solutions even at low concentrations as compared to other polysaccharide solutions. Xanthan gum solutions exhibit pseudoplastic behavior (viscosity is regained immediately even at high shear rates). Its pseudoplastic

property enhances mouth feel effect and flavor release. Xanthan gum solutions offer very good stability. They are least affected by changes in pH and are stable in both alkaline and acidic conditions. The solution properties of xanthan are not affected in a pH range of 1–13. Xanthan is compatible with most commercially available thickeners such as sodium alginate, carboxymethyl cellulose and starch [118].

Figure 6. Structure of Xanthan gum [52].

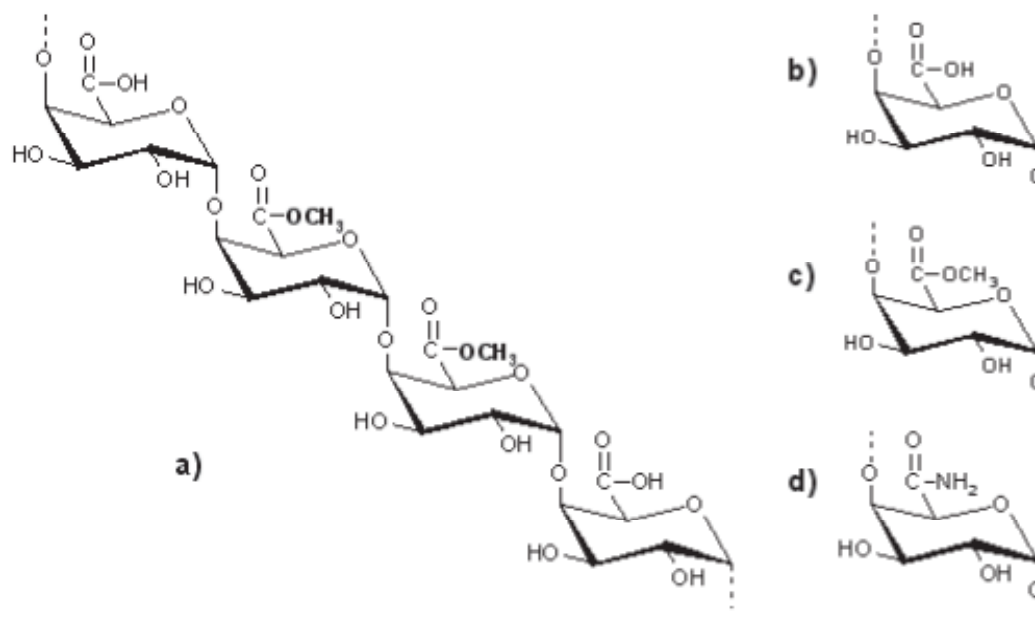


Xanthan gum is widely used in cosmetics and in toothpastes [119]. It can be easily extruded from the tube or dispenser because of the shear thinning flow behavior. It also ensures toothpaste that will keep a stable stand on the brush. The shear thinning characteristics also improve the dispersion on and the rinsing from the teeth. Toothpastes thickened with xanthan gum have a bright, shiny cord with short flow behavior. Xanthan gum is used as a thickener and stabilizer in personal care products like creams, eye gels and the like. Typical xanthan gels feel very gentle and soft due to their shear thinning low behavior. In emulsions or suspensions for pharmaceutical use xanthan gum prevents the separation of insoluble ingredients, e.g., barium sulphate in X-ray contrast media. Most of the ready to eat, semi-prepared foods and convenience foods would not be possible without stabilizers and thickeners. In order to adjust the desired flow behavior, xanthan gum is often used in combination with other hydrocolloids [119].

3.2. Pectins

Pectin is a made up of mixture of polysaccharides. Pectins are mainly obtained from citrus peel or apple pomades, both of which are by-products of juice manufacturing process Apple pomade contains 10–15% of pectin on a dry matter basis while Citrus peel contains of 20–30%. Pectin is mainly composed of D-galacturonic acid (GalA) units [120] joined in chains by means of α-(1-4) glycosidic linkage. These uronic acids have carboxyl groups, some of which are naturally present as methyl esters and others which are commercially treated with ammonia to produce carboxamide groups (Figure 7).

Figure 7. (a) A repeating segment of pectin molecule and functional groups; (b) carboxyl; (c) ester; (d) amide in pectin chain.



Pectins are soluble in pure water. Monovalent cation (alkali metal) salts of pectinic and pectic acids are soluble in water; di- and tri-valent cations salts are weakly soluble or insoluble. Dry powdered pectin, when added to water, forms clumps. This clump formation can be prevented by dry mixing pectin powder with water-soluble carrier material or by the use of pectin having improved dispersibility [121]. Other properties like viscosity, solubility, and gelation are generally related. For instance, factors that increase gel strength will increase the tendency to gel, decrease solubility, and increase viscosity, and vice versa. These properties of pectins are a function of their structure, which is that of a linear polyanion (polycarboxylate). Monovalent cation salts of pectins are highly ionized in solution, and the distribution of ionic charges along the molecule keeps it in an extended form by coulombic repulsion [122].

Pectin has been used in the pharmaceutical industry for a wide range of applications [123]. Pure and standardized pectin has been used as a binding agent in tablets. High Methoxy (HM) pectin is used as monolithic bioerodible system, preparation of directly compressible tablets along with HPMC. Low Methoxy (LM) Pectin has been used to prepare beads by ionotropic gelation technique, sustained release drug delivery using calcium pectinate gel beads. Pectin based microspheres were also prepared by emulsification technique. Film coated tablets can also be prepared using combination of HM-pectin and ethyl cellulose aqueous dispersion, HM or LM pectin with chitosan mixtures.

Pectin also has several unique properties which have enabled it to be used as a matrix for the entrapment and/or delivery of a variety of drugs, proteins and cells. Pectin helps in reduction of blood cholesterol in a diverse group of subjects. At least 6 g/day of pectin is necessary to reduce cholesterol levels. Amounts less than 6 g/day of pectin are not effective [124]. Pectin has been used as a thickening stabilizing and gelling agent stabilizer in food and beverage industry. It effectively removes lead and mercury from the gastrointestinal tract and respiratory organs [125]. Intravenous

administration of pectin shortens the coagulation time of drawn blood, thus helping in controlling hemorrhage or local bleeding.

Pectin hydrogels can be used as a binder in tablet formulations [126,127] and have been used in controlled-release matrix tablet formulations [128]. Using an extruder/spheronizer, spherical pellets containing calcium pectate were prepared. These were then coated in pectin solution resulting in the formation of insoluble calcium pectinate gel around the pellets. The use of pectin to develop other oral controlled release drug delivery systems has been reported by some authors.

3.3. Chitosan Derivatives

Chitin and chitosan have been used extensively in many areas ranging from food processing to waste management, medicine, biotechnology and pharmaceutical industries. Chitosan in particular has been used widely in pharmaceutical applications as a formulation excipient because it is biodegradable, biocompatible and less toxic. It has been used as a mucoadhesive, oral absorption enhancer and in protein and gene delivery [129].

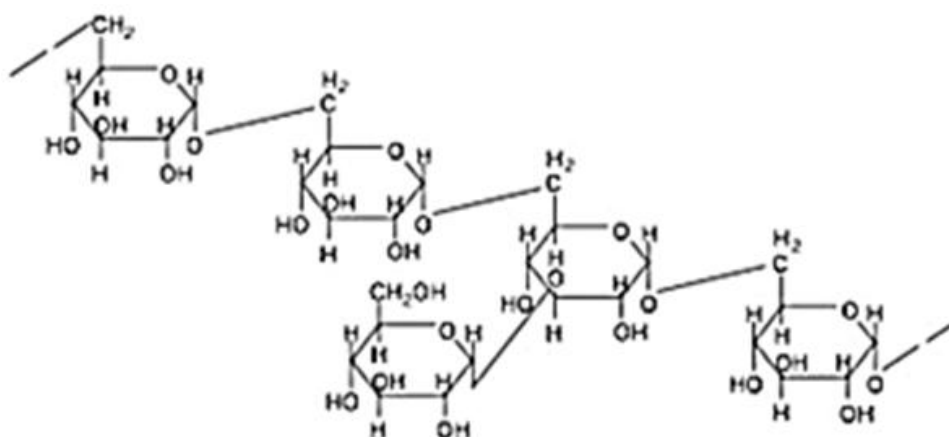
The main drawback with chitin and chitosan is that it is difficult to dissolve them in water and in neutral pH. So, water soluble derivatives of chitosan and chitosan have been synthesized by various researchers by chemical modification. These chemical modifications result in the formation of hydrophilic chitin or chitosan which have more affinity to water or organic solvents [130]. Limited solubility of chitosan and chitin has been overcome by chemical modification. For example, carboxymethylation of chitosan results in formation of N-carboxymethylchitosan (N-CMC) which is soluble in wide range of pH [131].

Chitin and chitosan derivatives are also used in treatment of industrial effluents because of their affinity to metal ions. N-CMC has been used widely in pharmaceutical areas for achieving controlled release of drugs, orthopedic devices and connective tissue [132-137].

3.4. Dextran

Dextran can be produced by fermentation of media containing sucrose by *Leuconostoc mesenteroides*. B512F Dextran is an α -D-1,6-glucose-linked glucan with side-chains 1–3 linked to the backbone units of the Dextran biopolymer. A fragment of the Dextran structure is shown in Figure 8 [138].

Figure 8. Fragment of Dextran.



Fractions of dextran are readily soluble in water to form clear, stable solutions. The solubility of dextran is not affected by pH. They are also soluble in other solvents like methyl sulfide, formamide, ethylene glycol, and glycerol. Dextran fractions are insoluble in alcohols like methanol, ethanol and isopropanol, and also most ketones, such as acetone and 2-propanone.

The research interest of past decades has focused on the use of dextran as macromolecular carriers, e.g., hydrogels, in which the drug can be incorporated. Dextran hydrogels can be obtained in various ways, based on either chemical or physical crosslinking. Dextran crosslinked with methacrylate (MA), hydroxyethylmethacrylate (HEMA) have been used as hydrogel implants, microspheres for scaffolds [139–144].

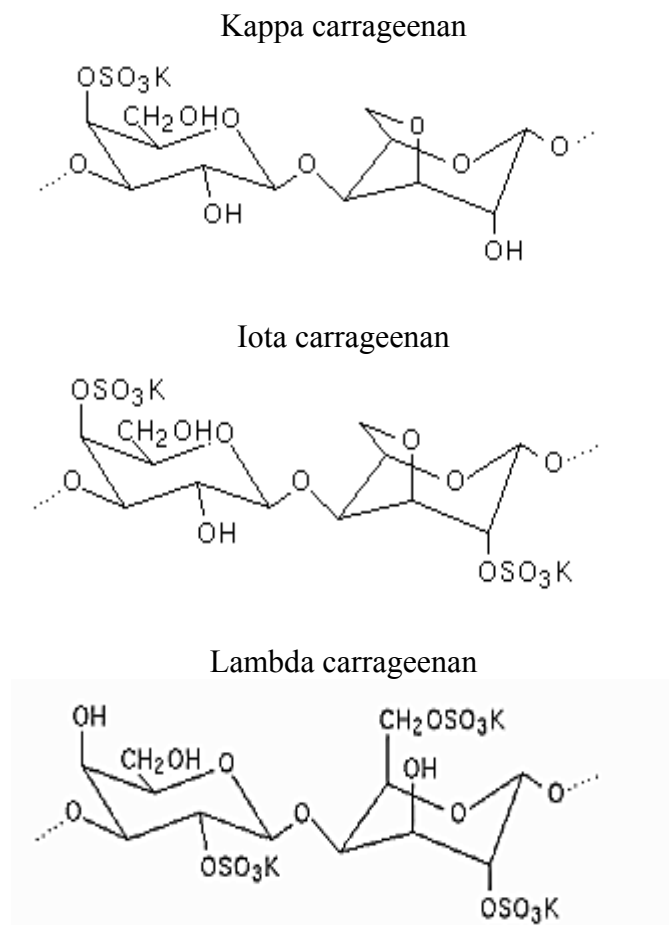
Thrombolytic enzymes are effective in treating myocardial infarction and other cardiac diseases. High costs, low availability due to low production, toxicity and antigenicity, lack of specificity to the affected area limit the clinical use of these enzymes. These problems can be overcome by using modified (immobilized) enzymes. Torchilin *et al.* [145] conjugated the enzyme with a water-soluble carrier like dextran, resulting in a stabilized enzyme preparation with longer circulation time and reduced immunogenicity [146]. They report the synthesis of streptokinase immobilized on activated dextran having a molecular weight of 35,000–50,000. This preparation is produced in Russia under the trademark Streptodekaza™ and is used for treatment of acute myocardial infarction, acute pulmonary artery thromboembolism, peripheral arterial and deep vein thrombosis [147,148]. In comparison with the native enzyme, Streptodekaza™ has a prolonged life-time in the circulation (increase in blood fibrinolytic activity can be observed even 80 h after administration) and causes few complications.

