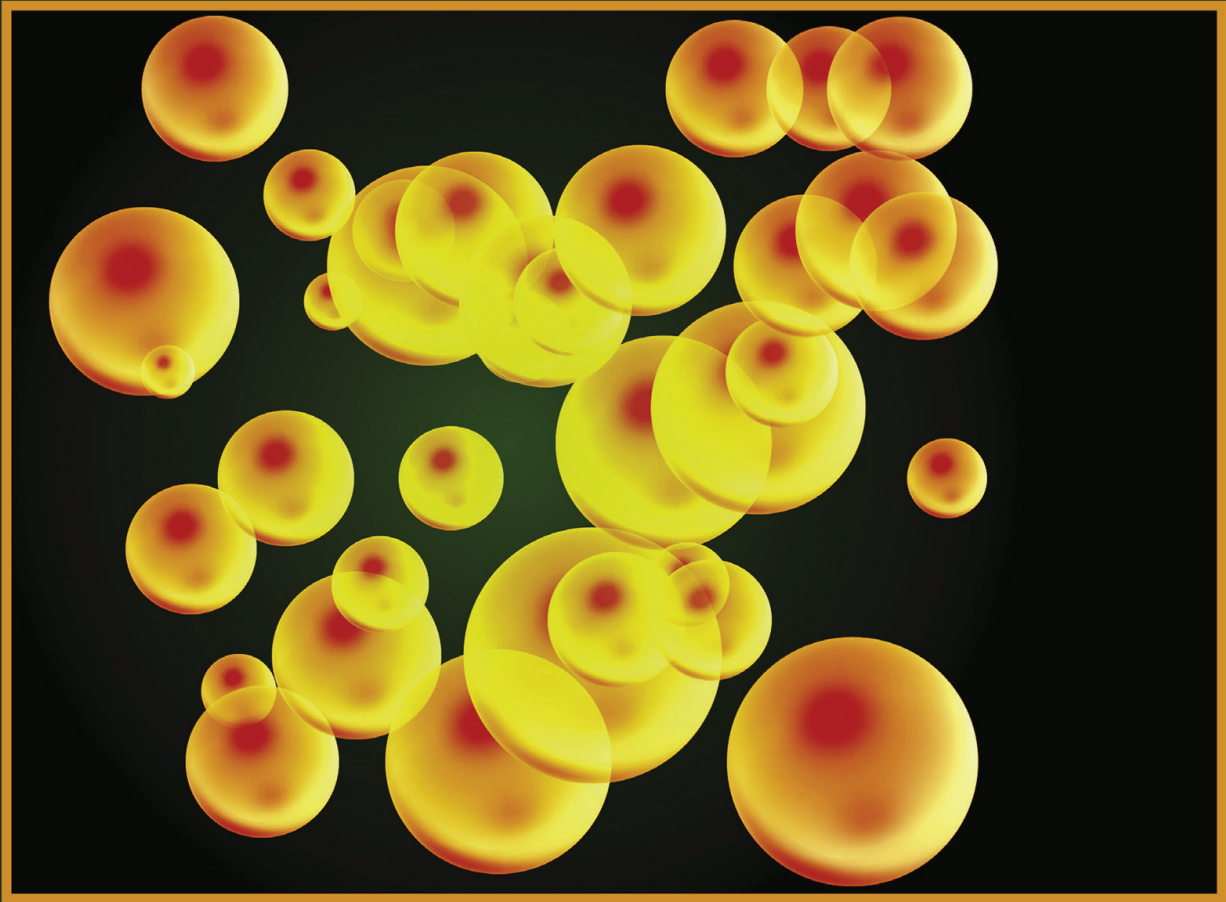
ELSEVIER

WOODHEAD PUBLISHING SERIES IN BIOMATERIALS



POLYSACCHARIDE CARRIERS FOR DRUG DELIVERY

Edited by
SABYASACHI MAITI
SOUGATA JANA

Polysaccharide Carriers for Drug Delivery

This page intentionally left blank

Woodhead Publishing Series in Biomaterials

Polysaccharide Carriers for Drug Delivery

Edited by

Sabyasachi Maiti
Sougata Jana

WP
WOODHEAD PUBLISHING
An imprint of Elsevier

Woodhead Publishing is an imprint of Elsevier
The Officers' Mess Business Centre, Royston Road, Duxford, CB22 4QH, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, OX5 1GB, United Kingdom

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-08-102553-6

Publisher: Matthew Deans
Acquisition Editor: Sabrina Webber
Editorial Project Manager: Leticia M. Lima
Production Project Manager:
Joy Christel Neumarin Honest Thangiah
Cover Designer: Greg Harris

Typeset by SPi Global, India

Contents

This page intentionally left blank

Contributors

Shavej Ahmad Research and Development Centre, Sun Pharmaceutical Industries Ltd., Gurgaon, India

Amani Alhibshi Department of Neuroscience, Institute for Research and Medical Consultations, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Javed Ali Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard (Hamdard University), New Delhi, India

Iman Almansour Epidemic Diseases Department, Institute for Research and Medical Consultations, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Sarah Almofty Department of Stem Cell Biology, Institute for Research and Medical Consultations, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Dana Almohazey Department of Stem Cell Biology, Institute for Research and Medical Consultations, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Munther Alomari Department of Stem Cell Biology, Institute for Research and Medical Consultations, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Leonard Ionut Atanase Department of Biomaterials, Faculty of Dental Medicine, "Apollonia" University of Iasi, Iasi, Romania

Sanjula Baboota Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard (Hamdard University), New Delhi, India

