RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Modified Biopolymer-Dextrin Based Crosslinked Hydrogels: Application in Controlled Drug Delivery

Dipankar Das and Sagar Pal*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

This review describes about hydrogels and its classifications along with the synthesis, properties of biopolymer-dextrin based crosslinked hydrogels and its potential application in controlled drug delivery. Modified dextrin based crosslinked hydrogels exhibit unique characteristics in terms of mechanical properties, stimuli-responsive behaviour and drug release characteristics. Herein, at first, an outline is given about the hydrogels and its classifications, various biopolymer based hydrogels and their synthetic procedures. Secondly, significance of biopolymer dextrin for developing hydrogels, requirements of modification, dextrin based various hydrogels developed in authors' laboratory have been discussed. Finally, the importance of crosslinked hydrogels in drug delivery applications and dextrin based various hydrogels used in sustained drug delivery study have been explored, which confirm that future clinical applications of these materials in the biomedical and pharmaceutical fields are feasible.

1. Introduction

In recent times, hydrogels have drawn significant attention because of their various applications in the pharmaceutical and biomedical fields.[1-6] Remarkable efforts have been made to develop novel hydrogels with combined features such as, tuneable chemical and 3-dimensional physical structure,[7-10] desired mechanical properties,[11-14] high water absorption ability, biodegradability and biocompatibility,[7-10] all of which are indispensable for biomedical applications.[15-17]

In addition, biopolymers/modified biopolymers based stimuli-responsive hydrogels are widely used as drugs carrier that improve drug release characteristics.[5, 18-20] The use of natural biopolymers over synthetic polymers for controlled drug release applications has increased markedly because of their inexpensive, easy availability, non-cytotoxic and biodegradable nature.[21] However, they are having certain shortcomings like microbial contamination, uncontrolled rate of hydration, and fall in viscosity during storage etc.[22] By grafting/crosslinking of synthetic polymer chains on natural polymer backbone in the presence of external crosslinkers, it is envisaged to develop hydrogels/crosslinked hydrogels having improved characteristics, that may be applicable as sustained drug release matrix.[23] Polymers synthesised from natural or synthetic sources having hydroxyl, amine, amide, ether, and sulfonate groups in their side chains are used for developing chemically crosslinked hydrogels, and might be suitable for both hydrophilic and hydrophobic drug molecules.[24]

For oral administration of drug delivery, safe, nontoxic biocompatible, biodegradable matrices are essential.[5] But in contrast to drug delivery requirements like better bioavailability of drugs, good biocompatibility between the drug and hydrogel, non-cytotoxic nature of the gel and sufficient drug stability in tablet formulations, chemically crosslinked hydrogels are less studied. From drug delivery perspective, covalently crosslinked hydrogels are interesting because of its unique characteristics like reducing burst release effects and prolonged drug release behaviour.

Various modified biopolymer based hydrogels have been developed and reported. However, we for the first time developed chemically crosslinked stimulus responsive hydrogels based on modified biopolymer-dextrin and their potential application in the field of controlled drug delivery. This review thus aims to provide an in-depth knowledge of various modified biopolymers based hydrogels, dextrin based chemically crosslinked hydrogels for controlled drug release applications. Here, we mainly focus on dextrin based chemically crosslinked hydrogels, proposed mechanism for their synthesis, detailed characteristics which includes surface morphology, cytoxicity study, biodegradability and finally their application as potential matrices for sustained release of various model drugs *in-vitro*. The release kinetics and mechanism have also been explored.

This review is organized in the following way: we commence with the brief overview of hydrogels and its classifications, biopolymer based hydrogels, various procedures for development of hydrogels. Afterwards, the significance of biopolymer-dextrin for developing hydrogels, requirements of modification and dextrin based various hydrogels, which were developed in authors' laboratory. In the next section, we present an idea about controlled drug delivery and the importance of crosslinked hydrogels in drug delivery application. Finally, we have explained in details about the release study of model drugs (such as ciprofloxacin, ornidazole) using synthesized modified dextrin based crosslinked hydrogels. In addition, we also explored the advantages of dextrin based hydrogels over other biopolymeric

hydrogels reported in the literature.

2. Polymeric hydrogels

According to literature, the name 'hydrogel' was first appeared in 1894 when it was depicted as colloidal gel of inorganic salts.[25, 26] In 1958, crosslinked PVA hydrogel was developed in presence of gamma irradiation.[26] In 1960, Wichterle and Lim were first to introduce hydrogels on poly (HEMA) as water-swollen crosslinked networks for contact lense application (Fig. 1).[27] Hydrogels are hydrophilic, physically or chemically crosslinked, three-dimensional natural or synthetic polymeric networks, which are capable of imbibing large amounts of water or biological fluids.[4-6, 28-30] Hydrogels also have a degree of flexibility which is resembled with natural tissue, owing to their significant water content. Their excellent water absorption efficacy is mainly because of the presence of hydrophilic groups like –OH, –CONH–, –$CONH_2$–, and –SO_3H in the polymeric network.[31] Due to the presence of these groups and domains in the network, the polymers are thus hydrated to different degrees (sometimes, more than 90% wt), depending on the nature of the aqueous environment and polymer composition.[32-35]

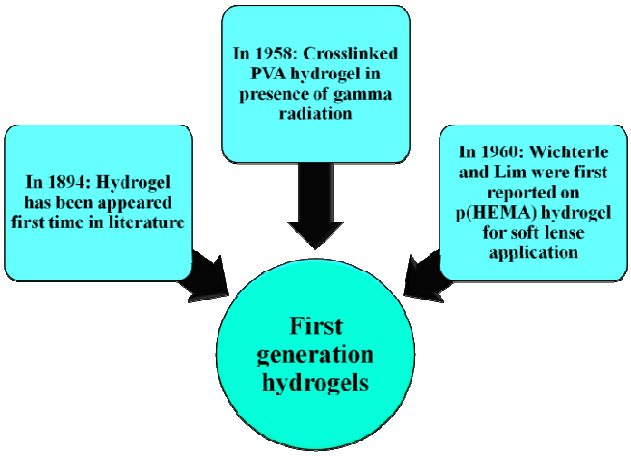


Fig. 1 Important events of hydrogel research

Hydrogels are commonly considered as highly biocompatible, owing to the high water content and also to the physiochemical similarity with the native extracellular matrix.[36] In spite of their high water absorbing ability, hydrogels swell rapidly instead of dissolved in the aqueous medium, because of the presence of crosslinker in the hydrogel network. These crosslinks are mainly of two types: (i) physical (entanglements or crystallites), and (ii) chemical (tie-points and junctions).[37-42] The crosslinks may remain in the polymer network in forms of covalent attachment, hydrogen bonding, van der Waals interactions or physical entanglements.[43]

Besides, hydrogels demonstrated phase transition with change in external conditions such as pH,[4, 44] temperature,[45] light,[46] electric field,[47] magnetic field[48] and are known as "stimuli-responsive" or "smart" gels.[49-51] These smart gels exhibit numerous outstanding characteristics like defined morphology, high porosity, flexible dimensions and the ability of their network to absorb large amount of water. These properties make them promising candidates for controlled drug release applications.[52-54]

There are several reports on synthetic polymer based hydrogel matrices used for controlled/sustained drug delivery applications.[55-77] Lalloo *at el.* was reported on poly (ethylene glycol) hydrogel for controlled delivery of the camptothecins.[55] Dadsetan *et al.* used oligo(poly(ethylene glycol) fumarate) hydrogel for the delivery of doxorubicin.[56] Controlled delivery of recombinant hirudin based on thermo-sensitive Pluronic F127(PF127) hydrogel was investigated by Liu *et al.*[57] PAE-PCL-PEG-PCL-PAE pentablock copolymer hydrogel as a sustained insulin delivery system was evaluated by Huynh *et al.*[58] Sustained release of paclitaxel by (pNIPAm-PEG-pNIPAm) hydrogel was investigated by Graaf *et al.*[59] Delivery of Ketoprofen and spironolactone drugs from PEG–PLGA–PEG triblock copolymeric hydrogel was described by Jeong *et al.*[60] Wang *et al.* described the controlled release of paclitaxel from poly(lactic acid)/(methoxyl poly(ethylene glycol)/itaconic acid based hydrogel.[61] Camptothecin release from PLGA–PEG–PLGA triblock copolymers hydrogel was developed by Yu *et al.*[62] Yu *et al.* described controlled release of anticancer drug doxorubicin from NPOD-PEG/α-CD hydrogels.[63] Riboflavin release was studied using PVA-star PDMAEMA based hydrogel by Wu *et al.*[64] Yu *et al.* also described Avastin release from crosslinked PEG hydrogel.[65] Pindolol, Quinine and Timolol maleate release from RADA 16 peptide hydrogel was detected by Briuglia *et al.*[66] The sustained release of dextran-fluorescent isothiocyanate (FITC) from MPEG-PCL-MPEG triblock copolymeric hydrogel was investigated by Wu *at al.*[67] PEOz-PCL-PEOz triblock hydrogel was used as controlled drug delivery matrix for Bevacizumab as studied by Wang *et al.*[68] Cavalieri *et al.* described doxorubicin release from PVA-PMA based hydrogel.[69] Wieduwild *et al.* investigated the release of ATIII-F drug from peptide hydrogel.[70] Dexamethasone acetate release from hyper branched polyester hydrogel was studied by Zhang *et al.*[71] The sustained release of model protein drug (bovine serum albumin) using PEG-α-cyclodextrin based hydrogel was described by Ma *et al.*[72] Release study of methylene blue and bovine serum albumin from NIPAm/Dextran/HEMA based hydrogel was studied by Huang *et al.*[73] Nugent *et al.* used PVA/poly(acrylic acid) hydrogel for theophyline delivery.[74] Poly(organophosphazene) hydrogel was used as controlled delivery of FITC-dextran and human serum albumin by Kang *et al.*[75] Mishra *et al.* reported on PEG–PVL–PEG copolymers hydrogel for sustained release of dexamethasone.[76] Babu *et al.* described on poly(HEMA-co-MMA) based hydrogel for controlled release of cisplatin.[77]

2.1. Classification of polymeric hydrogels

Hydrogels are broadly classified into two categories:

Permanent or chemical gel: These gels form stable covalently crosslinked networks.[78] They attain an equilibrium swelling state which depends on the polymer-water interactions as well as on crosslink density.[79]

Reversible or physical gel: These networks are held together by molecular entanglements, ionic interactions, hydrogen bonding or hydrophobic interactions. In physically crosslinked gels, dissolution is prevented due to physical interactions between different polymer chains.[78] The interactions are reversible, and can be interrupted by changing physical conditions or application of stress.[79]

Hydrogels can also be classified on the basis of various features (Fig. 2) [11] such as the nature of side groups, method of preparation, physical structure, mechanical and structural characters, and responsiveness to stimuli.[1, 28, 29, 35, 37-42, 80-84]

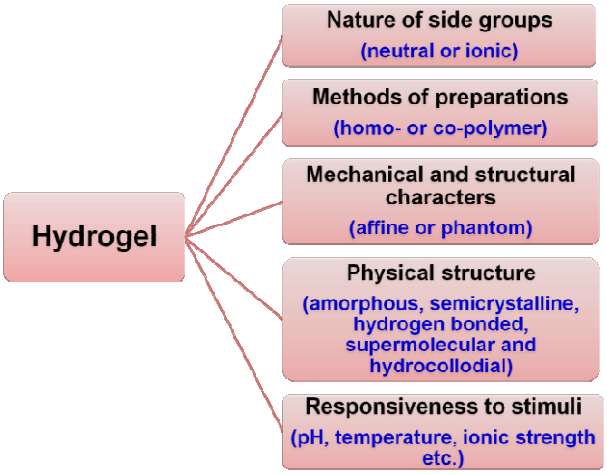


Fig. 2 Classifications of polymeric hydrogel

However, the hydrogels mainly used in biomedical applications have been synthesized from polymers of natural or synthetic origins.[1, 3, 85-88]

2.2. Biopolymer based hydrogels

The utilization of biopolymers, as materials is not new. For example, cellulose has been used frequently to provide structure for plants. Chitin is used as the exoskeleton of crawfish and shrimps. Collagen has been utilized for mechanical support in connective tissues, and silk in spider's webs.[89] Recently, these materials possess a great deal of significance as materials for biomedical applications owing to their better biocompatibility and low disposal expenses.[90, 91] Besides, the chemical structures of these materials assist for the synthesis of advanced modified materials which would be useful in multidisciplinary applications. The degradation properties of natural polymers into physiological metabolites make them potential candidates as drug delivery matrices or regenerative medicine.

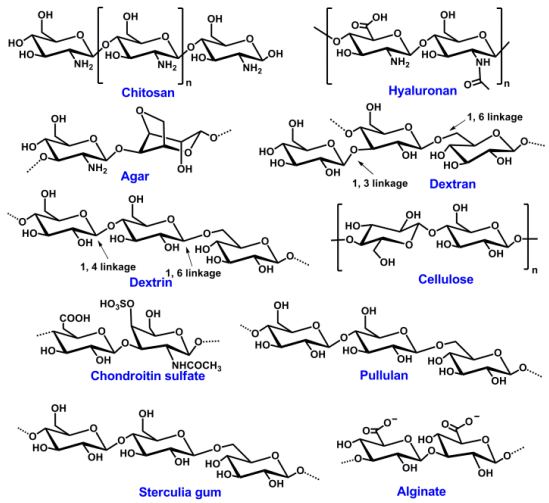


Fig. 3 Chemical structure of different polysaccharides

Among the biopolymers, polysaccharides have some esteemed characteristics, like non-toxicity, water solubility or high capability for swelling induce by simple chemical modifications, which make them suitable for biomedical applications.[1, 92, 93-95] Polysaccharides are obtained from numerous sources including seaweeds, plants, fungi, bacteria, insects, crustacea, animals and even humans.[96-99]

Chemically, polysaccharides contain large carbohydrates which are formed by only one type of repeating monosaccharide or by two or more different monomeric units. Polysaccharides can also be classified as non-polyelectrolites and polyelectrolites, which are either positively or negatively charged.[100] The typical examples of polysaccharides as biopolymers are chitosan, hyaluronan, agar, dextran, dextrin, cellulose, chondroitin sulphate, pullulan, sterculia gum, alginate etc (Fig. 3).[101, 102] The conformation of the polysaccharide chains depend on various factors like pH, ionic strength of the medium, temperature and the concentration of certain molecules (such as lecitins).[103] Polysaccharides usually respond to the external stimuli, which makes them attractive as potential candidate for sustained drug release applications. In addition, some polysaccharides also have unique features such as they provide nanocarriers with surface properties that control the interactions with blood, mucosa and target cells during absorption and biodistribution.[104] By biomimicking the surface of eukaryotic cells, bacteria and viruses, polysaccharides can assist the recognition and binding to desirable surfaces, while scaping from opsonization and complement activation.[105, 106]

However, polysaccharides have some limitations like microbial contamination, uncontrolled rate of hydration, and drop in viscosity on storing. Fortunately, several strategies have already been developed and reported to overcome these drawbacks by suitable chemical modification, which includes grafting/crosslinking of synthetic polymer chains onto their backbone.[4, 5] These modified biopolymers form a 3-dimensional, crosslinked, hydrophilic network which can absorb large amount of water when remain in contact with aqueous medium or in biological fluids without showing solubility. These materials are considered to be hydrogels or biomaterials based hydrogels.

The era of biomaterials based hydrogels started in 1960, when Wichterle and Lim was first developed poly (HEMA) based copolymer for contact lense application.[27] Later, various hydrogel materials were developed and reported using different techniques. The early methods of synthesis were focused on the development and structure determination, but later, the attention was shifted towards the applicability of hydrogels in various fields. The 3-dimensional polymeric networks at swollen state interact with the active compounds through covalent interactions or through H-bonding or ionic interactions. Biopolymer based hydrogels possess all the properties of synthetic counterparts as well as being inherently renewable, abundant in nature, nontoxic, biodegradable, and relatively cheap. In addition, these hydrogels possess a high content of functional groups, which are utilized in crosslinking with additional functional crosslinkers and can be bioconjugated with cell targeting materials.[107] The chemical and/or physical crosslinks are responsible for the insoluble nature of grafted/crosslinked hydrogels. It is also easy to tune the physico-chemical properties of grafted/crosslinked hydrogels,

which are sensitive towards various stimuli present in our body like pH, ionic strength, temperature etc.[108-111] Such hydrogels are called smart polymers. Thus, use of these modified biopolymer based hydrogels, specifically for drug delivery applications is advantageous than that of neat polysaccharides. This is because the drug release behaviour of these hydrogels not only depends on the extent of crosslinking but also on various other factors, including better swelling characteristics, restricted dissolution characteristics, pH of the release media and interaction between drugs and hydrogels.[4]

Therefore, the distinct features of the polysaccharides/biopolymers make these hydrogels to be efficient in various applications such as biomedical applications, agricultural applications and industrial applications (Fig. 4).

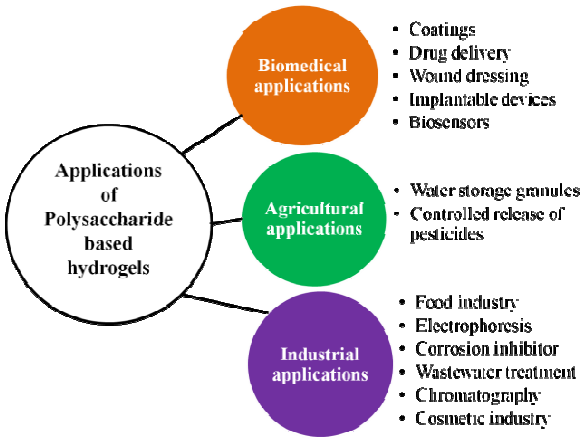


Fig. 4 Applications of polysaccharide based hydrogels in various fields

2.2.1. Applications of polysaccharide based hydrogels in various fields

2.2.1.1. Biomedical applications

Polysaccharides based hydrogels have been utilized in various biomedical applications because of their non-toxicity, biocompatibility, suitable performance towards *in-vivo* transplantation, capability to fabricate into an ample range of morphologies, structural similarity to natural materials and degradation by enzymes.[112]

Among different biomedical applications, hydrogel based drug delivery systems have become major area of interest and achieved success at the industrial level. There are several reports on hydrogels including modified biopolymeric hydrogels based on agar, chitosan, dextran, carrageenan, gelatin, gellan gum, konjac glucomanan, locust bean gum, cyclodextrin, guar gum, stereculis gum etc. for drug delivery applications.[113-142]

Usha Rani *et al.* reported on the synthesis and applications of polyacrylamide grafted agar based hydrogel as a matrix for controlled release of 5-ASA.[113] Cyclodextrin–agar hydrogels for ciprofloxacin delivery was studied by Fernandez *et al.*[114] Kulkarni *et al.* synthesized pH-responsive interpenetrating network hydrogel beads of polyacrylamide grafted carrageenan (PAAm-g-CG) and sodium alginate for targeting Ketoprofen to the intestine. [115] Hydrogel based oil encapsulation for controlled release of curcumin by using a ternary system of chitosan, kappa-carrageenan, and carboxymethylcellulose sodium salt was described by Nakagawa *et al.*[116] Hezaveh *et al.* designed kappa-carrageenan-based hydrogel for controlled release application.[117]

Gelatin–carrageenan hydrogels for quercetin delivery was designed by Varghese *et al.*[118] The controlled delivery formulations of caffeine in alginate hydrogel beads combined with pectin, carrageenan, chitosan and psyllium was described by Cvitanovic *et al.*[119] Kappa-carrageenan/polyvinyl alcohol crosslinked hydrogels was formulated using genipin as a natural and nontoxic crosslinker to achieve a controlled release of β-Carotene.[120] Sustained delivery of latanoprost by thermosensitive chitosan–gelatin-based hydrogel for controlling ocular hypertension was reported by Cheng *et al.*[121] Chitosan–gold hybrid hydrogel and its application for drug delivery was described by Chen *et al.*[122]

Synthesis of oxidized glycerol monooleate-chitosan polymer and its hydrogel formation for sustained release of trimetazidine hydrochloride was reported by Zhang *et al.*[123] Peng *et al.* described chitosan/glycerophosphate disodium thermosensitive hydrogels for the sustained delivery of venlafaxine hydrochloride.[124] Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery was depicted by Xu *et al.*[125] A magnetic chitosan hydrogel for sustained and prolonged delivery of Bacillus Calmettee Guérin in the treatment of bladder cancer was reported by Zhang *et al.*[126] van Dijk-Wolthuis *et al.*[127] reported dextran hydrogels, which were prepared by radical polymerization of aqueous solutions of glycidyl methacrylate-derivatized dextran (dex-MA), hydroxyethyl methacrylate-derivatized dextran (dex-HEMA), and HEMA-oligolactate-derivatized dextran (dex-lactate HEMA), using potassium peroxydisulfate and *N, N, N' ,N'*-tetramethylethylenediamine (TEMED) as the initiating system for controlled drug release application. Release characteristics of salmon calcitonin from dextran hydrogels for colon-specific delivery was reported by Basan *et al.*[128] *In-vivo* controlled release of cisplatin from biodegradable gelatin hydrogel was performed by Konishia *et al.*[129] *In-vivo* anti-tumour effect of dual release of cisplatin and adriamycin from biodegradable gelatin hydrogel was developed by Konishia *et al.*[130] Gaowa *et al.* reported gelatin based biodegradable hydrogel for *in-vivo* controlled release of anti-tumour activity.[131] Synthesis of polymethacrylamide-grafted-gellan gum (PMaa-g-GG) for controlled drug delivery application was reported by Nandi *et al.*[132] Chitosan/poly-γ-glutamic acid nanoparticles incorporated into pH-sensitive hydrogels were developed as an efficient carrier for amoxicillin delivery.[133] Cyclodextrin mediated controlled release of Naproxen from pH-sensitive chitosan/poly(vinyl alcohol) hydrogels for colon targeted delivery was described by Das *et al.*[134] The use of pH-sensitive cationic guar gum/poly (acrylic acid) polyelectrolyte hydrogels for controlled drug delivery application was described by Huang *et al.*[135] Synthesis of acryloyl guar gum and its hydrogel materials for use in the slow release of L-DOPA and L-tyrosine was reported by Thakur *et al.*[136] Thermoresponsive magnetic nanoparticle – aminated guar gum hydrogel system for sustained release of doxorubicin hydrochloride was described by Murali *et al.*[137] Chen *et al.* explained the synthesis and properties of degradable hydrogels of konjac glucomanan grafted acrylic acid for colon-specific drug delivery of 5-ASA.[138] Liu *et al* described the synthesis and characteristics of pH-sensitive semi-interpenetrating polymer network hydrogels based on konjac

glucomannan and poly (aspartic acid) for *in-vitro* drug delivery of 5-Fluorouracil.[139] Ibuprofen release from the pH- and electro-response cellulose nanofiber/sodium alginate hybrid hydrogels was described by Zheng *et al*.[140] Optimal response surface design of Gum tragacanth-based poly[(acrylic acid)-co-acrylamide] IPN hydrogel for the controlled release of antihypertensive drug losartan potassium was reported by Saruchi *et al*.[141] Photo thermally enhanced drug release from κ-carrageenan hydrogels reinforced with multi-walled carbon nanotubes was described by Estrada *et al*.[142]

Wound dressing is one of the most significant biomedical applications of the polysaccharides based hydrogels. The adhesive nature, antifungal/antibacterial activity and permeability to oxygen make the hydrogels suitable for the treatment of wounds and burns.[112] Chitosan and its derivative based hydrogels have been widely used as wound dressing materials.[143] Alginate/asiaticoside based hydrogels have been studied as wound dressing material by Sikareepaisan *et al*.[144] Balakrishnan *et al*. reported periodic-alginate crosslinked hydrogel as wound dressing agent.[145] Singh *et al*. synthesized sterculia gum crosslinked PVA–PVP hydrogel through radiation crosslinking method for the delivery of antimicrobial agent to the wounds.[146] Poly (vinyl alcohol)-alginate physically crosslinked hydrogel membranes for wound dressing applications has been reported by Kamoun *et al*.[147]

2.2.1.2. Agriculture Applications

Storage of water in industrial field is challenging. Hydrogels have been usually used as water storage materials in agricultural field.[112] Cellulose based hydrogels are the potential materials to absorb and retain water. Sannino and Coworkers reported cellulose based hydrogels for agricultural purposes.[148] The sodium alginate-glutaraldehyde crosslinked hydrogel has been investigated as matrix for natural liquid pesticide neem seed oil.[149] Starch-alginate-clay composite was used for the release of a fungicide thiram.[150] Microsphere of sodium alginate /starch crosslinked with Ca^{2+} has been used as controlled release matrix for the release of pesticide chlorpurifos.[151] Starch/ethylene glycol-co-methacrylic acid hydrogel was designed for controlled release of pesticides like fluometuron, thiophanate, thiophanate methyl, and trifluralin.[152]

2.2.1.3. Industrial Applications

Polysaccharide based hydrogels have wide range of industrial applications. In the food industry, pectin is used as gelling and thickening reagent. The inclusion of pectin in gel-like products achieves the desired firmness and alters the texture of the gel. For these reasons, pectin has been used in foods, cosmetics, and environmental applications to modify the release of fragrance compounds and enhance the perception of flavours.[153-155]

Heavy metal ion adsorption is an important application of polysaccharide based hydrogels. Psyllium husk and acrylic acid based crosslinked hydrogel was used for removal, separation, and enrichment of hazardous metal ions from aqueous solution.[156] Cellulose and its derivatives such as hydroxypropyl cellulose, cyanoethyl cellulose, hydroxyethyl cellulose, hydrazinodexy cellulose, cellulose phosphate with acrylamide and *N*, *N'*-methylene bisacrylamide based hydrogels are studied for sorption of $Fe^{2+,}$ Cu^{2+} and Cr^{2+} ions.[157] Polyacrylic acid and sodium alginate based hydrogel has been used for the adsorption of Cu^{2+}, Co^{2+}, and Ni^{2+} ions.[158] Hydrogel based on chitosan, maltodextrin and gum arabic has been employed as adsorbents for removing Cd^{2+} from aqueous solutions.[159] Calcium alginate hydrogel beads containing vineyard pruning waste has been used for dye removal.[160] Agarose based hydrogel has been utilized for stacking electrophoresis.[161] Cellulosic hydrogels were used for chromatographic supports.[162] Chitosan based hydrogels have been used as corrosion inhibitor.[163] Water soluble and biodegradable Pectin-grafted polyacrylamide and Pectin-grafted polyacrylic acid hydrogel as corrosion inhibitor on Mild Steel in 3.5% NaCl Media was described by Geethanjali *et al*.[164] Polyacrylamide grafted with Okra mucilage has been tested as corrosion inhibitor for mild steel in 0.5 M H_2SO_4 by Mukherjee *et al*.[165] Polyacrylamide grafted guar gum (GG-g-PAM) has been tested as potential green inhibitor against corrosion of mild steel in 1 M HCl by Roy *et al*.[166] Polysaccharides are also used as thickeners, bioadhesives, stabilizers, probiotic, and gelling agents in food and cosmetic industries.[167-169] Radiation synthesis of eco-friendly water reducing sulfonated starch/acrylic acid hydrogel designed for cement industry.[170]

2.2.2. Classifications of polysaccharide based hydrogels

Polysaccharide based hydrogels can be classified on the basis of method of preparation, types of monomers involved and ionic charges (Fig. 5).[112]

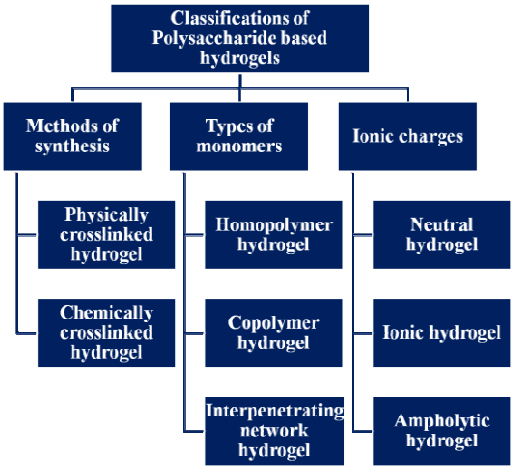


Fig. 5 Classifications of polysaccharide based hydrogels

On the basis of method of preparation, hydrogels are mainly of two types: (i) Physically crosslinked hydrogels, (ii) Chemically crosslinked hydrogels.