3.5. Carrageenan

The main sources for carrageenan are the *Chondrus crispus*, *Eucheuma cottonii* and *Eucheuma spinosum* species. It is a natural ingredient obtained from certain species of the red seaweed, class Rhodophyceae [149,150]. Chemically, it comprises repeating galactose units and 3,6-anhydrogalactose (3,6-AG), sulfated and non-sulfated, joined by alternating α (1-)- and β (1-4)-glycosidic linkages [151,152]. Three main types of carrageenan which are widely used in food industry are called iota, kappa and lambda carrageenan. Table 5 summarizes the characteristic features of each type of carrageenan and Figure 9 represents their corresponding structures.

Table 5. Types of carrageenan.

Iota	Kappa	Lambda
Gels most strongly with calcium salts	Gels most strongly with	No gel formation,
Elastic gel with no syneresis (weeping out of water)	potassium salts	forms high viscosity
Gel is freeze-thaw stable	Brittle gel with some syneresis	solutions
Completely soluble in hot water	Synergistic with locust bean gum	Fully soluble in cold
	Soluble in hot water	water

Figure 9. Structure of Kappa, Iota and Lambda type of carrageenan.

Carrageenan is considered to be a good substitute for gelatin (animal-based product) in hard and soft gel capsules. The incorporation in glycerin-water mixture masks the chalkiness of antacid gels. It can be used in both topical bases [153] and suppository bases [154]. The active ingredients can be trapped inside the fibres by spinning the insoluble carrageenan chitosan fibres. These systems help in wound healing by absorbing large quantities of water thereby keeping the wound clean. The texture of any formulation or polyols can be controlled by utilizing the property of unique interactions between carrageenan and polyols. Carrageenan is used as a thickening agent in hand lotions and shampoos thus promoting healthy skin and hair.

Contraceptive gels: Existing vaginal products have certain drawbacks like leakage because of their inability to maintain gel like structure when applied. Carrageenan gels can be modified suitably and can be used for quick rehealing and protection during intercourse.

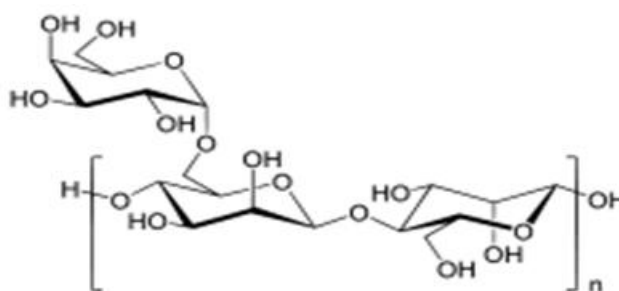
Carrageenan has unique properties like viscosity, continuous phase gel formation and specific interactions with the abrasive. Combination of these properties helps in stabilizing the toothpaste preparations. The continuous phase gel matrix entraps the abrasive and flavor oil micelles within the gel matrix thereby enhances the emulsion stability. The gel structure also imparts short texture to the toothpaste providing a clean (non-stringy) break on extrusion from the tube or pump. Carrageenan helps in dispersing and stabilizing the solids thus preventing hardening, caking and drying out. This is because of interaction between carrageenan and surface of the abrasives. These distinct properties of

carrageenan make it unique as compared to other binders used in dentrifice industry. It can be safely used with CMC as it does not contain enzymes while other binders like xanthan gum contain enzymes which attack CMC making it unsuitable for use in combinations. Apart from this, carrageenan is widely used in food industry as a thickening agent, stabilizer, gelling agents for a wide range of products like juices, dressings & sauces, beer and wine.

3.6. Guar Gum

Guar Gum is derived from endosperm of the guar plant (*Cyamopsis tetragonoloba*). Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. It consists chiefly of high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and shows degradation in the large intestine due the presence of microbial enzymes [155-158]. The backbone is a linear chain of β 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose, forming short side-branches (Figure 10).

Figure 10. Structure of Guar gum.



Guar gum is used as a binder, disintegrant in tablet formulations. It also acts as a stabilizers, emulsifier, thickening, and suspending agent in liquid formulations. It has been widely used for colonic drug delivery applications. The swelling ability of guar gum is used in the retardation of drug release from the dosage forms. Its utility as a carrier for colon specific drug delivery is based on its degradation by colonic bacteria [159-161].

3.7. Cellulose Ethers

A very wide range of products can be prepared using different cellulose ethers. They differ from each other with respect to type of substituents, substitution level, molecular weight (viscosity), and particle size. The most common types of cellulose ethers are:

- Hydroxypropylmethyl cellulose (HPMC)
- Hydroxypropyl cellulose (HPC)
- Hydroxyethyl cellulose (HEC)
- Sodium carboxy methyl cellulose (Na-CMC)

Pure cellulose as such is insoluble in hot or cold water due to strong intramolecular hydrogen bonding. So cellulose is converted to cellulose esters or cellulose ethers derivatives which are water soluble. These water soluble cellulose derivatives are used in wide range of applications. Thus,

modified cellulose derivatives enhance water retention capacity, pseudoplastic behavior, film forming properties and complexation. The advantages of cellulose ethers are that they are biocompatible and hence can be used for pharmaceutical purposes; cosmetics and food [162]. They are mainly used as binders, coating agents, emulsifying, stabilizing, agents, and tablet disintegrants.

3.7.1. Sodium CMC

It is used as an emulsifying agent in pharmaceuticals, and in cosmetics. It is a preferred polymer because it has wide range of functional properties like binding, thickening, stabilizing agent. Also, NaCMC can be used in preparation of microspheres by using glutaraldehyde as a crosslinker. Ketorolac tromethamine, an anti-inflammatory and analgesic agent, was successfully encapsulated into these microspheres and drug encapsulation of up to 67% was achieved [163].

3.7.2. HPC

It is non-ionic water-soluble and pH insensitive cellulose ether. It can be used as thickening agent, tablet binding, modified release and film coating. Buccal delivery formulations containing HPC and polyacrylic acid have been in use for many years [164,165], several researchers have reported the use of HPC in mucoadhesive delivery systems for several different drugs [166,167].

3.7.3. HPMC

It is a water soluble cellulose ether which is mainly used in the preparation of controlled release tablets. Viscosity is the main variable responsible for controlling the release. Ifat Katzhendler *et al.* studied the effect of molecular weight of HPMC on the mechanism of drug release of naproxen sodium (NS) and naproxen (N) [168]. The hydration and gel forming abilities of HPMC can be used to prolong the drug release of the active ingredient.

3.8. Hyaluronic acid (HA)

Hyaluronic acid (HA), a natural polyanionic polysaccharide distributed widely in the extracellular matrix and the joint liquid of mammals and approved for injections by the Food and Drug Administration (FDA) [169]. It is non-toxic, biocompatible mucoadhesive polysaccharide having negative charge and is biodegradable. It is mainly distributed in the connective tissue, eyes, intestine and lungs. Above all, the overexpression of CD-44 receptor which is an endogenous ligand for HA, makes this a good candidate for drug targeting [170,171].

HA is composed of two sugar units-glucuronic acid and N-acetylglucosamine which is polymerized into large macromolecules of over 30,000 repeating units. It is readily soluble in water, and produces a gel. The high solubility of hyaluronic acid has proven to be problematic in the development of polymers for tissue engineering. Although this property of HA is more helpful in orthopaedic surgery, it also requires more chemical stabilization and structural stability. The length of the chain, degree of entanglement, cross linking, pH, chemical variations all effect the viscosity of the gel [172,173].

Hyaluronic acid polymers are used in the preparation of gels for delivery of drugs to eye and installation into other cavities. They are used along with other polymers like alginic acid, HPMC,

poloxamers *etc.* for achieving the desired property in drug delivery systems (Bourlais *et al.* [174]. Combination of these polymers influences the biophysical properties and also alters the pharmacokinetics. HA-based corneal shields have demonstrated more prolonged steroid delivery than by direct application, with a consummate smoothing of dosage profile [175]. Insulin absorption from eye drops via the cornea is enhanced in the presence of HA. HA gel has been successfully studied as a carrier mechanism for antibiotics to the eye; the gel prevents tears from washing away the drug and gives a more prolonged release [176]. HA based nanosystems have been studied earlier for gene delivery, cancer and asthma [177-179]. Some of the commercial products containing HA are listed in Table 6.

Other applications of HA as reviewed by Price *et al.* [180] are as follows: (i) Wound healing by extracellular regeneration; (ii) Epithelial regeneration; (iii) Topical treatment of dry eye syndrome [181] and Sjögren's syndrome [182]; (iv) as a viscosity agent in pulmonary pathology for achieving alveolar patency [183]; (v) Commercial preparation (Synvist) available for intra-articular injection, (vi) as a filler in rejuvenative medicine for wrinkles and cutaneous lines.

Table 6. List of hyaluronic acid (HA) or HA-derived products developed by different companies (Adapted from [184]).

Company	Product/Application
Pharmacia & Upjohn Company	Healon surgical aid in cataract extraction
Fida	Hyalgan—osteoarthritis
Amgen	Blend of HA with Interleukin-1 receptor antagonist
Anika	Incert [®] , Amvisc [®] for surgery
	Orthovisc [®] , Hyvisc—osteoarthritis
	Ossigel bone fracture recovery
BioCoat	Hydak—HA surface coating
Biomatrix	HA derivatives
	Synvisc for viscosupplementation
	Hylashiel for viscoprotection
	Hylaform for viscoaugmentation
Clear Solutions Biotechnology	Halosol [™] , Halogel [™] , Halobeads [™] , HA-Quat [™] , Qualginate [™] , Halgin [™] } cosmetic use
	HA-Matricare [™] , Halosorb [™] —Medical applications
	Hazomes-B2 [™] , Cancept-HA [™] —drug delivery
	HA-Bed [™] —Tissue engineering purposes
Collaborative Laboratories	HA products in the cosmetic area: liposomes (Micasomes [™] HOH) and specialty products (Botanigel [™])
Genzyme	Hylucare—Cosmetic use (HyluMed [®]); Seprafilm [®] —Drug delivery
Seikagaku Corp.	HA-enzyme conjugates
Shiseido Company, Ltd.	HA products for cosmetics and drug delivery
SurModics Inc.	HA surface coating using PhotoLink [®] technology
Telios Pharmaceuticals, Inc.	HA hydrogels for tissue engineering

It is also interesting to note that HA is used in the field of viscosurgery, viscosupplementation. In reproductive medicine, HA enhances the retention of the mobility of cryo-preserved and thawed spermatozoa. This property can be used to select spermatozoa which are viable and improve artificial insemination and other *in vitro* fertilization methods.