Waisudin Badri School of Bio-Chemical Engineering and Technology, Sirindhorn International Institute of Technology (SIIT), Thammasat University, Pathum Thani, Thailand

Hemant Ramachandra Badwaik Rungta College of Pharmaceutical Sciences and Research, Bhilai, India

Subham Banerjee Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Guwahati, India

Azam Barzegari Department of Chemistry, Amirkabir University of Technology (Tehran Polytechnic), Tehran, Iran

Hriday Bera Faculty of Pharmacy, AIMST University, Bedong, Malaysia; Bengal School of Technology, Sugandha, Hooghly, India

Archana S. Bhadauria Department of Mathematics and Statistics, Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, India

Mallanagouda S. Biradar Shri. B. M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapur, India

Vasile Burlui Department of Biomaterials, Faculty of Dental Medicine, "Apollonia" University of Iasi, Iasi, Romania

Anca Niculina Cadinoiu Department of Biomaterials, Faculty of Dental Medicine, "Apollonia" University of Iasi, Iasi, Romania

Kusal K. Das Shri. B. M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapur, India

Hari Prasanna Deka Boruah Biological Sciences and Technology Division, Academy of Scientific & Innovative Research, CSIR-North East Institute of Science and Technology, Jorhat, India

Abdelhamid Elaissari School of Bio-Chemical Engineering and Technology, Sirindhorn International Institute of Technology (SIIT), Thammasat University, Pathum Thani, Thailand

Hatem Fessi School of Bio-Chemical Engineering and Technology, Sirindhorn International Institute of Technology (SIIT), Thammasat University, Pathum Thani, Thailand

Animesh Ghosh Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi, India

Tapan Kumar Giri NSHM Knowledge Campus, Kolkata Group of Institutions, Kolkata, India

Syed Z. Inamdar BLDEA's SSM College of Pharmacy and Research Centre, BLDE University Campus, Vijayapur, India

Sougata Jana Department of Pharmaceutics, Gupta College of Technological Sciences, Asansol; Department of Health and Family Welfare, Directorate of Health Services, Kolkata, India

Subrata Jana Department of Chemistry, Indira Gandhi National Tribal University, Amarkantak, India

Kai Jin School of Pharmacy, Key Laboratory of Smart Drug Delivery, Ministry of Education, Fudan University, Shanghai, China

Chariya Kaewsaneha School of Bio-Chemical Engineering and Technology, Sirindhorn International Institute of Technology (SIIT), Thammasat University, Pathum Thani, Thailand; Univ Lyon, University Claude Bernard Lyon-1, CNRS, LAGEP-UMR, Lyon, France

Chandrabose Karthikeyan Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, India

Rameshroo Kenwat Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, India

Raghavendra V. Kulkarni BLDEA's SSM College of Pharmacy and Research Centre, BLDE University Campus, Vijayapur, India

Pranesh Kumar Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University, Lucknow, India

Awanish Kumar Department of Biotechnology, National Institute of Technology Raipur, Raipur, India

Ashwini Kumar Department of Biotechnology, National Institute of Technology Raipur, Raipur, India

Shobhit Kumar Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology (MIET), Meerut, India

Dhanabal Kumarasamy NSHM Knowledge Campus, Kolkata Group of Institutions, Kolkata, India

Leena Kumari Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India

Balak Das Kurmi Institute of Pharmaceutical Sciences, Guru Ghasidas University, Bilaspur, India

Yiyang Liu School of Pharmacy, Key Laboratory of Smart Drug Delivery, Ministry of Education, Fudan University, Shanghai, China

Sabyasachi Maiti Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, India

Aanjaneya Mamgain Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, India

Thingreila Muinao Biological Sciences and Technology Division, Academy of Scientific & Innovative Research, CSIR-North East Institute of Science and Technology, Jorhat, India

Bushra Nabi Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard (Hamdard University), New Delhi, India

Chella Naveen Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, India

Amit Kumar Nayak Department of Pharmaceutics, Seemanta Institute of Pharmaceutical Sciences, Mayurbhanj, India

Mintu Pal Biological Sciences and Technology Division, Academy of Scientific & Innovative Research, CSIR-North East Institute of Science and Technology, Jorhat, India

Rishi Paliwal Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, India

Shivani Rai Paliwal Institute of Pharmaceutical Sciences, Guru Ghasidas University, Bilaspur, India

Zhiqing Pang School of Pharmacy, Key Laboratory of Smart Drug Delivery, Ministry of Education, Fudan University, Shanghai, China

M. Prabaharan Department of Chemistry, Hindustan Institute of Technology and Science, Chennai, India

Delia Mihaela Rata Department of Biomaterials, Faculty of Dental Medicine, “Apollonia” University of Iasi, Iasi, Romania

Somasree Ray Department of Pharmaceutics, Gupta College of Technological Sciences, Asansol, India

Saleha Rehman Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard (Hamdard University), New Delhi, India

Subhadeep Roy Department of Pharmaceutical Sciences, School of Bio-Sciences & Bio-Technology, Babasaheb Bhimrao Ambedkar University, Lucknow, India

Sudipta Saha Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University, Lucknow, India

Kalyan Kumar Sen Department of Pharmaceutics, Gupta College of Technological Sciences, Asansol, India

Zahra Shariatinia Department of Chemistry, Amirkabir University of Technology (Tehran Polytechnic), Tehran, Iran

Nalini R. Shastri Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, India

Ashok K. Singh Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University, Lucknow, India

P.R. Sivashankari Department of Chemistry, Hindustan Institute of Technology and Science, Chennai, India