2.2.2.1. Physically crosslinked hydrogels

These are reversible and unstable hydrogels in which polymeric units are connected to each other by secondary force of interactions such as hydrogen bonding, ionic or hydrophobic interactions. The stability of these hydrogels also depends on the external conditions and may obstruct by changing environment or by application of stress. These hydrogels have wide range of biomedical applications because of the absence of any external crosslinkers. There are several reports on physically crosslinked hydrogels used in biomedical applications like blends of starch/carboxymethyl cellulose, gelatine/agar, chitosan/glycerol-2-phosphate hydrogels.[171-174]

2.2.2.2. Chemically crosslinked hydrogels

Because of the presence of various functional groups like hydroxyl, amine, carboxylic acid groups in the polymeric backbone, it can covalently connect with the crosslinker and form chemically crosslinked hydrogels. These are irreversible in nature and stable due to the covalent attachment between the crosslinker and the polymer. Crosslinking may occur by various mechanisms such as condensation, addition and/ vulcanization. Because of stable network, which arises from covalent attachment, these types of hydrogels attain equilibrium swelling that depends on the polymer-solvent interactions as well as on crosslinking density. Polysaccharides like starch and its derivatives, cellulose, dextrin, dextran, chitosan, agar, alginate, guar gum, hyaluronan etc. was chemically crosslinked with crosslinker in the presence of initiator or radiations to form chemically crosslinked hydrogel.[175, 176]

2.2.2.3. Homopolymer hydrogels

When a single species act as building block in the network and form three dimensional polymeric network by crosslinking, then the hydrogel is considered as homopolymer hydrogel. The crosslinking may occur in the presence of crosslinker or with polymer molecules itself. Cellulose can form hydrogel in urea/NaOH solution in presence of epichlorohydrin crosslinker.[177] Whereas, irradiation of polysaccharide solutions can also form hydrogels in absence of gelating agent. In addition, polysaccharides such as chitin, chitosan, agar, alginate, xanthan, guar gum, hyaluronan etc. can form homopolymeric hydrogels in presence of high energy radiations.[178]

2.2.2.4. Copolymer hydrogel

When two or more polysaccharide units or one polysaccharide and one synthetic polymer took part in hydrogel formation (out of which one is hydrophilic), form 3-dimensional polymeric network. This is considered as copolymer hydrogel. The arrangements of copolymer hydrogels may be like random, block or alternate with respect to main polymeric network. The properties of these hydrogels depend on different combination of polymeric units as well as on the arrangements of polymeric network.[179, 180]

2.2.2.5. Interpenetrating network hydrogel

Interpenetrating polymer networks (IPNs) are crosslinked polymers[181] in which at least one polymer network is synthesized or crosslinked independently in the presence of the other, without any covalent bonds between them.[182] Synergistic effect was observed as the properties of both the polymers involved, which can reduce the limitations of natural as well as synthetic polymers. On the basis of synthesis, IPNs are of two types: (a) a sequential IPN in which one network is swollen and polymerized in the presence of the other, and (b) simultaneous IPN, in which both of the network precursors are synthesized at the same time by independent routes.

If only one component of the assembly is crosslinked leaving the other in a linear form, the system is termed as semi-IPN. The significant point during the fabrication of IPNs is the mutual miscibility of the interpenetrating polymers. Generally, polymers do not mix well with each other, resulting in the phase separation of the resultant blend.[183, 184] However, crosslinking provides an easy route for mixing the two components to form IPNs for a variety of applications.[185]

2.2.2.6. Neutral hydrogel

When neutral polysaccharides covalently crosslinked with neutral polysaccharides and/or neutral monomeric units like acrylamide, N-vinyl pyrollidone, hydroxyalkyl methacrylate etc. to form three dimensional polymeric networks then the network is called neutral hydrogel. These gels are irreversible and can absorb water without dissolution. These hydrogels demonstrate temperature sensitive swelling-deswelling behavior.[186]

pH sensitive N-succinyl chitosan grafted polyacrylamide hydrogel for oral insulin delivery was reported by Mukhopadhyay *et al.*[187] Cheng *et al.* described the sustained delivery of latanoprost by thermosensitive chitosan–gelatin-based hydrogel for controlling ocular hypertension.[188] Biodegradability and swelling capacity of kaolin based chitosan-g-PHEMA nanocomposite hydrogel was described by Pradhan *et al.*[189] Thermoresponsive chitosan–agarose hydrogel for skin regeneration was reported by Miguel *et al.*[190] Carboxymethyl cellulose-g-poly(2-(dimethylamino) ethyl methacrylate) hydrogel as adsorbent for dye removal was reported by Salama *et al.*[191] PVA/gelatin hydrogel beads and adsorption mechanism for advanced Pb(II) removal was depicted by Hui *et al.*[192]

2.2.2.7. Ionic hydrogels

Ionic hydrogels are two types: (a) cationic, and (b) anionic. When ionic polysaccharide covalently crosslinked with each other or synthetic/ionic polymers to form 3-D polymeric network, then it is called ionic hydrogels.

The only naturally existing cationic polysaccharide is chitosan, which is obtained from the partial alkaline deacetylation of chitin.[193, 194] The amine groups is responsible for pH-responsiveness of chitosan and also enhanced affinity for mammalian cell components as well as microbicide characteristics. Besides, these groups also provide affinity towards oppositely charged drugs and reactivity for crosslinking or grafting modifications.[193, 194]

Again, condensing agents like β-glycerophosphate, citrate, calcium phosphate, or tripolyphosphate can form ionically crosslinked hydrogels.[195-197]

The swelling of the cationic hydrogels is dependent on pH of the aqueous medium, which determines the extent of dissociation of the ionic chains. At acidic pH, cationic hydrogels show excellent swelling because their chain dissociation is favoured in low pH.

Anionic polysaccharides extracted from seaweeds (alginate, agar, carrageenan) and plant cell walls (pectin) and exudates (gum arabic) have been used in the food industry as thickening or gelling agents. At basic pH, anionic hydrogels dissociate more and show significant swelling than that of neutral solution. The sensitivity of alginate towards pH and calcium ions is mainly because of the different relative positions of the carboxylic acid groups in each block.[198] Alginate also offers large number of potential of derivatization for biomedical applications.[199] Agar or agar-agar is obtained from red algae or seaweed and is widely used as component of foods and microbial cultures, because of its performance as thickener and stabilizer. Agar is a heterogeneous mixture of agaropectin and agarose, where agaropectin is modified with acidic side-groups, such as sulphate and pyruvate and agarose has neutral charge and possesses longer chains.[200]

Due to this structural conformation it can form ionic hydrogel. The use of agar as drug delivery matrix is still quite recent and

mostly limited to physical blends with other polysaccharides.[201-204] Pectin and gum arabic are branched heteropolysaccharides having carboxylic acid groups and can form ionic hydrogels. These can be found in the cell wall of plants in the form of free acid, simple salt, ester or aminated polysaccharide. Pectin is suitable for colon delivery of drugs because of its selective digestion by the micro flora present in colon (*Bacteroids ovatus*) and its resistance to proteases and amylases of the upper gastrointestinal tract.[205, 206] Carrageenan or carrageenin are linear polysaccharides containing variable density of sulphated groups. They are extracted from red seaweeds and commercialized as kappa (κ, 1 sulphate group per dimer), iota (ι, 2 sulphate groups per dimer) and lambda (λ, 3 sulphate groups per dimer). Only the first two varieties can form stable physical gels and κ-carrageenan hydrogels show pH- and temperature-responsive behaviour.[201]

Wang *et al*. developed three ionic starch-based polymers, namely a cationic starch (C-Starch), an anionic starch (A-Starch) and a zwitter ionic starch (Z-Starch) via etherification reactions for the prevention of nonspecific protein adsorption.[207] Heparin is a highly sulphated glycosaminoglycan and has the highest negative charge density of any known biological molecule. It is widely used as an injectable anticoagulant. Recently it is gaining interest as component of growth factor delivery systems.[208, 209] Chondroitin sulphate is a linear polysaccharide based on (1, 3) – β – N – acetyl - D- galactosamine and (1, 4) – β - glucuronic acid presenting sulphates, hydroxyl and carboxylic acid functionalities. It can be found attached to proteoglycans in connective tissue matrices with structural functionalities or as a receptor on cell or basement membranes. Mainly, it has been used as component of scaffolds for cartilage repair in tissue engineering.[210] Nanocomposites hydrogel of calcium alginate and carboxymethyl-cellulose-g-poly (acrylic acid)/attapulgite for controlled release of ibuprofen was also reported.[211]

2.2.2.8. Ampholytic hydrogels

When polymeric hydrogels having 3-dimensional network contains both cationic and anionic moieties, are considered as ampholytic hydrogels. Cationic/anionic polysaccharides can covalently attach with oppositely charged synthetic polymer to form ampholytic hydrogel. At a definite pH, modified polysaccharides can also behave like ampholytic hydrogels. Zwitter ionic starch (Z-Starch) hydrogel via etherification reactions for the prevention of nonspecific protein adsorption was developed by wang *et al*.[212]

3. General procedures for development of polymeric hydrogels

Hydrogels open a new pathway for the advancement of various applications including tissue engineering,[213, 214] cell based biosensors,[215] coatings,[216] drug delivery, [4-6] packers in oil and gas recovery [217] and cell transplantation[218] and so on.

They are composed of hydrophilic polymer chains, which can be either natural or synthetic.[219] The structural integrity of hydrogels depends on crosslinks between the polymer chains, by chemical bonds and physical interactions. Besides, as the biomedical applications of hydrogels are increasing, so considerable efforts have been made to develop new hydrogel systems from a variety of synthetic and natural materials.[220]

It is essential to modify the properties of a polymer with tailor-made specifications, which are essential for target applications. There are various ways to modify the properties of polymers like blending, grafting/crosslinking, and curing. 'Blending' is the physical mixture of two or more polymers to get the required properties. 'Grafting' is a method wherein monomers are covalently bonded onto the polymer chain. 'Chemical crosslinking' is a method where monomers are covalently bonded onto the polymer chain in presence of crosslinker. In curing, the polymerization of an oligomer mixture forms a coating which adheres to the substrate by physical forces.[221] The schematic presentation of the polymer modifications is represented in Fig. 6.

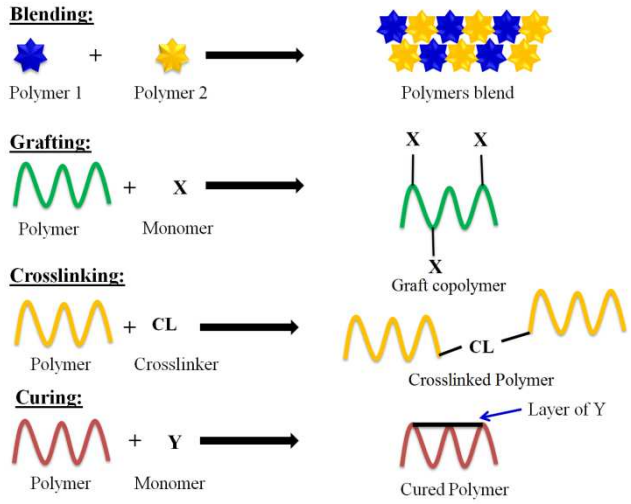


Fig. 6 Schematic representation of the methods for polymer modification

Although polysaccharides have several advantages, but polysaccharide itself is not sufficient for recent industrial requirements. Thus it is essential to modify the biopolymers for the advancement of their application in biomedical research, particularly in drug delivery applications. One of the easiest and efficient ways for modifications of natural polysaccharides is the "grafting" of synthetic polymer chains onto the polysaccharide backbone, followed by "chemical crosslinking" using an external crosslinker. This modification provides chemically crosslinked hydrogels which are having immense application in biomedical field with desired properties.

3.1. Blending

Polymer blend represents very important field to assist in the development of new low-cost products with better performance in comparison with the neat polymers. Blends and composites are extending the employment of polymers from renewable resource into new value-added products.[222] They are significant also from ecological and economical viewpoint. For example, municipal commingled plastic waste, composed of various immiscible polymers can be recycled by mixing in molten state, and so it can be transformed to the material, which would satisfy the relevant application.[223] The properties of natural polymers can be significantly advanced by blending with synthetic polymers. The objective for developing a novel blend of two or more polymers is not to change the properties of the components drastically, but to capitalize on the maximum feasible performance of the blend.

In the 1970s and 1980s, several blends of starch with various polyolefins were developed. However, these blends were not biodegradable, and thus the advantage of using a biodegradable polysaccharide was lost. Since most of natural polymers are water soluble, water has been used as a solvent, dispersion medium and plasticizer for blending purpose.[224]

3.1.1 Melt processed blends

Arvanitoyannis *et al*. reported on biodegradable blends based on gelatinized starch and 1,4-transpolyisoprene (gutta percha) by thermal pressing for food packaging or biomedical applications.[225] Carvalho *et al.* prepared the blend of thermoplastic starch/natural rubber polymer using natural latex and cornstarch at 150°C.[226] Kokini *et al*. reported protein/starch blend.[227] Matveev *et al.* studied protein/polysaccharide blend, considering inter-macromolecular hydrogen and dipole–dipole interactions.[228] Warth *et al.* developed starch/cellulose acetate blends.[229]

3.1.2 Aqueous blends

Several natural polymers cannot be melt processed, either because they degrade on or before melting (softening). For this reason, aqueous blending is the preferred technology to modify the polymers.[230] Pereira *et al.* reported on biodegradable hydrogels, based on cornstarch/cellulose acetate blends, produced by free-radical polymerization with methyl methacrylate and/or acrylic acid monomer.[231] Espigares *et al.* developed partially biodegradable acrylic bone cements based on cornstarch/cellulose acetate blends as bone cements.[232] Arvanitoyannis and Biliaderis reported on aqueous blends of methyl cellulose and soluble starch, plasticized with glycerol or sugars, prepared by casting or by extrusion and hot pressing.[233] Ikada *et al*. studied various poly(lactic acid) blends to improve their thermal properties.[234] A stereocomplex was formed from enantiomeric PLAs, poly(L-lactic acid) (PLLA) and poly(D-lactide) (i.e. poly(D-lactic acid) (PDLA)) due to the strong interactions between PLLA and PDLA chains.[234] Zhang *et al.* reported that poly(3-hydroxybutyrate)/poly(lactic acid) blends prepared by casting a film from a common solvent at room temperature.[235] Suyatma *et al.* reported on biodegradable film blends of chitosan with PLA by solution mixing and film casting.[236]

3.2 Grafting

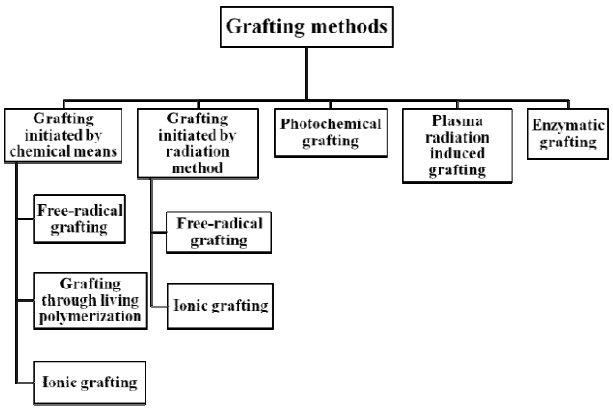


Fig. 7 Schematic presentation of the methods of grafting

Several methods (Fig. 7) have been used for the development of graft copolymeric hydrogels of different monomers on polymeric backbone. These techniques include chemical, radiation, photochemical, plasma-induced and enzymatic grafting techniques.[221]

3.2.1. Grafting initiated by chemical means

Graft copolymerization can be performed by two main processes, i.e. free radical and ionic. Besides, grafting can also be done by atom transfer radical polymerization (ATRP).

3.2.1.1. Free-radical grafting

In free radical grafting technique, an initiator first generates radicals on polysaccharide backbone, which further react with monomer to form the graft copolymers. Generally, the free radicals are generated by indirect or direct methods. A probable mechanism of grafting in presence of a radical initiator is as follows:

$$I_2 \rightarrow 2I^{\bullet}$$

$$I^{\bullet} + M \rightarrow IM^{\bullet}$$

$$I^{\bullet} + \text{Polym} - OH \rightarrow \text{Polym} - O^{\bullet} + IH$$

$$IMM^{\bullet} + \text{Polym} - OH \rightarrow \text{Polym} - O^{\bullet} + IMMH$$

$$\text{Polym} - O^{\bullet} + nM \rightarrow \text{Polym} - O - M_n^{\bullet}$$

$$IMM^{\bullet} + nM \rightarrow IM{-}M_n - H$$

$$\text{Polym} - O - M_n^{\bullet} + I^{\bullet} \rightarrow \text{Polym} - O - M_n - I$$

$$\text{Polym} - O - M_n^{\bullet} + IMM^{\bullet} \rightarrow \text{Polym} - O - M_{n+2} - I$$

An example of indirect method for free radicals production is redox reaction using M^{n+}/H_2O_2, persulphates.[237-241]

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^{\bullet}$$

$$Fe^{2+} + S_2O_8^{2-} \rightarrow Fe^{3+}\ SO_4^{2-} + SO_4^{-\bullet}$$

Again $SO_4^{-\bullet}$, $OH^{\bullet}$ can also directly react with the polymer backbone to generate the free radical species.

$$SO_4^{-\bullet} + \text{Polymer} - OH \rightarrow HSO_4 + \text{Polymer} - O^{\bullet}$$

$$OH^{\bullet} + \text{Polymer} - OH \rightarrow H_2O + \text{Polymer} - O^{\bullet}$$

Misra *et al.* described that $OH^{\bullet}$ is more reactive than SO_4^{2-} during grafting of vinylic monomers onto wool/cellulose.[239] Similarly, organic hydro peroxides, persulphates, Fe^{3+}, Cu^{2+} etc. along with a reducing agent like sodium bisulphite, thiosulphate or Ag^+ are also used in free radical grafting method.

$$S_2O_8^{2-} + HSO_3^- \rightarrow SO_4^{2-} + SO_4^{-\bullet} + HSO_3^{\bullet}$$

$$\text{Polymer} + SO_4^{-\bullet} \rightarrow \text{Polymer}^{\bullet} + HSO_4^-$$

$$SO_4^{-\bullet} + H_2O \rightarrow HSO_4^- + OH^{\bullet}$$

$$HSO_3^{\bullet} + H_2O \rightarrow H_2SO_3 + OH^{\bullet}$$

Bajpai *et al.* reported peroxydisulphate–ascorbic acid initiated graft copolymerization using Ag catalyst. [242] In this reaction the production of sulphate ion radicals act as chain carriers.[242] Besides, tertiary butyl hydroperoxides-Fe^{2+} system can also initiate the radical polymerisation as parallel with Fenton's reagent (Fe^{2+}/H_2O_2). As a result, t-butoxy radicals are formed

from one electron transfer between t-butyl-hydroperoxide (TBHP) and Fe^{2+}. The resulting t-butoxy radical basically abstracts hydrogen from monomer/polymer/water to generate corresponding radical species.[243]

Transition metals ions like Ce^{4+}, Cr^{6+}, V^{5+}, Co^{3+} can also generate free radical sites on a polymeric backbone by direct oxidation. The redox potential of the metal ions is the driving force in determining the grafting efficiency. Metal ions with low oxidation potential have better grafting efficiency than that of higher oxidation state. It is assumed that the reaction proceeds through the formation of a metal ion–polymer chelate complex as intermediate.[244-250] Sen *et al.* has been synthesized CMS-g-PAM using ceric ammonium nitrate as initiator.[251]

$$Ce^{4+} + Polymer - OH \rightarrow Chelate\ complex$$

$$Chelate\ complex \rightarrow Polymer - O^{\bullet} + Ce^{3+} + H^{+}$$

$$Polymer - O^{\bullet} + M \rightarrow Polymer - OM^{\bullet} \rightarrow Polymer - OMM^{\bullet}$$

MnO_4^- was also used for the formation of graft copolymers through radical polymerization. Here, MnO_4^- produces Mn^{3+} via Mn^{4+} in presences of acid solution. Highly reactive Mn^{3+} ions initiate the graft copolymerization and homopolymerization.[252] Tsubokawa *et al.* described the polymerization of azo groups incorporated organic pigments like quinacridone, Diketopyrrolopyrrole, anthraquinone etc. with vinyl monomers through radical mechanism.[253]

Chemical pre-treatment (e.g. ozonation, diazotization, xanthation) of the polymer moiety may also produce free-radical sites, which can offer sites for grafting.[254-264]

3.2.1.2. Grafting through living polymerization

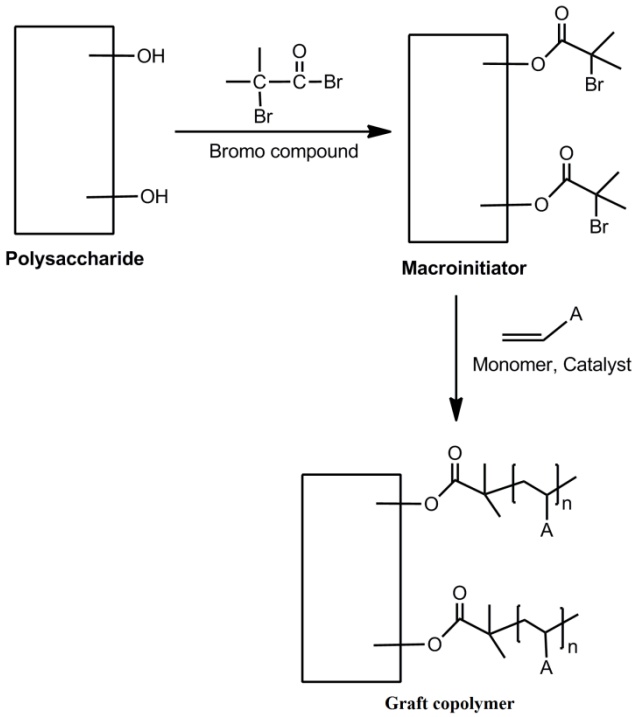
'Living Polymerization' technique offers a great potential for grafting reactions. Szwarc *et al.* depicts that a 'living polymer' is that which retains their ability to propagate for a long time and grow to a desired maximum size while their degree of termination or chain transfer is still negligible'.[265] Controlled free-radical polymerizations combine characteristics of both conventional free-radical and ionic polymerizations. In conventional free-radical polymerization, termination occurs through coupling or disproportionation reactions, which led to broad molecular weight distribution. While living polymerization provides living polymers with regulated molecular weights and low polydispersity.[266-273]

Controlled free-radical polymerization may be effective through ATRP. ATRP of styrene and various methacrylates has been reported, using various catalytic systems.[274, 275] In that method, inactive chains are capped by halogen atoms, which are reversibly transferred to metal complexes in the lower oxidation state. This creates the short-lived growing radicals and complexes in the higher oxidation state. ATRP reactions mainly proceed through the activation– deactivation dynamic equilibrium process.

$$M_n - X + Cu(I)/2L \rightleftharpoons M_n^{\bullet} + Cu(II)X/2L$$

Where, M_n-X is the polymeric halide and CuX/2L is Cu (I) (X = Cl /Br and L = 2, 2' bipyridine or a 4, 4' disubstituted 2, 2' bipyridine).

The copper (I) complex acts as a reversible halogen atom transfer agent between the active and inactive polymer chains (Scheme 1). The kinetically optimum ratio of ligands to copper (I) halide for these polymerization is found to be 2:1, which indicates that the coordinated copper (I) contains two bipyridine ligands.[275]



Scheme 1 Schematic representation of ATRP reaction

Multidentate amine based ligands such as tetramethylene diamine (TMEDA), *N*,*N*,*N*′,*N*′,*N*″-pentmethyl diethylene triamine (PMDETA), (tris-2-aminoethyl) amine (TREN) are also used in the copper mediated ATRP of styrene, methyl acrylate and methyl methacrylate.[276, 277] Grafting from polymers including poly (vinyl chloride) (PVC), polyisobutene, polyethylene, and ethylene-co-vinyl acetate copolymer through ATRP has been reported in various literatures.[278-282] Sonmez *et al.* reported acrylamide grafting by ATRP using N-chlorosulfonamide/CuBr catalyst.[283] Sakaguchi and Shimada depicted the grafting of polystyrene on a polypropylene backbone in presence of γ-irradiation in air with 2, 2, 6, 6-tetramethyl-1-piperidinoxyl (TEMPO).[284] Janata *et al.* reported the design of a multifunctional ATRP macroinitiator for the preparation of graft copolymer.[285] Carlmark *et al.* has reported surface grafting by controlled radical polymerization using 2-bromoisobutyryl bromide by reaction with the hydroxyl groups on the filter paper. Then, grafting is achieved by immersing the modified paper into a reaction mixture containing methyl acrylate, Cu(I)Br, tris 2-(dimethyl amino) ethyl amine (Me_6-TREN), sacrificial initiator and ethyl acetate.[286] Mishra *et al.* reported grafting of 4-aminoantipyrine from guar gum through graft ATRP using Cu(I)Br / 2, 2'-bipyridyl as initiator.[287] Wang *et al.* Developed ethyl cellulose-graft-PDEAEMA copolymer through ATRP for drug (rifampicin) release application. [288] In this reaction, pyridine was used as base for the first step and CuBr/bpy as initiator.[288] Huang *et al.* described poly (methacrylic acid)-grafted chitosan microsphere via surface initiated ATRP technique for Cd(II) ions

removal from aqueous solution. In the first step of reaction, 2-bromoisobutyryl bromide was used for the synthesis of macroinitiator by TEA as base. Then grafting of sodium methacrylate was performed with CuBr, $CuBr_2$ and PMDTEA as catalyst.[289]

3.2.1.3. Ionic grafting

In this method, grafting is performed by ionic approach. Alkali metal suspensions in a Lewis base liquid, organometallic compounds and sodium naphthalenide are useful initiators. Alkyl aluminium (R_3Al) and the halide form of polymer (PCl) combine to form carbonium ions in the polymer chain, which is responsible for copolymerization. The reaction follows cationic and anionic polymerization mechanism. Cationic catalyst BF_3 can also be used.[221]

Cationic mechanism:

$$PCl + R_3Al \rightarrow P^+R_3AlCl^-$$

$$A^+ + M \rightarrow AM^+ - M \rightarrow \text{Graft copolymer}$$

Sodium–ammonia or the methoxide of alkali metals forms the alkoxide of polymer (PO^-Na^+), which reacts with monomer to produce the graft copolymer.

Anionic mechanism:

$$P - OH + NaOR \rightarrow PO^-Na^+ + ROH$$

$$PO^- + M \rightarrow POM^- - M \rightarrow \text{Graft copolymer}$$

3.2.2. Grafting initiated by irradiation technique

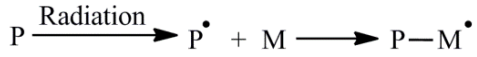
3.2.2.1. Free-radical grafting

The irradiation of polymers creates free radicals through homolytic fission. In the radiation technique, the presence of an initiator is not necessary rather the medium. Thus, if irradiation is performed in open air, peroxides may be generated on the polymer backbone. While lifetime of the free radicals depends on the nature of the polymer moiety. Grafting usually takes place in three different ways: (a) pre-irradiation (b) peroxidation and (c) mutual irradiation technique (Scheme 2).[221]

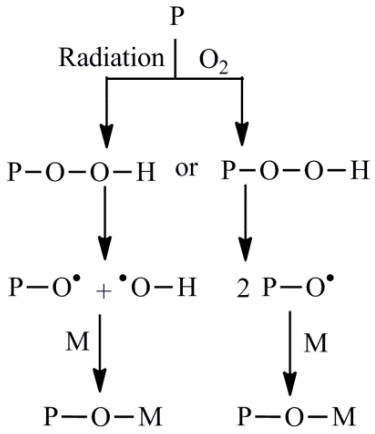
In pre-irradiation grafting method, at first, the polymer backbone is irradiated in vacuum or in an inert gas to form free radicals. Then, the irradiated polymer is treated with the monomer, in liquid or vapour state or in a suitable solvent.[290-294]

In peroxidation grafting process, high-energy irradiation is applied to the polymer molecule in the presence of air or oxygen to form hydroperoxides or diperoxides. Radiation is used on the basis of nature of the polymeric backbone and the irradiation conditions, resulting formation of a stable peroxy compound. After that, it is treated with the monomer at higher temperature when the peroxides undergo decomposition to radical species. This initiates the grafting process. The advantage of this method is the formation of intermediate peroxy products that can be stored for long period for grafting. On the other hand, in the mutual irradiation method, the polymer and the monomers are irradiated simultaneously to form free radicals and consequent addition.[295-301] The advantage of the pre-irradiation method is that the process is relatively free from homopolymer formation because the monomers are not irradiated. But, the certain disadvantage of the pre-irradiation method is scission of the base polymer due to its direct irradiation, which can result in the development of block copolymers.

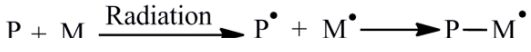
(a) Pre-irradiation grafting method:



(b) Peroxidation grafting method:



(c) Mutual irradiation grafting method:



Scheme 2 Schematic representation for grafting through irradiation method

3.2.2.2. Ionic grafting

Ionic grafting can also proceed via ions formation in presence of high-energy irradiation. Ionic grafting may be of two different types: cationic or anionic. The polymer is irradiated to produce the polymeric ion, and afterwards reacted with the monomer to form the graft copolymer. The advantage of the ionic grafting is of high reaction rate.