3.7.5. Albumin

Albumin has a molecular weight of 66.5 kDa and is the most abundant plasma protein (35–50 g/L human serum) synthesized in the liver. Human serum albumin (HSA) has a half-life of 19 days. It acts as a solubilising agent for long chain fatty acids and is therefore essential for the metabolism of lipids. It binds very well to penicillins, sulfonamides, indole compounds, and benzodiazepines, copper(II) and nickel(II) in a specific and calcium(II) and zinc(II) in a relatively nonspecific manner, it is responsible for osmotic pressure of the blood [185].

Albumin is an acidic and very soluble protein that is soluble in 40% ethanol. It is stable in the pH range of 4–9, soluble in 40% ethanol, and highly thermostable even when heated at 60 °C for up to 10 h. It is biodegradable in nature and lacks toxicity & immunogenicity. It is very well taken up by the tumor tissues. All these properties make it an ideal candidate for drug delivery. It is a versatile protein carrier which is used in drug targeting for achieving better pharmacokinetic profile of peptide or protein based drugs.

It is easy to purify, soluble in water which makes it convenient to delivery by injection and thus is considered as an ideal candidate for nanoparticle preparation [186,187]. Protein based nanoparticles have the advantage of greater stability during storage and are easy to scale up as compared to other delivery systems [188–191].

Covalent derivatization of albumin nanoparticles with drug targeting ligands is possible, due to the presence of functional groups (*i.e.*, amino and carboxylic groups) on the nanoparticle surfaces [192,193]. HAS based formulations such as Abraxane [194,195] and Albunex [196] have shown good tolerability as evident from the clinical studies. So their efficacy of albumin formulations with minimum side effects is guaranteed. It is also suitable for gene delivery [197,198].

3.7.6. Starch or Starch Based Derivatives

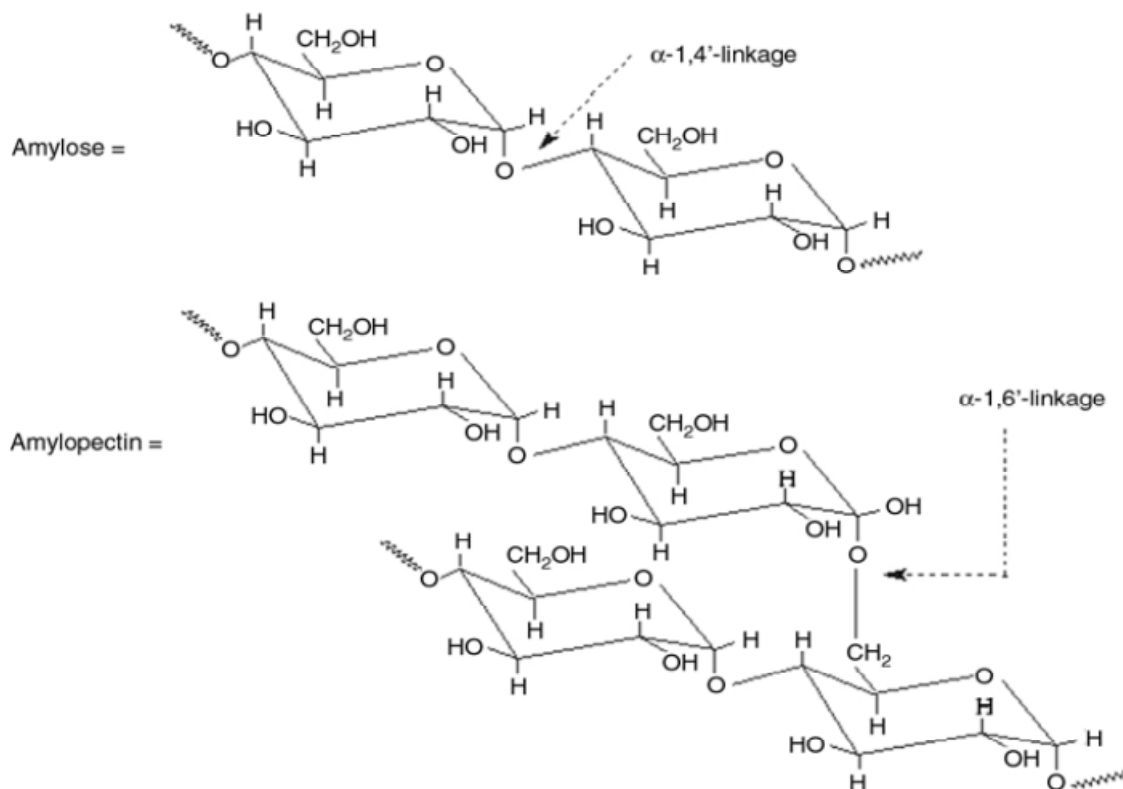
Starch is a natural polymer which has widespread application ranging from a simple filler or binder [199] to a more functional ingredient in the formulation of capsules [200], coatings [201], subcutaneous implants [202], and tablets. In tablets, starch has been mainly used as a binder, diluents, disintegrant and also as a sustained release agent in matrix systems [203,204]. It is also used as a thickening and gelling agent in food industry.

It is synthesized from carbon dioxide and water by photosynthesis in plants [205]. Its low cost, biodegradability and renewability make it a suitable candidate for developing sustainable materials [206,207]. In order to conserve petrochemical resources and reduce environmental burden many efforts have been made to develop starch based polymers.

Starch is mainly composed of two homopolymers of D-glucose [208]: amylose, a mostly linear D (1, 4′)-glucan and branched amylopectin, having the same backbone structure as amylose but with many α -1, 6′-linked branch points (Figure 11). Starch has many hydroxyl functional groups in its

structure and so it is hydrophilic in nature. Hydrophilicity of starch can be used to improve the degradation rate of some degradable hydrophobic polymers. Native starch is not used because of its poor processability, and poor mechanical properties of the end products [209].

Figure 11. Structure of Amylose and Amylopectin units of starch.



Lu *et al.* have described in detail the preparation of starch based biodegradable polymers by physical blend, chemical modification and their applications in various fields [210]. Starch is either chemically or physically modified to improve the properties of starch. Such derivatives have physicochemical properties that are different from the parent while still maintaining the biodegradability.

Chemically, starch is modified by Hydroxypropylation to enhance starch clarity and cold-storage stability because the presence of hydroxypropyl groups increases water holding and reduces reassociation of starch chains. This results in formation of a more stable gel [211].

PCL and PLA are chemically bonded onto starch and can be used directly as thermoplastics or compatibilizer. Starch-g-PVA behaves good properties of both components such as processability, hydrophilicity, biodegradability and gelation ability [212-216].

Starch-based biodegradable polymers (SBBP) have good biocompatibility, its degradation products are non-toxic and have good mechanical properties [217-222]. These SBBPs have been widely used in bone tissue engineering scaffolds [223,224], in drug delivery as microspheres or hydrogels [225,226]. Modified starches have been studied as functional ingredients in sustained release applications because of their improved functionality over their native counterparts [227-231]. Among them, crosslinked high amylose corn starch is the most extensively studied one. The sustained release properties of crosslinked and substituted high amylose corn starch matrices and their swelling behavior in media with various pH and ionic strengths has been reported by Mulhbachter *et al.* [232]. The matrix

characteristics of cross-linked high amylose starches have been studied by Dumoulin *et al.* [233] and Le Bail *et al.* [229]. The reasons for starch acting as a sustained release agent is due to its gel-forming ability, biodegradability, and biocompatibility [234]. The molecular structure of the gel layer and the mechanical and physicochemical characteristics of the matrix such as gel strength and porosity contribute to the sustained release properties of the matrix.

Onofre and Wang [235] investigated the sustained release properties of hydroxypropylated corn starches with varying amounts of amylase. They characterized the matrices for water holding capacity, porosity, rheological properties, and morphology. Hydroxypropylation increased the water holding capacity and reduced the porosity of the tablets thus enhancing the sustained release ability of amylase containing starches.

4. Conclusions

Scientists around the globe are trying to find ways of improving therapeutic efficacy of drugs by modifying the formulation technique, polymeric systems, *etc.* The drawbacks associated with conventional dosage forms have been overcome by utilizing polymers synthesized specifically to solve the problems. The use of novel polymers not only offers benefits but also can prove to be harmful because of the toxicity and other incompatibilities associated with them. Care should be taken to properly select polymers while designing a delivery system. The ultimate goal is to introduce cost effective, biocompatible, multifunctional, less toxic polymers so that the delivery systems pass through the various phases of clinical trials and benefit the society. It is believed that the advances in polymer sciences will revolutionize the design, development and performance of polymer based drug delivery systems.

Acknowledgments

The authors wish to thank the Department of Pharmaceutical sciences, Western University of Health Sciences, Pomona, CA, USA, for providing the facilities and necessary assistance.

References

1. Will, R.; Loechner, U.; Yokose, K. Synthetic Water Soluble Polymers. Available online: <http://www.sriconsulting.com/CEH/Public/Reports/582.0000/> (accessed on 28 June 2011).
2. Veronese, F.M.; Pasut, G. PEGylation, Successful Approach to Drug Delivery. *Drug Discovery Today* **2005**, *10*, 1451-1458.
3. Knop, K.; Hoogenboom, R.; Fischer, D.; Schubert, U.S. Poly (ethylene glycol) in Drug Delivery: Pros and Cons as Well as Potential Alternatives. *Angew. Chem. Int. Ed.* **2010**, *49*, 6288-6308.
4. Ruel-Gariepy, E.; Leroux, J.-C. *In situ*-Forming Hydrogels—Review of Temperature-Sensitive Systems. *Eur. J. Pharm. Biopharm.* **2004**, *58*, 409-426.
5. Martens, P.; Holland, T.; Anseth, K.S. Synthesis and Characterization of Degradable Hydrogels Formed from Acrylate Modified Poly(vinyl alcohol) Macromers. *Polymer* **2002**, *43*, 6093-6100.
6. Bhadra, D.; Bahdra, S.; Jain, P.; Jain, N.K. Pegnology: A Review of PEG-ylated Systems. *Pharmazie* **2002**, *57*, 5-29.