Saundray Raj Soni Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi, India

Kunjbihari Sulakhiya Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, India

Kishor Kumar Suryavanshi Department of Chemistry, Indira Gandhi National Tribal University, Amarkantak, India

Harsh Yadav Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, India

Yuefei Zhu School of Pharmacy, Key Laboratory of Smart Drug Delivery, Ministry of Education, Fudan University, Shanghai, China

Polysaccharide-based stimuli-sensitive graft copolymers for drug delivery

7

Raghavendra V. Kulkarni[*], *Syed Z. Inamdar*[*], *Kusal K. Das*[†] *and Mallanagouda S. Biradar*[†]

[*]BLDEA's SSM College of Pharmacy and Research Centre, BLDE University Campus, Vijayapur, India, [†]Shri. B. M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapur, India

7.1 Introduction

Compounds which contain more than 10 monosaccharide units are called polysaccharides. Generally, these are represented by the formula $C_x(H_2O)_y$ where x represents a number ranging from 200 to 2500, since the repeating units include six carbon monosaccharides present in the polymer backbone, hence they can also be generally denoted as $(C_6H_{10}O_5)n$ where $40 \leq n \leq 3000$. A polymeric carbohydrate molecule containing lengthy chains of monosaccharide joined together by a glycosidic link and which on hydrolysis yields mono and oligosaccharides termed as polysaccharides. Their structure varies from linear to an extremely branched manner. With slight modification in the repeating units, they are often heterogeneous and have distinctive properties based on the structure resulting out of monosaccharide building blocks as amorphous or crystalline compound [1, 2]. The classification of polysaccharides is depicted in Fig. 7.1.

Use of polysaccharides overcame the disadvantages of using synthetic polymers in the field of drug delivery [3]. The renewable resources like selected strains of microbial culture, algal and plant kingdoms, recombinant DNA techniques etc. have made polysaccharides readily available and in abundant form with greater range of compositions, distinctive properties limiting their imitation in the laboratory, and with the ease of production, renders them cost effective compare to synthetic polymers. The recent scientific developments in polysaccharidic hydrogel networks have contributed significantly to this unique material in the development of numerous drug delivery approaches, not only for its greater versatility but also in being used as matrices to encapsulate living cells, as bio-friendly scaffolds for tissue engineering and a polymer for controlled release of proteins. An huge number of polysaccharides have been studied for the development of drug delivery systems; attention was focused on the most recent studies and utilization related to such systems. The intricate structure of polysaccharides attributes to their versatility and variability which is not evident in other polymer classes in terms of chemical derivatizations and extensive applications.

Natural polysaccharides are used in pharmaceutical fields as controlled release carriers for drugs to achieve an optimized concentration, for prolonging the release time,

Polysaccharide Carriers for Drug Delivery. https://doi.org/10.1016/B978-0-08-102553-6.00007-6

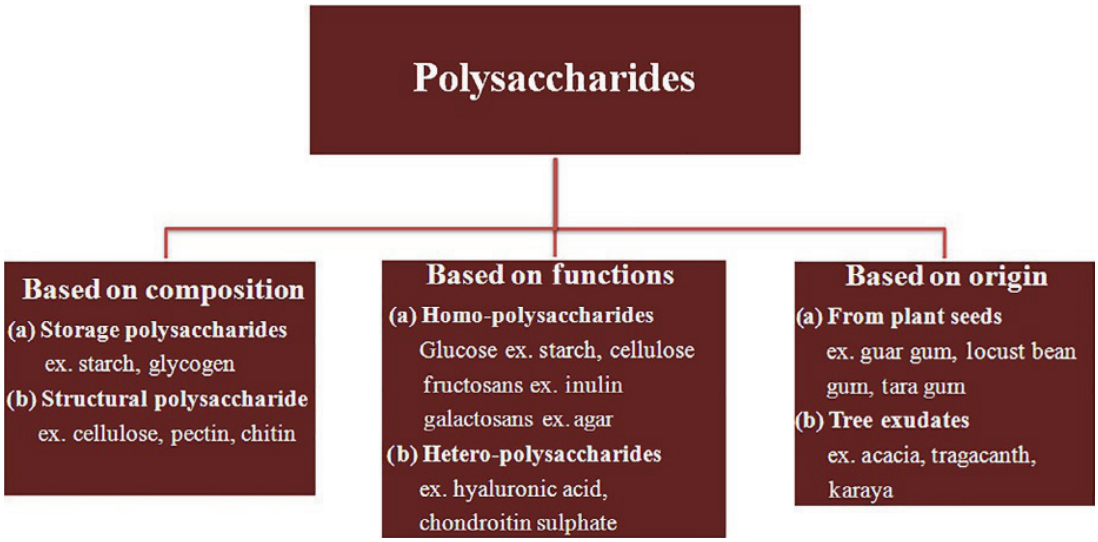


Fig. 7.1 Classification of polysaccharides.

the enhancement of drug activity, and diminishing of side effects [4]. Polysaccharides, when compared to synthetic polymers, are biodegradable, nontoxic, economic, and easily available in nature and their structure can be altered for custom-made drug delivery [5]. Many polysaccharides including sodium alginate [6–10], chitosan [11–15], guar gum [16–18], xanthan gum [19–22], pectin [23, 24], and gellan gum [25, 26] are being utilized either in combination or alone with their indigenous or customized forms to enable controlled release of drugs.