The cationic grafting mechanism can also proceed through the formation of monomer radical cation, which then forms a dimer. Charge localization in the dimer occurs in such a way that the dimer radical cation then reacts with the radical formed by the irradiation of the polymer.[302]

Similarly in anionic grafting mechanism, an anion controls the grafting, acting as the initiator. Kitamuru *et al.* and Mazzi *et al.* applied proton beams as ionizing radiation to prepare amidoxime type adsorbents on PE film using acrylonitrile.[303, 304] The H-atoms liberated from chemically active sites of polymer film irradiated by the ion beam; which basically reacts with carbon radicals, C=C bonds, C-C bonds and crosslinking to form the graft-polymer.

3.2.3. Photochemical grafting

Because of the presence of chromophores in polymeric chain, it can absorb light. As a result, molecule goes to an excited state and dissociate into reactive free-radicals, which initiates the grafting process. Sometimes, the absorption of light does not form free-radicals through bond rupture. Then the reaction can be promoted by the addition of photosensitizers, e.g. benzoin ethyl ether, dyes (Na-2, 7 anthraquinone sulphonate or acrylated azo dye), aromatic ketones (benzophenone, xanthone) or metal ions

UO_2^{2+}. Thus the photochemical grafting process can proceed in two ways: with or without a sensitizer.[305]

Generally, when sensitizer is not involved in the reaction, the generated free radicals of polymeric backbone react with the monomer free radical to form the graft copolymer. On the contrary when sensitizer is involved, it forms free radicals. These free radicals can undergo diffusion so that they abstract H-atoms from the polymer. This results the formation of radical sites, which are required for grafting.[306]

3.2.4. Plasma radiation induced grafting

Recently, the plasma radiation induced polymerization method has gained increasing significance. This method proceeds through the similar mechanistic way as with ionizing radiation.[307, 308] It involves electron-induced excitation, ionization and dissociation. Thus, the accelerated electrons from the plasma having adequate energy cleave the chemical bonds in the polymeric structure. This results the formation of polymeric radicals, which consequently initiate graft copolymerization.

3.2.5. Enzymatic grafting

Enzymes are also used in grafting technology. In this method an enzyme initiates the chemical/electrochemical grafting reaction.[309] For example; tyrosinase can convert phenol into reactive o-quinone, which undergoes consequent non-enzymatic reaction with chitosan. Cosnier *et al*. reported the enzymatic grafting on a poly (dicarbazole-*N*-hydroxysuccinimide) film.[310]

3.3. Method of crosslinking

Both physical and chemical crosslinking methods (Fig. 8) have been used to prepare hydrogels. In chemically crosslinked gels, covalent bonds are present between different polymer chains or with an external crosslinking agent and polymer molecules. Whereas, in physically crosslinked gels, polymer chains are bounded by physical interactions.[311]

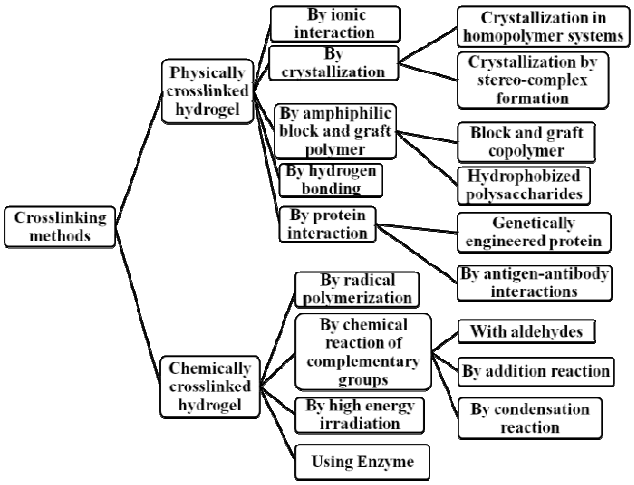


Fig. 8 Schematic representation of methods of crosslinking

3.3.1. Physically crosslinked hydrogels

3.3.1.1. Crosslinking by ionic interactions

Physically crosslinked hydrogels can be developed by ionic interactions. Alginate is an example of a polymer that can be crosslinked by ionic interactions. Alginate is a polysaccharide with mannuronic and glucuronic acid residues and can be crosslinked by calcium ions.[312] Crosslinking can be performed at room temperature and physiological pH. Consequently, alginate gels are usually used as matrices for encapsulation of living cells[313] and for release of proteins.[314]

The gels can be destabilized by extraction of the Ca-ions from the gel by a chelating agent. The ionotropic hydrogels degrade under physiological conditions. The degradation rate was increased by incorporating hydrolysis-sensitive glycinato groups in the polymer.[315] Polycations can also be crosslinked with anions. For example, chitosan-based hydrogels were obtained by crosslinking with glycerol-phosphate disodium salt.[316] It was observed that below room temperature, chitosan solutions remain liquid in this salt solution, but it formed gel when heated. With increasing degree of deacetylation, sol–gel transition temperature declined. Histological evaluations exposed that the gel can deliver active protein (BP) inducing bone and cartilage formation.[317]

The presence of ionic groups in the polymer chains is not essential to form hydrogel by ionic interactions. For example, Watanabe *et al*. described dextran forms hydrogel in the presence of potassium ions.[318] They pointed out that it forms microstructure as the ionic radius of the potassium ion fits into the cage formed by six oxygen atoms of glucose units of three polymer chains.[318] On the other hand, dextran/potassium gel is unstable in water and consequently is less suitable for drug delivery applications. Carrageenan also contained variable portion of sulphate groups which can form gel with potassium ions, but also exhibits gelation under salt-free conditions. However, gels obtained in presence of metallic ions were considerably stronger than that of under salt-free conditions.[319] Besides, anionic polymers can crosslinked with metallic ions to form hydrogels. Ionically crosslinked chitosan hydrogels were formed by complex formation between chitosan and dextran sulphate or polyphosphoric acid.[320] Doxorubicin was encapsulated in nanoparticles of this chitosan hydrogels. These particles act as controlled drug delivery matrix by showing non-cytoxicity and minimal burst release.

3.3.1.2. Crosslinking by crystallization

Aqueous solution of poly(vinyl alcohol) forms gel at room temperature with low mechanical strength. Besides, aqueous solutions of PVA form highly elastic gel through Freeze-thawing process.[321] The properties of the gel depend on the molecular weight of PVA, PVA-concentration, temperature and time of freezing and the number of freezing cycles. Gel formation was attributed to the development of PVA crystallites which act as physical crosslinking in the polymer network.[321] The synthesized optimized gel were stable upto 6 months at 37 °C.[322] BSA loaded PVA gels were obtained by dissolving the protein in the aqueous PVA solution through Freeze-thawing cycles.[323]

It was verified that with the addition of alginate to the PVA solution before freeze-thawing, the mechanical strength of the gel was increased drastically which was related with the release behaviour of the model drug.[324]

3.3.1.3. Crosslinking by amphiphilic block and graft copolymers

Amphiphilic block and graft copolymers can form hydrogels through self-assembly in water, where the hydrophobic segments of the polymers are aggregated. Amphiphilic diblock copolymers form micelles, lamellar phases, etc.[325] Physically crosslinked hydrogels are usually obtained from multiblock copolymers or

graft copolymers.

The biodegradability of poly (glycolic acid) and the biocompatibility of poly (ethylene glycol) offered to design block copolymer based hydrogels for drug delivery applications. For example, PEG-PLGA based triblock polymers were developed and reported.[326-328] The thermo-reversible gels were formed at low concentrations in water via micelle formation. The critical gel concentration and gel-to-sol transition temperature (i.e. UCST) depend on the molecular weight as well as on the composition of the blocks. The PEG-PLGA-PEG block copolymers also exhibits LCST, which make them attractive for drug delivery applications, since the polymers remain in liquid state at room temperature and gel state at body temperature.[327]

Triblock copolymers with PEG and lactides were prepared by ring opening polymerization (ROP) for the release of BSA and fibrinogen.[329-333] Contrary to BSA, fibrinogen showed almost linear release rate. This indicates a reservoir drug delivery system and incompatibility of the protein with the aqueous PEG phase. Kissel *et al.* described the synthesis, characteristics of microspheres of triblock and star-branched block copolymers for protein delivery System.[334-338]

Multiblock copolymers of PEG and PLGA were prepared by polycondensation of dicarboxylated PLA and PEG.[339, 340] Graft copolymers of PEG and PLA were developed for protein release.[341] Multiblock copolymers of PEG and poly (butylene terephthalate) were investigated by Feijen and coworkers.[342] Anirudhan *et al.* developed a novel composite hydrogel, namely maleated cyclodextrin-grafted-silylated montmorillonite (MACD-g-MPTMS/MMT) for colon specific tetracycline hydrochloride (TCH) delivery.[343] Anirudhan *et al.* also reported a novel pH switchable gelatin based hydrogel via grafting method for the controlled delivery of the anti cancer drug 5-fluorouracil.[344] Boruah *et al.* described the preparation of a biocompatible nanocomposite hydrogel based on CMC-g-PAA and organo-MMT nanoclay by using methylene bis-acrylamide (MBA) as a crosslinker and potassium persulfate (KPS) as an initiator through radical graft polymerization for release of vitamin B12.[345] Kajjari *et al.* described acrylamide-grafted-guar gum (pAAm-g-GG) blended with chitosan (CS) hydrogel for ciprofloxacin delivery.[346] A Stimuli-responsive bacterial cellulose-g-poly-(acrylic acid) hydrogels were investigated as an oral delivery system for proteins by Ahmed *et al.*[347]

3.3.1.4. Crosslinking by hydrogen bonds

The complex was prepared using poly (acrylic acid), poly (methacrylic acid) with poly (ethylene glycol) and mainly the hydrogen bonding interactions between the oxygen of the poly (ethylene glycol) and the carboxylic group of poly (methacrylic acid) predominates. [348] While for poly (methacrylic acid), hydrophobic interactions also play a role.[348] Hydrogen bonding interactions were also observed in poly (methacrylic acid-g-ethylene glycol).[349, 350] The hydrogen bonds are only formed when the carboxylic acid groups get protonated. This suggests that the swelling of these gels is strongly dependent on the pH.

Using the concept of hydrogen bonding of the double strands in DNA, Nagahara *et al.* was designed a hydrogel system in which crosslinking was established by hybridization. They developed oligodeoxyribonucleotides and poly (*N, N'*-dimethylacrylamide-co-N-acryolyloxysuccinimide) based hydrogels at room temperature, which were dissociated at higher temperature.[351]

3.3.1.5. Crosslinking by protein interactions

Tirrell and Cappello first established a new class of hydrogels using protein engineering in materials chemistry research.[352, 353] The main benefit of these hydrogels are the sequence of peptides. This characteristic helps to control the physical and chemical properties by the proper design of the genetic code in synthetic DNA sequences.[354]

With the help of genetic engineering, Cappello and his co-workers developed sequential block copolymers which contain silk-like as well as elastine-like blocks. The silk-like segments were associated through hydrogen bonding to form beta strands or sheets.[353, 355] They undergo an irreversible sol to gel transition with time in physiological conditions owing to crystallization of the silk-like domains. The rate of gelation and subsequent drug release depends on various factors like concentration, polymer composition, and temperature. The drug release rate depends on the water content of the gels and the molecular weights of the incorporated species and follows first-order release kinetics.

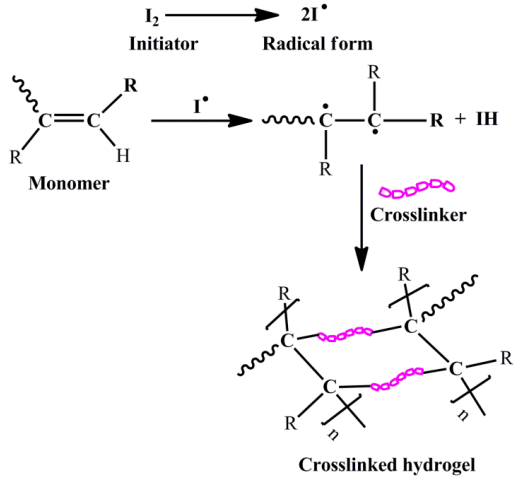
Some natural proteins having α-helices (coiled coils) structure were characterized by a hydrophilic and a hydrophobic part due to the repeating unit of amino acids with different polarities. The proteins undergo conformational transition in response to temperature and pH.

Tirell and co-workers genetically engineered a polypeptide which is called 'leucine zipper', also demonstrated the above characteristics.[356] The hydrogel formed by the coiled-coil interactions slowly make a viscous solution with increasing temperature and pH (above 8.0). Kopecek and co-workers used coiled-coil forming natural and engineered proteins as crosslinkers for poly [N-(2-hydroxypropyl) methacrylamide] [357, 358] The proteins were connected with one end of the polymer backbone through metal complexes between histidine tags and metal-chelating ligands on the polymer.[357]

3.3.2. Chemically crosslinked hydrogels

3.3.2.1. Crosslinking by radical polymerization

Chemically crosslinked gels can be synthesized by radical polymerization of low molecular weight monomers in the presence of crosslinking agents (Scheme 3).



Scheme 3 Mechanism for synthesis of crosslinked hydrogel through radical polymerization

Wichterle and Lim first described poly (2-hydroxyethyl

methacrylate) based chemically crosslinked hydrogel using ethylene glycol as crosslinker.[27]

Using this technique, various hydrogel systems were synthesized.[359] The hydrogel's features, mainly the swelling can be controlled using the amount of crosslinker. Moreover, stimuli responsive materials can be obtained by the addition of e.g. methacrylic acid as pH-sensitive gels[360] or N-isopropylacrylamide as temperature responsive gels.[361] Additionally, by radical polymerization of mixtures of vinylic monomers, chemically crosslinked hydrogels can also be obtained.

Hovgaard *et al*. reported dextran crosslinked with diisocyanate hydrogel through radical polymerization for colon specific delivery of hydrocortisone.[362] Edman *et al*. described dextran-glycidylacrylate based hydrogel by radical polymerization using N, N, N', N'-Tetramethylenediamine and ammonium peroxydisulphate as initiator and *N, N'*- methylene bisacrylamide as crosslinker.[363, 364] Water-soluble polymers other than dextran, namely albumin,[365] hydroxyethyl starch,[366-368] poly-aspartamide,[369-371] poly (vinyl alcohol)[372] and hyaluronic acid[373] were also derivatized with methacrylic groups using the process developed by Edman *et al*. Synthesis of methacrylated dextran using glycidylmethacrylate and catalyzed by 4-(*N, N'*-dimethylamino) pyridine was described by van Dijk-Wolthuis *et al*.[374]

Methacrylate groups were also introduced into dextran molecule using methacryloyl chloride,[375, 376] methacrylic anhydride,[377] bromoacetyl bromide and sodium acrylate.[378] Besides, hydrogels were also prepared by introducing methacrylic groups in mono- and di-saccharides using enzymes as catalyst.[379-381] The synthesis was carried out in anhydrous pyridine and the products obtained were of high yield (75%). In contrast to chemical methods, enzymatic synthesis also results in a very good regioselectivity.

Hubbell and co-workers developed macromers having a poly (ethylene glycol) central block, extended with oligomers of a hydroxy acid and terminated with acrylate groups. By radical polymerization of the acrylate groups of the macromer, hydrogel was formed. Radicals were produced after exposure to UV light of an aqueous solution of the macromer and in presence of 2, 2' dimethoxy-2-phenylacetophenone photo-initiator dissolved in N-vinylpyrrolidone solvent.[382] The UV-curable PEG-PLA-acrylate gels were used as matrices for protein delivery.[383-385] van Dijk-Wolthuis *et al.* synthesized dextran derivatives by introducing hydrolytically sensitive groups to a dextran backbone. The hydrolysable groups are either a carbonate ester in Dex-HEMA or a combination of carbonate ester and lactic acid groups (Dex-lactate-HEMA).[386]

Dextran-based hydrogels were also developed via UV-induced polymerization technique by Zhang *et al.* Dextran was modified with acryloyl chloride[387] or allyl isocyanate.[388] The dextran derivatives were dissolved in DMF with a poly (D, L-lactic acid) diacrylate macromer (PDLLAM). These gels were investigated as matrices for the release of albumin. Its release was dependent on the gel composition and was expressed by a combination of diffusion and degradation of the matrix.[389]

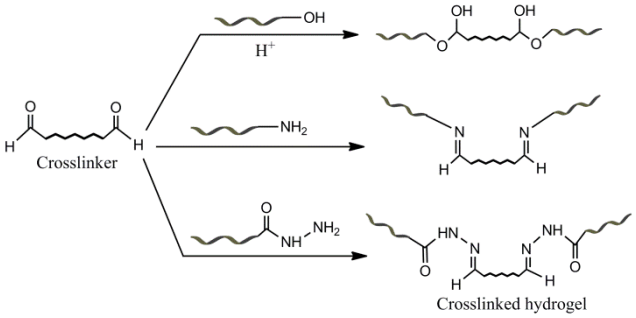
3.3.2.2. Crosslinking by chemical reaction of complementary groups

Water-soluble polymers containing -OH, -COOH, -NH groups are used for the formation of hydrogels. Polymers can be covalently connected with complementary groups, like an amine-carboxylic acid or an isocyanate OH/NH reaction, or by Schiff base formation.

3.3.2.2.1. Crosslinking with aldehydes

Polymers containing hydroxyl groups, like poly (vinyl alcohol) was crosslinked using glutaraldehyde.[390, 391] In drastic conditions like low pH, high temperature and in presence of quencher (methanol), they form hydrogel. Besides, amine-polymers were crosslinked with the similar reagent under mild conditions by forming Schiff (Scheme 4).

This was observed previously during the preparation of crosslinked proteins (e.g. albumin, [392] gelatin [393, 394] and amine containing polysaccharides [395]). Crosslinking of gelatin using polyaldehydes obtained by partial oxidation of dextran was developed for the application of wound treatment.[396]



Scheme 4 Mechanism of crosslinking by chemical reaction of complementary groups

The *in-vitro* and *in-vivo* biocompatibility of dextran dialdehyde crosslinked hydrogels was assessed.[397] Poly (aldehyde guluronate) was used to develop hydrogel by crosslinking with adipic acid dihydrazide.[398] Herein, daunomycin was covalently connected with the gel during hydrogel formation. Daunomycin was released from 2 days to 6 weeks due to hydrolysis of crosslinking linkage.[399] Aleuronic acid hydrogel films were developed with adipic dihydrazide followed by crosslinking with poly (ethylene glycol)-propiondialdehyde. These hydrogels were enzymatically degradable and used as matrices for the controlled release of antibacterial and anti-inflammatory drugs.[400]

3.3.2.2.2. Crosslinking by addition reactions

Water soluble polymers can be converted into hydrogels using functional crosslinking agents through addition reactions. Polysaccharides can be crosslinked with 1, 6-hexamethylenediisocyanate,[401] divinylsulfone,[402] or 1, 6 hexanedibromide.[403] The properties of these hydrogels can be modified by the changing the concentration of the polymer and the amount of crosslinking agent. Organic solvents are more preferable for this type of crosslinking reactions than that of water, because water can also react with the crosslinking agent. Besides as the crosslinking agents are very toxic, thus either the gels were extracted or crosslinkers were removed for biomedical applications.[402, 403]

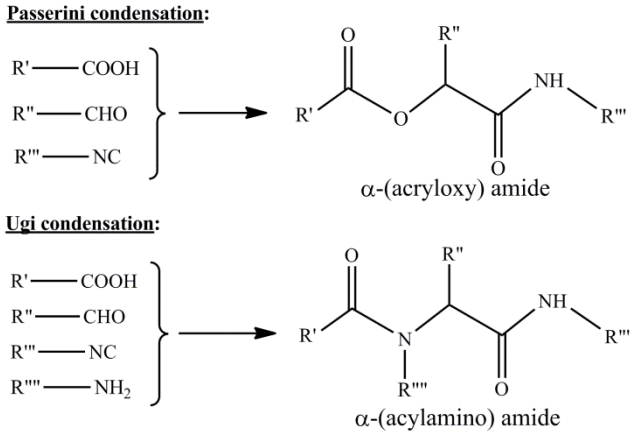
Recently, Hubbell and co-workers developed a degradable crosslinked hydrogel by reaction of PEG-dithiol with PEG-acrylate for delivery of albumin.[404] Gel formation occurred at room temperature and physiological pH. The hydrogels were degraded in physiological conditions because of the hydrolysis of

the ester bonds in the network within 5-25 days.[404]

3.3.2.2.3. Crosslinking by condensation reactions

Condensation reactions between hydroxyl or amines groups with carboxylic acids or derivatives are commonly formed polyesters or polyamides, which can also be utilized for the synthesis of hydrogels. Feijen and co-workers described the preparation of gelatin hydrogels using 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide / N-hydroxysuccinimide (EDC/NHS) mixtures. The hydrogels were synthesized for the release of antibacterial proteins.[405] Mooney *et al.* developed covalently crosslinked alginate and PEG-diamines using EDC. The mechanical property was modified by the amount of PEG-diamine and the molecular weight of PEG.[406]

Crescezi *et al.* synthesized polysaccharide hydrogels using the Passerini and Ugi condensation reactions (Scheme 5).[407, 408]



Scheme 5 Passerini and Ugi condensation reactions

In the Passerini condensation reaction, a carboxylic acid and an aldehyde or ketone are condensed with an isocyanide to produce α-(acryloxy) amide. On the contrary, in the Ugi condensation an amine is added to a carboxylic acid and an aldehyde or ketone mixture yielding α-(acylamino) amide. The reaction can be carried out in water at slightly acidic condition and at room temperature. Passerini condensation creates ester bonded crosslinked hydrogels, which are generally degrade at ambient temperature and pH 9.5. While synthesized gels from the Ugi condensation contain amide crosslinking were stable under the above conditions.

Yui *et al.* developed PEG-hydrogel crosslinked by a hydrolyzable polyrotaxane. This hydrogel has ester linkages, which was degraded by the hydrolysis of this bond. The hydrogel was developed to be used as scaffolds for the regeneration of soft tissue.[409]

3.3.2.3. Crosslinking by high energy irradiation

High energy irradiation, in particular gamma and electron beam are used to polymerize unsaturated compounds. The water-soluble polymers which have vinyl groups can form hydrogels in presence of high energy irradiations.[410] Hydrogels can also be synthesized by radiation-induced polymerization of acryloyl-proline methyl ester and a suitable crosslinker.[411] Besides, high energy irradiations also produce crosslinked water-soluble polymers without additional vinyl groups. Irradiation of aqueous solutions of polymers can also form radicals on the polymer chain by homolytic scission of C–H bonds. Moreover, radiolysis of water molecules generates hydroxyl radicals, which can react with polymer chains and form a macroradicals.[412] These macroradicals on different chains connect with each other to form crosslinked hydrogel by covalent bonding. Radiation induced hydrogel formation reaction is generally performed in inert atmosphere (of nitrogen or argon), because the generated macroradicals can react with oxygen in the propagation step. In presence of high energy irradiation, poly (vinyl alcohol),[413] poly (ethylene glycol)[414–416] and poly (acrylic acid)[417] were crosslinked to form hydrogels. Thermo sensitive hydrogel was synthesized and reported by irradiation of aqueous solutions of poly (methyl vinyl ether).[418, 419]

The advantage of hydrogel formation using radiation-induced crosslinking method is based on the fact that this process can be carried out in water medium under mild conditions (room temperature and physiological pH). Moreover, the utilization of crosslinkers (which are normally toxic) is also avoided. Biologically active materials are generally loaded after their preparation because the radicals formed during irradiation may damage the materials.

3.3.2.4. Crosslinking using enzymes

Sperinde *et al.* synthesized PEG-based hydrogels using an enzyme.[420] PEG was modified with glutaminyl groups (PEG-Q_a).[420] Then, trans-glutaminase was added to the aqueous solutions of PEG-Q and poly (lysine-co-phenylalanine) to form hydrogel.[420] The enzyme catalyzed the reaction between the γ-carboxamide group of the PEG-Q_a and the ε-amine group of lysine to produce an amide linkage between the polymers.[420] Westhaus *et al.* developed a triggered hydrogel containing mixture of Ca-loaded liposomes, fibrinogen and a Ca -dependent transglutaminase.[421] This mixture formed gel rapidly when heated to 378 °C. On heating, the liposomes were destabilized and Ca-ions were released in the surrounding fluid and simultaneously activate the enzyme.

3.4. Methods of curing

The curing process for developing the advanced polymer composites is based on thermal curing, in which the oven or autoclave is widely used. According to the curing mechanism, the curing technologies can be categorized as radiation curing and thermal curing.[422]

3.4.1. Radiation curing

Radiation curing is based on the bond breaking of radiation sensitive polymers in presence of high energy electromagnetic radiation such as accelerated electron beams[423-427], gamma ray and x-ray, [428, 429] ultraviolet curing. [430, 431] The radiation curing offers some distinctive technological advantages compared to thermal curing, including improved resin stability, handling flexibility, fast curing speed, energy efficiency and so on.

3.4.2. Thermal curing

Thermal curing is the most popular curing method for polymer composites. Recently, various thermal heating processes for thermal curing has been used, including infrared, laser, microwave, hot shoe, hot gas, flame, oven, induction, ultrasonic, resistance heating and etc. Based on heating mechanism, radiation curing can be classified as- radiation heating (infrared, laser and microwave),[432-437] convection and conduction heating (hot gas, flame, oven, and hot shoe),[438-439] induction heating,[440] ultrasonic heating,[440] resistance heating[441-443] and thermal

additive-based heating.[444-448]

4. Conventional Drug Delivery Systems (CDDS) and Controlled Drug Delivery Systems (CRDDS)

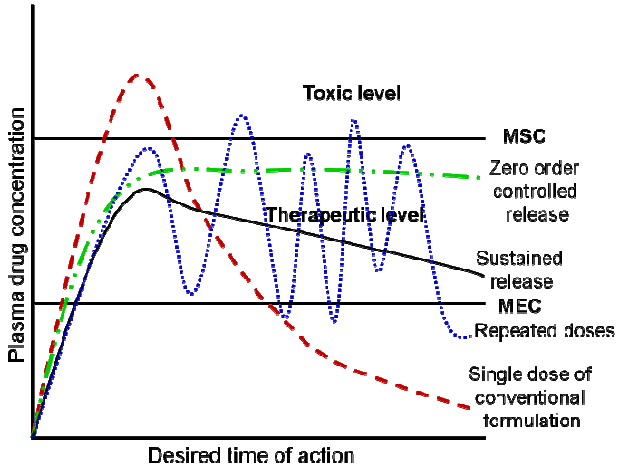


Fig. 9 A Schematic diagram for conventional and controlled drug delivery. (MSC = Maximum Safe Concentration, MEC = Minimum Effective Concentration).

4.1. Conventional Drug Delivery System

Drug delivery systems developed for oral delivery are generally through conventional delivery systems. These are the systems which are designed for immediate release of drugs for rapid absorption.[449, 450] From Fig. 9, it is obvious that the conventional dosage does not maintain the required drug concentration in plasma for an extended period of time. The short duration of action is because of the inability of conventional dosage form to control temporal delivery.

The conventional dosage forms such as capsule, tablets etc. have some drawbacks like drugs with short half-life need frequent administration, which increases the probability of missing the drug doses. This leads to poor patient compliance. The unavoidable fluctuations of the drug concentration in the blood may lead to under medication or over medication as the steady state concentration values fall or rise beyond the therapeutic range. The overdosing results the fluctuation of drug concentrations, which causes adverse effects particularly of a drug with minute therapeutic index. In order to overcome the shortcomings of conventional drug delivery systems, controlled drug delivery systems were designed that revolutionized the drug release system and offer several therapeutic benefits.[451]

4.2. Controlled Release Drug Delivery Systems (CRDDS):

A controlled drug delivery system is typically designed to deliver the drug at a controlled rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics. Besides, it localized the drug action by spatial placement to the targeted cell.[450]

CRDDS overcomes patient compliances, reduce or eliminate local side effects, minimize or eliminate systemic side effects, reduce drug accumulation with chronic dosing. It also improves efficiency in treatment, reduced the fluctuation in drug level, and enhanced the bioavailability of drugs. The average cost of treatment over an extended period of time may be less. It enhanced therapeutic benefits and reduced the side effects. The time required for health care was also reduced.[450]

4.2.1. Oral Controlled Drug Delivery Systems:

Oral controlled drug delivery systems provide constant oral delivery of drugs at expected and reproducible kinetics for a programmed period during the course of GI transport. It also delivered the drug to a specific targeted region in the GI tract for either a local or systemic action.[452]

Fig. 10 Common modes of drug delivery

4.2.1.1. Challenges of oral mode of drug delivery

Among the various modes of drug delivery (Fig. 10),[453-467] the oral mode is the most convenient one. However, still the current knowledge on mechanism of drug absorption, transit and microenvironment of human gastrointestinal tract is incomplete and poorly understood. The physiology of the gastrointestinal tract is beset with constraints like chemical degradation in the stomach, gastric emptying, intestinal motility, mucosal surface area, specific absorption sites and metabolic degradation during passage through mucosa and subsequently the liver. The animal models (e.g. beagle dog) used during the design phase of the oral controlled release products have different anatomical and physiological aspects (specially, the marked difference in transit time and pH in various parts of gastrointestinal tract) relative to human subjects.[452]

The most prominent among these challenges is the harsh environment of the stomach, where enzymatic degradation of many drugs like the polypeptides (e.g. insulin) takes place. Further, certain drugs like the salicylates can damage the stomach lining, leading to gastric ulcer. The only solution to these problems is to enclose the drug in a matrix that protects it during passage through the harsh environment of the stomach and should release the drug in the lower gastrointestinal tract. This gastric bypass can be achieved through the following strategies:

4.2.1.1.1. Delayed release formulation: In this case, the matrix

released the drug after a time delay. This time delay can be adjusted to cover the gastric region transit time. The matrix in this case essentially consists of crosslinked polymers. Here the extent of crosslinking controls the time delay.