7. Monfardini, C.; Veronese, F.M. Stabilization of Substances in Circulation. *Bioconjugate Chem.* **1998**, *9*, 418-450.
8. Pasut, G.; Veronese, F.M. Polymer Drug Conjugation, Recent Achievements and General Strategies. *Prog. Polym. Sci.* **2007**, *32*, 933-961.
9. Allen, T.M.; Cullis, P.R. Drug Delivery Systems: Entering the Mainstream. *Science* **2004**, *303*, 1818-1822.
10. Duncan, R.; Vicent, M.J.; Greco, F.; Nicholson, R.I. Polymer—Drug Conjugates: Towards a Novel Approach for the Treatment of Endocrine-Related Cancer. *Endocr. Relat. Cancer* **2005**, *12*, S189-S199.
11. Savient Pharmaceuticals, Inc. Product Pipeline—Overview. Available online: <http://savientpharma.com/pipeline/> (accessed on 13 August 2011).
12. Pasut, G.; Veronese, F.M. PEG Conjugates in Clinical Development or Use as Anticancer Agents: An Overview. *Adv. Drug Deliv. Rev.* **2009**, *61*, 1177-1188.
13. Burnham, B. Polymers for Delivering Peptides and Proteins. *Am. J. Hosp. Pharm.* **1994**, *51*, 210-218.
14. Eldon, M.A.; Staschen, C.M.; Viegas, T.; Bentley, M. NKTR-102, a Novel PEGylatedirinotecan Conjugate, Results in Sustained Tumor Growth Inhibition in Mouse Models of Human Colorectal and Lung Tumors that is Associated with Increased and Sustained Tumor SN38 Exposure. Presented at *AACR-NCI-EORTC International Conference*, San Francisco, CA, USA, 22–26 October 2007; poster C157.
15. Von Hoff, D.D.; Jameson, G.S.; Borad, M.J.; Rosen, L.S.; Utz, J.; Basche, M.; Alemany, C.; Dhar, S.; Acosta, L.; Barker, T.; *et al.* First Phase I Trial of NKTR-102 (PEG-Irinotecan) Reveals Early Evidence of Broad Anti-Tumour Activity in Three Different Schedules. Presented at *the 20th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics*, Geneva, Switzerland, 21–24 October 2008; poster #595.
16. NKTR-105. Available online: http://www.nektar.com/product_pipeline/oncology_nktr-105.html (accessed on 12 August 2011).
17. Zhao, H.; Lee, C.; Sai, P.; Choe, Y.H.; Boro, M.; Pendri, A.; Guan, S.; Greenwald, R.B. 20-Oacylcamptothecin Derivatives: Evidence for Lactone Stabilization. *J. Org. Chem.* **2000**, *65*, 4601-4606.
18. Scott, L.C.; Yao, J.C.; Benson, A.B.; Thomas, A.L.; Falk, S.; Mena, R.R.; Picus, J.; Wright, J.; Mulcahy, M.F.; Ajani, J.A.; *et al.* A Phase II Study of Pegylatedcamptothecin (Pegamotecan) in the Treatment of Locally Advanced and Metastatic Gastric and Gastro-Oesophageal Junction Adenocarcinoma. *Cancer Chemother. Pharmacol.* **2009**, *63*, 363-370.
19. Sapra, P.; Zhao, H.; Mehlig, M.; Malaby, J.; Kraft, P.; Longley, C.; Greenberger, L.M.; Horak, I.D. Novel Delivery of SN38 Markedly Inhibits Tumor Growth in Xenografts, Including a Camptothecin-11-Refractory Model. *Clin. Cancer Res.* **2008**, *14*, 1888-1896.
20. Jeong, B.; Bae, Y.H.; Kim, S.W. Thermoreversible Gelation of PEG-PLGA-PEG Triblock Copolymer Aqueous Solutions. *Macromolecules* **1999**, *32*, 7064-7069.
21. Chowhan, Z.T. Role of Binders in Moisture-Induced Hardness Increase in Compressed Tablets and Its Effect on *in vitro* Disintegration and Dissolution. *J. Pharm. Sci.* **1980**, *69*, 1-4.

22. Chowhan, Z.T.; Amaro, A.A.; Ong, J.T.H. Punch Geometry and Formulation Considerations in Reducing Tablet Friability and Their Effect on *in vitro* Dissolution. *J. Pharm. Sci.* **1992**, *81*, 290-294.
23. Jun, Y.B.; Min, B.H.; Kim, S.I.; Kim, Y.I.J. Preparation and Evaluation of Acetaminophen Tablets. *Kor. Pharm. Sci.* **1989**, *19*, 123-128.
24. Sinchalpanid, N.; Mitrevej, A. Comparative Evaluation of Hydroxypropyl Cellulose and Povidone in Paracetamol Tablet Formulations. *Mahidol J. Pharm. Sci.* **1993**, *20*, 33-39.
25. Stone, I.M. Water Dispersible Antibiotics. U.S. Patent 3,089,818, 14 May 1963.
26. Forster, A.; Hempenstall, J.; Rades, T. Characterization of Glass Solutions of Poorly Water-Soluble Drugs Produced by Melt Extrusion with Hydrophilic Amorphous Polymers. *J. Pharm. Pharmacol.* **2001**, *53*, 303-315.
27. Jijun, F.; Lishuang, X.; Xiaoli, W.; Shu, Z.; Xiaoguang, T.; Xingna, Z.; Haibing, H.; Xing, T. Nimodipine (NM) Tablets with High Dissolution Containing NM Solid Dispersions Prepared by Hot-Melt Extrusion. *Drug Dev. Ind. Pharm.* **2011**, *37*, 934-944.
28. He, H.; Yang, R.; Tang, X. *In vitro* and *in vivo* Evaluation of Fenofibrate Solid Dispersion Prepared by Hot-Melt Extrusion. *Drug Dev. Ind. Pharm.* **2010**, *36*, 681-687.
29. Chokshi, R.J.; Sandhu, H.K.; Iyer, R.M.; Shah, N.H.; Malick, W.A.; Zia, H. Characterization of Physico-Echanical Properties of Indomethacin and Polymers to Assess their Suitability for Hot-Melt Extrusion Process as a Means to Manufacture Solid Dispersion/Solution. *J. Pharm. Sci.* **2005**, *94*, 2463-2474.
30. Jachowicz, R. Dissolution Rates of Partially Water Soluble Drugs from Solid Dispersion Systems. II. Phenytoin. *Int. J. Pharm.* **1987**, *35*, 7-12.
31. White, R.K. Pharmaceutical Compositions Containing Polyvinylpyrrolidone and a Tri-Ester and a Process of Manufacture Thereof. Internat. Patent WO/1994/025008, 10 November 1994.
32. Bühler, V. *Kollidon® Polyvinylpyrrolidone for the Pharmaceutical Industry*, 4th ed.; BASF: Ludwigshafen, Germany, 1998.
33. Tubbs, R.K. Sequence Distribution of Partially Hydrolyzed Poly(vinyl acetate). *J. Polym. Sci.* **1966**, *4*, 623-629.
34. Tacx, J.C.J.F.; Schoffeleers, H.M.; Brands, A.G.M.; Teuwen, L. Dissolution Behavior and Solution Properties of Polyvinylalcohol as Determined by Viscometry and Light Scattering in DMSO, Ethylene glycol and Water. *Polymer* **2000**, *41*, 947-957.
35. Hassan, C.M.; Peppas, N.A. Structure and Applications of Poly(vinyl alcohol) Hydrogels Produced by Conventional Crosslinking or by Freezing/Thawing Methods. *Adv. Polym. Sci.* **2000**, *153*, 37-65.
36. Reneker, D.H.; Yarin, A.L.; Fong, H.; Koombhongse, S. Bending Instability of Electrically Charged Liquid Jets of Polymer Solutions in Electrospinning. *J. Appl. Phys.* **2000**, *87*, 4531-4547.
37. Krishna, N.; Brow, F. Polyvinyl Alcohol as an Ophthalmic Vehicle. Effect on Regeneration of Corneal Epithelium. *Am. J. Ophthalmol.* **1964**, *57*, 99-106.
38. Paton, T.F.; Robinson, J.R. Ocular Evaluation of Polyvinyl Alcohol Vehicle in Rabbits. *J. Pharm. Sci.* **1975**, *64*, 1312-1316.

39. Wan, L.S.C.; Lim, L.Y. Drug Release from Heat Treated Polyvinyl Alcohol Films. *Drug Dev. Ind. Pharm.* **1992**, *18*, 1895-1906.
40. Saunders, G.; MacCreath, B. *Biodegradable Polymers Analysis of Biodegradable Polymers by GPC-SEC. Application Compendium*; Agilent Technologies Inc.: Santa Clara, CA, USA, 2010.
41. Bromberg, L. Polyether-Modified Poly(acrylic acid): Synthesis and Applications. *Ind. Eng. Chem. Res.* **1998**, *37*, 4267-4274.
42. Craig, D.Q.M.; Tamburic, S.; Buckton, G.; Newton, J.M. An Investigation into the Structure and Properties of Carbopol® 934 Gels Using Dielectric Spectroscopy and Oscillatory Rheometry. *J. Control. Release* **1994**, *30*, 213-223.
43. Ayers, D.; Cuthbertson, J.M.; Schroyer, K.; Sullivan, S.M. Polyacrylic Acid Mediated Ocular Delivery of Ribozymes. *J. Control. Release* **1996**, *38*, 167-175.
44. Magny, B.; Iliopoulos, I.; Audebert, R. Aggregation of Hydrophobically Modified Polyelectrolytes in Dilute Solution: Tonic Strength Effects. In *Macromolecular Complexes in Chemistry and Biology*; Dubin, P., Bock, J., Davis, R., Schulz, D.N., Thies, C., Eds.; Springer-Verlag: Berlin, Germany, 1994; pp. 50-62.
45. Wang, T.K.; Iliopoulos, I.; Audebert, R. Aqueous-Solution Behavior of Hydrophobically Modified Poly(acrylic acid). In *Water Soluble Polymers*; Shalaby, S.W., McCormick, C.L., Butler, G.B., Eds.; American Chemical Society: Washington, DC, USA, 1991.
46. *Polymers for Pharmaceutical Applications*; Lubrizol Pharmaceutical Bulletin 1; Lubrizol: Wickliffe, OH, USA, 11 August 2010.
47. Weintraub, R.S. Acrylamide Gel as a Supporting Medium for Zone Electrophoresis. *Science* **1959**, *130*, 711-713.
48. Raymond, S. Protein Purification by Elution Convection Electrophoresis. *Science* **1964**, *146*, 406-407.
49. Chrambach, A.; Rodbard, D. Polyacrylamide Gel Electrophoresis. *Science* **1971**, *172*, 440-451.
50. Davis, B.K. Control of Diabetes with Polyacrylamide Implants Containing Insulin. *Experientia* **1972**, *28*, 348.
51. Hussain, M.D.; Rogers J.A.; Mehvar, R.; Vudathala, G.K. Preparation and Release of Ibuprofen from Polyacrylamide Gels. *Drug Dev. Ind. Pharm.* **1999**, *25*, 265-271.
52. Sairam, M.; Babu, V.R.; Vijaya, B.; Naidu, K.; Aminabhavi, T.M. Encapsulation Efficiency and Controlled Release Characteristics of Crosslinked Polyacrylamide Particles. *Int. J. Pharm.* **2006**, *320*, 131-136.
53. Gao, D.; Xu, H.; Philbert, M.A.; Kopelman, R. Ultrafine Hydrogel Nanoparticles: Synthetic Approach and Therapeutic Application in Living Cells. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 2224-2227.
54. Patton, J.N.; Palmer, A.F. Physical Properties of Hemoglobinpoly(acrylamide) Hydrogel-Based Oxygen Carriers: Effect of Reaction pH. *Langmuir* **2006**, *22*, 2212-2221.
55. Risbud, M.V.; Bhone, R.R. Polyacrylamide-Chitosan Hydrogels: *In Vitro* Biocompatibility and Sustained Antibiotic Release Studies. *Drug Deliv.* **2000**, *7*, 69-75.
56. Yang, T.H. Recent Applications of Polyacrylamide as Biomaterials. *Recent Patents Mater. Sci.* **2008**, *1*, 29-40.