7.2 Grafting reaction

Grafting reaction is a technique wherein the different blocks connect to the main chain of a host polymer as side chains with genuine features which are different from the main chain features (Fig. 7.2). Graft copolymerization acts as a tool for researchers to

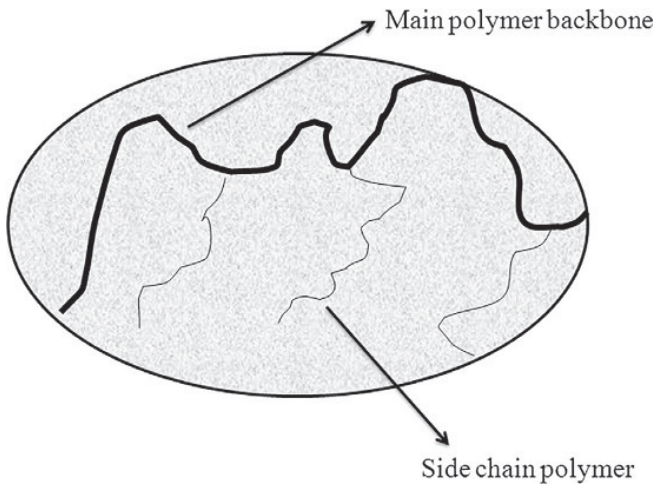


Fig. 7.2 Schematic representation of graft copolymer.

add desired characteristics on the backbones of native polysaccharides for specialty applications. It is a method to hybridize both natural and synthetic polymers and assist in the elemental study of structure-property understanding. Grafting is used to modify the characteristics of host polymers like solubility, glass transition temperature, permeation capability, reactivity, and elasticity as per the need [27–29]. In recent years, modification of natural polysaccharides through graft copolymerization has gained much importance [30–35].

7.3 Principle of grafting reaction

The copolymer generally consists of replicating units of two diverse monomers. Such copolymers are categorized as random copolymers, alternate copolymers, block copolymers, and graft copolymers. In random copolymers, repeating units are randomly positioned; in alternate copolymers, they are in an ordered form, while in the block copolymers, monomers are positioned at terminals; in graft copolymers, the monomer chains are positioned at varied sites on host polymers [36]. Having reactive functional groups on the structure of the host polymer is an essential parameter for the grafting reaction [37].

7.4 Different types of grafting techniques

The principle involved in graft copolymerization is the generation of free radicals on functional groups on the host polymer and, further, polymerization of monomers onto free radical sites brings graft copolymerization. Numerous methods have been explored and reported for the synthesis of graft copolymers [38, 39].

7.4.1 Chemical method

This method involves chemical initiators to produce active sites or free-radicals on the host polymer. Redox initiators such as Lewis acids, strong bases, and metal carbonyls are being used as initiators. An array of free radical initiators and redox schemes viz dibenzoyl peroxide, Azobis(isobutyronitrile), ceric ammonium nitrate, potassium persulphate, and potassium permanganate were utilized to graft the vinyl monomers on polymer backbones [40–43]. Atom transfer radical polymerization is a contemporary method to breed free radical sites on quiescent chains. The method involves capping of halogen atoms onto dormant sites to be transferred to metal complexes in lower states in a reversible manner. The schematic synthetic pathway for free radical graft copolymerization is shown in Fig. 7.3.

7.4.2 Microwave radiation-induced grafting

A greater extent of control can be achieved on the number and length of grafted chains with the approach of radiation induced grafting. The method is most convenient for graft copolymerization, but must be done in a precise manner to select the appropriate