4.2.1.1.2. pH triggered drug release: pH of stomach is acidic, while that of lower gastrointestinal tract is neutral/alkaline. This difference in pH can act as a trigger for drug release into the lower gastrointestinal tract (bypassing the gastric region). Evidently, this involves a drug delivery matrix which does not significantly release the drug in acidic pH (of stomach) and releases it at a much faster rate in the neutral/alkaline pH (of lower gastrointestinal tract).

4.2.1.1.3. Drug release from matrix degradable by colonic micro flora: The drug can be enclosed in a matrix that is not affected (and can protect the drug) by the stomach environment, but undergoes biodegradation by colonic micro flora. Obviously, the drug remains protected during the gastric transit and as the matrix gets degraded in the colonic region, the enclosed drug gets released for subsequent absorption.

4.2.1.2 Classification of Oral Controlled Drug Delivery Systems: The classification of oral controlled drug delivery systems is shown in Fig. 11.

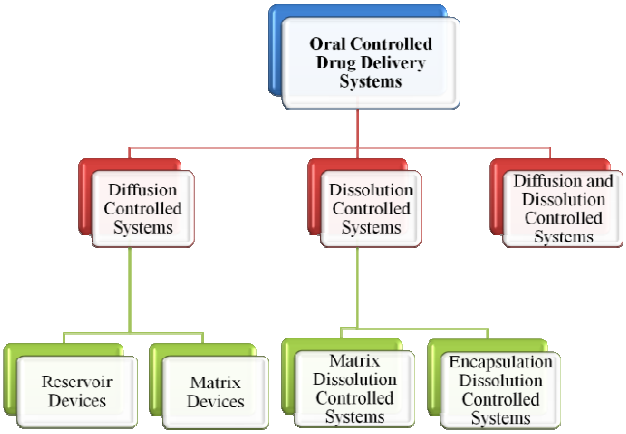


Fig. 11 Classification of oral controlled drug delivery systems

4.2.1.2.1. Diffusion Controlled Systems:

4.2.1.2.1.1. Reservoir Devices:

Reservoir systems are hollow devices in which an inner core of the drug is surrounded by a polymer membrane. In this device, the drug core is encapsulated in a polymeric membrane. Drug diffusion through the membrane is rate limiting and controls the overall drug release rate. A saturated concentration of drug inside the reservoir is essential to maintain a constant concentration gradient across the membrane. The drug transport mechanism through the membrane is usually a solution-diffusion mechanism. Drug transport occurs first by dissolution of the drug in the membrane on one side followed by diffusion through the membrane and desorption from the other side of the membrane.[452, 468] The drug release rate is dependent on the type of polymer. High molecular weight compounds are difficult to deliver through the device.

4.2.1.2.1.2. *Matrix Devices*: It consists of drug dispersed homogeneously on a matrix surface. A matrix (or monolith) device is easy to formulate and gives a higher initial release rate than a reservoir device and can be made to release at a nearly constant rate. High molecule weight compounds are delivered through the devices.

4.2.1.2.2. Dissolution controlled systems

Sustained release of the oral products empoly the dissolution as the rate limiting step. In this system, the drug particles can be coated with material of varying thickness or by dispersing them in a polymer matrix.

4.2.1.2.2.1. *Matrix Dissolution Controlled System*: It is also called as monoliths. The drug is dispersed in media such as bees wax, carnauba wax, castor oil and so on, which controls drug dissolution by controlling the penetration of dissolution fluid into matrix. This can be controlled by altering the porosity of the tablet matrix.

4.2.1.2.2.2. *Encapsulation Dissolution Controlled System*: This method involves the coating of particles or granules of drug with slow dissolving materials. Particles, seeds or granules can be coated by microencapsulation. There are several ways for coating. A common method is to coat the seeds with the drug followed by a coat of slow dissolving materials such as carbohydrate sugar, cellulose, polyethylene glycol, polymeric material and wax.

4.2.1.2.3. Diffusion and Dissolution Controlled System

The main feature of this system is that the drug is enclosed with a partially soluble membrane. In this system, the drugs were homogenously dispersed in a matrix. However, the drug is released from these system is either through swelling controlled mechanism or by hydrolysis or enzymatic attack. The drug release from this type of matrix follows zero order kinetics.

5. Polymeric hydrogels as matrices for drug delivery

A smart polymeric drug delivery system must overcome all the restrictions and drawbacks of conventional therapeutic agents and should hold the characteristic properties of biodegradability, biocompatibility, as well as non-toxicity.[469] Recent advancements in polymer science have led to the development of biopolymers based various hydrogels for biomedical applications. Biopolymers are generally of two types, natural and synthetic polymers. They have a strong backbone as an efficient factor of drug delivery. For example, for colonic drug delivery systems, polymers should efficiently release the drug in the colon and should not release at the stomach or small intestine due to degradation. For instance, guar gum, HPMC, dextran etc. have proven to be best suited for colonic delivery as its enzymatic degradation occurs via the hydrolytic cleavage of glycosidic bonds.[470] Consequently the individual properties of polymers are vital for their use for specific organs. The synthetic biodegradable polymers have showed an immense role for their use in drug delivery devices.

5.1. Application of various hydrogels in controlled drug delivery

Controlled drug delivery systems considered as advanced materials which improve the fundamental area in biomedical field for human health care. These delivery systems offer various advantages over conventional drug delivery systems. These include improved efficacy, reduced toxicity, improved patient compliance and convenience along with the release of the drug at

a specific rate with spatial manner within the body to accomplish the specific therapeutic requirements. Hydrogels, among the different controlled-release systems developed so far, have particular properties such as capability to mimic many physical properties of tissues, biocompatibility, potential responsiveness to small environmental changes (e.g., temperature, pH, and ion concentration), and their ability to store functional chemicals and nanoparticles. These characteristics make them to be potentially considered as one of the ideal future controlled release systems.

The hydrogel-based drug delivery systems are generally of two types: (i) time-controlled systems and (ii) stimuli-induced release systems.[471, 472] The stimuli-induced release systems are also referred to as 'stimuli-sensitive', 'stimuli-responsive', 'environment-sensitive', 'environment-responsive', or 'responsive' hydrogel systems. Responsive hydrogel systems are designed to deliver the drugs in response to a variable condition so that it can fulfil the physiological requirements at the accurate time and suitable place.[473] There are several reports on hydrogels including modified biopolymeric hydrogels based on agar, chitosan, dextran, carrageenan, gelatin, gellan gum, konjac glucomanan, locust bean gum, cyclodextrin, guar gum, stereculis gum etc. for drug delivery applications.[113-142]

5.2. Release mechanism from hydrogel matrices

The drug release mechanism from hydrogels is mainly classified as: (i) diffusion-controlled, (ii) swelling-controlled, and (iii) chemically-controlled. According to Fick's first law of diffusion, the diffusion-controlled release is mostly applicable mechanism to explain the drug release from hydrogels.[474] The drug diffusion from the hydrogel matrix is mainly dependent on the mesh sizes within the matrix of the gel,[475] which is influenced by numerous factors such as the degree of crosslinking, chemical structure of the monomers as well as intensity of the external stimuli. Besides, mechanical strength, degradability, diffusivity, and other physical properties of a hydrogel network are also dependent on its mesh size.[474-476] Typical mesh sizes reported for biomedical hydrogels are in the range of 5-100 nm (in their swollen state),[476, 477] which are much larger than most small-molecule drugs. Therefore, diffusion of these drugs is not significantly retarded in swollen state. For the swelling-controlled mechanism, diffusion of the drug is significantly faster than hydrogel swelling. Here swelling is considered to be the controlling factor for the release behavior.[478, 479]

Besides, chemically-controlled release is determined by chemical reactions, which took place within the hydrogel matrix. The reactions include polymeric chain cleavage through hydrolytic or enzymatic degradation, or reversible/irreversible reactions. This is occurred between the polymer network and the released drug. In addition, under certain circumstances, the surface or bulk erosion of hydrogels or the binding equilibrium among the drug binding moieties within the hydrogels are two different mechanisms which also controlled the rate of drug release.[474, 480]

6. Dextrin, a potential biopolymer

Although developments of various biopolymeric hydrogels based on agar, chitosan, dextran, carrageenan, gelatin, gellan gum, konjac glucomanan, locust bean gum, guar gum, stereculis gum etc. have already been developed and reported for biomedical applications by different research groups,[113-142] but the development of modified dextrin based chemically crosslinked hydrogels as oral administration for controlled drug release applications were reported for the first time by our group.[4-6] Dextrin is low molecular weight saccharine polymer, produced by acid and/or enzymatic partial hydrolysis of starch or glycogen. It consists of α-(1→ 4)-D-glucose units of amylose and the α-(1→4) and α-(1→4, 6)-D-glucose units of amylopectin with lower polymerization.[481] They contain only less than 5% α-(1→ 6) links, therefore show minimal branching (Fig. 12).[482] It has same general formula as of starch, but smaller and less complex. The degree of hydrolysis is expressed in "dextrose equivalent" (DE) which is a measure of the total reducing power.[483, 484] Dextrin with the same DE can exhibit different characteristics in hygroscopicity, fermentability, viscosity, sweetness, stability, gelation, solubility, and bioavailability, which may be because of the different structural features.[483]

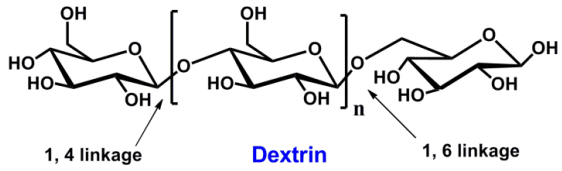


Fig. 12 Chemical structure of dextrin

Dextrin is an inexpensive raw material, generally regarded as safe (GRAS).[485] It is a widely used material with a variety of applications such as adhesives, foods, textiles and cosmetics.[481] In biomedical applications, dextrin is still relatively unfamiliar than other polysaccharides. It is biocompatible and non-immunogenic material, degradable *in-vivo* by α-amylases and its molecular weight ensures renal elimination avoiding tissue accumulation because of the repeated administration.[486, 487] In spite of its limited number of recent biomedical applications,[488-490] the numerous advantages of dextrin ensure its use in the biomedical field. Thus the solubility in water, presence of hydroxyl groups, biocompatibility and degradability give immense prospective to dextrin for the design and fabrication of hydrogels. The proven clinical tolerability and proficient absorption due to degradation by amylases[491, 492] also provide sufficient worth to dextrin in biomedical applications.

The surface morphology of dextrin was investigated using SEM and FESEM analyses. After complete drying, dextrin was sputter-coated with gold, and the surface morphologies were analyzed by SEM (Model: S-3400N, HITACHI, Japan) and FESEM (Supra 55, Zeiss, Germany) analyses. From SEM (Fig. 13a) and FESEM (Fig. 13b) analyses, it is obvious that dextrin has fine oval shaped granular morphology.

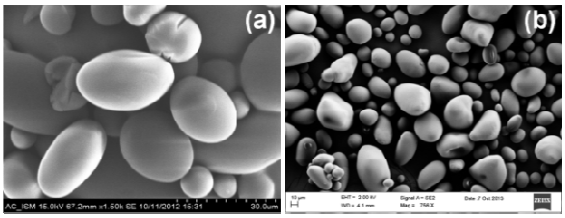


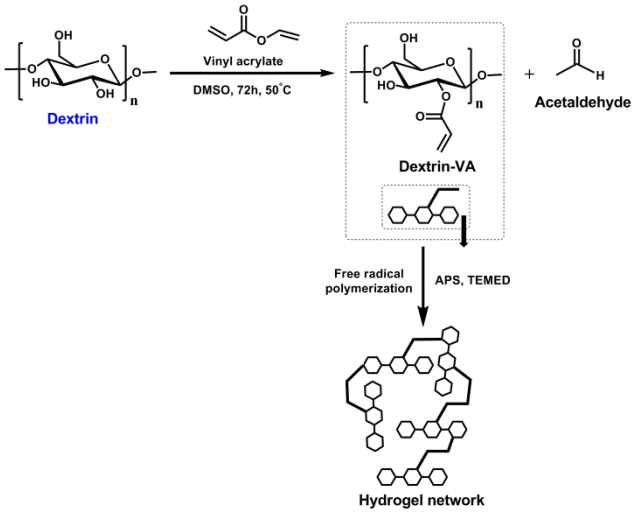
Fig. 13 Images of dextrin (a) SEM (Magnification 1.50 k, scale bar = 30 μm) and (b) FESEM(Magnification 756 X, scale bar = 10 μm).

Hreczuk-Hirst *et al*. and Molinos *et al.* described the ^{1}H-NMR spectrum of dextrin in D_2O. It was observed that the peaks between δ 4.0 and δ 3.4 ppm are assigned to protons at positions 2, 3, 4, 5 and 6, whereas the peak at δ 5.4 ppm is attributed to the glucose anomeric proton. The spectrum also showed a small peak at δ 5.3 ppm corresponding to the anomeric proton corresponding to α-1, 6 linkages (< 5% of the total dextrin).[486, 493]

6.1. Dextrin based various hydrogels

Abo-Shosha *et al.* reported polyacrylic acid/dextrin (PAA/D) adduct which was prepared by free radical polymerization of highly concentrated, partially neutralized acrylic acid using $Na_2S_2O_8/Na_2S_2O_3$ redox system. [494] Rheological properties of 7% aqueous solutions of these adduct, including Na-alginate (Alg) showed non-Newtonian, shear-thinning, thixotropic behavior. Within the range of shear rate studied, the apparent viscosities of adducts were also measured.[494]

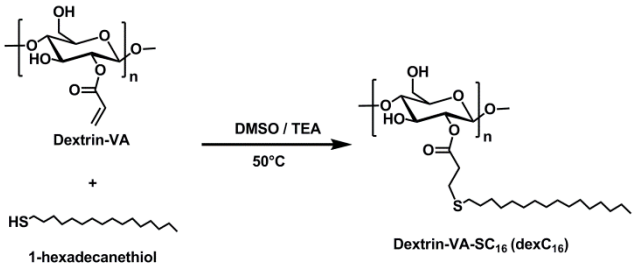
There are also few reports on dextrin-adducts for biomedical applications. For example, Carvalho *et al.* reported on the synthesis of hydrogels obtained by free radical polymerization of dextrin-VA (Scheme 6), with different degrees of substitution and monomer concentration in water. [495] These hydrogels were developed as scaffold materials for bioactive molecule and cell delivery, tissue engineering and a variety of other biomedical applications.[495]



Scheme 6 Dextrin-VA synthesis and formation of the hydrogel networks (Reproduced with permission from Ref. 495, Copyright 2007, Elsevier Ltd.)

The hydrogels were characterized using the solid state ^{13}C CP/MAS nuclear magnetic resonance (NMR) spectral analysis. The NMR spectrum of dextrin-VA hydrogel (containing cross-linked acrylate groups) demonstrated that the carbonyl resonance was broadened and shifted from 167 ppm in dextrin-VA to 175 ppm in the hydrogel.[495] The broadening reveals the heterogeneity of crosslinked VA environments and the low field shift results from the chemical changes taking place around the carbonyl groups upon the crosslinking process.[495]

Goncalves *et al.* used the dextrin derivatives (Dextrin-VA) for the preparation of self-assembled hydrogel nanoparticles (Dextrin-VA-SC_{16}), dexC_{16} by controlling the degree of substitution with hexadecanethiol (Scheme 7).[496] DexC16 self-aggregates in water, stable (over 2 months) nanoparticles with a narrow size distribution.[496] A diameter of about 20 nm was determined by DLS and AFM. The cmc value, around 0.001 g/dL, was determined using pyrene as a fluorescent probe and confirmed by DLS.[496]



Scheme 7 Schematic representation of the synthesis of DexC_{16}. (Reproduced with permission from Ref. 496, Copyright 2007, American Chemical Society.)

Again, the influence of the degree of substitution on the self-assembly process of a hydrophobized dextrin polymer, dex$_{C16}$ was evaluated by Goncalves *et al.*[497] Size distribution was also evaluated by dynamic light scattering and transmission electron microscopy which showed that the particles were spherical having a diameter of about 20 nm. The size of self assembled hydrogel nanoparticles was assessed as a function of DS_{C16} also. Goncalves *et al.* pointed out that the nanoparticles size was only slightly influenced by DS_{C16} or polymer concentration. The nanoparticles were stable in the presence of urea and at different pH and ionic strength.[497]

A novel superabsorbent nanocomposite was synthesized through intercalation polymerization of partially neutralized acrylic acid, gelatinized dextrin, and an organic-montmorillonite powder using *N*, *N*′-methylene bisacrylamide as a crosslinker, Span-60 as a dispersant, and ammonium persulfate together with sodium sulphite as a type of mixed redox initiator.[498] The blood compatibility of the composite was primarily measured.[498]

Dextrin-vinylacrylate hydrogels were prepared by radical polymerization of aqueous solutions of vinylacrylate (VA)-derivatized dextrin for the controlled release of bioactive molecules.[499]

The degree of acrylate substitution (DS) was determined by proton nuclear resonance spectroscopy (^{1}H NMR) in D_2O. They also prepared dextrin-VA/amyloglucosidase (AMG) hydrogels using different amounts of enzyme solution (diluted to 10 U/mL in phosphate buffer) to the dextrin-VA solution.[499] SEM analysis of three dimensional hydrogel slabs revealed a highly porous structure.[499] Hydrogels with lower DS (10% and 20%) exhibit irregular pores, in the size range 20–70 μm.[499] It was observed that DS alter the pore morphology by up to DS 70%, thereby obtained a material with much lower porosity. For the DS 70%, a smooth surface was observed by SEM and large pores, and consequently interconnectivity, were no longer observed.[499]

The protein (bovine serum albumin) diffusion coefficients on the hydrogels were analysed using the lag-time analysis.[499] The release nature revealed that it depends on the diffusivity on the crosslinking density. The release of BSA (Fig. 14) from dextrin-VA hydrogels, in the presence of amyloglucosidase was mainly dependent on the diffusion and on the degradation kinetics. The protein release can be tailored from days to months by varying

the degree of substitution.[499]

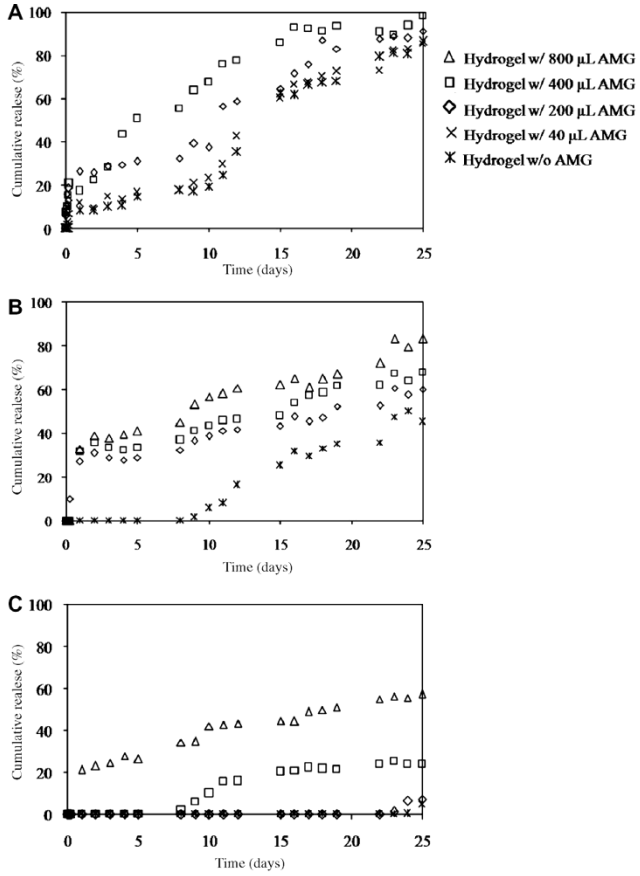
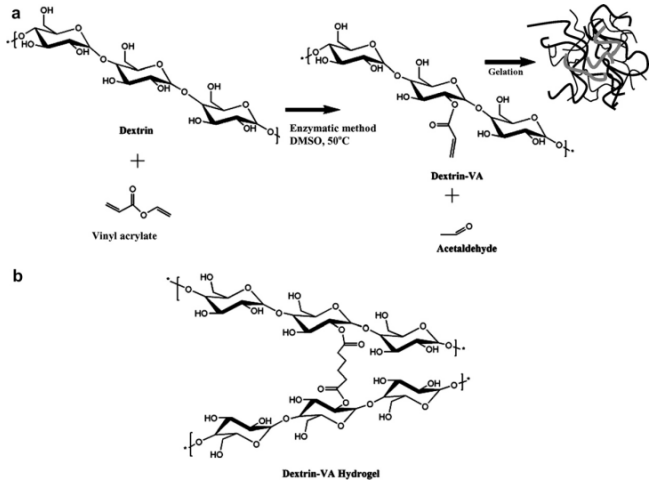


Fig. 14 Cumulative release of BSA (2 g/L) from dextrin-VA hydrogels, DS 20 (A), 40 (B) and 70 (C). The data points are averages of at least three repeats that deviated less than 5% of the total amount of protein in the hydrogels. (Reproduced with permission from Ref. 499, Copyright 2008, Elsevier)

Garcia *et al*. studied the structural changes of dextrin owing to grafting of vinyl acrylate (VA) (Scheme 8).[500]



Scheme 8 Schematic representation of: (a) synthesis of dextrin-VA and hydrogel networks and (b) hydrogel cross-links. (Reproduced with permission from Ref. 500, Copyright 2008, Elsevier)

The degrees of VA substitution (DS) and polymerization (DP) were quantified up to 40%VA by FTIR intensity measurements and partial least squares (PLS)/FTIR, the latter being a faster and less error-prone method. In addition, the solid state ^{13}C cross polarization and magic angle spinning (CP/MAS) showed high carbon content for hydrogels and improved PLS/NMR models were achieved for DS and DP determination.[500] Besides, a correlation FTIR/NMR study suggested that ring conformations are significantly affected in hydrogels, compared to neat dextrin.[500]

Wannachaiyasit *et al.* synthesized dextrin–zidovudine (AZT) conjugate designed as a sustained release prodrug of AZT for parenteral administration.[501] The release *in-vitro* of free AZT and succinoylated AZT was explored in buffer solutions at pH 5.5 and 7.4 and in human plasma. AZT and succinoylated AZT release from the conjugate was 1.4% (pH 5.5), 41.7% (pH 7.4) and 78.4% in human plasma after 24 h as reported by Wannachaiyasit *et al.*[501] Release was complete in human plasma after 48 h. A pharmacokinetic study in rats following intravenous administration of the conjugate showed prolonged plasma levels of AZT compared to free AZT.[501] This study imply the potential of the dextrin–AZT conjugate as a new intravenous preparation of AZT.[501]

A new class of degradable dextrin-based hydrogels (dextrin-HEMA) was developed by Carvalho *et al.*[502] The hydroxyethyl methacrylate ester (HEMA) hydroxyl groups were activated with *N*, *N'*-carbonyldiimidazole (CDI), followed by coupling between dextrin and the produced derivatized material which was polymerized in aqueous solution to formed hydrogels.[502] A comparative study of the stability of the dextrin-HEMA hydrogels and dextrin-vinyl acrylate has been performed and it was observed that only the first one is effectively hydrolyzed under physiological conditions. Rheology study suggested that physical structuring is less pronounced when dextrin is modified with methacrylate side groups.[502] The biocompatibility results revealed that the dextrin hydrogels have negligible cell toxicity, irrespective of the hydrogel type (HEMA and VA).[502] Assembled the biocompatibility and the ability to tailor the release profiles, it was concluded that hydrogel would be a promising candidate for controlled release application.[502]

Treetharnmathurot *et al.* reported a new biodegradable, polymer–protein conjugates of dextrin and trypsin with improved stability properties.[503] The dextrin II–trypsin conjugate was more stable than the other conjugates and native trypsin at all temperatures between 30 and 70°C, and also exhibited improved thermal stability in the autolysis assays at 40 °C.[503] The dextrin II–trypsin conjugate underlines the potential of higher molecular weight dextrin II for protein conjugation in the context of protein masking with subsequent regeneration of activity (PUMPT).[503]

Silva *et al.* depicted a comprehensive structural characterization of several commercial dextrins, which were used to produce oxidized dextrin hydrogels reticulated with adipic acid dihydrazide.[481] The cytotoxicity of the crosslinking agent was evaluated and compared with that of glutaraldehyde.[481]

The development of hydrogel networks based on agarose (Aga) and chitosan using oxidized dextrins as low cytotoxicity crosslinking agents was described by Gómez-Mascaraque *et al.*[504] Spectroscopic, thermal and swelling analyses revealed good compatibility of the components of the hydrogels, with an absence of phase separation of the two polysaccharides at

Aga/Ch proportions of 50:50 and 25:75.[504] Viscoelastic analysis illustrated a constant storage modulus independent of frequency, typical of gels, for all materials, and indicated that their stiffness was strongly influenced by the degree of oxidation of the crosslinker. The overall results showed that by adjusting the Aga content and varying the degree of oxidation of the crosslinker it was possible to obtain IPN polymer networks of physical gels of Aga and chemical gels of crosslinked Ch, or that semi-IPN networks formed between the crosslinked Ch and Aga polysaccharides (Fig. 15).

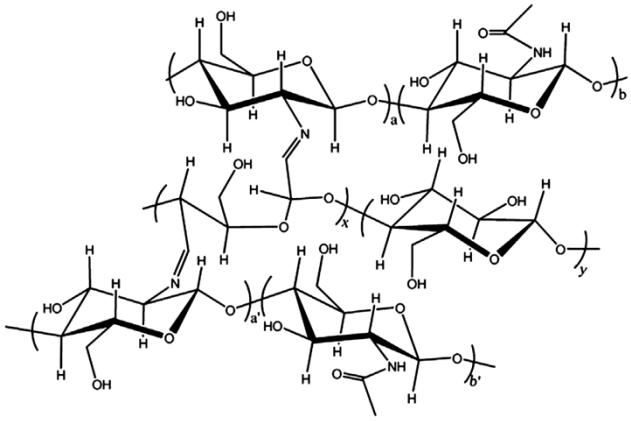


Fig. 15 The chemical structure of chitosan network obtained by crosslinking with oxidised Dextrin. (Reproduced with permission from Ref. 504, Copyright 2013, Elsevier Ltd.)

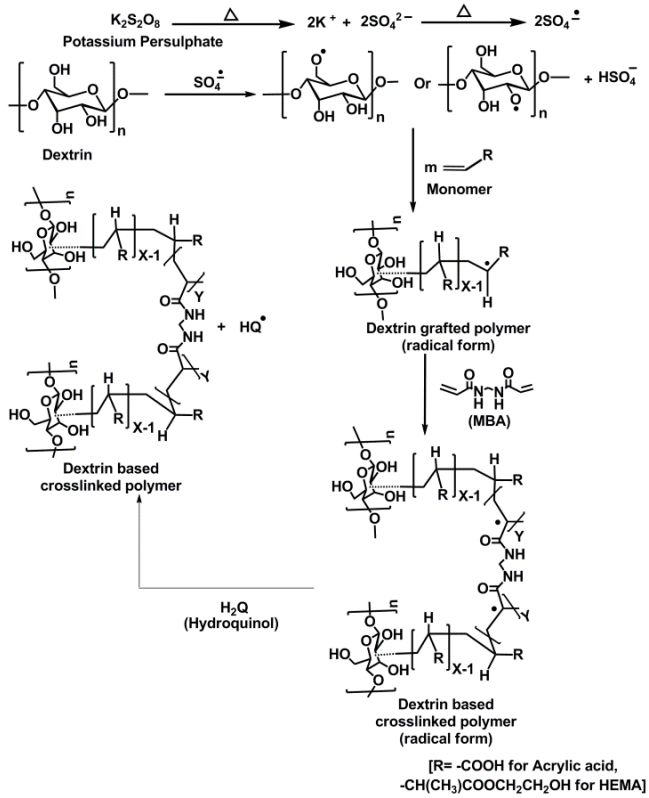
Finally, biological assays explained that cell adhesion and proliferation was dependent on an array of properties of the hydrogels that should be analysed in order to choose a particular material for tissue engineering purposes.[504]

A novel biodegradable, non-cytotoxic, chemically crosslinked, porous hydrogel was developed in authors' laboratory by grafting poly (hydroxyethyl methacrylate) in presence of *N, N′*-methylene bisacrylamide (MBA) crosslinker through free radical polymerization technique, which finds potential application as matrix for controlled release of colonic drug, antibiotic.[4] We also propose that this polymerization reaction is Michael-type addition (Scheme 9). We synthesized dextrin based hydrogels by two techniques: (i) addition of *N, N′*-methylene bisacrylamide as crosslinker to radical form of dextrin grafted polymer (Reaction-I, Scheme 9), and (ii) addition of crosslinker on radical form of dextrin, after that monomer was added (Reaction-II, Scheme 10). The two different types of synthetic techniques significantly affect the gel strength and accordingly release pattern was also changed.