57. Soppimath, K.S.; Kulkarni, A.R.; Aminabhavi, T.M. Chemically Modified Polyacrylamide-g-Guar Gum-Based Crosslinked Anionic Microgels as pH-Sensitive Drug Delivery Systems: Preparation and Characterization. *J. Control. Release* **2001**, *75*, 331-345.
58. Murakami, Y.; Mizuo, M. DNA-Responsive Hydrogels that can Shrink or Swell. *Biomacromolecules* **2005**, *6*, 2927-2929.
59. Schmidt, B. Membranes in Artificial Organs. *Artif. Organs* **1996**, *20*, 375-380.
60. Puetz, G.; Eckes, J. Method for Eliminating Potentially Toxic and/or Harmful Substances. WO 02081006, 17 October 2002.
61. Botto, S.A.; Roeth, P.J.; Faramus, E.L.; Nair, C.H. Removal of Metabolic Components from Blood. U.S. Patent 7,066,900, 27 June 2006.
62. Kopecek, J.; Bazilova, H. Poly[N-(2-hydroxypropyl)methacrylamide]. I. Radical Polymerization and Copolymerization. *Eur. Polym. J.* **1973**, *9*, 7-14.
63. Kopeček, J.; Kopečková, P. HPMa Copolymers: Origins, Early Developments, Present and Future. *Adv. Drug Deliv. Rev.* **2010**, *62*, 122-149.
64. De Duve, C.; De Barse, T.; Poole, B.; Trouet, A.; Tulkens, P.; van Hoof, F. Lysosomotropic Agents. *Biochem. Pharmacol.* **1974**, *23*, 2495-2531.
65. Vasey, P.A.; Duncan, R.; Kaye, S.B.; Cassidy, J. 929 Clinical Phase I Trial of PK1 (HPMA Copolymer Doxorubicin). *Eur. J. Cancer* **1995**, *31A*, S193.
66. Vasey, P.A.; Kaye, S.B.; Morrison, R.; Twelves, C.; Wilson, P.; Duncan, R.; Thomson, L.S.; Murray, A.H.; Hilditch, T.E.; Murray, T.; *et al.* Cancer Research Campaign Phase I/II Committee, Phase I Clinical and Pharmacokinetic Study of PK1 [N-(2-hydroxypropyl)-methacrylamide copolymer doxorubicin]: First Member of a New Class of Chemotherapeutic Agents-Drug-Polymer Conjugates. *Clin. Cancer Res.* **1999**, *5*, 83-94.
67. Bilim, V. Technology Evaluation: PK1, Pfizer/Cancer Research UK. *Curr. Opin. Mol. Ther.* **2003**, *5*, 326-330.
68. Lammers, T. Improving the Efficacy of Combined Modality Anticancer Therapy Using HPMa Copolymer-Based Nanomedicine Formulations. *Adv. Drug Deliv. Rev.* **2010**, *62*, 203-230.
69. Julyan, P.J.; Seymour, L.W.; Ferry, D.R.; Daryani, S.; Boivin, C.M.; Doran, J.; David, M.; Anderson, D.; Christodoulou, C.; Young, A.M.; *et al.* Preliminary Clinical Study of the Distribution of HPMa Copolymers Bearing Doxorubicin and Galactosamine. *J. Control. Release* **1999**, *57*, 281-290.
70. Seymour, L.W.; Ferry, D.R.; Anderson, D.; Hesslewood, S.; Julyan, P.J.; Poyner, R.; Doran, J.; Young, A.M.; Burtles, S.; Kerr, D.J. Cancer Research Campaign Phase I/II Clinical Trials Committee, Hepatic Drug Targeting: Phase I Evaluation of Polymer-Bound Doxorubicin. *J. Clin. Oncol.* **2002**, *20*, 1668-1676.
71. Seymour, L.W.; Ulbrich, K.; Wedge, S.R.; Hume, I.C.; Strohal, J.; Duncan, R. N-(2-hydroxypropyl)methacrylamide Copolymers Targeted to the Hepatocyte Galactose-Receptor: Pharmacokinetics in DBA2 Mice. *Br. J. Cancer* **1991**, *63*, 859-866.
72. Lin, X.; Zhang, Q.; Rice, J.R.; Stewart, D.R.; Nowotnik, D.P.; Howell, S.B. Improved Targeting of Platinum Chemotherapeutics. The Antitumour Activity of the HPMa Copolymer Platinum Agent AP5280 in Murine Tumour Models. *Eur. J. Cancer* **2004**, *40*, 291-297.

73. Rademaker-Lakhai, J.M.; Terret, C.; Howell, S.B.; Baud, C.M.; De Boer, R.F.; Pluim, D.; Beijnen, J.H.; Schellens, J.H.; Droz, J.P. A Phase I and Pharmacological Study of the Platinum Polymer AP5280 Given as an Intravenous Infusion Once Every 3 Weeks in Patients with Solid Tumors. *Clin. Cancer Res.* **2004**, *10*, 3386-3395.
74. Rice, J.R.; Gerberich, J.L.; Nowotnik, D.P.; Howell, S.B. Preclinical Efficacy and Pharmacokinetics of AP5346, a Novel Diaminocyclohexane-Platinum Tumor Targeting Drug Delivery System. *Clin. Cancer Res.* **2006**, *12*, 2248-2254.
75. Campone, M.; Rademaker-Lakhai, J.M.; Bennouna, J.; Howell, S.B.; Nowotnik, D.P.; Beijnen, J.H.; Schellens, J.H. Phase I and Pharmacokinetic Trial of AP5346, a DACHplatinum-Polymer Conjugate, Administered weekly for Three out of Every 4 Weeks to Advanced Solid Tumor Patients. *Cancer Chemother. Pharmacol.* **2007**, *60*, 523-533.
76. Nowotnik, D.P.; Cvitkovic, E. ProLindac (AP5346): A Review of the Development of an HPMa DACH Platinum Polymer Therapeutic. *Adv. Drug Deliv. Rev.* **2009**, *61*, 1214-1219.
77. Morahan, P.S.; Munson, J.A.; Baird, L.G.; Kaplan, A.M.; Regelson, W. Antitumor Action of Pyran Copolymer and Tilorone against Lewis Lung Carcinoma and B-16 Melanoma. *Cancer Res.* **1974**, *34*, 506-511.
78. Harmel, R.P., Jr.; Zbar, B. Tumor Suppression by Pyran Copolymer: Correlation with Production of Cytotoxic Macrophages. *J. Natl. Cancer Inst.* **1975**, *54*, 989-992.
79. Santoni, A.; Puccetti, P.; Riccardi, C.; Herberman, R.B.; Bonmassar, E. Augmentation of Natural Killer Activity by Pyran Copolymer in Mice. *Int. J. Cancer* **1979**, *24*, 656-661.
80. Oda, T.; Akaike, T.; Hamamoto, T.; Suzuki, F.; Hirano, T.; Maeda, H. Oxygen Radicals in Influenza-Induced Pathogenesis and Treatment with Pyran Polymer-Conjugated SOD. *Science* **1989**, *244*, 974-976.
81. Kaneda, Y.; Yamamoto, Y.; Kamada, H.; Tsunoda, S.; Tsutsumi, Y.; Hirano, T.; Mayumi, T. Antitumor Activity of Tumor Necrosis Factor Conjugated with Divinyl Ether and Maleic Anhydride Copolymer on Solid Tumors in Mice. *Cancer Res.* **1998**, *58*, 290-295.
82. Adams, N.; Schubert, U.S. Poly(2-oxazolines) in Biological and Biomedical Application Contexts. *Adv. Drug Deliv. Rev.* **2007**, *59*, 1504-1520.
83. Park, J.S.; Akiyama, Y.; Winnik, F.M.; Kataoka, K. Versatile Synthesis of End-Functionalized Thermosensitive Poly(2-isopropyl-2-oxazolines). *Macromolecules* **2004**, *37*, 6786-6792.
84. Persigehl, P.; Jordan, R.; Nuyken, O. Functionalization of Amphiphilic Poly(2-oxazoline) Block Copolymers: A Novel Class of Macroligands for Micellar Catalysis. *Macromolecules* **2000**, *33*, 6977-6981.
85. Ansari, A.M.; Scaria, P.V.; Woodle, M.C. Polymers for Delivering Peptides and Small Molecules *in vivo*. WO 2003/066069, 14 August 2003.
86. Hoogenboom, R.; Fijten, M.W.M.; Schubert, U.S. Parallel Kinetic Investigation of 2-Oxazoline Polymerisations with Different Initiators as Basis for Designed Copolymer Synthesis. *J. Polym. Sci. A: Polym. Chem.* **2004**, *42*, 1830-1840.
87. Wiesbrock, F.; Hoogenboom, R.; Leenen, M.; Van Nispen, S.F.G.M.; van der Loop, M.; Abeln, C.H.; van den Berg, A.M.J.; Schubert, U.S. Microwaveassisted Synthesis of a 42-Membered Library of Diblock Copoly(2-oxazoline)s and Chain-Extended Homo Poly(2-oxazoline)s and Their Thermal Characterization. *Macromolecules* **2005**, *38*, 7957-7966.

88. Huang, H.; Hoogenboom, R.; Leenen, M.A.M.; Guillet, P.; Jonas, A.M.; Schubert, U.S.; Gohy, J.F. Solvent-Induced Morphological Transition in Corecross-Linked Block Copolymer Micelles. *J. Am. Chem. Soc.* **2006**, *128*, 3784-3788.
89. Hoogenboom, R.; Wiesbrock, F.; Huang, H.; Leenen, M.A.M.; Thijs, H.M.L.; van Nispen, S.F.G.M.; van der Loop, M.; Fustin, C.A.; Jonas, A.M.; Gohy, J.-F.; Schubert, U.S. Microwave-Assisted Cationic Ring-Opening Polymerization of 2-Oxazolines: A Powerful Method for the Synthesis of Amphiphilic Triblock Copolymers. *Macromolecules* **2006**, *39*, 4719-4725.
90. Woodle M.C. New Amphiphatic Polymer-Lipid Conjugates Forming Longcirculating Reticuloendothelial System-Evading Liposomes. *Bioconjugate Chem.* **1994**, *5*, 493-496.
91. Lasic, D.D.; Martin, F.J.; Gabizon, A.; Huang, S.K.; Papahadjopoulos, D. Sterically Stabilized Liposomes: A Hypothesis on the Molecular Origin of Extended Circulation Times. *Biochim. Biophys. Acta* **1991**, *1070*, 187-192.
92. Mao, H.Q.; Kdaiyala, I.; Leong, K.W.; Zhao, Z.; Dang, W. Biodegradable Polymers: Poly (phosphoester)s. In *Encyclopaedia of Controlled Drug Delivery*; Mathowitz, E., Ed.; John Wiley and Sons: New York, NY, USA, 1999; Volume 1, pp. 45-60.
93. Penczek, S.; Duda, A.; Kaluzynski, K.; Lapienis, G.; Nyk, A.; Szymanski, R. Thermodynamics and Kinetics of Ring-Opening Polymerization of Cyclic Alkylene Phosphates. *Makromol. Chem. Macromol. Symp.* **1993**, *73*, 91-101.
94. Penczek, S.; Klosinski, P. Synthetic Polyphosphates Related to Nucleic and Teichoic Acids. In *Models of Biopolymers by Ring-Opening Polymerization*; Penczek, S., Ed.; CRC Press: Boca Raton, FL, USA, 1990; pp. 291-378.
95. Penczek, S.; Lapienis, G.; Kaluzynski, K.; Nyk, A. Models of Biopolymers and Bioanalogous Polymers with Backbones of Poly(alkylene phosphate)s. *Pol. J. Chem.* **1994**, *68*, 2129-2142.
96. Penczek, S.; Pretula, J.; Kaluzynski, K. Models of Biomacromolecules and Other Useful Structures Based on the Poly (alkylene phosphate) Chains. *Pol. J. Chem.* **2001**, *75*, 1171-1181.
97. De Smedt, S.C.; Demeester, J.; Hennink, W.E. Cationic Polymer Based Gene Delivery Systems. *Pharm. Res.* **2000**, *17*, 113-126.
98. Garnett, M.C. Gene-Delivery Systems Using Cationic Polymers. *Crit. Rev. Ther. Drug Carrier Syst.* **1999**, *16*, 147-207.
99. Kabanov, A.V. Taking Polycation Gene Delivery Systems from *in vitro* to *in vivo*. *Pharm. Sci. Technol. Today* **1999**, *2*, 365-372.
100. Pouton, C.W.; Seymour, L.W. Key Issues in Non-Viral Gene Delivery. *Adv. Drug Deliv. Rev.* **2001**, *46*, 187-203.
101. Zhaob, Z.; Wanga, J.; Maa, H.Q.C.; Leong, K.W. Polyphosphoesters in Drug and Gene Delivery. *Adv. Drug Deliv. Rev* **2003**, *55*, 483-499.
102. Wang, J.; Mao, H.Q.; Leong, K.W. A Novel Biodegradable Gene Carrier Based on Polyphosphoester. *J. Am. Chem. Soc.* **2001**, *123*, 9480-9481.
103. Wang, J.; Zhang, P.C.; Lu, H.F.; Ma, N.; Wang, S.; Mao, H.Q.; Leong, K.W.; Ong, L.; Leong, H.K.W. New Polyphosphoramidate with a Spermidine Side chain as a Gene Carrier. *J. Control. Release* **2002**, *83*, 157-168.