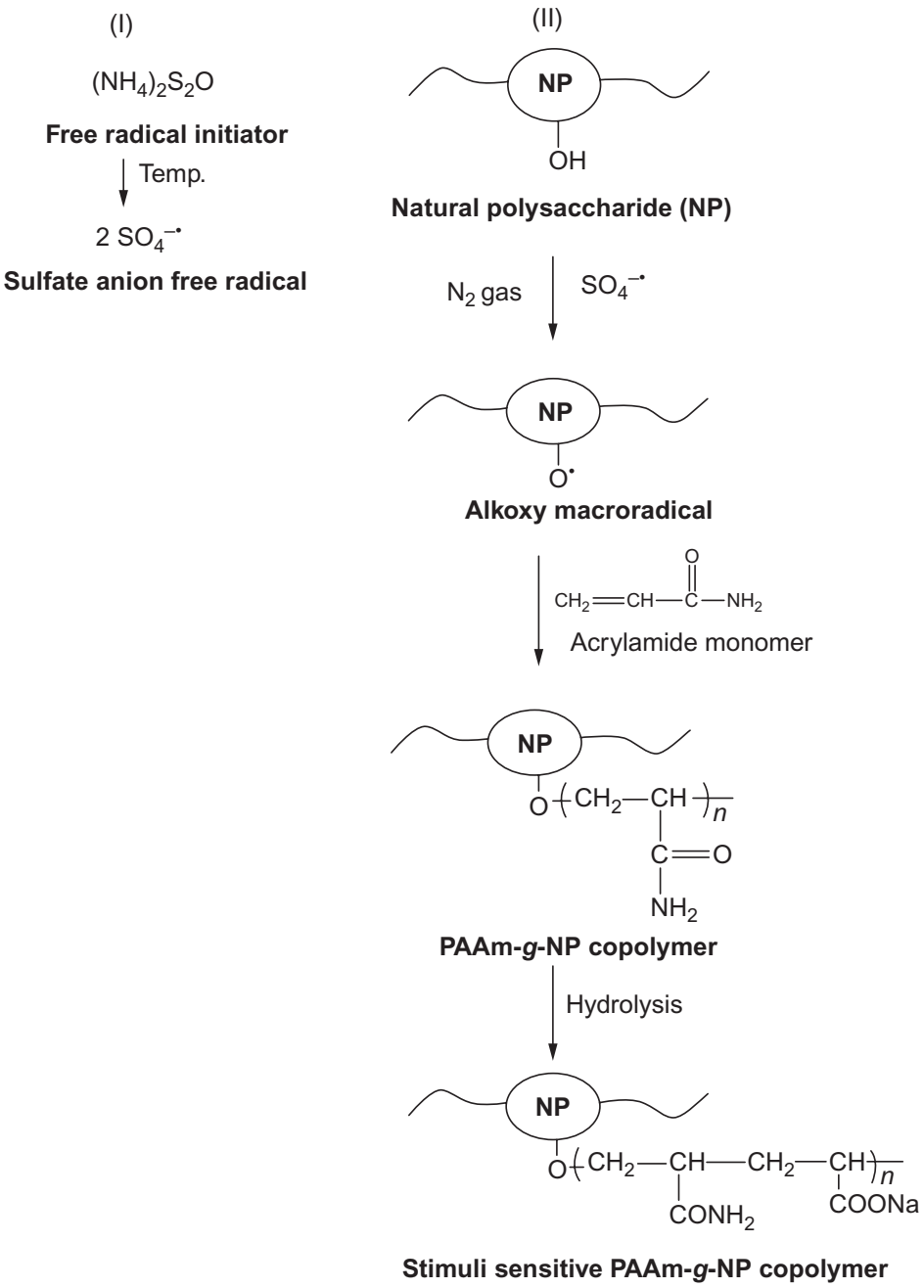


Fig. 7.3 Schematic synthetic pathway for free radical based graft copolymerization.

dose and rate. The active sites or free radicals for the reaction are created when electromagnetic radiation is passing through the host polymer structure. The yield obtained from the radiation technique maintains the highest purity since it is free from contamination. Depending upon the penetration ability of radiation, it facilitates to perform the reaction at different depths of backbone and the molecular weight of the product can be modified in case of radiation-induced grafting. Hence, the radiation technique is preferred because of its unique features [44, 45].

Microwave radiation is a unique energy source for grafting; they can quickly pass the energy into the reaction mixture homogeneously which leads to quick reaction of

reactants in the mixture [46]. Microwave irradiation gives high yields, avoids toxic solvents, and reduces the reaction time for grafting. The polysaccharide copolymers synthesized by microwave radiation methods exhibit better properties for commercial applications when compared to those prepared by conventional methods [47]. The schematic synthetic pathway for microwave-assisted graft copolymerization is shown in Fig. 7.4 and the comparative advantages of grafting reaction using microwaves and conventional methods are given in Table 7.1.

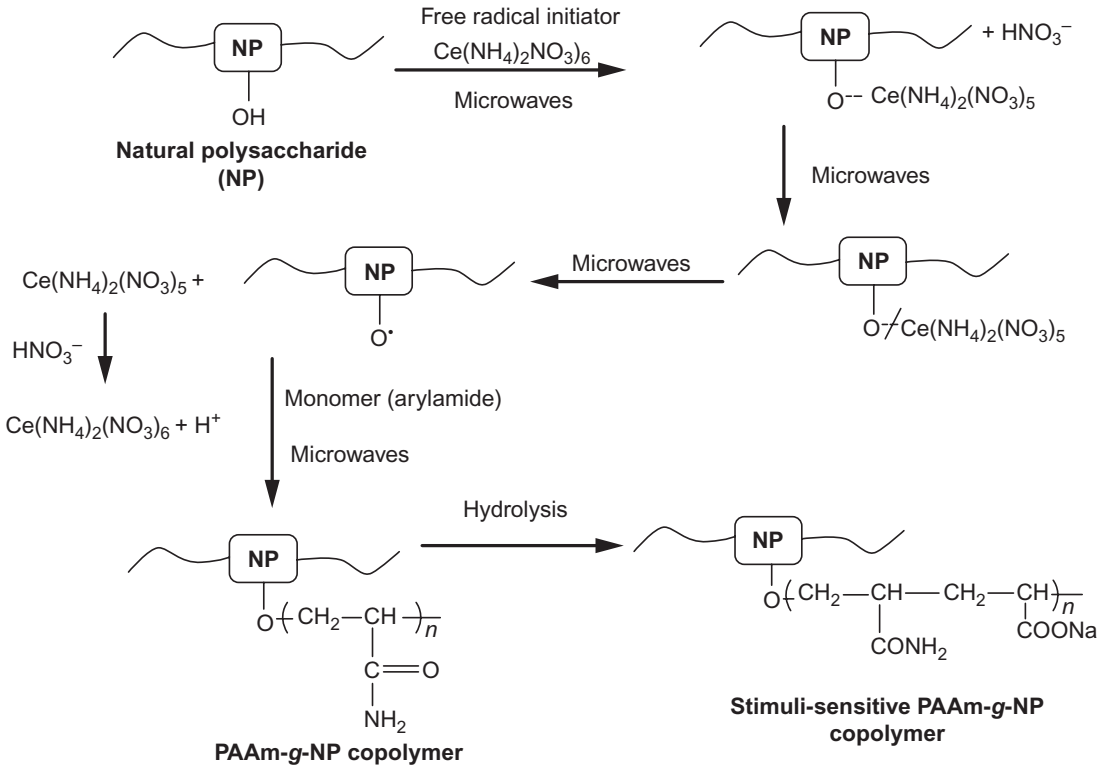


Fig. 7.4 Schematic synthetic pathway for microwave-assisted graft copolymerization.