We explained in details on the synthesis and characterization of a novel hydrogel based on dextrin and poly(HEMA) and its application as matrix for delivery of colonic drug as well as antibiotic (for colonic drug -ornidazole and for antibiotic -ciprofloxacin).[4, 6] We also proposed that the hydrogel was developed through the schematic steps as shown in Reaction - I.[4] After modification, the physical and chemical properties were also investigated in details.

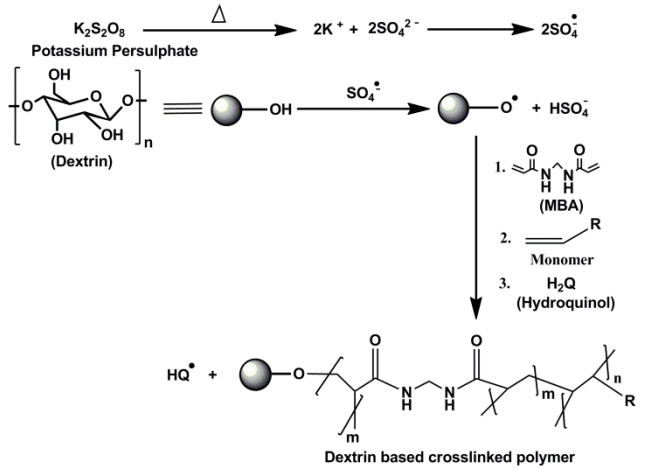
SEM analyses showed that the granular appearance of dextrin was distorted after crosslinking and the morphology of the hydrogel became porous (Fig. 16).[4, 6] The incorporation of poly (HEMA) and crosslinker onto dextrin backbone affects the crosslinking ratio as well as the structure of the hydrogel.

Reaction-I:



Scheme 9 Probable mechanism of the formation of dextrin based crosslinked hydrogel (Reaction-I)

Reaction-II:



Scheme 10 Probable mechanism of the formation of dextrin based crosslinked hydrogel (Reaction-II)

This leads to a change in microstructure of dextrin/pHEMA hydrogel. Due to several interconnected pores in the hydrogel, water molecules can easily spread and hence affect the rate of swelling. It was also expected that these pores are the regions of water permeation and interaction sites of external stimuli like pH, temperature, ionic strength etc.[4]

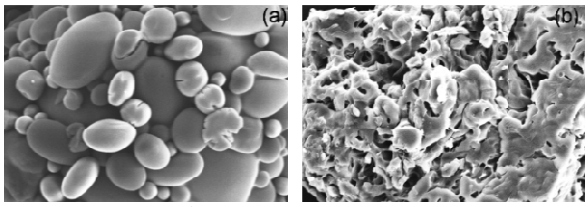


Fig. 16 SEM images of (a) dextrin and (b) Dxt/p(HEMA) 5 hydrogel. (Reproduced from Ref. 4, Copyright 2013, Royal Society of Chemistry)

The E-SEM image of c-Dxt/pHEMA 5 in swollen state (Fig.17), indicates that because of its excellent swelling characteristics, the higher amount of water was retained in the hydrogel structure, which results larger pore size after lyophilization.[6]

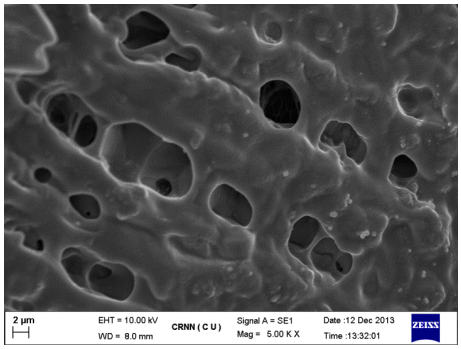


Fig. 17 E-SEM image of c-Dxt/pHEMA hydrogel (Reproduced with permission from Ref. 6, Copyright 2014, Elsevier.)

The stimuli responsive behavior of Dxt/p(HEMA) hydrogel was investigated by measuring the equilibrium swelling ratio at pH 1.2, 6.8 and 7.4 buffer solutions at 37 °C. It was observed that dextrin showed a declining trend of swelling with time which indicates its solubility in aqueous solution. The hydrogel attained its equilibrium swelling at ~ 5 h (Fig. 18).[4] It was also obvious that c-Dxt/pHEMA demonstrate a faster swelling rate. This observation can be explained on the basis of the presence of poly (HEMA) and MBA in the hydrogel structure, which enhanced the hydrophilicity of the network and facilitates the hydration as well as expansion of the network. In addition to that, the porous morphology of the hydrogel also enhanced the diffusion of water into the hydrogel network.[4] As obvious from Fig. 18 that the hydrogel showed pH dependent swelling behaviour. This may be because at acidic pH (i.e. pH 1.2), the hydrophilic groups present in the hydrogel network got protonated which hindered the formation of H-bonding with water. However, at pH 7.4, all the hydrophilic groups remain free and thus able to form more H-bonding with the media. This results higher swelling.[4]

The cell viability study suggested that the hydrogel is non-cytotoxic against HaCaT cell lines.[4]

The c-Dxt/pHEMA hydrogel was also used as an oral route administration for ciprofloxacin hydrochloride delivery.[6] Biodegradation study showed that the hydrogel is biodegradable in nature. FTIR, XRD along with solid state UV-VIS-NIR analyses explain the good compatibility between the drug and the hydrogel matrix.[6] The viscoelastic behavior of c-Dxt/p(HEMA) hydrogel was investigated through measurement of rheological parameters. The non-Newtonian shear thinning behavior of hydrogel was observed.[6] The shear thinning behavior of the hydrogel was attributed to the breakdown of the crosslinked network of the p(HEMA) crosslinked to dextrin.[6]

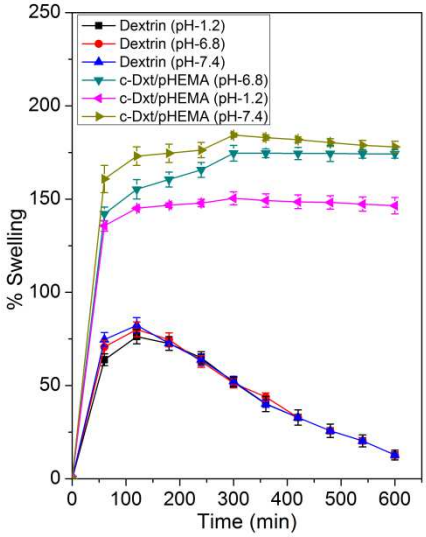


Fig. 18 Swelling characteristic of dextrin and various hydrogels at pH 1.2 and pH 7.4 (results represented are mean ± SD, n = 3). (Reproduced from Ref. 4, Copyright 2013, Royal Society of Chemistry)

Further, the gel strength of c-Dxt/p(HEMA) was studied via amplitude sweep oscillatory measurement. It was observed that both G' and G" are independent of frequency, which is the characteristics feature of gel structure.[505] At all shear stress, G' was higher than G" (G'/G" = ~ 2.41), suggesting elastic nature of the hydrogel. Besides, it was also seen that beyond critical stress value (σ = ~1000 Pa), both G' and G" were declined to a lower value (Fig. 19a), which suggests the flow behavior of the hydrogel.[505] c-Dxt/p(HEMA) also showed temperature dependent swelling and deswelling behaviour which suggest the reversible nature of the gel. Moreover the swelling and deswelling kinetics were also studied using Voigt model.[4, 6]

Thus the distinct features, such as soft tissue like behaviour, non-cytoxicity, biodegradability, pH and temperature dependent swelling characteristics make c-Dxt/p(HEMA) hydrogel an ideal candidate for sustained drug release applications.

Our group also developed a new class of biodegradable crosslinked hydrogel, consisting of hydrophobic poly (lactic acid) (PLA) and hydrophilic dextrin (c-Dxt/pLA) in presence of crosslinker *N, N'*-methylene bisacrylamide (MBA).[5] The reaction was carried out via free radical polymerization technique as proposed in Reaction-II (Scheme 10).

By variation of reaction parameters, a series of hydrogels were prepared and the optimized grade was selected on the basis of higher % crosslinking efficiency and lower % equilibrium swelling.[5]

The rheological features of c-Dxt/pLA 3 hydrogel (1 wt%) was studied in PBS media (pH 7.4) after reaching the equilibrium swelling (6 h), using Bohlin Gemini-2 rheometer (Malvern, UK). The storage modulus (G') and loss modulus (G") of c-Dxt/pLA 3 were evaluated to measure the gel strength, at a constant frequency of 0.5 Hz and different shear stress ranging from 0 to 400 Pa using parallel plate geometry, with a fixed tool gap of 500 µm. From Fig. 19b, it has been observed that at all shear stress G′ was observed to be higher than G″ (G′/G″= ~ 1.21) which

suggests the elastic nature of the hydrogel. It has also been observed that beyond critical stress value, both G′ and G″ declined sharply to a lower value, which suggests the flow behaviour of the hydrogel.[505] This is also known as yield stress (σ) of the hydrogel. It has been found that the yield stress of c-Dxt/pLA hydrogel is ~ 250 Pa (Fig.19b). Higher is the yield stress value stronger will be the gel. However, the gel strength of c-Dxt/pLA is lower compared to c-Dxt/pHEMA (Fig.19)

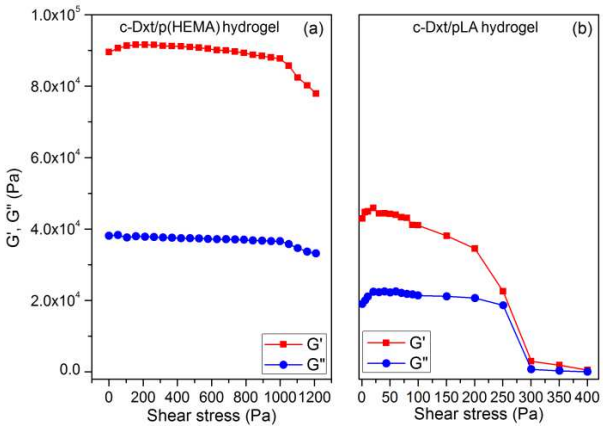


Fig. 19 variation of G' and G" vs. shear stress of (a) c-Dxt/p(HEMA) hydrogel, and (b) c-Dxt/pLA hydrogel

The hydrogel also showed pH responsive swelling characteristics.[5] The acute oral toxicity study of dextrin and pLA based hydrogel was executed using five nulliporous and nonpregnant 5 weeks old female mice (Swiss albino strain).[5] It was observed that there was no mortality found within the study period of 14 days after dosing, confirming the non-toxic nature of the hydrogel.[5]

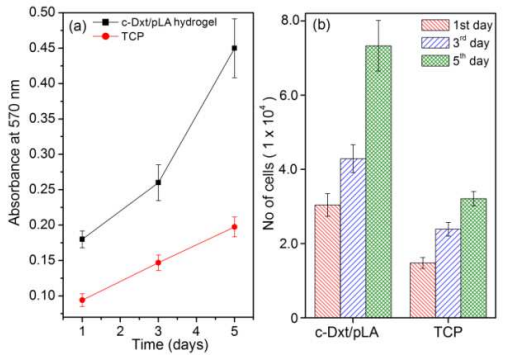


Fig. 20 Cell viability study of c-Dxt/pLA hydrogel using HaCaT cell line.

Cell viability and proliferation study of c-Dxt/pLA hydrogel was performed using HaCaT cell line and MTT assay at 37 °C. Briefly, the powdered samples were made into pellets for assessing cell viability and proliferation. The pellets were sterilized using 70% alcohol and UV followed by washing with sterilized PBS, pH 7.4. HaCaT cell lines (NCCS, Pune) were cultured in 5% CO_2 atmosphere at 37 °C (Heracell 150i, Thermo, USA) in DMEM (Himedia) supplemented with 10% foetal bovine serum, 1% antibiotics, 3.7% sodium bicarbonate, and 1% L-glutamine (all Himedia). The cells were harvested from tissue culture flasks using 0.25% trypsin in 1 mM EDTA (Himedia) and plated onto pellets. To seed similar cell density, cell suspension was counted using countess (Invitrogen, USA). 10^4 cells were plated on both samples and wells of tissue culture plate (TCP). For cell proliferation MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide] assay of the adherent HaCaT cells on the pellets was examined after 1, 3 and 5 days. After predetermined time intervals, culture medium was discarded, washed thoroughly with PBS and incubated with 5 mg/mL MTT solution (Sigma, US) at 37 °C for 4 h. The insoluble formazan crystals formed were allowed to dissolve in dimethyl sulfoxide and absorbance was read in 96-well plates at 570 nm on a microplate reader (RMS Instruments, India).

Cell attachment, viability and proliferation indicate cellular compatibility towards a material. MMT reduction assay was used to determine cell viability after 1, 3, 5 days (Fig. 20). The c-Dxt/pLA 3 hydrogel as well as tissue culture plate (TCP) maintained viable population of HaCaT cells throughout the study period (Fig. 20a). However, compared to 1st day of cell seeding, the hydrogel showed significantly higher viability than TCP. Thus, the synthesized material is not toxic for HaCaT cells. The absorbance values were further converted to rate of cell proliferation using a standard curve. After 5 days, the no. of cells on c-Dxt/pLA 3 hydrogel and TCP were $7.33 \pm 0.68 \times 10^4$ and $3.21 \pm 0.19 \times 10^4$, respectively (Fig. 20b). This may be because hydrogel being hydrophilic in nature, swells to form three dimensional structure that provide more surface area for cells to attach and proliferate whereas cell proliferation is restricted on two dimensional surface like TCP.[4] Being biodegradable and non-cytotoxic as well as the stimuli responsive behavior of c-Dxt/pLA, this hydrogel was also found to be an excellent matrix for controlled drug release.

6.2. Drug delivery study using synthesized crosslinked hydrogel based on modified dextrin

We have used the synthesized crosslinked hydrogels as matrices for oral route administrations in controlled drug delivery. We investigated the *in-vitro* drug delivery study through tablet formulations using two different types of drugs: ornidazole-colon specific drug and ciprofloxacin- antibiotic. The interactions between the drugs and the hydrogels (Fig. 21 and Fig. 22) were confirmed through FTIR analysis, XRD analysis and UV-VIS-NIR studies. Excellent compatibity was observed between the drugs and the hydrogels synthesised in authors' laboratory.[4-6] The drug release mechanism and release kinetics were determined using various mathematical models.[4-6] The diffusion coefficients values of drugs from tablet formulation were determined by Fick's law. Finally, we also investigated the drug stability study upto 3 months.[4-6]

6.2.1. Drug loading method

Some most commonly used techniques for drug loading are:

6.2.1.1 Solvent swelling technique: The matrix can be left to swell in the highly concentrated drug solution. Afterwards, the solvent was removed by suitable physical treatment (e.g. evaporation).[506]

6.2.1.2 Supercritical fluid technique: Supercritical fluids are dense as liquids but have viscosity as low as that of gas. In this technique, a solution of the drug in a supercritical fluid easily and efficiently swells the matrix. The solvent (supercritical fluid) was then easily removed by decreasing the pressure (leaving the drug behind, in the matrix).[507, 508]

6.2.1.3 Direct compression method: In this method, the drug is grounded and mixed with the matrix and a binder in a definite proportion, in presence of a volatile solvent like ethanol. Afterwards, they were compressed into tablets under high pressure (2-3 tons/cm^2).[509-511]

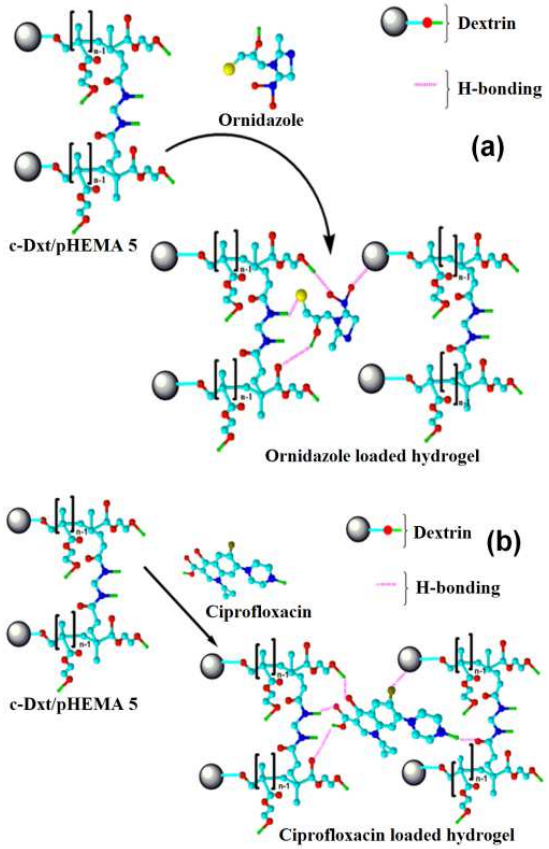


Fig. 21 Probable interaction between c-Dxt/p(HEMA) and (a) ornidazole, (b) ciprofloxacin. (Reproduced from Ref. 4, Copyright 2013, Royal Society of Chemistry and Reproduced with permission from ref. 6, copyright 2014, Elsevier)

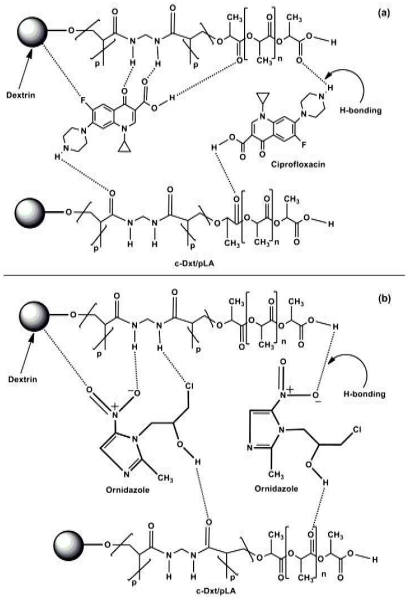


Fig. 22 Probable interaction between c-Dxt/pLA and (a) ciprofloxacin and (b) ornidazole. (Reproduced with permission from Ref. 5, Copyright 2013, Wiley Periodicals, Inc.)

6.2.2. *In-vitro* drug release study

Evaluation of amount of drug release from solid oral dosage formulations (e.g. tablets) is an established practice in controlled drug release study. The rationale for conducting drug dissolution tests is based on the fact that the drug should be released via gastrointestinal tract. Being a critical part of drug formulation development, all aspects of '*in-vitro*' drug dissolution studies have been extensively standardized by USP guidelines.[512]

In fact, dissolution testing is basically a specific form of solubility testing. However, it differs from the later by the fact that here the measurements are taken multiple times, usually below saturation and at physiological temperature (37 °C). While solubility is measured at a single point i.e. at the point of saturation and usually at 20°C, if otherwise mentioned.

Drug dissolution testing for oral mode formulations were performed in various buffer solutions, corresponding to the pH of different regions of the gastrointestinal tract. The tests were conducted in paddle type standard USP drug dissolution rate test apparatus (Fig. 23), in 900 mL of the buffer solution maintained at the physiological temperature of 37 °C (using isothermal bath). The spindle rotation was maintained between 50 -150 rpm. Aliquots were withdrawn at equal intervals of time. Drug content was assayed and was graphically expressed as drug release profile (% cumulative drug release vs. time).

6.2.2.1. Evaluation of drug release kinetics and drug release mechanism

To investigate the release kinetics and mechanism of drugs from modified dextrin based crosslinked hydrogels developed in authors' laboratory, the release data were analyzed using zero order,[513] first order,[514] Korsmeyer-Peppas,[515] Higuchi,[516] Hixson-Crowell,[517] and Kopcha models.[518] Since, no single model successfully predicts the release kinetics as well as release mechanism of drug from a hydrogel matrix; various mathematical models were used to explain the experimental observations during drug release.

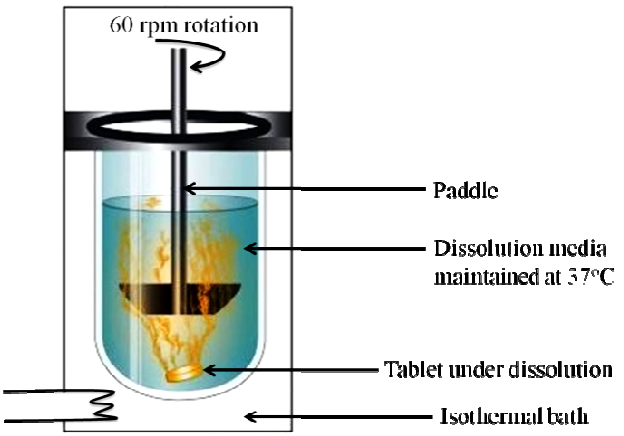


Fig. 23 Schematic diagram of a drug dissolution test apparatus (paddle type).

6.2.2.2. Erosion rate determination

During drug release, some tablets partially disintegrated which also affect the rate of drug release.[4-6] The degree of erosion (D)

was calculated using eq.(1), based on the difference between the initial dry weight of the tablet (W_i) and the dry weight of the tablet ($W_{d(t)}$) at time t, considering the initial amount of drug in tablet (W_d) and fraction of drug (M_t / M_∞) release at time t,

$$D\,(t)(\%) = \frac{W_i - W_{d(t)} - W_d\left(1 - {}^{M_t}/_{M_\infty}\right)}{W_i} \times 100 \quad ----- \quad \text{eq. (1)}$$

6.2.2.3. Stability study

We further investigated the efficacy of the developed hydrogels as carriers for drugs like ciprofloxacin/ornidazole, mainly to find out the compatibility in accelerated conditions. The stability study was performed upto 3 months under the influence of various environmental factors like temperature, humidity etc.[519] For this process, a tablet was packed in a glass bottle and placed in the humidity chamber where the temperature was kept at 40 ± 2 °C and relative humidity (RH) was maintained at 75 ± 5% throughout the study period.

6.2.3. Release study using developed hydrogels

For all the synthesized crosslinked hydrogels, the tablets were prepared using the direct compression method using 450 mg of matrix, 500 mg of drug and 50 mg of binder. After mixing and sieving (20 meshes), tablets of 1 g each were prepared by compression in a tablet making machine at a pressure of 2-3 t/cm^2.[4-6]

In-vitro ornidazole release study was performed from c-Dxt/p(HEMA) and dextrin, under a constant rotation of 60 rpm at 37 ± 0.5 °C (Fig. 24a). The amount of drug release was measured with the help of UV-Visible spectrophotometer (Shimadzu, Japan; Model - UV 1800). It was observed that c-Dxt/p(HEMA) showed more sustained release (~ 68.7% release after 18 h) characteristics (Fig. 24a) than that of dextrin.[4] This can be attributed on the basis of the chemical structure of hydrogel as well as the equilibrium swelling ratio. The higher swelling ratio of hydrogels creates a larger surface area for diffusion of the drug from the inside of the hydrogel to the environment.[4]

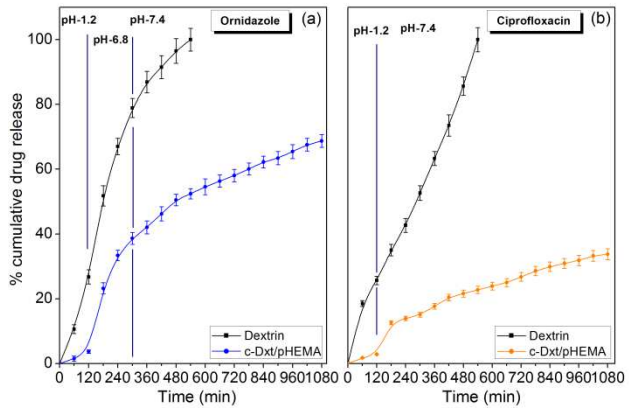


Fig. 24 Drug release profiles from dextrin and c-Dxt/p(HEMA) hydrogels (a) ornidazole, and (b) ciprofloxacin. Results represented here ± SD (n = 3) (Reproduced from Ref. 4, Copyright 2013, Royal Society of Chemistry and Reproduced with permission from Ref. 6, Copyright 2014, Elsevier)

Also, the presence of poly (HEMA) as well MBA in the hydrogel structure enhanced the hydrophilicity of the network, which offers more functional groups as well as higher surface area. This provides the release of the enclosed drug in a more sustained way.[4] It was also pointed out that the interaction between the hydrogel and ornidazole is mainly physical interaction as shown in Fig. 21a. The *in-vitro* release of ornidazole from hydrogel followed first order kinetic and non-Fickian diffusion mechanism.[4] The drug stability study confirmed that ~ 98% ornidazole remain stable in the hydrogel upto 3 months.[4] The dextrin and poly (HEMA) based hydrogel also showed excellent release characteristics for antibiotic-ciprofloxacin (33.75% release after 18 h) (Fig. 24b).[6] It was also observed through various characterizations that mainly physical interactions predominate between ciprofloxacin and hydrogel in tablet formulation (Fig. 21b).[6] Besides, c-Dxt/pHEMA demonstrated excellent potential as ciprofloxacin carrier till 3 months, as ~98.5% drug was stable.

Considering the above characteristics of c-Dxt/p(HEMA) hydrogel such as stimuli responsive behaviour, biodegradable nature, non-cytotoxic character, compatibility with drugs upto 3 months, and most importantly the controlled release behaviour; it is obvious that this hydrogel is an excellent alternative as dual drugs (ciprofloxacin, ornidazole) carrier.

Dextrin/poly (lactic acid) (c-Dxt/pLA) based hydrogel was also used as controlled drug delivery matrix.[5] It was obvious that c-Dxt/pLA showed excellent sustained release behaviour that that of neat dextrin (Fig. 25).[5] In addition, the drug release behavior of c-Dxt/pLA was compared with hydroxypropyl methyl cellulose (HPMC), which is an usual matrix for sustained release applications. It was apparent that c-Dxt/pLA demonstrated much better sustained release characteristics than that of HPMC for both ciprofloxacin (Fig. 25a) and ornidazole (Fig. 25b) drugs.[5] Besides, c-Dxt/pLA also exhibited physical interactions with both the drugs (as shown in Fig. 22).[5] This observation indicates that the presence of hydrophilic-hydrophobic segments, and crosslinker moiety in the network structure control the swelling ratio. This helps the release of the enclosed drug in more sustained way. Finally, drug stability study confirmed the efficacy of c-Dxt/pLA as proficient carrier for ciprofloxacin and ornidazole.

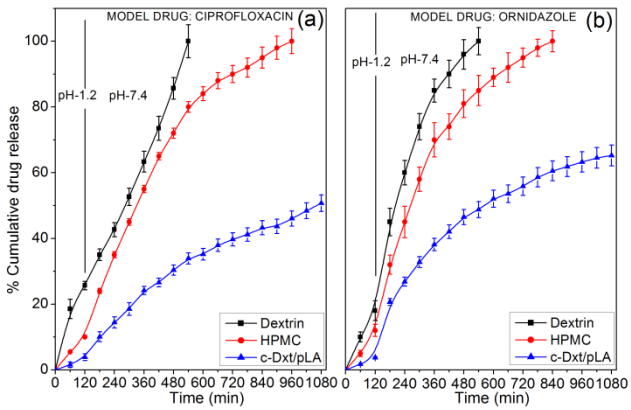


Fig. 25 Ciprofloxacin release studies from (a) dextrin, c-Dxt/pLA hydrogel and HPMC and ornidazole release studies from (b) dextrin, c-Dxt/pLA hydrogel and HPMC. Results represented here ± SD (n = 3). (Reproduced with permission from Ref. 5, Copyright 2013, Wiley Periodicals, Inc.)

6. 3. Comparison of dextrin based hydrogels with other hydrogel

Dextrin based hydrogels are the potential and most promising hydrogels for drug delivery application in compared to many others polysaccharide based hydrogels. This is because –

(i) In contrast to the other polysaccharides like dextran, agar, carrageenan, chitosan, gelatin, gellan gum, hydroxypropyl methyl cellulose, locust bean gum, xanthan gum, amylopectin, glycogen etc., dextrin is more cheaper material. Thus, the average cost of the treatment would be less when dextrin based hydrogels would use in drug delivery applications compared to other polysaccharides based hydrogels.

(ii) Owing to its inherent non-cytotoxicity and biodegradable nature, which are essential requirements for drug delivery application, dextrin based hydrogels probably suitable alternatives as drug release matrices.

(iii) Dextrin is completely soluble in water and DMSO, while chitosan is insoluble in water. Thus, compared to chitosan, dextrin is an easier alternative for modification with different of substituted groups in aqueous/organic media.