104. Wang, J.; Zhang, P.C.; Mao, H.Q.; Leong, K.W. Enhanced Gene Expression in Mouse Muscle by Sustained Release of Plasmid DNA Using PPE-EA as a Carrier. *Gene Ther.* **2002**, *9*, 1254-1261.
105. Singh, A.; Krogman, N.R.; Sethuraman, S.; Nair, L.S.; Sturgeon, J.L.; Brown, P.W.; Laurencin, C.T.; Allcock, H.R. Effect of Side Group Chemistry on the Properties of Biodegradable L-Alanine Cosubstituted Polyphosphazenes. *Biomacromolecules* **2006**, *7*, 914-918.
106. Nair, L.S.; Bhattacharyya, S.; Bender, J.D.; Greish, Y.E.; Brown, P.W.; Allcock, H.R.; Laurencin, C.T. Fabrication and Optimization of Methylphenoxy Substituted Polyphosphazene Nanofibers for Biomedical Applications. *Biomacromolecules* **2004**, *5*, 2212-2020.
107. Seong, J.Y.; Jun, Y.J.; Kim, B.M.; Park, Y.M.; Sohn, Y.S. Synthesis and Characterization of Biocompatible Poly(organophosphazenes) Aiming for Local Delivery of Protein Drugs. *Int. J. Pharm.* **2006**, *314*, 90-96.
108. Zhang, J.X.; Qiu, L.Y.; Zhu, K.J.; Jin, Y. Thermosensitive Micelles Self-Assembled by Novel N-Isopropylacrylamide Oligomer Grafted Polyphosphazene. *Macromol. Rapid Commun.* **2004**, *25*, 1563-1567.
109. Zhang, J.X.; Li, X.J.; Qiu, L.Y.; Li, X.H.; Yan, M.Q.; Jin, Y.; Zhu, K.J. Indomethacin-Loaded Polymeric Nanocarriers Based on Amphiphilic Polyphosphazenes with Poly(N-isopropylacrylamide) and Ethyl Tryptophan as Side Groups: Preparation, *in vitro* and *in vivo* Evaluation. *J. Control. Release* **2006**, *116*, 322-329.
110. Zheng, C.; Qiu, L.; Zhu, K. Novel Polymersomes Based on Amphiphilic Graft Polyphosphazenes and Their Encapsulation of Water-Soluble Anti-Cancer Drug. *Polymer* **2009**, *50*, 1173-1177.
111. Allcock, H.R.; Kwon, S. An Ionically Crosslinkable Polyphosphazene: Poly[bis(carboxylatophenoxy)phosphazene] and Its Hydrogels and Membranes. *Macromolecules* **1989**, *22*, 75-79.
112. Allcock, H.R.; Austin, P.E.; Neenan, T.X.; Sisko, J.T.; Blonsky, P.M.; Shriver, D.F. Polyphosphazenes with Etheric Side Groups: Prospective Biomedical and Solid Electrolyte Polymers. *Macromolecules* **1986**, *19*, 1508-1512.
113. Andrianov, A.K. Water-Soluble Polyphosphazenes for Biomedical Applications. *J. Inorg. Organomet. Polym. Mater.* **2006**, *16*, 397-406.
114. Andrianov, A.K.; Chen, J. Polyphosphazene Microspheres: Preparation by Ionic Complexation of Phosphazene Polyacids with Spermine. *J. Appl. Polym. Sci.* **2006**, *101*, 414-419.
115. Andrianov, A.K.; Payne, L.G. Protein Release from Polyphosphazene Matrices. *Adv. Drug Deliv. Rev.* **1998**, *31*, 185-196.
116. Andrianov, A.K.; Payne, L.G. Polymeric Carriers for Oral Uptake of Microparticulates. *Adv. Drug Deliv. Rev.* **1998**, *34*, 155-170.
117. Andrianov, A.K.; Cohen, S.; Visscher, K.B.; Payne, L.G.; Allcock, H.R.; Langer, R. Controlled Release Using Ionotropic Polyphosphazene Hydrogels. *J. Control. Release* **1993**, *27*, 69-77.
118. Sharma, B.R.; Naresh, L.; Dhuldhoya, N.C.; Merchant, S.U.; Merchant, U.C. Xanthan Gum—A Boon to Food Industry. *Food Promot. Chron.* **2006**, *1*, 27-30.
119. Katzbauer, B. Properties and Applications of Xanthan Gum. *Polym. Degrad. Stabil.* **1998**, *59*, 81-84.

120. Mukhiddinov, Z.K. Isolation and Structural Characterization of a Pectin Homo and Ramnogalacturonan. *Talanta* **2000**, *53*, 171-176.
121. Rolin, C. Pectin. *Industrial Gums*, 3rd ed.; Whistler, R.L., BeMiller, J.N., Eds.; Academic Press: New York, NY, USA, 1993.
122. Paoletti, S. *Chemistry and Function of Pectins*; Fishman, M.L., Jen, J.J., Eds.; American Chemical Society: Washington, DC, USA, 1986.
123. Sriamornsak, P. Chemistry of Pectin and Its Uses: A Review. *Silpakorn Univ. Int. J.* **2003**, *3*, 206-228.
124. Ginter, E. Natural Hypocholesterolemic Agent: Pectin Plus Ascorbic acid. *Int. J. Vitic. Nat. Res.* **1979**, *49*, 406-408.
125. Kohn, R. Binding of Toxic Cations to Pectin, Its Oligomeric Fragment and Plant Tissues. *Carbohydr. Polym.* **1982**, *2*, 273-275.
126. Slany, J. Study of Functional Action of Citrus Pectins in Tablets. *Ceska a Slovenska Farmacie* **1981**, *30*, 195-200.
127. Slany, J. Evaluation of Tablets with Pectin as a Binding Agent. *Farmaceuticky Obzor.* **1981**, *50*, 491-498.
128. Krusteva, S. Pharmaceutical Investigation of a Bioerodible Nystatin System. *Pharmazie* **1990**, *45*, 195-197.
129. Khan, T.A.; Khiang, P.K. Reporting Degree of Deacetylation values of Chitosan: The Influence of Analytical Methods. *J. Pharm. Pharm. Sci.* **2002**, *5*, 25-212.
130. Masatoshi, S.; Minoru, M.; Hitoshi, S.; Hiroyuki, S.; Yoshihiro, S. Preparation and Characterization of Water-Soluble Chitin and Chitosan Derivatives. *Carbohydr. Polym.* **1998**, *36*, 49-59.
131. TienAn, N.; Thien, D.T.; Dong, N.T.; Dung, P.L. Water-Soluble N-Carboxymethylchitosan Derivatives: Preparation, Characteristics and Its Application. *Carbohydr. Polym.* **2009**, *75*, 489-497.
132. Chen, X.-G.; Park, H.-J. Chemical Characteristics of O-Carboxymethylchitosans Related to the Preparation Conditions. *Carbohydr. Polym.* **2003**, *53*, 355-359.
133. de Abreu, F.R.; Campana-Filho, S.P. Preparation and Characterization of Carboxymethylation. *Polímeros* **2005**, *15*, 79-83.
134. Ge, H.C.; Luo, D.K. Preparation of Carboxymethylchitosan Inaqueous Solution under Microwave Irridiation. *Carbohydr. Res.* **2005**, *340*, 1351-1356.
135. Paulino, A.T.; Minasse, F.A.; Guilherme, M.R.; Reis, A.V.; Muniz, E.C.; Nozaki, J. Novel Adsorbent Based on Silkwormchrysalides for Removal of Heavy Metals froms Wastewater. *J. Colloid Interface Sci.* **2006**, *301*, 479-487.
136. Shengling, S.; Ai Qin, W. Adsorption Properties and Mechanism of Crosslinked-Carboxymethyl Chitosan Resin with Zn(II) as Template Ion. *React. Funct. Polym.* **2006**, *66*, 819-826.
137. Shengling, S.; Wang, L.; Wang, A. Adsorption Properties of Crosslinked-Carboxymethyl Chitosan Resin with Pb(II) as Template Ions. *J. Hazard. Mater.* **2006**, *136*, 930-937.
138. Pharmacosmos. Dextran Structure. Available online: <http://www.dextran.net/dextran-structure.html> (accessed on 28 June 2011).

139. van Dijk-Wolthuis, W.N.E.; Hoogeboom, J.A.M.; van Steenberg, M.J.; Tsang, S.K.Y.; Hennink, W.E. Degradation and Release Behavior of Dextran-Based Hydrogels. *Macromolecules* **1997**, *30*, 4639-4645.
140. Stenekes, R.J.H.; Franssen, O.; van Bommel, E.M.G.; Crommelin, D.J.A.; Hennink, W.E. The Preparation of Dextran Microspheres in an All-Aqueous System: Effects of the Formulation Parameters on Particle Characteristics. *Pharm. Res.* **1998**, *15*, 557-561.
141. Franssen, O.; Vandervennet, L.; Roders, P.; Hennink, W.E. Degradable Dextran Hydrogels: Controlled Release of a Model Protein from Cylinders and Microspheres. *J. Control. Release* **1999**, *60*, 211-221.
142. Lévesque, S.G.; Shoichet, M.S. Synthesis of Cell-Adhesive Dextran Hydrogels and Macroporous Scaffolds. *Biomaterials* **2006**, *27*, 5277-5285.
143. Ferreira, L.; Gil, M.H.; Cabrita, A.M.S.; Dordick, J.S. Biocatalytic Synthesis of Highly Ordered Degradable Dextran-Based Hydrogels. *Biomaterials* **2005**, *26*, 4707-4716.
144. De Jong, S.J.; De Smedt, S.C.; Demeester, J.; van Nostrum, C.F.; Kettenes-van den Bosch, J.J.; Hennink, W.E. Biodegradable Hydrogels Based on Stereocomplex Formation between Lactic Acid Oligomers Grafted to Dextran. *J. Control. Release* **2001**, *72*, 47-56.
145. Torchilin, V.P.; Maksimenko, A.V.; Mazaev, A.V. Immobilized Thrombolytic Enzymes for Systemic and Local Application. *Ann. N. Y. Acad. Sci.* **2006**, *501*, 481-486.
146. Torchilin, V.P. Immobilized Enzymes and the Use of Immobilization Principles for Drug Targeting. In *Targeted Drugs*; Goldberg, E.D., Ed.; Wiley: New York, NY, USA, 1983; pp. 127-152.
147. Torchilin, V.P.; Voronkov, I.; Mazaev, A.V. Use of Immobilized Streptokinase (Streptodecase) for Treating Thromboses. *Terapevt Arkh.* **1982**, *54*, 21-25.
148. Voronkov, Y.; Torchilin, V.P. Immobilized Streptokinase (Streptodekaza) in Treatment of Intravitreal Haemorrhage. *Vestnik Oftalmologii (Russ.)* **1982**, *4*, 61-64.
149. Kalia, A.N. *Text Book of Industrial Pharmacognosy*; CBS Publishers: New Delhi, India, 2005; p. 217.
150. Evans, W.C.; Evans, D.; Trease, G.E. *Trease and Evans Pharmacognosy*, 15th ed.; Saunders/Elsevier: Edinburgh, UK, 2002; p. 206.
151. Paul, C.S.; Richard, L.M. *McGraw-Hill Encyclopedia of Science and Technology*, 7th ed.; McGraw-Hill Publishing Company: New York, NY, USA, 1992; p. 285.
152. Gennaro, A.R. *Remington the Science and Practice of Pharmacy*, 20th ed.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2000; Volume 1, p. 1031.
153. Lev, R.; Long, R.; Mallonga, L.; Schnaram, R.; Reily, W. Evaluation of Carrageenan as Base for Topical Gels. *Pharm. Res.* **1997**, *14*, 42.
154. Lui, Y.; Schnaram, R.; Reily, W. Evaluation of Carrageenan as Suppository Base. *Pharm. Res.* **1997**, *14*, 41.
155. Tomolin, J.; Taylor, J.S.; Read, N.W. The Effect of Mixed Faecal Bacteria on a Selection of Viscous Polysaccharide *in vitro*. *Nutr. Rep. Int.* **1989**, *39*, 121-135.
156. Bayliss, C.E.; Houston, A.P. Degradation of Guar Gum by Faecal Bacteria. *Appl. Environ. Microbiol.* **1986**, *48*, 626-632.