Table 7.1 Comparison of conventional and microwave-assisted methods of grafting

Conventional method	Microwave-assisted method
A mandatory requirement of inert atmosphere	Can be carried out in atmospheric conditions
Reaction initiators need to be used	Reaction can be carried out without initiator
Longer duration for reaction to be complete	Shorter duration, in a few minutes reaction will be complete
It is a wet reaction either in solution or suspension form	Reaction can be performed in a dry medium
Chances of lower grafting efficiency	Possibilities of higher grafting efficiency
Chances of formation of homopolymer are greater	Homopolymer formation is restricted

7.4.3 Enzymatic grafting

In this method, an enzyme induces a chemical grafting on the host polymer, which requires specific surface alteration and mild reaction conditions to obtain a polymer backbone with a nondestructive transformation to attract its attention. The grafting of natural polysaccharides by enzymatic method has been explored for wider industrial applications. The aqueous solubility of chitosan in basic environment can be achieved through grafting a hydrophilic compound chlorogenic chitosan acid onto chitosan in the presence of a tyrosinase enzyme which bring about conversion of phenolic substrate into *o*-quinone, which further reacts with the amino group of chitosan to produce graft copolymer [48].

7.4.4 Plasma-initiated grafting

Increasing attention has been garnered for polymer surface modification by the plasma polymerization approach. Plasma conditions accomplished during slow discharge give equivalent possibilities as that of ionizing radiations [49, 50]. The main sequences in plasma-initiated grafting are electron-induced excitation and ionization followed by dissociation. Macromolecular radicals initiate the process of graft copolymerization through the accelerated electrons which have sufficient energy to bring on cleavage of the chemical bonds of polymers [51]. Plasma-initiated grafting can be performed by utilizing polymerizing gases and precursors like fluorocarbons, hydrocarbons and silicone-containing monomers. Inert gas like helium or argon, if implied as a carrier gas, can play a significant role in plasma-surface interactions [52].

7.5 Polysaccharides in drug delivery

Polysaccharide-based controlled drug delivery systems are becoming popular because of the following advantages: they can maintain the concentration within the therapeutic range over a desired period of time with a single dose, target drugs to particular organs, reduce the follow-up care and increase patient comfort. Though, these controlled release systems have advantages over the traditional drug delivery systems, they are not responsive to the altering physiological environment in the body; hence novel drug delivery systems are required that can respond to alteration in the physiological environment and accordingly modify the drug release patterns. Consequently, an optimization of drug delivery need is warranted for self-regulated mechanisms. Trying to understand the concept of chronopharmacology and variations in disease symptoms has realized the importance of drug delivery systems which mimic the symptomatic requirement of disease. According to the recent findings, the time of treatment is also an important factor in delivering drugs into the body. These considerations have taken into focus the view of researchers towards the advancement in stimuli responsive drug delivery wherein the requisite quantity of drug is delivered at a specific time to the preferred site in the body [53].

7.6 Stimuli-sensitive polysaccharides in drug delivery

Advancement and improvement in polymer science has developed newer polymers/copolymers for controlled delivery of medicines. A novel such improvement is stimuli-sensitive polymer or smart polymer which has a characteristic physiochemical responsive property to environmental signals and an array of triggering stimuli, such as temperature, ultrasound, light, electricity, pH, ionic strength, enzymes, glucose etc., can be applied. These signals can be unnaturally provided through "external" sources or "internal" atmosphere provided by certain pathophysiological conditions. Remarkable features of smart polymers include tunable sensitivity and flexibility. Several monomers have specific sensitivity to certain stimuli. A customized monomer or homopolymer that will respond to a particular signal or a copolymer responding to multiple stimuli can be adapted. Tuning of polymer sensitivity to a given stimuli within a restricted range was only possible due to polymer resourcefulness and their combination methods. These advantages make smart polymer deliver drugs in an accurate and programmable manner [54].

"Intelligent" or "smart" polysaccharides respond to an array of internal or external stimuli in a distinctive manner with theatrical changes observed in their swelling pattern, network configuration, and mechanical strength or permeability. Such polysaccharides can be effectively used to develop stimuli sensitive drug delivery systems. The utility of smart polysaccharides can release the required amount of drug at an appropriate time and at a defined place in the body upon stimuli application. Moreover, these can be effectively used to mimic in vivo pulsatile release of numerous endogenous hormones. Various stimulus-generating devices are available to produce an external stimulus whereas an internal stimulus is produced within the body to exhibit the desired drug release [55].

7.7 Stimuli-sensitive polysaccharide hydrogels

Hydrogels constitute three-dimensional polymer networks which undergo swelling without dissolving in water. Wichterle and Lim pioneered the development of hydrophilic polymer networks for biological use by utilizing hydrogels as biomaterials [56]. An array of biocompatible products have been developed by diverse physical and chemical cross-linking methods using polysaccharide hydrogels viz; drug delivery systems, implants, surgical sutures, artificial organs, hemodialysis membranes, and soft contact lenses. Upon application of stimuli, stimuli-sensitive hydrogels undergo volume changes (Fig. 7.5.). Hydrogels are rubbery in nature since they absorb large quantity of water and thus are similar to muscles and they are biocompatible. This makes sure that when hydrogels are inserted subcutaneously into the body as implants, minimum mechanical irritation to the surrounding tissues is produced.