(iv) Because of the presence of primary and secondary hydroxyl groups in the dextrin backbone, it is ideal for the formation of hydrogels through free radical polymerization technique with high grafting and crosslinking efficiency than that of others polysaccharides like hyaluronan, chondroitin sulphate, alginate, chitosan etc. This dense hydrogels structure hindered the erosion phenomena during the extended drug delivery.

(v) From the developed modified dextrin based drug delivery systems, it was observed that during drug release, the rate of erosion was very less. This characteristic of the modified dextrin based hydrogels make it suitable for controlled release applications.

(vi) In spite of the development of various drug delivery systems, like carboxymethyl chitosan hydrogel, hydrogel based on sterculia gum–polyHEMA–polyacrylic acid, hydrogel derived from sterculia gum and poly (vinyl pyrrolidone), HPMC, and ethyl cellulose for ornidazole delivery; dextrin based hydrogels (i.e. c-Dxt/pHEMA and c-Dxt/pLA) developed in our laboratory released ornidazole as well as ciprofloxacin in more controlled way. For example, Singh *et al.*[520] reported that ~65% of ornidazole drug was released from sterculia-cl-poly(HEMA-co-AAc) hydrogel in 5 h, Vaghani *et al.*[521] reported ~100% ornidazole was released in 12 h from the carboxymethyl chitosan hydrogel system. Patel *et al.*[522] studied the ornidazole release from HPMC based coated system, which released the drug ~ 65% in 12 h and the stability of drug loaded tablet after 2 months for 12 h is ~74–78% and for 24 h is ~96–98% at 40 ± 2°C/75 ± 5% RH. On the other hand, dextrin based hydrogels like c-Dxt/pHEMA hydrogel released ~ 68.7 % even after 18 h in colonic region than that of earlier reports, which is the most important prerequisite, as fast release of ornidazole may lead to severe side effects. Also % of drug stability using c-Dxt/pHEMA hydrogel as carrier for ornidazole is ~ 96 % upto 3 months, which is quite promising and restricts the degradation of drug in stomach region.[4] Besides, c-Dxt/pLA hydrogel released ~65.2% ornidazole 18 h with ~98% stability upto1 month.[5]

(vii) In recent years, several drug delivery systems have also been developed for ciprofloxacin release which includes HPMC (K100M)/xanthan gum tablet formulation,[523] Poloxamer-graft-hyaluronic acid hydrogel,[524] HPMC/poly(vinyl alcohol) microsphere,[525] Sterculia-cl-poly (MAAm) hydrogel,[526] carboxymethyl locust bean gum (CMLBG), [527] chitosan/(PAAm-g-GG) hydrogel,[528] HPMC (K15M)/sodium alginate tablet formulation,[529] calcium phosphate/chitosan hydrogel,[530] Such systems deliver the drug in different fashion. For example, Mostafavi *et al.* reported ~65-90% ciprofloxacin release from HPMC (K100M), xanthan Gum, NaCMC, crospovidone in 12 h,[523] Cho *et al.* reported that ~90% ciprofloxacin drug was released from Poloxamer-graft-hyaluronic acid hydrogel after 20 h,[524] YerriSwamy *et al.* reported ~60% ciprofloxacin was released from HPMC/poly(vinyl alcohol) microsphere in 13 h,[525] Singh *et al.* reported ~50% ciprofloxacin was released from Sterculia-cl-poly (MAAm) hydrogel after 5 h,[526] Kaity *et al.* reported ~70% drug was released from sodium carboxymethyl locust bean gum (CMLBG) after 12 h,[527] Kajjari *et al.* reported ~50-60% ciprofloxacin was released from different grades of chitosan/(PAAm-g-GG) hydrogel at 12 h,[528] Tadros *et al.* reported ~50% ciprofloxacin has been released from HPMC (K15M)/Sodium alginate based tablet formulation,[529] Nardecchia *et al.* reported ~40% ciprofloxacin was released from calcium phosphate/chitosan hydrogel after 9 h.[530] Whereas, c-Dxt/pLA released ~50.7% ciprofloxacin after 18h with ~97.5 % stability upto 1 month.[5] c-Dxt/pHEMA hydrogel released ~33.75% ciprofloxacin in 18 h with ~98.5% stability up to 3 months.[6]

(viii) Again, the drug release from various dextrin based hydrogels generally followed first order and non-Fickian diffusion mechanism (with negligible amount of erosion effect) which also supports the hydrogel systems as ideal matrices for controlled drug release application.

7. Summary

Biopolymer based hydrogels possess some unique properties, such as biodegradability, non-cytotoxicity, excellent water absorption capability which make them superior candidate for biomedical applications. Chemically crosslinked biopolymer based hydrogels, because of their excellent gel stability showed unique characteristics towards controlled release applications. Various synthetic strategies including free radical polymerization technique were explored to develop chemically crosslinked hydrogels.

Out of several polysaccharides/biopolymers, dextrin is one of the most important polymers which can be used in biomedical field owing to its biocompatible and non-immunogenic nature. Although compared to other polysaccharides, dextrin is less studied in biomedical applications, but more recently, dextrin based chemically crosslinked hydrogels have been developed and reported for controlled release application. However, still it is essential to finely tune the properties of dextrin based chemically crosslinked hydrogels for *in-vivo* applications. Additionally, modified dextrin based hollow nanogels are required to be developed, which might be potential candidate for anti-cancer drug delivery. In this perspective, development of hollow nanogels derived from chemically crosslinked dextrin based hydrogel will be investigated and studied in near future.

Acknowledgement

The first author wishes to acknowledge University Grant Commission, New Delhi, India (Ref. No. 19-06/2011(i) EU-IV; Sr. No.2061110303, Dated: 30.11.2011) for providing financial

assistance under Junior Research Fellowship Scheme. S.P. acknowledges the financial support from Department of Science and Technology, New Delhi, India in form of a research grant (NO:SR/FT/CS-094/2009) to carry out the reported investigation. Authors also acknowledge the kind help of Dr. Santanu Dhara, School of Medical Science & Technology, Indian Institute of Technology, Kharagpur, India for providing the cell viability study and Dr. Animesh Ghosh, Department of Pharmaceutical Sciences, BIT, Mesra, Ranchi, India for providing drug stability study.

Notes

Polymer Chemistry Laboratory, Department of Applied Chemistry, Indian School of Mines, Dhanbad-826004, India. E-mail: sagarpal1@hotmail.com; pal.s.ac@ismdhanbad.ac.in; Fax: +91-326-2296615; Tel: +91-326-2235769.

References

1 T. Coviello, P. Matricardi, C. Marianecci and F. Alhaigue, *J. Controlled Release*, 2007, **119**, 5-24.
2 L. Pescosolido, T. Piro, T. Vermonden, T. Coviello and F. Allhaique, *Carbohydr. Polym.*, 2011, **86**, 208-213.
3 A. S. Hoffman, *Adv. Drug Delivery Rev*., 2002, **54**, 3-12.
4 D. Das, R. Das, P. Ghosh, S. Dhara, A. B. Panda and S. Pal, *Rsc Adv.*, 2013, **3**, 25340.
5 D. Das, R. Das, A. Ghosh and S. Pal, *J. Appl. Polym. Sci*., 2014, **131**, 40039.
6 D. Das and S. Pal, *Int. J. Biol. Macromol*., 2015, **72**, 171-178.
7 P. Kurian and J. P. Kennedy, *J. Polym. Sci., Part A: Polym. Chem*., 2002, **40**, 1209-1217.
8 A. Finne and A. C. Albertsson, *J. Polym. Sci., Part A: Polym. Chem*., 2003, **41**, 1296–1305.
9 B. V. Slaughter, S. S. Khurshid and O. Z. Fisher, *Adv. Mater*., 2009, **21**, 3307-3329.
10 N. A. Peppas, J. Z. Hilt and A. Khademhosseini, *Adv.Mater*., 2006, **18**, 1345-1360.
11 M. Hamidi, A. Azadi and P. Rafiei, *Adv. Drug Delivery Rev*., 2008, **60**, 1638-1649.
12 E. Soussan, S. Cassel and M. Blanzat, *Angew. Chem., Int. Ed.*, 2009, **48**, 274-288.
13 L. Pan, Q. He, J. Liu, Y. Chen, M. Ma, L. Zhang and J. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 5722-5725.
14 L. Tang, T. M. Fan, L. B. Borst and J. Cheng, *ACS Nano*, 2012, **6**, 3954-3966.
15 J. A. Killion, L. M. Geever, D. M. Devine, J. E. Kennedy and C. L. Higginbotham, *J. Mech. Behav. Biomed. Mater*., 2011, **4**, 1219-1227.
16 S. G. Lee, G. F. Brunello, S. S. Jang and D. G. Bucknall, *Biomaterials*, 2009, **30**, 6130-6141.
17 H. Shin, B. D. Olsen and A. Khademhosseini, *Biomaterials*, 2012, **33**, 3143-3152.
18 Y. Cao, Y. Gu, H. Ma, J. Bai, L. Liu, P. Zhao and H. He, *Int. J. Biol. Macromol*., 2010, **46**, 245.
19 W. Wu, M. Aiello, T. Zhou, A. Berliner, P. Banerjee and S. Zhou, *Biomaterials*, 2010, **31**, 3023.
20 T. F. Vandamme, A. Lenourry, C. Charrueau and J. C. Chaumeil, *Carbohydr. Polym*., 2002, **48**, 219.
21 X. Huang, B. R. Nayak and T. L. Lowe, *J. Polym. Sci. Part A: Polym. Chem.*, 2004, **42**, 5054.
22 V. Vijan, S. Kaity, S. Biswas, J. Isaac and A. Ghosh, *Carbohydr. Polym*., 2012, **90**, 496.
23 B. Singh and N. Sharma, *Carbohydr. Polym*., 2008, **74**, 489.
24 J. K. Oh, D. I. Lee and J. M. Park, *Prog. Polym. Sci*., 2009, **34**, 1261–1282.
25 J. M. Van Bemmelen, *Z. Anorg. Chem*., 1894, **5**, S. 466.
26 S. J. Buwalda, K. W. M. Boere, P. J. Dijkstra, J. Feijenc, T. Vermonden and W. E. Hennink, *J. Controlled Release*, 2014, **190**, 254-273.
27 O. Wichterle and D. Lím, *Nature*, 1960, **185**, 117-118.
28 N. A. Peppas and A. G. Mikos, Preparation methods and structure of hydrogels, in: N.A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy, vol. 1, CRC Press, Boca Raton, FL, 1986, pp. 1-27.
29 L. Brannon-Peppas, Preparation and characterization of crosslinked hydrophilic networks, in: L. Brannon-Peppas, R.S. Harland (Eds.), Absorbent Polymer Technology, Elsevier, Amsterdam, 1990, pp. 45-66.
30 J. A. Bouwstra and H. E. Jungiger, in: J. Swarbrick, J.C. Boylan (Eds.), 1st ed., Encyclopedia of Pharmaceutical Technology, vol. 7, Marcel Dekker Inc., New York, 1993, p. 441.
31 N. A. Peppas and A. R. Khare, *Adv. Drug Delivery Rev*., 1993, **11**, 1-35.
32 P. J. Flory and J. Rehner, *J. Chem. Phys*., 1943, **11**, 521-526.
33 P. J. Flory, *J. Chem. Phys*., 1950, **18**, 108-111.
34 P. J. Flory, Principles of Polymer Chemistry, Cornell University Press, Ithaca, NY, 1953.
35 N. A. Peppas, *J. Bioact. Compat. Polym*., 1991, **6**, 241-246.
36 M. Molinos, V. Carvalho, D. M. Silva and F. M. Gama, *Biomacromolecules*, 2012, **13**, 517−527.
37 N. A. Peppas and E. W. Merrill, *J. Polym. Sci. Polym. Chem. Ed*., 1976, **14**, 441-457.
38 N. A. Peppas and E. W. Merrill, *J. Appl. Polym. Sci*., 1976, **20**, 1457–146.
39 N. A. Peppas, Hydrogels of poly(vinyl alcohol) and its copolymers, in: N. A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy, vol. 2, CRC Press, Boca Raton, FL, 1986, pp. 1-48.
40 S. R. Stauffer, N. A. Peppas, *Polymer*, 1992, **33**, 3932-3936.
41 A. S. Hickey and N. A. Peppas, *J. Membr. Sci*., 1995, **107**, 229-237.
42 N. A. Peppas and N. K. Mongia, *Eur. J. Pharm. Biopharm*., 1997, **43**, 51–58.
43 K. Kamath and K. Park, *Adv. Drug Delivery Rev*., 1993, **11**, 59-84.
44 J. H. Jeong, J. J. Schmidt, C. Cha and H. Kong, *Soft Matter*, 2010, **6**, 3930-3938.
45 D. P. Huynh, G. J. Im, S. Y. Chae, K. C. Lee, and D. S. Lee, *J. Controlled Release*, 2009, **137**, 20-24.
46 J. S. Im, B. C. Bai, S. J. In, and Y. S. Lee, *J. Colloid Interface Sci.*, 2010, **346**, 216-221.
47 S. Jin, J. Gu, Y. Shi, K. Shao, X. Yu, and G. Yue, *Eur. Polym. J.*, 2013, **49**, 1871-1880.
48 S. A. Meenach, J. Z. Hilt and K.W. Anderson, *Acta Biomater*., 2010, **6**, 1039-1046.
49 P. R. Ninawe, and S. J. Parulekar, *Ind. Eng. Chem. Res.*, 2012, **51**, 1741-1755.
50 L. E. Nita, M. T. Nistor, A. P. Chiriac and I. Neamtu, *Ind. Eng. Chem. Res*., 2012, **51**, 7769-7776.
51 L. Chen, Z. Tian and Y. Du, *Biomaterials*, 2004, **25**, 3725-3732.
52 N. Patil, S. G. Roy, U. Haldar and P. De, *J. Phys. Chem. B*., 2013, **117**, 16292-16302.
53 J. Wang, K. P. Loh, Z. Wang, Y. Yan, Y. Zhong, Q. H. Xu and P. C. Ho, *Angew. Chem., Int. Ed.*, 2009, **48**, 6282-6285.
54 T. M. L. Taylor-Pashow, J. D. Rocca, R. C. Huxford and W. Lin, *Chem. Commun*., 2010, **46**, 5832-5849.
55 A. Lalloo, P. Chao, P. Hu, S. Stein and P. J. Sinko, *J. Control. Release*, 2006, **112**, 333–342.
56 M. Dadsetan, Z. Liu, M. Pumberger, C. V. Giraldo, T. Ruesink, L. Lu and M. J. Yaszemski, *Biomaterials*, 2010, **31**, 8051-8062.
57 Y. Liu, W. L. Lu, J. C. Wang, X. Zhang, H. Zhang, X. Q. Wang, T. Y. Zhou and Q. Zhang, *J. Controlled Release*, 2007, **117**, 387–395.
58 D. P. Huynh, G. J. Im, S. Y. Chae, K. C. Lee and D. S. Lee, *J. Controlled Release*, 2009, **137**, 20-24.
59 A. J. de Graaf, I. I. A. Próspero dos Santos, E. H. E. Pieters, D. T. S. Rijkers, C. F. van Nostrum, T. Vermonden, R. J. Kok,

W. E. Hennink and E. Mastrobattista, *J. Controlled Release*, 2012, **162**, 582-590.
60 B. Jeong, Y. H. Bae and S. W. Kim, *J. Control. Release*, 2000, **63**, 155-163.
61 K. Wang, Q. Fu, X. Chen, Y. Gaoa and K. Donga, *RSC Adv.*, 2012, **2**, 7772-7780.
62 L. Yu, G. T. Chang, H. Zhang and J. D. Ding, *Int. J. Pharm.*, 2008, **348**, 95–106.
63 J. Yu,W. Ha, J. Chena and Y.Shi, *RSC Adv*., 2014, **4**, 58982-58989.
64 W. Wu, J. Liu, S. Cao, H. Tan, J. Li, F. Xu and X. Zhanga, *Int. J. Pharm.*, 2011, **416**, 104–109.
65 J. Yu, X. Xu, F. Yao, Z. Luo, L. Jin, B. B. Xie, S. Shi, H. Ma, X. Y. Li and H. Chen, *Int. J. Pharm*., 2014, **470**, 151–157.
66 M. L. Briuglia, A. J. Urquhart and D. A. Lamprou, *Int. J. Pharm*., 2014, **474**, 103-111.
67 D. Q. Wu, T. Wang, B. Lu, X. D. Xu, S. X. Cheng, X. J. Jiang, X. Z. Zhang and R. X. Zhuo, *Langmuir*, 2008, **24**, 10306-10312.
68 C. H. Wang, Y. S. Hwang, P. R. Chiang, C. R. Shen, W. H. Hong and Ging-Ho Hsiue, *Biomacromolecules*, 2012, **13**, 40-48.
69 F. Cavalieri, E. Chiessi, R. Villa, L. Vigano, N. Zaffaroni, M. F. Telling and G. Paradossi, *Biomacromolecules*, 2008, **9**, 1967-1973.
70 R. Wieduwild, W. Lin, A. Boden, K. Kretschmer and Y. Zhang, *Biomacromolecules*, 2014, **15**, 2058-2066.
71 H. Zhang, A. Patel, A. K. Gaharwar, S. M. Mihaila, G. Iviglia, S. Mukundan, H. Bae, Huai Yang and Ali Khademhosseini, *Biomacromolecules*, 2013, **14**, 1299-1310.
72 D. Ma, K. Tu and L. M. Zhang, *Biomacromolecules*, 2010, **11**, 2204–2212.
73 X. Huang and T. L. Lowe, *Biomacromolecules*, 2005, **6,** 2131-2139.
74 M. J. D. Nugent and C. L. Higginbotham, *Euro. J. Pharm. Biopharm*., 2007, **67**, 377–386.
75 G. D. Kang, S. H. Cheon, G. Khang and S. C. Song, *Eur. J. Pharm. Biopharm*., 2006, **63**, 340–346.
76 G. P. Mishra, R. Kinser, I. H. Wierzbicki, R. G. Alany and A. W. G. Alani, *Eur. J. Pharm. Biopharm*., 2014, **88**, 397–405.
77 M. Babu, H. S. Yadav, A. Moin, H. G. Shivkumar, *Acta Pharma. Sinica B*, 2011, **1**, 261–267.
78 W. E. Hennink and C. F. van Nostrum, *Adv. Drug Delivery Rev*., 2002, **54**, 13–36.
79 J. M. Rosiak and F. Yoshii, *Nucl. Ins. Method. Phy. Res. B*, 1999, **151**, 56-64.
80 V. A. Kabanov and I. M. Papisov, *Vysokolmol. Soedin. A* 1979, **21**, 243–281.
81 E. A. Bekturov and L. A. Bimendina, *Adv. Polym. Sci*., 1981, **43**, 100–147.
82 E. Tsuchida and K. Abe, *Adv. Polym. Sci*., 1982, **45**, 1-19.
83 J. Klier and N. A. Peppas, Structure and swelling behavior of poly(ethylene glycol)/poly(methacrylic acid) complexes, in: L. Brannon-Peppas, R. S. Harland (Eds.), Absorbent Polymer Technology, Elsevier, Amsterdam, 1990, pp. 147-169.
84 C. L. Bell and N. A. Peppas, *Adv. Polym. Sci*., 1995, **122**, 125-175.
85 S. Drotleff, U. Lungwitz, M. Breunig, A. Dennis, T. Blunk, J. Tessmar and A. Göpferich, *Eur. J. Pharm. Biopharm*., 2004, **58**, 385-407.
86 C. C. Lin and A. T. Metters, *Adv. Drug Delivery Rev*., 2006, **58**, 1379-1408.
87 K. A. Davis and K. S. Anseth, *Crit. Rev. Ther. Drug Carr. Syst*., 2002, **19**, 385-423.
88 N. A. Peppas, P. Bures, W. Leobandung and H. Ichikawa, *Eur. J. Pharm. Biopharm*., 2000, **50**, 27-46.
89 D. Pasqui, M. D. Cagna and R. Barbucci, *Polymers*, 2012, **4**, 1517-1534.
90 D. L. Kaplan, Introduction to polymers from renewable resources. In Biopolymers from Renewable Resources; D. L. Kaplan, Ed.; Springer Verlag: Berlin, Germany, 1998; pp. 1-29.
91 Yannas, I.V. Natural materials. In Biomaterials Science. An Introduction to Materials in Medicine; B. D. Ratner, A. S. Hoffman, F. J. Schoen and J. E. Lemons, Eds.; Academic Press California: San Diego, CA, USA, 1996; pp. 84–94.
92 S. S. Stalling, S. O. Akintoye, S. B. Nicol, *Acta Biomater*., 2009, **5**, 1911–1918.
93 R. Jin, L. S. Moreira-Teixeira, A. Krouwels, P. J. Dijstra, C. A. van Blitterswilk, M.Karperien and J. Feijen, *Acta Biomater*., 2010, 6, 1968–1977.
94 R. Jin, L. S. Moreira-Teixeira, P. J. Dijstra, C. A. van Blitterswilk, M. Karperien and J. Feijen, *J. Controlled Release*, 2011, **152**, 186–195.
95 R. Barbucci, R. Giardino, M. de Cagna, L. Golini and D. Pasqui, *Soft Matter*, 2010, **6**, 3524–3532.
96 J. Kost, R. Goldbart, Natural and modified polysaccharides, in: A.J. Domb, J. Kost, D.M. Wiseman (Eds.), Handbook of Biodegradable Polymers, Harwood Academic Publisher, Amsterdam, 1997, pp. 275–289.
97 I. J. Colquhoun, A. J. Jay, J. Eagles, V. J. Morris, K. J. Edwards, A. M. Griffin and M. J. Gasson, *Carbohydr. Res*., 2001, **330**, 325–333.
98 G. Gomez d'Ayala, M. Malinconico and P. Laurienzo, *Molecules*, 2008 **13**, 2069–2106.
99 P. Laurienzo, *Mar. Drugs*, 2010, **8**, 2435–2465.
100 Z. Liu, Y. Jiao, Y. Wang, C. Zhou and Z. Zhang, *Adv. Drug Delivery Rev*., 2008, **60**, 1650–1662.
101 G. F. Payne and S. R. Raghavan, *Soft Matter*, 2007, **3**, 521-527.
102 R. Stern and M. J. Jedrzejas, *Chem Rev*., 2008, **108**, 5061–5085.
103 A. Shrivastava, R.G. Rhodes, S. Pochiraju, D. Nakane, M.J. McBride, *J. Bacteriol*., 2012, **194**, 3678–3688.
104 C. A. Lorenzo, B. B. Fernandez, Ana M. Puga and Angel Concheiro, *Adv. Drug Delivery Rev*., 2013, **65**, 1148-1171.
105 C. Vauthier, I. Bertholon and D. Labarre, Integrated development of glycobiologics: fromdiscovery to applications in the design of nanoparticular drug delivery systems, in: S. Coxgad (Ed.), Handbook of Pharmaceutical Biotechnology, Wiley-Interscience, New Jersey, 2007, pp. 125-160.
106 I. Y. Tsai, C. C. Kuo, N. Tomczyk, S. J. Stachelek, R. J. Composto and D. M. Eckmann, *Soft Matter*, 2011, **7**, 3599-3606.
107 J. K. Oh, D. I. Lee and J. M. Park, *Prog. Polym. Sci*., 2009, **34**, 1261-1282.
108 J. O. Karlsson and P. Gatenholm, *Polymer*, 1997, **38**, 4727-4731.
109 K. Pal, A. K. Banthia and D. K. Majumdar, *Des. Monomers Polym*., 2009, **12**, 197-220.
110 N. A. Peppas, P. Bures, W. Leobandung and H. Ichi, *Eur. J. Pharm. Biopharm.*, 2000, **50**, 27-46.
111 Y. Qiu and K. Park, *Adv. Drug Delivery Rev*., 2001, **53**, 321-339.
112 S. Kalia, M. W. Sabaa (Eds.), Polysaccharide Based Graft Copolymers, in: J. K. Bhatia, B. S, Kaith and S. Kalia, Polysaccharides hydrogels: Syntheis, Characterization, and Applications, Springer-Verlag Berlin Heidelberg, 2013, pp. 271-289.
113 G. Usha Rani, A. K. Konreddy, S. Mishra and G. Sen, *Int. J. Biol. Macromol*., 2014, **65**, 375-382.
114 B. B. Fernandez, M. L.Viota, A. Concheiro and C. A. Lorenzo, *Carbohydr. Polym*., 2011, **85**, 765-774.
115 R. V. Kulkarni, R. Boppana, G. K. Mohan, S. Mutalik and N. V. Kalyane, *J. Colloid Interface Sci*., 2012, **367**, 509-517.
116 K. Nakagawa, N. Sowasod, W. Tanthapanichakoon and T. Charinpanitkul, *LWT - Food Sci. Tech*., 2013, **54**, 600-605.
117 H. Hezaveh and I. I. Muhamad. *J. Taiwan Institute of Chem. Eng*., 2013, **44**, 182-191.
118 J. S. Varghese and Nisha Chellappa and N. N. Fathima, *Colloids Surf. B: Biointerf*., 2014,**11**, 346-351.

119 A. B. Cvitanovic, D. Komes, S. Karlovic, S. Djakovic, I. Špoljaric, G. Mršic and D. Jezek, *Food Chemistry*, 2015, **167**, 378-386.

120 H. Hezaveh and I. I. Muhamad, *Chem. Eng. Res. Des*., 2013, **91**, 508-519.

121 Y. H. Cheng, K. H. Hung, T. Hu Tsai, C. J. Lee, R. Y. Ku, A. W. Chiu, S. H. Chiou, C. J. Liu, *Acta Biomater.*, 2014, **10**, 4360-4366.

122 Rui Chen, Qi Chen, Da Huo, Yin Ding, Yong Hu, Xiqun Jiang, *Colloids Surf. B: Biointerf*., 2012, **97**, 132-137.

123 J. Zhang, M. Fu, M. Zhang, L. Xu and Y. Gao, *Int. J. Pharm*., 2014, **465**, 32-41.

124 Y. Peng, J. Li, J. Li, Y. Fei, J. Dong and W. Pan, *Int. J. Pharm.*, 2013, **441**, 482- 490.

125 J. Xu, S. Strandman, J. X. X. Zhu, J. Barralet and M. Cerruti, *Biomaterials*, 2015, **37**, 395-404.

126 D. Zhang, P. Sun, P. Li, A. Xue, X. Zhang, H. Zhang and X. Jin, *Biomaterials*, 2013, **34**, 10258-10266.

127 W. N. E. van Dijk-Wolthuis, J. A. M. Hoogeboom, M. J. van Steenbergen, S. K. Y. Tsang, and W. E. Hennink, *Macromolecules*, 1997, **30**, 4639-4645.

128 H. Basan, M. Gumusderelioglu and M. T. Orbey, *Eur. J. Pharm. Biopharma*., 2007, **65**, 39-46.

129 M. Konishia, Y. Tabatab, M. Kariyaa, A. Suzukia, M. Mandaia, K. Nanbua, K. Takakuraa and S. Fujiia, *J. Controlled Release*, 2003, **92**, 301-313.

130 M. Konishia, Y. Tabatab, M. Kariyaa, H. Hosseinkhanib, A. Suzukia, K. Fukuharaa, M. Mandaia, K. Takakuraa and S. Fujii, *J. Controlled Release*, 2005, **103**, 7 -19.

131 A. Gaowa, T. Horibe, M. Kohno, K. Sato, H. Harada, M. Hiraoka,Y. Tabata and K. Kawakami, *J. Controlled Release*, 2014, **176**, 1–7.

132 G. Nandi, P. Patra, R. Priyadarshini, S. Kaity and L. K. Ghosh, *Int. J. Biol. Macromol*., 2015, **72**, 965-974.

133 C. H. Chang, Y. H. Lin, C. L. Yeh, Y. C. Chen, S. F. Chiou, Y. M. Hsu, Y. S. Chen and C. C. Wang, *Biomacromolecules* 2010, ***11***, 133-142.