157. Macfarlane, G.T.; Hay, S.; Macfarlane, S.; Gibson, G.R. Effect of Different Carbohydrates on Growth Polysaccharidases and Glycosidase Production of *Bacteroides Ovatus* in Batch and Continuous Culture. *J. Appl. Bacteriol* **1990**, *68*, 179-187.
158. Chourasia, M.K.; Jain, S.K. Potential of Guar Gum Microspheres for Target Specific Drug Release to Colon. *J. Drug Target*. **2004**, *2*, 1-8.
159. Rama Prasad, Y.V.; Krishnaiah, Y.S.R.; Satyanarayana, S. *In vitro* Evaluation of Guar Gum as a Carrier for Colon-Specific Drug Delivery. *J. Control. Release* **1998**, *51*, 281-287.
160. Krishnaiah, Y.S.R.; Satyanarayana, S.; Rama Prasad, Y.V.; Narasimha Rao, S. Gamma Scintigraphic Studies on Guar Gum Matrix Tablets for Colonic Drug Delivery in Healthy Subjects. *J. Control. Release* **1998**, *55*, 245-252.
161. Krishnaiah, Y.S.R.; Satyanarayana, S.; Rama Prasad, Y.V.; Arasimha Rao, S. Evaluation of Guar Gum as a Compression Coat for Drug Targeting to Colon. *Int. J. Pharm.* **1998**, *171*, 137-146.
162. Clasen, C.; Kulicke, W.M. Determination of Viscoelastic and Rheo-Optical Material Functions of Water Soluble Cellulose Derrivatives. *Prog. Polym. Sci.* **2001**, *26*, 1839-1919.
163. Rokhade, A.P.; Agnihotri, S.A.; Patil, S.A.; Mallikarjuna, N.N.; Kulkarni, P.V.; Aminabhavi, T.M. Semiinterpenetrating Polymer Network Microspheres of Gelatin and Sodium Carboxymethyl Cellulose for Controlled Release of Ketorolac Tromethamine. *Carbohydr. Polym.* **2006**, *65*, 243-252.
164. Nagai, T.; Machida, Y. Advances in Drug Delivery: Mucosal Adhesive Dosage Forms. *Pharm. Int.* **1985**, *6*, 196-200.
165. Satoh, K.; Takayama, K.; Machida, Y.; Suzuki, Y.; Nakagaki, M.; Nagai, T. Factors Affecting the Bioadhesive Property of Tablets Consisting of Hydroxypropyl Cellulose and Carboxyvinyl Polymer. *Chem. Pharm. Bull.* **1989**, *37*, 1366-1368.
166. Senel, S.; Hincal, A.A. Drug Permeation Enhancement via Buccal Route: Possibilities and Limitations. *J. Control. Release* **2001**, *72*, 133-144.
167. Okamoto, H.; Nakamori, T.; Arakawa, Y.; Iida, K.; Danjo, K. Development of Polymer Film Dosage Forms of Lidocaine for Buccal Administration. II. Comparison of Preparation Methods. *J. Pharm. Sci.* **2002**, *91*, 2424-2432.
168. Katzhendler, I.; Mader, K.; Friedman, M. Structure and Hydration Properties of Hydroxypropyl Methylcellulose Matrices Containing Naproxen and Naproxen Sodium. *Int. J. Pharm.* **2000**, *200*, 161-179.
169. Ito, T.; Iida-Tanaka, N.; Koyama, Y. Efficient *in vivo* Gene Transfection by Stable DNA/PEI Complexes Coated by Hyaluronic Acid. *J. Drug Target*. **2008**, *16*, 276-281.
170. Abetamann, V.; Kern, H.F.; Elsasser, H.P. Differential Expression of the Hyaluronan Receptors CD44 and RHAMM in Human Pancreatic Cancer Cells. *Clin. Cancer Res.* **1996**, *2*, 1607-1618.
171. Li, H.; Guo, L.; Li, J.W.; Liu, N.; Qi, R.; Liu, J. Expression of Hyaluronan Receptors CD44 and RHAMM in Stomach Cancers: Relevance with Tumor Progression. *Int. J. Oncol.* **2000**, *17*, 927-932.
172. Kobayashi, Y.; Okamoto, A.; Nishinari, K. Viscoelasticity of Hyaluronic Acid with Different Molecular Weights. *Biorheology* **1994**, *31*, 235-244.
173. Parka, J.W.; Chakrabartib, B. Conformational Transition of Hyaluronic Acid Carboxylic Group Participation and Thermal Effect. *Biochim. Biophys. Acta* **1978**, *541*, 263-269.

174. Bourlais, C.L.; Acar, L.; Zia, H.; Sado, P.A.; Needham, T.; Leverge, R. Ophthalmic Drug Delivery Systems—Recent Advances. *Prog. Retin. Eye Res.* **1998**, *17*, 33-58.
175. Bucolo, C.; Mangiafico, S.; Spadaro, A. Methylprednisolone Delivery by Hyalobend Corneal Shields and Its Effects on Rabbit Ocular Inflammation. *J. Ocul. Pharmacol. Ther.* **1996**, *12*, 141-149.
176. Cho, K.Y.; Chung, T.W.; Kim, B.C.; Kim, M.K.; Lee, J.H.; Wee, W.R.; Cho, C.S. Release of Ciprofloxacin from Poloxamer-graft-Hyaluronic Acid Hydrogels *in vitro*. *Int. J. Pharm.* **2003**, *260*, 83-91.
177. de la Fuente, M.; Csaba, N.; Garcia-Fuentes, M.; Alonso, M.J. Nanoparticle as Protein and Gene Carriers to Mucosal Surfaces. *Nanomedicine* **2008**, *3*, 845-857.
178. Platt, V.M.; Szoka, F.C., Jr. Anticancer Therapeutics: Targeting Macromolecules and Nanocarriers to Hyaluronan or CD44, a Hyaluronan Receptor. *Mol. Pharm.* **2008**, *5*, 474-486.
179. Oyarzun-Ampuero, F.A.; Brea, J.; Loza, M.I.; Torres, D.; Alonso, M.J. Chitosanhyaluronic Acid Nanoparticles Loaded with Heparin for the Treatment of Asthma. *Int. J. Pharm.* **2009**, *381*, 122-129.
180. Price, R.D.; Berry, M.G.; Navsaria, H.A. Hyaluronic Acid: The Scientific and Clinical Evidence. *J. Plast. Reconstruct. Aesth. Surg.* **2007**, *60*, 1110-1119.
181. McDonald, C.C.; Kaye, S.B.; Figueiredo, F.C.; Macintosh, G.; Lockett, C. A Randomised, Crossover, Multicentre Study to Compare the Performance of 0.1% (w/v) Sodium Hyaluronate with 1.4% (w/v) Polyvinyl Alcohol in the Alleviation of Symptoms Associated with Dry Eye Syndrome. *Eye* **2002**, *16*, 601-607.
182. Aragona, P.; Di Stefano, G.; Ferreri, F.; Spinella, R.; Stilo, A. Sodium Hyaluronate Eye Drops of Different Osmolarity for the Treatment of Dry Eye in Sjogren's Syndrome Patients. *Br. J. Ophthalmol.* **2002**, *86*, 879-884.
183. Bray, B.A. The Role of Hyaluronan in the Pulmonary Alveolus. *J. Theor. Biol.* **2001**, *210*, 121-130.
184. Prestwich, G.D.; Vercruysse, K.P. Therapeutic Applications of Hyaluronic Acid and Hyaluronan derivatives. *PSTT* **1998**, *1*, 42-43.
185. Peters, T. Serum Albumin. *Adv. Protein Chem.* **1985**, *37*, 161-245.
186. Kratz, F.; Fichtner, I.; Schumacher, P.; Roth, T.; Feibig, H.H.; Unger, C. Antitumor Activity of Acid Labile Transferrin and Albumin Doxorubicin Conjugates *in vitro* and *in vivo* Human Tumor Xerograft Models. *Eur. J. Cancer* **1997**, *33*, S175.
187. Rahimnejad, M.; Jahanshahi, M.; Najafpour, G.D. Production of Biological Nanoparticles from Bovine Serum Albumin for Drug Delivery. *Afr. J. Biotechnol.* **2006**, *5*, 1918-1923.
188. Langer, K.; Balthasar, S.; Vogel, V.; Dinauer, N.; Von Briesen, H.; Schubert, D. Optimization of the Preparation Process for Human Serum Albumin (HSA) Nanoparticles. *Int. J. Pharm.* **2003**, *257*, 169-180.
189. Rubino, O.P.; Kowalsky, R.; Swarbrick, J. Albumin Microspheres as a Drug Delivery System: Relation among Turbidity Ratio, Degree of Cross-Linking and Drug Release. *Pharm. Res.* **1993**, *10*, 1059-1065.