A hydrogel can be synthesized by polymerization of monomers simultaneously or linear polymers cross-linkage and cross-linking with polyfunctional monomers. Naturally occurring polymers or polymers from synthetic or semisynthetic origin with

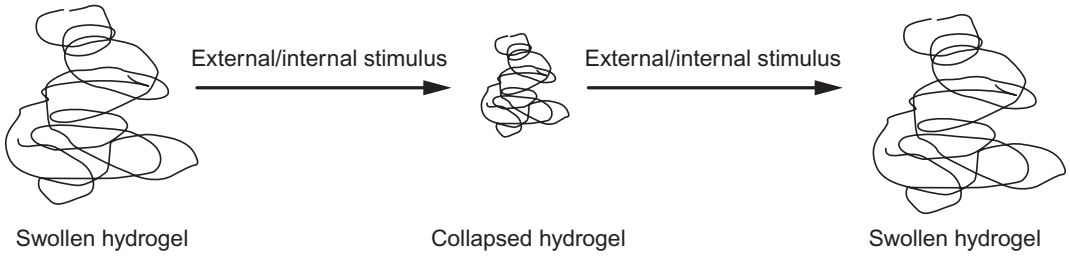


Fig. 7.5 Volume changes of hydrogels in response to external/internal stimulus.

functional groups like hydroxyl, amine, amide, ether, carboxylate, and sulfonate can be used for the synthesis of hydrogels. The cross-linking of linear polymers provides a link between linear chains which leads to the formation of a three-dimensional network structure. Regular covalent bonds (chemical cross-linking) or hydrogen bonds (physical cross-linking) can be used for cross-linking. While, a physically cross-linked hydrogel could be melted to a liquid and again cooled back to solid reversibly, a chemically cross-linked hydrogel can neither be melted nor dissolved in a solvent. The hydrogel networks exhibit viscoelastic and/or elastic behavior, once the cross-links between different polymers chains are introduced. Enzymatic or chemical and more often hydrolysis techniques are employed under normal physiological conditions to break down the labile bonds which are frequently introduced into the polymer to prepare biodegradable hydrogels [57].

7.8 Electrically-sensitive polysaccharides

Electrically responsive polymers are polyelectrolytes carrying cations or anions on their backbone. The required amount of drug "on-demand" from nanoparticles and implants can be released by such polymers. The electrically responsive polymers also show response to pH as they contain greater concentrations of ionizable functional groups. The polymers so far studied include polyanions, polycations, and amphoteric polyelectrolytes. The natural polysaccharides, such as chondroitin sulphate, hyaluronic acid, agarose, xanthan gum, alginates etc., have been investigated [58].

7.8.1 Mechanism of drug release

The drug release behavior from electrically responsive polymers under the electrical stimulus can be controlled by several events such as electrodiffusion, electroosmotic, or electrophoretic, and electrostatic partitioning of charged drugs into the polymer matrix. Three challenging forces such as rubber elasticity, polymer-polymer affinity and ionic pressure play an important role during drug release. These three forces are collectively known as osmotic pressure. The change in balance of these forces leads the polymer to undergo volume change. The osmotic pressure of the polymer matrix is identical to that of the adjacent aqueous solution at equilibrium. The counterion of the polyion (H^+) moves in the direction of the negative electrode (cathode) while the polyions are static when an electric stimulus is applied on the negatively charged polymer

in an aqueous solution. Also, free ions in the adjacent solution go in the direction of their counter electrodes and enter the polymer network. Thus the osmotic pressure of the polymer near a positive electrode (anode) increases and becomes greater than the osmotic pressure near the negative electrode [58]. Therefore, the osmotic pressure difference builds up within the polymer matrix and acts as a driving force for the release of drugs. (A schematic image is shown in Fig. 7.6.)

Recently, a polysaccharide-based electrically responsive poly(acrylamide)-grafted-sodium alginate copolymer was synthesized and studied in its application as a transdermal drug delivery system. The study revealed that the swollen graft copolymer hydrogel underwent shrinking when an electric stimulus was applied. (A schematic image is shown in Fig. 7.7.) It was noticed that an enhanced drug release was seen when the electric stimulus was applied and, further, that the drug release was increased with an increase in electric current density. The synthesized copolymer demonstrated "on and off" a pulsated drug release when the electric stimulus was switched "on and off" respectively. The histopathology study confirmed that the applied electric stimulus altered the structural and cellular integrity of the stratum corneum which could be reversible [59].

The same authors synthesized another polysaccharide-based electro-responsive poly(acrylamide)-grafted-xanthan gum hydrogel for an electro-responsive transdermal delivery of ketoprofen by free radical polymerization in the nitrogen ambiance followed by alkaline hydrolysis. A de-swelling of hydrogel in the electrically charged environs of the electrode was observed when a swollen hydrogel was positioned between two electrodes. The membrane moderated transdermal delivery system was fabricated utilizing ketoprofen loaded hydrogel as the reservoir and cross-linked films

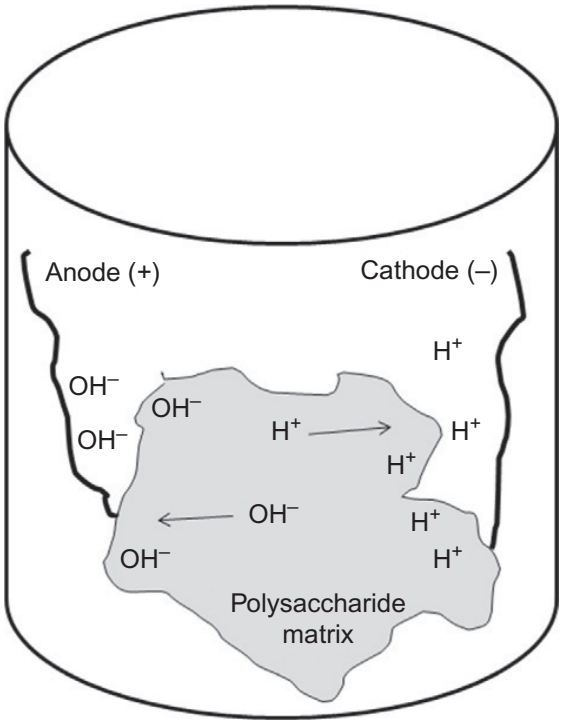


Fig. 7.6 Schematic drug release mechanism from electrically-sensitive polysaccharides.