134 S. Das and U. Subuddhi, *Ind. Eng. Chem. Res*., 2013, **52**, 14192-14200.

135 Y. Huang, H. Yu and C. Xiao, *Carbohydr. Polym*., 2007, **69**, 774–783.

136 S. Thakur, G. S. Chauhan and J. H. Ahn, *Carbohydr. Polym*., 2009, **76**, 513–520.

137 R. Murali, P. Vidhya and P. Thanikaivelan, *Carbohydr. Polym*., 2014, **110**, 440–445.

138 L. G. Chen, Z. L. Liu and R. X. Zhuo, *Polymer*, 2005, **46**, 6274–6281.

139 C. Liu, Y. Chen and J. Chen, *Carbohydr. Polym*., 2010, **79**, 500–506.

140 X. Shi, Y. Zheng, G. Wang, Q. Lina and J. Fana, *RSC Adv*., 2014, **4**, 47056-47065.

141 Saruchi, B. S. Kaith, R. Jindal, V. Kumar and M. S. Bhatti, *RSC Adv*., 2014, **4**, 39822-39829.

142 A. C. Estrada, A. L. Daniel-da-Silva and T. Trindadea, *RSC Adv*., 2013,**3**, 10828-10836.

143 R. Jayakumar, M. Parbaharam, P. T. S.. Kumar, S. V. Nair and H. Tamura, *Biotech. Adv*., 2011, **29**, 322-337.

144 P. Sikareepaisan, U. Ruktanonchai and P. Supaphol, *Carbohydr. Polym*., 2011, **83**, 1457-1469.

145 B. Balakrishnan, M. Mohanty, P. R. Umashankar and A. Jayakrishnan, *Biomaterials*, 2005, **26**, 6335-6342.

146 B. Singh and L. Pal, *Int. J. Biol. Macromol*., 2011, **48**, 501-510.

147 E. A. Kamoun, E. R. S. Kenawy, T. M. Tamer, M. A. El-Meligy, M. S. M. Eldin, *Arab. J. Chem*., 2015, **8**, 38-47.

148 K. Kiran and B. S. Kaith, *Fibres Polym*., 2010, 11, 147-152.

149 F. A. Aouada, M. R. de Moura, L. Henrique and C. Mattaso, Biodegradable hydrogel as delivery vechile for the controlled release of pesticide. In: Stoytecheva M (ed) Pesticides-formulations, effects, fate., 2011, CC BY-NC-SA.

150 B. Singh, D. K. Sharma, R. Kumar and A. K. Gupta, *Appl. Clay Sci*., 2009, **45**, 76-82.

151 A. Roy, J. Bajpai and A. K. Bajpai, *Carbohydr. Polym*., 2009, **76**, 222-231.

152 H. L. A. El-Mohdy, E. A. Hegazy, E. M. El-Nesr and M. A. El-Wahab, *J. Appl. Polym. Sci*., 2011, **122**, 1500-1509.

153 B.M.Yapo, *Carbohydr. Polym*., 2011, **86**, 373–385.

154 P. A. Markov, S.V. Popov, I. R. Nikitina, R. G. Ovodova, and Y. S. Ovodov, *Russ. J. Bioorg. Chem*., 2011, **7**, 817-821.

155 A. Gregorova, N. Saha, T. Kitano and P. Saha, *Carbohydr. Polym.*, 2015, **117**, 559-568.

156 B. Singh, G. S. Chauhan, S. S. Bhatt and K. Kumar, *Carbohydr. Polym.*, 2006, **64**, 50-56.

157 G. S. Chauhan, B. S. Singh, S. Chauhan, M. Verma and S. Mahajan, *Desalination*, 2006, **181**, 217-224.

158 H. M. Nizam El-Din, M. F. Abou Taleb, A. M. Abdel Waheb and A. M. El-Naggar, *Nucl. Inst. Meth. Phys. Res. B Beam*, 2008, **266**, 2607-2613.

159 A. T. Paulinoa, L. A. Belfiore, L. T. Kubotac, E. C. Munizd, E. B. Tambourgia, *Chem. Eng. J*., 2011, **168**, 68-76.

160 X. Vecinoa, R. Devesa-Reya, J. M. Cruza, A. B. Moldesa, *Carbohydr. Polym*., 2015, **115**, 129-138.

161 F. P. Curtis, S. Nochumson and F. H. Kirkpatrick, Fmc Corporation, Jonathan Hart Morgan, Polysaccharide resolving gels and gel system for stacking electrophoresis, Publication number- CA2042381 C, 1997.

162 W. D. Oliveira and W. G. Glasse, *J. Appl. Polym. Sci*., 1996, **60**, 63-73.

163 M. H. M. Hussein, M. F. El-Hady, H. A. H. Shehata, M. A. Hegazy and H. H. H. Hefni, *J. Surfactants Deterg*., 2013, **16**, 233-242.

164 R. Geethanjali, A. A. F. Sabirneeza and S. Subhashini, *Ind. J. Materials Sci*., 2014, Article ID 356075, 1-9, doi:10.1155/2014/356075.

165 S. Banerjee, V. Srivastava and M. M. Singh, *Corrosion Sci*., 2012, **59**, 35-41.

166 P. Roy, P. Karfa, U. Adhikari and D. Sukul, *Corrosion Sci*., 2014, **88**, 246-253.

167 F. Donot, A. Fontana, J. C. Baccou and S. Schorr-Galindo, *Carbohydr. Polym*., 2012, **87**, 951-962.

168 F. Freitas, V. D. Alves and M. A. M. Reis, *Trends. Biotechnol*., 2011, **29**, 388-398.

169 B. Nicolaus, M. Kambourova and E. O. Toksoy, *Environ. Technol.*, 2010, **31**, 1145-1158.

170 H. A. Abd El-Rehim, E. S. A. Hegazy, D. A. Diaa, *Rad. Phys. Chem*., 2013, **85**, 139-146.

171 J. Liu, S. Lin, L. Li and E. Liu, *Int. J. Pharm.*,2005, **298**, 117-125.

172 A. K. Bajpai and J. Shrivastava, *Polym. Int.*, 2005, **54**, 1525-1536.

173 D. Gupta, C.H. Tator and M. S. Soichet, *Biomaterials*, 2006, **27**, 2370-2379.

174 A. Chenite, C. Chaput, D. Wang, C. Combes, M.D. Buschmann, C. D. Hamann, J. C. Leroux, B. L. Atkinson, F. Binette and A. Selmani, *Biomaterials*, 2000, **21**, 2155-2161.

175 C. Gau, M. Liu, J. Chen and X. Zhang, *Polym. Degrad. Stab*., 2009, **94**, 1405-1410.

176 H. Mittal, B. S. Kaith and R. Jindal, *Der. Chemica. Sinica*., 2010, **1**, 59-69.

177 J. Zhou, C. Cheng, R. Zhang and L. Zhang, *Macromol. Biosci*., 2007, **7**, 804-809.

178 G. O. Phillips, T. A. Du Plessis, S. Al-Assaf and P. A. Williams, 2005, Biopolymers obtained by Solid state irradiation in a unsaturated gaseous atmosphere, US Patent 6841644.

179 S. G. Hirsch and R. J. Spontak, *Polymer*, 2002, **43**, 123-129.

180 T. Mitsumata, Y. Suemitsu, K. Fujii, T. Fujii, T. Taniguchi and K. Koyama, *Polymer*, 2003, **44**, 7103-7111.

181 B. Suthar, H. X. Xiao, D. Klempner, K. C. Frisch, *Polym. Adv. Technol.*, 1996, **7**, 221-233.

182 V. Bhardwaj, G. Harit and S. Kumar, *Int. J. Drug Dev. & Res*., 2012, **4**, 41-54.
183 P. J. Flory, Principles of Polymer Chemistry. Ithaca: Cornell University Press; 1953.
184 O. Olabisi, L. M. Robeson, M. T. Shaw, Polymer-Polymer Miscibility. New York: Academic Press; 1979.
185 D. Myung, D. Waters, M. Wiseman, P. E. Duhamel, J. Noolandi, C. N. Ta, and C. W. Frank1, *Polym. Adv. Technol*., 2008, **19**, 647-657.
186 J. Ostroha, M. Pong, A. Lowman and N. Dha, *Biomaterials*, 2004, **25**, 4345-4353.
187 P. Mukhopadhyay, K. Sarkar, S. Bhattacharya, A. Bhattacharyya, R. Mishra and P. P. Kundu, *Carbohydr. Polym.*, 2014, **112**, 627-637.
188 Y. H. Cheng, K. H. Hung, T. H. Tsai, C. J. Lee, R. Y. Ku, A. Wen-hsiang Chiu, S. H. Chiou and C. J. Liu, *Acta Biomater*., 2014, **10**, 4360-4366.
189 A. K. Pradhan, P. K. Rana and P. K. Sahoo, *Int. J. Biol. Macromol.*, 2014, http://dx.doi.org/10.1016/j.ijbiomac.2014.12.024.
190 S. P. Miguel, M. P. Ribeiro, H. Brancal, P. Coutinho and I. J. Correia, *Carbohydr. Polym*., 2014, **111**, 366-373.
191 A. Salama, N. Shukry and M. El-Sakhawy, *Int. J. Biol. Macromol.*, 2015, **73**, 72-75.
192 B. Hui, Y. Zhang and L. Ye, *J. Ind. Eng. Chem*., 2015, **21**, 868-876.
193 L. Illum, *Pharm. Res*., 1998, **15**, 979-993.
194 C. Alvarez-Lorenzo, A. Concheiro, Stimuli-sensitive chitosan interpenetrating networks. Current research and developments on chitin and chitosan in biomaterials science, in: R. Jayakumar, M. Prabaharan (Eds.), Current Research and Developments on Chitin and Chitosan in Biomaterials Science, vol. 1, Research Signpost, Kerala (India), 2008, pp. 55-81.
195 J. Berger, M. Reist, J. M. Mayer, O. Felt, N. A. Peppas and R. Gurny, *Eur. J. Pharm. Biopharm*., 2004, **57**, 19-34.
196 J. Berger, M. Reist, J.M. Mayer, O. Felt and R. Gurny, *Eur. J. Pharm. Biopharm.*, 2004, **57**, 35-52.
197 R. Barreiro-Iglesias, R. Coronilla, A. Concheiro, C. Alvarez-Lorenzo, *Eur. J. Pharm. Sci*., 2005, **24**, 77-84.
198 Y. K. Lee and D. J. Mooney, *Prog. Polym. Sci*., 2012, **37**, 106-126.
199 S. N. Pawar and K. J. Edgar, *Biomaterial*s, 2012, **33**, 3279–3305.
200 Y. F. Pelegrín and E. Murano, *Bioresour. Technol*., 2005, **96**, 295-302.
201 H. Sjöberg, S. Persson and N. Caram-Lelham, *J. Controlled Release*, 1999, **59**, 391-400.
202 J. Liu, S. Lin, L. Li and E. Liu, *Int. J. Pharm*., 2005, **298**, 117-125.
203 E. Amici, A. H. Clark, V. Normand and N. B. Johnson, *Biomacromolecules*, 2002, **3**, 466-474.
204 W. J. Frith, *Adv. Colloid Interf*., 2010, **161**, 48-60.
205 M. K. Chourasia and S.K. Jain, *Drug Deliv*., 2004, **11**, 129-148.
206 T. W. Wong, G. Colombo and F. Sonvico, *AAPS Pharm. Sci. Tech*., 2011, **12**, 201-214.
207 J. Wang, H. Sun, J. Li, D. Dong, Y. Zhang and F. Yao, *Carbohydr. Polym*., 2015, **117**, 384-391.
208 N. Yamaguchu, L. Zhang, B. S. Chae, C. S. Palla, E.M. Furst and K. L. Kiick, *J. Am. Chem. Soc*., 2007, **129**, 3040-3041.
209 S.H. Kim and K.L. Kiick, *Macromol. Rapid Commun*., 2010, **31**, 1231-1240.
210 A. D. Baldwin and K. L. Kiick, *Biopolymers*, 2009, **94**, 128-140.
211 Q. Wang, W. Wang, J. Wu and A. Wang, *J. Appl. Polym. Sci*., 2012, **124**, 4424-4432.
212 J. Wang, H. Sun, J. Li, D. Dong, Y. Zhang and F. Yao, *Carbohydr. Polym*., 2015, **117**, 384-391.
213 A. H. Faraji, J. J. Cui, Y. Guy, L. Li, C. A. Gavigan, T. G. Strein and S. G. Weber, *Langmuir*, 2011, **27**, 13635-13642.
214 D. R. Albrecht, V. L. Tsang, R. L. Sah, S. N. Bhatia, *Lab on a Chip*. 2005, **5**, 111-118.
215 D. Q. Wu, J. Wu and C. C. Chu, *Soft Matter*, 2013, **9**, 3965-3975.
216 Y. Nakayama, J. Y. Kim, S. Nishi, H. Ueno and T. Matsuda, *J. Bio. Mat. Res.*, 2001, **57**, 559–566.
217 S. Lin, C. Cao, Q. Wang, M. Gonzalez, J. E. Dolbow and X. Zhao, *Soft matter*, 2014, **10**, 7519-7527.
218 J. Elisseeff, W. McIntosh, K. Anseth, S. Riley, P. Ragan and R. Langer, *J. Bio. Mat. Res.*, 2000, **51**, 164-171.
219 J. Carvalho, C. Goncalves, A. M. Gil and F. M. Gama, *Eur. Polym. J*., 2007, **43**, 3050-3059.
220 J. L. Drury and D. J. Mooney, *Biomaterials*, 2003, **24**, 4337-4351.
221 A. Bhattacharya and B. N. Misra, *Prog. Polym. Sci*., 2004, **29**, 767-814.
222 L. Yua, K. Dean and L. Li, *Prog. Polym. Sci*., 2006, **31**, 576-602.
223 B. A. Ibrahim and K. M. Kadum, *Mod. Appl. Sci*, 2010, **4**, 157-161.
224 Y. I. Matveev, V. Y. Grinberg and V. B. Tolstoguzov, *Food Hydrocolloid*., 2000, **14**, 425-437.
225 I. Arvanitoyannis, A. Nakayama and S. Aiba, *Carbohydr. Polym.*, 1998, **37**, 371-382.
226 A. Carvalho, A. Job, N. Alves, A. Curvelo, A. Gandini, *Carbohydr. Polym.*, 2003, **53**, 95-99.
227 J. L. Kokini, G. Baumann, K. Breslauer, P. K. Chedid, L. S. Herh and H. Madeka. A kinetic model for starch gelatinization and effect of starch/protein interactions on rheological properties of 98% amylopectin and amylose rich starches. In: Spiess WEL, Schubert H, editors. Engineering and food-physical properties and process control. London: Elsevier Applied Science; 1990. p. 109-121.
228 Y. I. Matveev, V. Y. Grinberg and V. B. Tolstoguzov, *Food Hydrocolloid*., 2000, **14**, 425-437.
229 H. Warth, R. Mulhaupt and J. Schatzle, *J. Appl. Polym. Sci*., 1997, **64**, 231-242.
230 S. Lepeniotis, B. I. Feuer and J. M. Bronk, *Chemometr. Intelligent Lab. Syst.*, 1998, **44**, 293-306.
231 C. S. Pereira, A. M. Cunha, R. L. Reis, B. Vazquez and J. San Roman, *J. Mater. Sci. Mater. Med*., 1998, **12**, 825-833.
232 I. Espigares, C. Elvira, J. F. Mano, B. Va´ zquez, J. San Roman and R. L. Reis, *Biomaterials*, 2002, **23**, 1883-1895.
233 I. Arvanitoyannis and C. G. Biliaderis, *Carbohydr. Polym*., 1999, 38, 47-58.
234 Y. Ikada, K. Jamshidi, H. Tsuji and S. H. Hyon, *Macromolecules*, 1987, **20**, 904-906.
235 L. Zhang, C. Xiong and X. Deng, *Polymer*, 1996, **37**, 235-241.
236 N. E. Suyatma, A. Copinet, L. Tighzert and V. Coma, *J. Polym. Environ.*, 2004, **12**, 1-6.
237 M. A. Pepenzhik, A. D. Virnik and Z. A. Rogovin, *Vysokomol Soedin Ser. B*, 1969, **11**, 245-250.
238 B. N. Misra, R. Dogra and I. K. Mehta, *J. Polym. Sci. Polym. Chem.*, 1980, **18**, 749-752.
239 B. N. Mishra, I. K. Mehta and R. C. Khetrapal, *J. Polym. Sci. Polym. Chem*., 1984, **22**, 2767–2775.
240 K. V. H. Prasanth and R. N. Tharanathan, *Carbohydr. Polym*., 2003, **54**, 43-51.
241 W. Xie, P. Xu, W. Wang and Q. Liu, *Carbohydr. Polym*., 2002, **50**, 35-40.
242 U. D. N. Bajpai, A. Jain and S. Ray, *J. Appl. Polym. Sci*., 1990, **39**, 2187–2204.
243 B. N. Misra and D. S. Sood, Graft copolymerization of vinyl monomers onto wool by use of TBHP–FAS system as redox initiators. In: Mittal KL, editor. Physicochemical aspects of polymer surfaces. New York: Plenum Press; 1981. p. 881–891.
244 G. Mino, S. Kaizerman and E. Rasmussen, *J. Polym. Sci*., 1958, **31**, 242-247.

245 B. N. Misra, I. Kaur and R. Dogra, *J. Appl. Polym. Sci*., 1979, **24**, 1595-1602.
246 J. Zhang, Z. Yuan, Y. Yuan, J. Shen and S. Lin, *Colloids Surf. B: Biointerf.*, 2003, **30**, 249-257.
247 C. L. Hsueh, Y. J. Peng, C. C. Wang and C. Y Chen, *J. Membr. Sci*., 2003, **219**, 1-13.
248 T. L. Han, R. N. Kumar, H. D. Rozman and M. A. Md Noor, *Carbohydr. Polym*., 2003, **54**, 509-516.
249 J. Zhang, Y. Youling, W. K. Kehua, J. Shen and S. Lin, *Colloids Surf. B: Biointerf*., 2003, **30**, 249-257.
250 Zhang, Y. Youling, J. Shen and S. Lin, *Eur. Polym. J*., 2003, **39**, 847-850.
251 G. Sen, R. Kumar, S. Ghosh, S. Pal, *Carbohydr. Polym*., 2009, **77**, 822-831.
252 S. Moharana, S. B. Mishra and S. S. Tripathy, *J. Appl. Polym. Sci*., 1991, **40**, 345-357.
253 N. Tsubokawa, M. Kobayashi and T. Ogasawara, *Prog. Org. Coatings*, 1999, **36**, 39-44.
254 H. Kubota and Y. Ogiwara, *J. Appl. Polym. Sci*., 1980, **25**, 683-689.
255 H. Kubota and Y. Ogiwara, *J. Appl. Polym. Sci*., 1978, **22**, 3363-3370.
256 H. Kubota and Y. Ogiwara, *J. Appl. Polym. Sci*., 1979, **23**, 241-247.
257 Y. Ogiwara, T. Umasaka and H. Kubota, *J. Appl. Polym. Sci*., 1979, **23**, 837-845.
258 B. V. Kokta, J. L. Valade and C. Daneault, *Transactions*, 1981,7, 5–10.
259 C. I. Simonescu and C. Dumitrice, *J. Polym. Sci*.,1972, 37, 187–203.
260 A. Hebeish, E. M. A. Bary, A. Waly and M. S. Bedawy, *Angew. Makromol. Chem*., 1980, **86**, 47–63.
261 Z. A. Rogovin, editor. Advances in polymer science (translated from the Russian). New York: Halsted Press; 1974, 331 p.
262 V. Hornof, B. V. Kokta and J. L. Valade, *J. Appl. Polym. Sci*., 1975, **19**, 545-556.
263 V. Hornof, B. V. Kokta and J. L.Valade, *J. Appl. Polym. Sci*., 1976, **20**, 1543-1554.
264 Y. Yun, J. Zhang, F. Di, J. Yuan, J. Zhou, J. Shen and S. Lin., *Colloids Surf. B: Biointerf*., 2003, **29**, 247-256.
265 M. Szwarc, *J. Polym. Sci. Part A: Polym. Chem*., 1998, **36**, 1X-XV.
266 K. E. Russell, *Prog. Polym. Sci*., 2002, **27**,1007–1038.
267 U. M. Stehling, E. E. Malmstrom, R. M. Waymouth and C. J. Hawker, *Macromolecules*, 1998, **31**, 4396–4398.
268 V. Percec nad B. Barboiu. *Macromolecules*, 1995, **28**, 7970–7972.
269 J. S. Wang and K. Matyjaszewski, *J. Am. Chem. Soc*.,1995, **117**, 5614–5615.
270 K. Matyjaszewski, J. Xia, *Chem. Rev*., 2001, **101**, 2921–2990.
271 K. Matyjaszewski, *Chem. Eur. J*., 1999, **5**, 3095–3102.
272 V. Coessens, T. Pintauer and K. Matyjaszewski, *Prog.Polym. Sci*., 2001, **26**, 337–377.
273 M. Kato, M. Kamigaito, M. Sawamoto and T. Higashimura, *Macromolecules*, 1995, **28**, 1721–1723.
274 J. S. Wang and K. Matyjaszewski, *Macromolecules*, 1995, **28**, 7901-7910.
275 K. Matyjaszewski, T. E. Patten and J. Xia, *J. Am. Chem. Soc*., 1997, **119**, 674-680.
276 J. Xia and K. Matyjaszewski, *Macromolecules*, 1997, **30**, 7697-7700.
277 J. Xia, S. G. Gaynor and K. Matyjaszewski, *Macromolecules*, 1998, **31**, 5958-5959.
278 H. G. Borner and K. Matyjaszewski, *Macromol. Symp*., 2002, **177**, 1-15.
279 H. J. Paik, S. G. Gaynor and K. Matyjaszewski, *Macromol. Rapid Commun*., 1998, **19**, 47-52.
280 S. C. Hong, T. Pakula and K. Matyjaszewski, *Macromol. Chem. Phys*., 2001, **202**, 3392-3402.
281 K. Matyjaszewski, M. Teodorescu, P. J. Miller and M. L. Peterson, *J. Polym. Sci., Part A: Polym. Chem*., 2000, **38**, 2440-2448.
282 F. G. Garcia, M. R. Pinto and B. G. Soares, *Eur. Polym. J*., 2002, **38**, 759-769.
283 H. B. Sonmez, B. F. Senkal, D. C. Sherrington and N. Bleak, *React. Funct. Polym.*, 2003, **55**, 1-8.
284 M. Sakaguchi and S. Shimada, *Macromolecules*, 2001, **34**, 2089-2094.
285 M. Janata, B. Masar, L. Toman, P. Vlcek, P. Policka, J. Brus and P. Holler, *React. Funct. Polym*., 2001, **50**, 67-75.
286 A. Carlmark and E. Malmstroem, *J. Am. Chem. Soc*., 2002, **124**, 900-901.
287 V. Mishra and R. Kumar, *Carbohyr. Polym*., 2011, **86**, 296-303.
288 D. Wang, J. Tan, H. Kang, L. Ma and X. Jin, *Carbohydr. Polym*., 2011, **84**, 195-202.
289 L. Huang, S. Yuan, L. Lv, G. Tan, B. Ling and S. O. Pehkonen, *J. Colloid Interface Sci*., 2013, **405**, 171-182.
290 I. E. Uflyand, I. A. Ilchenko, V. N. Sheinker and V. S. Savostyanov, *React. Funct. Polym*., 1992, **17**, 289-296.
291 A. Bhattacharya, A. Das and A. De, *Ind. J. Chem. Tech*., 1998, **5**, 135-138.
292 J. Chen, H. Iwata, Y. Maekawa, M. Yoshida and N. Tsubokawa, *Radiat. Phys. Chem*., 2003, **67**, 397–401.
293 P. Marmey, M. C. Porte and C. Baquey, *Nucl. Instrum. Methods B*, 2003, **208**, 429-433.
294 T. Yamaki, M. Asano, Y. Maekawa, Y. Morita, T. Suwa, J. Chen, N. Tsubokawa, K. Kobayashi, H. Kubota and M. Yoshida, *Radiat. Phys. Chem.*, 2003, **67**, 403-407.
295 I. Kaur, R. Barsola, A. Gupta and B. N.Misra, *J. Appl. Polym. Sci.*, 1994, **54**, 1131-1139.
296 I. Kaur, B. N. Misra, M. S. Chauhan, S. Chauhan and A. Gupta, *J. Appl. Polym. Sci*., 1996, **59**, 389-397.
297 I. Kaur, B. N. Misra, R. Barsola and K. Singla, *J. Appl. Polym. Sci*., 1993, **47**, 1165-1174.
298 S. Basu, A. Bhattacharya, P. C. Mondal and S. N. Bhattacharyya, *J. Polym. Sci., Polym. Chem*., 1994, **32**, 2251-2255.
299 S. Aich, A. Bhattacharya and S. Basu, *Radiat. Phys. Chem*., 1997, **50**, 347-354.
300 S. Aich, T. Sengupta T, A. Bhattacharya and S. Basu, *J. Polym. Sci. Polym. Chem*., 1999, **37**, 3910-3915.
301 S. N. Bhattacharyya, D. Maldas and V. K. Pandey, *J. Polym. Sci.*, 1986, **24**, 2507-2515.
302 S. N. Bhattacharyya and D. Maldas, *Prog. Polym. Sci*., 1983, **10**, 171–270.
303 A. Kitamura, S. Hamamoto, A. Taniike, Y. Ohtani, N. Kubota and Y. Furuyama, *Radiat. Phys. Chem*., 2004, **69**, 171-178.
304 R. Mazzei, D. Tadey, E. Smolko and C. Rocco, *Nucl. Instrum. Methods B*., 2003, **208**, 411-415.
305 H. Kubota, I. G. Suka, S. Kuroda and T. Kondo, *Eur. Polym. J*., 2001, **37**, 1367-1372.
306 S. N. Bhattacharyya and D. Maldas, *Prog. Polym. Sci*., 1983, **10**, 171–270.
307 A. Wenzel, H. Yamgishita, D. Kitamoto, A. Endo, K. Haraya, T. Nakane, N. Hanai, H. Matsuda, H. Kamuswetz and D. Paul, *J. Membr. Sci.*, 2000, **179**, 69-77.
308 T. Yamaguchi, S. Yamahara, S. Nakao, S. Kimura, *J. Membr. Sci.*, 1994, **95**, 39-49.
309 T. Chen, G. Kumar, M. T. Harries, P. J. Smith and G. F. Payne, *Biotechnol. Bioeng*., 2000, **70**, 564-573.
310 S. Cosnier, D. Fologen, S. Szunerits and R. S. Marks, *Electrochem. Commun*., 2000, **2**, 827-831.
311 W. E. Hennink and C. F. van Nostrum, *Adv. Drug Delivery Rev*., 2002, **54**, 13-36.
312 P. Gacesa, *Carbohydr. Polym*., 1988, **8**, 161-182.
313 M. F. A. Goosen, G. M. O'Shea, H. M. Gharapetian, S. Chou andd A. M. Sun, *Biotechnol. Bioeng*., 1985, **27**, 146-150.
314 W. R. Gombotz and S. F. Wee, *Adv. Drug Delivery Rev*., 1998, **31**, 267-285.

315 A. K. Andrianov, L. G. Payne, K. B. Visscher, H. R. Allcock and R. Langer, *J. Appl. Polym. Sci*., 1994, **53**, 1573-1578.

316 A. Chenite, C. Chaput, D. Wang, C. Combes, M. D. Buschmann, C. D. Hoemann, J. C. Leroux, B. L. Atkinson, F. Binette and A. Selmani, *Biomaterials*, 2000, **21**, 2155-2161.

317 T. Watanabe, A. Ohtsuka, N. Murase, P. Barth and K. Gersonde, *Magn. Reson. Med*., 1996, **35**, 697-705.

318 K. S. Hossain, K. Miyanaga, H. Maeda and N. Nemoto, *Biomacromolecules*, 2001, **2**, 442-449.

319 K. S. Hossain, K. Miyanaga, H. Maeda and N. Nemoto, *Biomacromolecules*, 2001, **2**, 442-449.

320 K. A. Janes, M. P. Fresneau, A. Marazuela, A. Fabra and M. J. Alonso, *J. Controlled Release*, 2001, **73**, 255-267.

321 F. Yokoyama, I. Masada, K. Shimamura, T. Ikawa and K. Monobe, *Colloid Polym. Sci*., 1986, **264**, 595-601.

322 C. M. Hassan and N. A. Peppas, *Macromolecules*, 2000, **33**, 2472-2479.

323 N. A. Peppas and J. E. Scott, *J. Controlled Release*, 1992, **18**, 95-100.

324 A. Takamura, F. Ishii and H. Hidaka, *J. Controlled Release*, 1992, **20**, 21-27.

325 S. Forster and M. Antonietti, *Adv. Mater*., 1998, **10**, 195-217.

326 D. S. Lee, B. Jeong, Y. H. Bae and S. W. Kim, Proc. *Int. Symp. Controlled Release Bioact. Mater*., 1996, **23**, 228-229.

327 B. Jeong, Y.H. Bae and S.W. Kim, *Macromolecules*, 1999, **32**, 7064–7069.

328 B. Jeong, D.S. Lee, J. I. Shon, Y. H. Bae and S.W. Kim, *J. Polym. Sci., Part A Polym. Chem.*, 1999, **37**, 751-760.