190. Kommareddy, S.; Amiji, M. Preparation and Evaluation of Thiol-Modified Gelatin Nanoparticles for Intracellular DNA Delivery in Response to Glutathione. *Bioconjugate Chem.* **2005**, *16*, 1423-1432.
191. Azarmi, S.; Tao, X.; Chen, H.; Wang, Z.; Finlay, W.H.; Löbenberg, R.; Roa, W.H. Formulation and Cytotoxicity of Doxorubicin Nanoparticles Carried by Dry Powder Aerosol Particles. *Int. J. Pharm.* **2006**, *319*, 155-161.
192. Ulbrich, K.; Hekmatara, T.; Herbert, E.; Kreuter, J. Transferrin- and Transferrin-Receptor-Antibody-Modified Nanoparticles Enable Drug Delivery across the Blood-Brain Barrier (BBB). *Eur. J. Pharm. Biopharm.* **2009**, *71*, 251-256.
193. Steinhäuser, I.M.; Langer, K.; Strebhardt, K.M.; Spänkuch, B. Effect of trastuzumab-Modified Antisense Oligonucleotide-Loaded Human Serum Albumin Nanoparticles Prepared by Heat Denaturation. *Biomaterials* **2008**, *29*, 4022-4028.
194. Damascelli, B.; Cantù, G.; Mattavelli, F.; Tamplenizza, P.; Bidoli, P.; Leo, E.; Dosio, F.; Cerrotta, A.M.; di Tolla, G.; Frigerio, L.F.; *et al.* Intraarterial Chemotherapy with Polyoxyethylated Castor Oil Free Paclitaxel, Incorporated in Albumin Nanoparticles (ABI-007): Phase II Study of Patients with Squamous Cell Carcinoma of the Head and Neck and Anal Canal: Preliminary Evidence of Clinical Activity. *Cancer* **2001**, *92*, 2592-2602.
195. Ibrahim, N.K.; Desai, N.; Legha, S.; Soon-Shiong, P.; Theriault, R.L.; Rivera, E.; Esmaeli, B.; Ring, S.E.; Bedikian, A.; Hortobagyi, G.N.; Ellerhorst, J.A. Phase I and Pharmacokinetic Study of ABI-007, a Cremophor-Free, Protein-Stabilized, Nanoparticle Formulation of Paclitaxel. *Clin. Cancer. Res.* **2002**, *8*, 1038-1044.
196. Geny, B.; Mettauer, B.; Muan, B.; Bischoff, P.; Epailly, E.; Piquard, F.; Eisenmann, B.; Haberey, P. Safety and Efficacy of a New Transpulmonary Echo Contrast Agent in Echocardiographic Studies in Patients. *J. Am. Coll. Cardiol.* **1993**, *22*, 1193-1198.
197. Brzoska, M.; Langer, K.; Coester, C.; Loitsch, S.; Wagner, T.O.; Mallinckrodt, C. Incorporation of Biodegradable Nanoparticles into Human Airway Epithelium Cells—*In vitro* study of the Suitability as a Vehicle for Drug or Gene Delivery in Pulmonary Diseases. *Biochem. Biophys. Res. Commun.* **2004**, *318*, 562-570.
198. Simoes, S.; Slepishkin, V.; Pires, P.; Gaspar, R.; de Lima, P.M.C.; Duzgunes, N. Human Serum Albumin Enhances DNA Transfection by Lipoplexes and confers Resistance to Inhibition by Serum. *Biochim. Biophys. Acta* **2004**, *1463*, 459-469.
199. Roper, H. Applications of Starch and Its Derivatives. *Carbohydr. Eur.* **1996**, *15*, 14-21.
200. Vilivalam, V.D.; Illum, L.; Iqbal, K. Starch Capsules: An Alternative System for Oral Drug Delivery. *Pharm. Sci. Technol. Today* **2000**, *3*, 64-69.
201. Milojevic, S.; Newton, J.M.; Cummings, J.H.; Gibson, G.R.; Botham, R.L.; Ring, S.G.; Stockham, M.; Allwood, M.C. Amylose as a Coating for Drug Delivery to the Colon: Preparation and *in vitro* Evaluation Using 5-Aminosalicylic Acid Pellets. *J. Control. Release* **1996**, *38*, 75-84.
202. Désévaux, C.; Dubreuil, P.; Lenaerts, V.; Girard, C. Tissue Reaction and Biodegradation of Implanted Cross-Linked High Amylose Starch in Rats. *J. Biomed. Mater. Res.* **2002**, *63*, 772-779.

203. Mulhbachter, J.; Ispas-Szabo, P.; Lenaerts, V.; Mateescu, M.A. Cross-Linked High Amylose Starch Derivatives as Matrices for Controlled Release of High Drug Loadings. *J. Control. Rel.* **2001**, *76*, 51-58.
204. Nabais, T.; Brouillet, F.; Kyriacos, S.; Mroueh, M.; Amores da Silva, P.; Bataille, B.; Chebli, C.; Cartilier, L. High-Amylose Carboxymethyl Starch Matrices for Oral Sustained Drug-Release: *In vitro* and *in vivo* Evaluation. *Eur. J. Pharm. Biopharm.* **2007**, *65*, 371-378.
205. Teramoto, N.; Motoyama, T.; Yosomiya, R.; Shibata, M. Synthesis, Thermal Properties, and Biodegradability of Propyl-Etherified Starch. *Eur. Polym. J.* **2003**, *39*, 255-261.
206. Araújo, M.A.; Cunha, A.; Mota, M. Enzymatic Degradation of Starch-Based Thermoplastic Compounds Used in Protheses: Identification of the Degradation Products in Solution. *Biomaterials* **2004**, *25*, 2687-2693.
207. Zhang, J.F.; Sun, X.Z. Mechanical Properties of PLA/Starch Composites Compatibilized by Maleic Anhydride. *Biomacromolecules* **2004**, *5*, 1446-1451.
208. Pareta, R.; Edirisinghe, M.J. A Novel Method for Thepreparation of Starch Films and Coatings. *Carbohydr. Polym.* **2006**, *63*, 425-431.
209. Choi, E.J.; Kim, C.H.; Park, J.K. Synthesis and Characterization of Starch-g-Polycaprolactone Copolymer. *Macromolecules* **1999**, *32*, 7402-7408.
210. Lu, D.R.; Xiao, C.M.; Xu, S.J. Starch-Based Completely Biodegradable Polymer Materials *eXPRESS Polym. Lett.* **2009**, *3*, 366-375.
211. Pal, J.; Singhal, R.S.; Kulkarni, P.R. Physicochemical Properties of Hydroxypropyl Derivative from Corn and Amaranth Starch. *Carbohydr. Polym.* **2002**, *48*, 49-53.
212. Fanta, G.F.; Burr, R.C.; Doane, W.M.; Russell, C.R. Graft Polymerization of Vinyl Acetate onto Starch. Saponification to Starch-g-Poly(vinyl alcohol). *J. Appl. Polym. Sci.* **1979**, *23*, 229-240.
213. Simi, C.K.; Abraham, T.E. Hydrophobic Grafted and Crosslinked Starch Nanoparticles for Drug Delivery. *Bioprocess Biosyst. Eng.* **2007**, *30*, 173-180.
214. Samaha, S.H.; Nasr, H.E.; Hebeish, A. Synthesis and Characterization of Starch-Poly(vinyl acetate) Graft Copolymer and Their Saponified Form. *J. Polym. Res.* **2005**, *12*, 343-353.
215. Xiao, C.M.; Yang, M.L. Controlled Preparation of Physical Cross-Linked Starch-g-PVA Hydrogel. *Carbohydr. Polym.* **2006**, *64*, 37-40.
216. Zhu, Z.F.; Zhuo, R.X. Slow Release behavior of Starch-g-Poly(vinyl alcohol) Matrix for 2,4,5-Trichlorophenoxyacetic Acid Herbicide. *Eur. Polym. J.* **2001**, *37*, 1913-1919.
217. Marques, A.P.; Reis, R.L.; Hunt, J.A. The Biocompatibility of Novel Starch-Based Polymers and Composites: *In vitro* Studies. *Biomaterials* **2002**, *23*, 1471-1478.
218. Mendes, S.C.; Reis, R.L.; Bovell, Y.P.; Cunha, A.M.; van Blitterswijk, C.A.; de Bruijn, J.D. Biocompatibility Testing of Novel Starch-Based Materials with Potential Application in Orthopaedic Surgery: A Preliminary Study. *Biomaterials* **2001**, *22*, 2057-2064.
219. Azevedo, H.S.; Gama, F.M.; Reis, R.L. *In vitro* Assessment of the Enzymatic Degradation of Several Starch Based Biomaterials. *Biomacromolecules* **2003**, *4*, 1703-1712.
220. Defaye, J.; Wong, E. Structural Studies of Gum Arabic, the Exudate Polysaccharide from Acacia Senegal. *Carbohydr. Res.* **1986**, *150*, 221-231.
221. Reddy, S.M.; Sinha, V.R.; Reddy, D.S. Novel Oral Colon-Specific Drug Delivery Systems for Pharmacotherapy of Peptides and Nonpeptide Drugs. *Drugs Today* **1999**, *35*, 537-580.

222. Sinha, V.R.; Kumria, R. Polysaccharides in Colon-Specific Drug Delivery. *Int. J. Pharm.* **2001**, *224*, 19-38.
223. Boesel, L.F.; Mano, J.F.; Reis, R.L. Optimization of the Formulation and Mechanical Properties of Starch Based Partially Degradable Bone Cements. *J. Mater. Sci. Mater. Med.* **2004**, *15*, 73-83.
224. Gomes, M.E.; Sikavitsas, V.I.; Behraves, E.; Reis, R.L.; Mikos, A.G. Effect of Flow Perfusion on the Osteogenic Differentiation of Bone Marrow Stromal Cells Cultured on Starch-Based Three-Dimensional Scaffolds. *J. Biomed. Mater. Res. Part A* **2003**, *67*, 87-95.
225. Balmayor, E.R.; Tuzlakoglu, K.; Marques, A.P.; Azevedo, H.S.; Reis, R.L. A Novel Enzymatically Mediated Drug Delivery Carrier for Bone Tissue engineering applications: Combining Biodegradable Starch Based Microparticles and differentiation Agents. *J. Mater. Sci. Mater. Med.* **2008**, *19*, 1617-1623.
226. Reis, A.V.; Guilherme, M.R.; Moia, T.A.; Mattoso, L.H.C.; Muniz, E.C.; Tambourgi, E.B. Synthesis and Characterization of a Starch-Modified Hydrogel as Potential Carrier for Drug Delivery System. *J. Polym. Sci. Part A: Polym. Chem.* **2008**, *46*, 2567-2574.
227. Herman, J.; Remon, J.P. Modified Starches as Hydrophilic Matrices for Controlled Oral Delivery. II. *In vitro* Drug Release Evaluation of Thermally Modified Starches. *Int. J. Pharm.* **1989**, *56*, 65-70.
228. Te Wierik, G.H.P.; Eissens, A.C.; Bergsma, J.; Arends-Scholte, A.W.; Lerk, C.F. A New Generation of Starch Products as Excipient in Pharmaceutical Tablets. II. High Surface Area Retrograded Pregelatinized Potato Starch Products in Sustained Release Tablets. *J. Control. Release* **1997**, *45*, 25-33.
229. Le Bail, P.; Morin, F.G.; Marchessault, R.H. Characterization of a Crosslinked High Amylose Starch Excipient. *Int. J. Biol. Macromol.* **1999**, *26*, 193-200.
230. Chebli, C.; Cartilier, L.; Hartman, N.G. Substituted Amylose as a Matrix for Sustained-Drug Release: A Biodegradation Study. *Int. J. Pharm.* **2001**, *222*, 183-189.
231. Yoon, H.-S.; Kweon, D.-K.; Lim, S.-T. Effects of Drying Process for Amorphous Waxy Maize Starch on Theophylline Release from Starch-Based Tablets. *J. Appl. Polym. Sci.* **2007**, *105*, 1908-1913.
232. Mulhbach, J.; Ispas-Szabo, P.; Mateescu, M.A. Cross-Linked High Amylase Tarch Derivatives for Drug Release. II. SWELLING Properties and Mechanistic Study. *Int. J. Pharm.* **2004**, *278*, 231-238.
233. Dumoulin, Y.; Alex, S.; Szabo, P.; Cartilier, L.; Mateescu, M.A. Cross-Linked Amylase as Matrix for Drug Controlled Release. X-Ray and FT-IR Structural Analysis. *Carbohydr. Polym.* **1998**, *37*, 361-370.
234. Zhang, L.M.; Yang, C.; Yan, L. Perspectives on: Strategies to Fabricate Starchbased Hydrogels with Potential Biomedical Applications. *J. Bioact. Compat. Polym.* **2005**, *20*, 297-314.
235. Onofre, F.O.; Wang, Y.J. Hydroxypropylated Starches of Varying Amylose Contents as Sustained Release Matrices in Tablets. *Int. J. Pharm.* **2010**, *385*, 104-112.