329 I. Rashkov, N. Manolova, S. Li, J. Espartero and M. Vert, *Macromolecules*, 1996, **29**, 50-56.

330 S. Li, I. Rashkov, J. Espartero, N. Manolova and M. Vert, *Macromolecules*, 1996, **29**, 57-62.

331 D. S. G. Hu and H. J. Liu, *J. Appl. Polym. Sci*., 1994, **51**, 473-482.

332 H. Kricheldorf and J. Meier-Haack, *Makromol. Chem.*, 1993, **194**, 715-725.

333 Y. Li and T. Kissel, *J. Controlled Release*, 1993, **27**, 247–257.

334 C. Witt, K. Mader and T. Kissel, *Biomaterials*, 2000, **21**,931-938.

335 C. Witt and T. Kissel, *Eur. J. Pharm. Biopharm*., 2001, **51**, 171-181.

336 K. Pistel, B. Bittner, H. Koll, G. Winter and T. Kissel, *J. Controlled Release*, 1999, **59**, 309-325.

337 B. Bittner, C. Witt, K. Mader and T. Kissel, *J. Controlled Release*, 1999, **60**, 297-309.

338 Y. Li, C. Volland, T. Kissel, *J. Controlled Release*, 1994, **32**, 121-128.

339 K. M. Huh and Y. H. Bae, *Polymer*, 1999, **40**, 6147-6155.

340 Y. H. Bae, K. M. Huh, Y. Kim and K. H. Park, *J. Controlled Release*, 2000, **64**, 3-13.

341 B. Jeong, M. R. Kibbey, J. C. Birnbaum, Y.Y. Won and A. Gutowska, *Macromolecules*, 2000, **33**, 8317-8322.

342 J. M. Bezemer, R. Radersma, D. W. Grijpma, P. J. Dijkstra, J. Feijen and C. A. van Blitterswijk, *J. Controlled Release*, 2000, **64**, 179-192.

343 T. S. Anirudhan, S. Sandeep and P. L. Divya, *RSC Adv*., 2012, **2**, 9555-9564.

344 T. S. Anirudhan and A. M. Mohana, *RSC Adv.*, 2014, **4**, 12109-12118.

345 M. Boruah, P. Gogoi, A. K. Manhar, M. Khannam, M. Mandal and S. K. Dolui, *RSC Adv*., 2014, **4**, 43865-43873.

346 P. B. Kajjari, L. S. Manjeshwar, and T. M. Aminabhavi, *Ind. Eng. Chem. Res*., 2011, **50**, 13280-13287.

347 N. Ahmad, M. C. I. M. Amin, S. M. Mahali and I. Ismail, *Mol. Pharmaceutics*, 2014, **11**, 4130−4142.

348 D. Eagland, N. J. Crowther and C. J. Butler, *Eur. Polym. J*., 1994, **30**, 767-773.

349 C. L. Bell and N. A. Peppas, *J. Controlled Release*, 1996, **39**, 201-207.

350 A. M. Mathur, K. F. Hammonds, J. Klier and A. B. Scanton, *J. Controlled Release*, 1998, **54**,177-184.

351 S. Nagahara and T. Matsuda, *Polym. Gels Networks*,1996, **4**, 111-127.

352 K. P. McGrath, M. J. Fournier, T. L. Mason and D. A. Tirrell, *J. Am. Chem. Soc*., 1992, **114**, 727-733.

353 J. Cappello, J. Crissman, M. Dorman, M. Mikolajczak, G. Textor, M. Marquet anf F. Ferrari, *Biotechnol. Prog*., 1990, **6**, 198-202.

354 E. Yoshikawa, M. J. Fournier, T. Mason and D. A. Tirrell, *Macromolecules*, 1994, **27**, 5471-5475.

355 J. Cappello, J. W. Crissman, M. Crissman, F. A. Ferrari, G. Textor, O. Wallis, J. R. Whitledge, X. Zhou, D. Burman, L. Aukerman and E. R. Stedronsky, *J. Controlled Release*, 1998, **53**, 105-117.

356 W. Petka, J. Harden, K. McGrath, D. Wirtz and D. A. Tirrell, *Science*, 1998, **281**, 389-392.

357 C. Wang, R.J. Stewart and J. Kopecek, *Nature*, 1999, **397**, 417-420.

358 A. Tang, C. Wang, R. J. Stewart and J. Kopecek, J. *Controlled Release*, 2001, **72**, 57-70.

359 R. S. Langer and N. A. Peppas, *Biomaterials*, 1981, **2**, 201-214.

360 R. Bettini, P. Colombo and N. A. Peppas, *J. Controlled Release*, 1995, **37**, 105-111.

361 H. Cicek and A. Tuncel, *J. Polym. Sci., Part A Polym. Chem*., 1998, **36**, 543-552.

362 L. Hovgaard and H. Brondsted, *J. Controlled Release*, 1995, **36**, 159-166.

363 P. Edman, B. Ekman and I. Sjoholm, *J. Pharm. Sci*., 1980, **69**, 838-842.

364 I. P. Sjoholm and P. Edman, The use of biocompatible microparticles as carriers of enzymes and drugs in vivo, in: S.S. Davies, L. Illum, J.G. Vie, E. Tomlinson (Eds.), Microspheres and Drug Therapy. Pharmaceutical, Immunological and Medical Aspects, Elsevier, Amsterdam, 1984, pp. 245-262.

365 K. Park, *Biomaterials*, 1998, **9**, 435-441.

366 P. Artursson, P. Edman, T. Laakso, I. Sjoholm, *J. Pharm. Sci*., 1984, **73**, 1507-1513.

367 J. Heller, S.H. Pangburn, K.V. Roskos, *Biomaterials*, 1990, **11**, 345-350.

368 C. Sturesson and L. D. Wikingsson, *J. Controlled Release*, 2000, **68**, 441-550.

369 G. Giammona, V. Tomarchio, G. Pitarresi and G. Cavallaro, *Polymer*, 1997, **38**, 3315-3323.

370 G. Giammona, G. Pitarresi, G. Cavallaro, S. Buscemi and F. Saiano, *Biochim. Biophys. Acta*, 1999, **1428**, 29-38.

371 G. Giammona, G. Pitarresi, G. Cavallaro and G. Spadaro, *J. Biomed. Sci. Polym. Ed*., 1999, **10**, 969-987.

372 P. Martens and K. S. Anseth, *Polymer*, 2000, **41**, 7715-7722.

373 Y. Jin, J. Yamanaka, S. Sato, I. Miyata, C. Yomota and M. Yonese, , *J. Controlled Release*, 2001, **73**, 173-181.

374 W. N. E. van Dijk-Wolthuis, O. Franssen, H. Talsma, M. J. van Steenbergen, J. J. Kettenes-van den Bosch and W. E. Hennink, *Macromolecules*, 1995, **28**, 6317-6322.

375 E. Marsano, E. Bianchi, S. Gagliardi and F. Ghioni, *Polymer*, 2000, **41**, 533-538.

376 L. K. Huang, R. C. Metha and P. P. DeLucca, *Pharm. Res.*, 1997, **14**, 475-482.

377 S. H. Kim and C. C. Chu, *J. Biomed. Mater. Res.*, 2000, **49**, 517-527.

378 S. H. Kim, C. Y. Won and C. C. Chu, *Carbohydr. Polym*., 1999, **40**, 183-190.

379 N. S. Patil, J. S. Dordick and D. G. Rethwisch, *Biomaterials*, 1996, **17**, 2343-2350.

380 B. D. Martin, R. J. Linhardt and J. S. Dordick, *Biomaterials*, 1998, **19**, 69-76.

381 N. S. Patil, Y. Li, D. G. Rethwisch and J. S. Dordick, *J. Polym. Sci., Part A Polym. Chem*., 1997, **35**, 2221-2229.

382 A. S. Sawhney, C. P. Pathak and J. A. Hubbell, *Macromolecules*, 1993, **26**, 581-587.

383 J. L. West and J. A. Hubbell, *React. Polym*., 1995, **25**, 139-147.
384 J. A. Hubbell, *J. Controlled Release*, 1996, **39**, 305-313.
385 S. Lu and K. S. Anseth, *Macromolecules*, 2000, **33**, 2509-2515.
386 W. N. E. van Dijk-Wolthuis, S. K. Y. Tsang, J. J. Kettenes-vanden Bosch and W. E. Hennink, *Polymer*, 1997, **38**, 6235-6242.
387 Y. Zhang, C. Y. Won and C. C. Chu, *J. Polym. Sci., Part A. Polym. Chem.*, 1999, **37**, 4554–4569.
388 Y. Zhang, C. Y. Won and C. C. Chu, *J. Polym. Sci.,Part A Polym. Chem.*, 2000, 38, 2392-2404.
389 Y. Zhang and C. C. Chu, *J. Biomed. Mater. Res*., 2000, **54**, 1-11.
390 N. A. Peppas and R. E. Benner, *Biomaterials*, 1980, **1**, 158–162.
391 W. S. Dai and T. A. Barbari, *J. Membr. Sci*., 1999, **156**, 67-79.
392 N. Willmott, H. M. H. Kamel, J. Cummings, J.F.B. Stuart, A.T. Florence, Adriamycin-loaded albumin microspheres: lung entrapment and fate in the rat, in: S. S. Davies, L. Illum, J. G. Vie, E. Tomlinson (Eds.), Microspheres and Drug Therapy. Pharmaceutical, Immunological and Medical Aspects, Elsevier, Amsterdam, 1984, pp. 189-205.
393 Y. Tabata and Y. Ikada, *Pharm. Res*., 1989, **6**, 422–427.
394 M. Yamamoto, Y. Tabata, L. Hong, S. Miyamoto, N. Hashimoto and Y. Ikada, *J. Controlled Release*, 2000, **64**, 133-142.
395 S. R. Jameela and A. Jayakrishnan, *Biomaterials*, 1995, **16**, 769-775.
396 J. P. Draye, B. Delaey, A. van de Voorde, A. van den Bulcke, B. Bogdanov and E. Schacht, *Biomaterials*, 1998, **19**, 99-107.
397 J. P. Draye, B. Delaey, A. van de Voorde, A. van den Bulcke, B. de Reu and E. Schacht, *Biomaterials*, 1998, **19**, 1677-1687.
398 K. Y. Lee, K. H. Bouhadir and D. J. Mooney, *Macromolecules*, 2000, **33**, 97–101.
399 K. H. Bouhadir, G. M. Kruger, K. Y. Lee and D. J. Mooney, *J. Pharm. Sci.*, 2000, **89**, 910-919.
400 Y. Luo, R. K. Kirker and G. D. Prestwich, *J. Controlled Release*, 2000, **69**, 169-184.
401 H. Brondsted, L. Hovgaard and L. Simonsen, *Stp. Pharma Sci*., 1995, **5**, 65-69.
402 S. H. Gehrke, L. H. Uhden and J. F. McBride, *J. Controlled Release*, 1998, **55**, 21-33.
403 T. Coviello, M. Grassi, G. Rambone, E. Santucci, M. Carafa, E. Murtas, F.M. Riccieri and F. Alhaique, *J. Controlled Release*, 1999, **60**, 367-378.
404 D. L. Elbert, M. P. Luthof, A. B. Pratt, S. Halstenberg and J. A. Hubbell, *Proc. Int. Symp. Control. Release Bioact. Mater*., 2001, 28, 987-988.
405 A. J. Kuijpers, P. B. van Wachum, M. J. A. van Luyn, G. H. M. Engbers, J. Krijsveld, S. A. J. Zaat, J. Dankert and J. Feijen, *J. Controlled Release*, 2000, **67**, 323-336.
406 P. Eiselt, K. Y. Lee and D. J. Mooney, *Macromolecules*, 1999, **32**, 5561-5566.
407 A. E. J. de Nooy, G. Masci and V. Crescenzi, *Macromolecules*, 1999, **32**, 1318-1320.
408 A. E. J. de Nooy, D. Capitani, G. Masci and V. Crescenzi, *Biomacromolecules*, 2000, **1**, 259-267.
409 T. Ichi, J. Watanabe, T. Ooya and N. Yui, *Biomacromolecules*, 2001, **2**, 204-210.
410 G. Giammona, G. Pitarresi, G. Cavallaro, G. Spadaro, *J. Biomed.Sci. Polym. Ed.*,1999, **10**, 969-987.
411 P. Caliceti, S. Salmaso, A. Lante, M. Yoshida, R. Katakai, F.Martellini, L. H. I. Mei, M. Carenza, *J. Controlled Release*, 2001,**75**, 173-181.
412 N.A. Peppas, A.G. Mikos, Preparation methods and structureof hydrogels, in: N.A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy, Vol. I, CRC Press, Boca Raton, FL, 1986, Chapter 1.
413 N.A. Peppas, E.W. Merrill, *J. Appl. Polym. Sci*., 1977, **21**, 1763-1770.
414 P. Kofinas, V. Athanasssiou, E. W. Merrill, *Biomaterials*, 1996, **17**, 1547-1550.
415 E. W. Merrill, K. A. Dennison, C. Sung, *Biomaterials*, 1993, **14**, 1117-1126.
416 J. L. Stringer, N. A. Peppas, *J. Controlled Release*, 1996, **42**, 195-202.
417 E. Jabbari, S. Nozari, *Eur. Polym. J.*, 2000, **36**, 2685-2692.
418 R. Moerkerke, F. Meeussen, R. Koningsveld, H. Berghmans, W. Mondelaers, E. Schacht, K. Dusek, K. Solc, *Macromolecules*, 1998, **31**, 2223-2229.
419 K. F. Arndt, T. Schmidt, R. Reichelt, *Polymer*, 2001, **42**, 6785–6791.
420 J. J. Sperinde, L. G. Griffith, Macromolecules, 1997, **30**, 5255-5264.
421 E. Westhaus, P. B. Messersmith, *Biomaterials*, 2001, **22**, 453-462.
422 D. Abliz, Y. Duan, L. Steuernagel, L. Xie, D. Li and G. Ziegmann, *Polyms. & Polym. Composites*, 2013, **21**, 341-348.
423 A. Singh, *Nucl. Instrum. Meth. B.*, 2001, **185**, 50-57.
424 C. Decker, *Macromol. Rapid Comm*., 2002, **23**, 1067-1093.
425 D. Bezier, P. Perilleux and Y. Grenie, *Radiat. Phys. Chem.*, 1996, **48**, 171-177.
426 C. Saunders, V. Lopata, J. Barnard and T. Stepanik, *Radiat. Phys. Chem*., 2000, **57**, 441-445.
427 A. J. Berejka and C. Eberle, *Radiat. Phys. Chem*., 2002, **63**, 551-556.
428 C. Dispenza, S. Alessi and G. Spadaro, *Adv. Polym. Tech*., 2008, **27**, 163-171.
429 A. J. Berejka, M. R. Cleland, R. A. Galloway and O. Gregoire, *Nucl. Instrum. Meth. B.*, 2005, **241**, 847-849.
430 A. Endruweit, M. S. Johnson and A. C. Long, *Polym. Composite.*, 2006, **27**, 119-128.
431 Q. Yuan, M. B. Yang and Y. W. Mai, *Adv. Compos. Lett*., 2000, **9**, 341-346.
432 R. Schledjewski, *Plast. Rubber Compos*., 2009, **38**, 379-386.
433 V. Tartrattanakul and D. Jaroendee, *J. Appl. Polym. Sci*., 2006, **102**, 1059-1070.
434 A. M. Visco, L. Calabrese, P. Cianciafara, L. Bonaccorsi and E. Proverbio, *J. Mater. Eng. Perform*., 2007, **16**, 792-799.
435 E. T. Thostenson and T. Chou, *Polym. Composite*., 2001, **22**, 197-212.
436 F. Boey, I. Gosling and S. W. Lye, *J. Mater. Process.Tech*., 1992, **29**, 311-319.
437 F. Boey and C. Y. Yue, *Mater. Sci. Lett*., 1991, **10**, 1333-1334.
438 R. Pitchumani, J. W. Gillespie Jr and M. A. Lamontia M.A., *J. Compos. Mater.*, 1997, **31**, 244-275.
439 J. Tierney and J. W. Gillespie, *J. Compos. Mater*., 2006, **40,** 1487-1506.
440 S. Sharma and I. Luzinov, *J. Compos. Mater*., 2011, **45**, 2217-2224.
441 C. Ageorges and L.Ye, *Compos. Part A.-Appl. S*., 2001, **32**, 1603-1612.
442 Z. S. Colak, F. O. Sonmez and V. Kalenderoglu, *J. Compos. Mater*., 2002, **36**, 721-744.
443 D. Stavrov and H. Bersee, *Compos. Part A.- Appl. S*., 2005, **36**, 39-54.
444 L. Ye, Y. Lu, Z. Q. Su and G. Meng, *Compos. Sci. Technol.*, 2005, **65**, 1436-1446.
445 R. F. Gibson, *Compos. Struct.*, 2010, **92**, 2793-2810.
446 L. Y. Sun, R. F. Gibson, F. Gordaninejad and J. Suhr, *Compos. Sci. Technol.*, 2009, **69**, 2392-2409.
447 J. Baur and E. Silverman, *Mrs Bull.*, 2007, **32**, 328-334.
448 F. H. Gojny, M. Wichmann, B. Fiedler and K. Schulte, *Compos. Sci. Technol.*, 2005, **65**, 2300-2313.
449 J. R. Robinson and V. H. L. Lee, Controlled Drug Delivery: Fundamentals and Applications, 2nd ed. New York, Marcel Dekker, Inc.1987.

450 R. Narasimharao, M. R. Anusha, N. R. Swetha, P. Divyasagar and K. Keerthana, *Int. J. Res. Pharm. Bio. Sci*., 2011, **2**,1118-1133.

451 Y. W. Chien, Novel drug delivery systems. 2nd ed. New York, Marcel Dekker, Inc.1992.

452 B. Vora, A. J. Khopade, V. V. D Jain, Shelly and N. K. Jain, *Indian Drugs*, 1996, **33**, 365-373.

453 X. Xu, Y. Shen, W. Wang, C. Sun, C. Li, Y. Xiong and J. Tu, *Eur. J. Pharm. Biopharm*., 2014, **88**, 998-1004.

454 J. Wu, W. Wei, L.Y. Wang, Z. G. Su, G. H. Ma, *Biomaterials*, 2007, **28**, 2220-2232.

455 J. Kim and A. Chauhan, *Int. J. Pharm*., 2008, **353**, 205–222.

456 I. P. Kaur, A. K. Mitra and D. Aggarwal, *J. Drug Delivery Sci. Tech*., 2007, **17**, 33-41.

457 E. L. Nissenbaum, W. Khan, R. P. Pawar, R. Tabakman , E. Naftali, I. Winkler, O. Kaufman, L. Klapper, A. J. Domb, *Eur. J. Pharm. Biopharm.*, 2012, **82**, 85-93.

458 J. Y. Leea, K. S. Kim, Y. M. Kang, E. S. Kim, S. J. Hwang, H. B. Lee, B. H. Min, J. H. Kim and M. S. Kima, *Int. J. Pharm*., 2010, **392**, 51–56.

459 N. H. Bhanji, G. Chouinard, H. C. Margolese, *Euro. Neuropsychopharm*., 2004, **14**, 87-92.

460 J. Xu, S. Strandman, J. X. X. Zhu, J. Barralet and M. Cerruti, *Biomaterials*, 2015, **37**, 395-404.

461 K. Ertopcu, C. Nayki, P. Ulug, U. Nayki, E. Gultekin, A. Donmez, Y. Yildirim, *Int. J. Gyn. Obs*., 2015, **128**,10-13.

462 H. Shiohira, M. Fujii, N. Koizumi, M. Kondoh and Y. Watanabe, *Int. J. Pharma*., 2009, **379**, 119-124.

463 Y. Yuan, C. Ying, Z. Li, Z. H. ping, G. Y. Sha, Z. Bo, H. Xia, Z. Ling, W. Xiao-hui and C. Li, *Int. J. Pharm*., 2012, **430**, 114-119.

464 L. Wei-Ze, Z. Ning, Z. Y. Qiang, Y. Li-Bin, W. Xiao-Ning, H. Bao-Hua, K. Peng and Z. Chun-Feng, *Eur. J. Pharm. Sci*., 2012, **47**, 162–169.

465 A. Abruzzo, F. Bigucci, T. Cerchiara, B. Saladini, M.C. Gallucci, F. Cruciani, B. Vitali and B. Luppi, *Carbohydr. Polym*., 2013, **91**, 651-658.

466 S. Mazzitelli, C. Pagano, D. Giusepponi,C. Nastruzzi and L. Perioli, *Int. J. Pharm*., 2013, **454**, 47–57.

467 H. J. Lim, E. C. Cho, J. A. Lee and J. Kim, *Colloid Surf, A: Physicochem. Eng. Aspects*, 2012, **402**, 80–87.

468 T. Chandy and C. P. Sharma, *J. Appl. Polym. Sci*., 1992, **44**, 2145-2156.

469 J. H. Kim, J. Y. Kim, Y. M. Lee and K. Y. Kim, *J. Appl. Polym. Sci.*, 1992, **14**, 1823-1828.

470 A. Vashist, A. Vashist, Y. K. Gupta and S. Ahmad, *J. Mater. Chem. B*, 2014, **2**,147-166.

471 C. M. Ji, H. N. Xu and W. Wu, *J. Biomater. Appl*., 2009, **23**, 311-329.

472 C. C. Lin and A. T. Metters, *Adv. Drug Delivery Rev.*, 2006, **58**, 1379-1408.

473 A. Kikuchi and T. Okano, *Adv. Drug Delivery Rev*., 2002, **54**, 53-77.

474 B. Amsden, *Macromolecules*, 1998, **31**, 8382–8395.

475 T. Canal and N. A. Peppas, *J. Biomed. Mater. Res.*, 1989, **23**, 1183–1193.

476 M. N. Mason, A. T. Metters, C. N. Bowman and K. S. Anseth, *Macromolecules*, 2001, **34**, 4630–4635.

477 G. M. Cruise, D. S. Scharp and J. A. Hubbell, *Biomaterials*, 1998, **19**, 1287–1294.

478 J. Siepmann and N. A. Peppas, *Adv. Drug Delivery Rev.*, 2001, **48**, 139–157.

479 R. Bettini, P. Colombo, G. Massimo, P.L. Catellani and T. Vitali, *Eur. J. Pharm. Sci*., 1994, **2,** 213–219.

480 D.G. Kanjickal, S.T. Lopina, *Critical Rev. Ther. Drug Carrier Syst*., 2004, **21**, 345–386.

481 D. M. Silva, C. Nunes, I. Pereira, A. S. P. Moreira, M. R. M. Domingues, M. A. Coimbra and F. M. Gamaa, *Carbohydr. Polym*., 2014, **114**, 458-466.

482 D. H. Hirst, D. Chicco, L. German and R. Duncan, *Int. J. Pharm*., 2001, **230**, 57-66.

483 I. S. Chronakis, *Food Sci. Nutrition*, 1998, **38**, 599-637.

484 D. R. White, P. Hudson and J. T. Adamson, *J. Chrom. A*, 2003, **997**, 79-85.

485 K. Alvani, X. Qi and R. F. Tester, *Starch-Starke*, 2011, **63**, 424-431.

486 M. Molinos, V. Carvalho, D. M. Silva and F. M. Gama, *Biomacromolecules*, 2012, **13**, 517−527.

487 S. Moreira, R. M.G. da Costa, L. Guardao, F. Gartner, M. Vilanova and M. Gama, J. Bio. Comp. Polym., 2010, **25**, 141–153.

488 E. Peers and R. Gokal, *Artificial Organs*, 1998, **22**, 8–12.

489 Y. Takatori, S. Akagi, H. Sugiyama, J. Inoue, S. Kojo, H. Morinaga, K. Nakao, J. Wada and H. Makino, *Clin. J. Am. Soc. Nephr*., 2011, **6**, 1337–1344.

490 A. DeBusk and T. Alleman, Method for preparing medical dressings. Vol. US2006/0018955 A1. Powell, TN: DeRoyal Industries, Inc.

491 J. E. Frampton and G. L. Plosker, *Drugs*, 2003, **63**, 2079-2105.

492 D. H. Hirst, D. Chicco, L. German and R. Duncan, *Int. J. Pharm.*, 2001, **230**, 57-66.

493 D. Hreczuk-Hirst, D. Chicco, L. German and R. Duncan, *Int. J. Pharm*., 2001, **230**, 57−66.

494 M. H. Abo-Shosha, N. A. Ibrahim, E. Allam, M. R. El-Zairy and E. M. El-Zairy, *J. Appl. Polym. Sci*., 2006, **101**, 4290-4300.

495 J. Carvalho, C. Goncalves, A. M. Gil and F. M. Gama, *Eur. Polym. J*., 2007, **43**, 3050-3059.

496 C. Goncüalves, J. A. Martins and F. M. Gama, *Biomacromolecules*, 2007, **8**, 392-398.

497 C. Gonçualves and F. M. Gama, *Eur. Polym. J*., 2008, **44**, 3529–3534.

498 X. Ding, L. Li, P. Liu, J. Zhang, N. Zhou, S. Lu, S. Wei and J. Shen, *Polym. Composites*, 2009, **30**, 976-981.

499 J. Carvalho, M. A. Coimbra and F. M. Gama, *Carbohydr. Polym*., 2009, **75**, 322-327.

500 H. Garcia, A. S. Barros, C. Gonçalves, F. M. Gama and Ana M. Gil, *Eur. Polym. J*., 2008, **44**, 2318–2329.

501 S. Wannachaiyasit, P. Chanvorachote and U. Nimmannit, *AAPS Pharm. Sci. Tech*., 2008, **9**, 840-850.

502 J. Carvalho, S. Moreira, J. Maia and F. M. Gama, *J. Biomed. Mater. Res*., 2010, **93**, 389–399.

503 B. Treetharnmathurot, L. Dieudonné, E. L. Ferguson, D. Schmaljohann, R. Duncan and R. Wiwattanapatapee, *Int. J. Pharm*., 2009, **373**, 68–76.

504 L. G. Gómez-Mascaraque, J. A. Méndez, M. F. Gutiérrez, B. Vázquez and J. S. Román, *Acta Biomater*., 2014, **10**, 798–811.

505 A. Pal and J. K. Dey, *Langmuir*, 2011, **27**, 3401-3408.

506 D. S. Hsieh; Ed. Controlled Release Systems: Fabrication Technology, Volume I, CRC Press, Inc., Boca Raton, Florida, 1987.

507 R. Ghaderi, P. Artusson and J. Carlfors, *Eur. J. Pharm. Sci*., 2000, **10**, 1-9

508 R. Falk, T. W. Randolph, J. D. Meyer, R. M. Kelly and M. C. Manning, *J. Controlled Release*, 1997, **44**,77-85.

509 S. Geresh, G. Y. Gdalevsky, I. Gilboa, J. Voorspoels, J. P. Remon and J. Kost, *J. Controlled Release*, 2004, **94**, 391-399.

510 S. Pal, G. Sen, S. Mishra, R. K. Dey and U. Jha, *J. Appl. Polym. Sci*., 2008, **110**, 392-400.

511 G. Sen and S. Pal, *Int. J. Biol. Macromol*., 2009, **45**, 48-55.

512 USP. General chapter <711> Dissolution, USP 27 - The United states pharmacopeial convention, Inc., Rockville, MD, pp.2303 (2003).

513 M. Donbrow and Y. Samuelov, *J. Pharm. Pharmacol*., 1980, **32**, 463-470.

514 M. Gibaldi and S. Feldman, *J. Pharm. Sci*., 1967, **56**, 1238–1242.

515 R. W. Korsemeyer, R. Gurny, E. Doelker, P. Buri and N. A. Peppas, *Int. J. Pharm*., 1983, **15**, 25–35.

516 T. Higuchi, *J. Pharm. Sci*., 1961, **50**, 874–875.

517 A. W. Hixson and J. H. Crowell, *Ind. Eng. Chem*., 1931, **23**, 923–931.

518 M. Kopcha, N. G. Lordi and K. J. Toja, *J. Pharm. Pharmacol*., 1991, **43**, 382–387.

519 WHO, Technical Report Series, no. 953, Annex. 2, 2009.

520 B. Singh and M. Vashistha, *Nucl. Instrum. Methods Phys. Res., Sect. B*, 2008, **266**, 2009–2020.

521 S. S. Vaghani, M. M. Patel and C. S. Satish, *Carbohydr. Res*., 2012, **347**, 76–82.

522 P. Patel, A. Roy, V. K. SM and M. Kulkarni, *Int. J. Drug Dev. Res*., 2011, **3**, 52–61.

523 A. Mostafavi, J. Emami, J. Varshosaz, N. M. Davies, M. Rezazadeh, *Int. J. Pharmacetics*, 2011, **409**, 128-136.

524 K.Y. Cho, T.W. Chung, B.C. Kim, M.K. Kim, J.H. Lee, W.R. Wee , C.S. Cho, *Int. J. Pharmacetics*, 2003, **260**, 83-91.

525 B. YerriSwamy, C. V. Prasad, C.L.N. Reddy, B. Mallikarjuna, K. C. Rao, M.C.S. Subha, *Cellulose*, 2011, **18**, 349-357.

526 B. Singh, N. Sharma, *Biomacromolecules*, 2009, **10**, 2515–2532.

527 S. Kaity, A. Ghosh, *Ind. Eng. Chem. Res*., 2013, **52**, 10033-10045.

528 P. B. Kajjari, L. S. Manjeshwar, T. M. Aminabhavi, *Ind. Engg. Chem. Res*., 2011, **50**, 13280-13287.

529 M.I. Tadros, *Eur. J. Pharm. and Biopharm*., 2010, **74**, 332-339.

530 S. Nardecchia, M. C. Gutierrez, M. C. Serrano, M. Dentini, A. Barbetta, M. L. Ferrer, F. del Monte, *Langmuir*, 2012, **28**, 15937-15946.