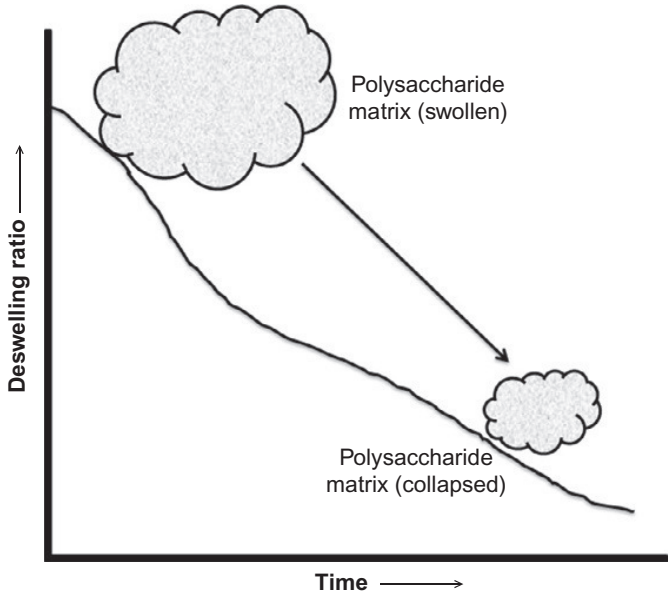


Fig. 7.7 Schematic image of polysaccharide collapse in response to electrical stimulus.

of poly (vinyl alcohol) as rate controlling membranes. The drug permeation study was performed using an excised abdominal rat skin as the biological barrier. The permeation of the drug was greatly enhanced in the electrically stimulated environment against passive diffusion and was directly reliant on the strength of the electric current and the density of the rate controlling membrane. When the electric stimulus was put "on" or "off," it was observed that the drug released in a pulsated manner. The electric stimulus bought alteration in the structure of the stratum corneum and its cells, which was demonstrated by a skin histopathology study. Thus synthesized graft copolymer hydrogel can be effectively used to provide drug release on demand actuated by an electric signal [60].

7.9 pH-sensitive polysaccharides

A very significant parameter that needs to be considered while formulating an oral drug delivery system is gastrointestinal (GI) tract physiology. The GI tract runs into the varied environment of different pH compared to more subtle change in pH ranges among other body tissues. The pH varies between 7.4 and 5.4 for chronic wounds and cancer tissue is acidic in nature extra-cellularly. The same applies to the diverse cellular compartments in the body. This property can be utilized to direct a response to a certain tissue or cellular compartment's changes in pH that occur within the body. In response to external stimulus, local pH varies, which can be utilized for modulating drug release [61].

A pH-sensitive polymer or polyelectrolyte comprising weak acidic or basic functional groups tends to release or accept protons in accordance with the variations in surrounding pH. The acidic or basic functional groups on polyelectrolytes endure ionization similar to that of monoacids or monobases. The electrostatic repulsion

bought by a charged polymer backbone greatly enhances the hydrodynamic volume of the polymer. Any surrounding environment viz pH, ionic strength, and type of counter-ions which tend to vary in terms of electrostatic repulsion will amend this transition between de-swelling and swelling state. This switching from collapsed to swollen state has been explicated by alteration in the osmotic pressure put forth by mobile counterions neutralizing the network charges [62].

Gene and drug delivery systems are the most sought after biomedical application areas where pH sensitive polymers are being used. A variety of polysaccharides viz; dextran, inulin, amylose, guar gum, pectin, chitosan, chondroitin sulphate, and locust beam gum have been explored for pH-sensitive drug release and more often utilize the enteric polymer approach which avoids degradation of the acidic medium and releases the drug in alkaline surroundings of the GI tract owing to salt formation and variation in the pH.

7.9.1 Swelling mechanism of pH-sensitive polysaccharides

The three parameters—namely, hydrophilicity of polymer, the static charges on the polymer, and the counterions within the matrix—which are responsible for swelling/de-swelling of polysaccharides are together termed as "osmotic pressure." Swelling of the polysaccharide matrix usually occurs in three stages [63, 64]:

(a) Diffusion of water molecules into network.
(b) Loosening the polymer network due to hydration.
(c) Expansion of the network due to polymer chain relaxation.

According to the theory of Flory and Rehner, the swelling of polysaccharides occurs because of polymer chains' elasticity and the compatibility of polymer chains with water. The swelling of ionic polysaccharides can be controlled by two parameters [65]:

(a) Properties of the network, such as: cross-link density, ionic charge and hydrophilicity, hydrophobicity.
(b) Properties of fluid medium, such as: ionic strength, pH, and counterion strength.

Thus the pH of the surrounding medium relative to respective pK_a and pK_b values of the pendant groups describe the swelling of polysaccharides with acidic or basic pendant groups. For the anionic matrix (with −COOH groups), if the medium pH is more than the pK_a of acidic groups of polymers, there occurs ionization of acidic groups of the polymer matrix resulting in the formation of set negative charges ($-COO^-$) on the polymer backbone and the positive charges (H^+) are mobile in the fluid medium. Hence, there exists an electrostatic repulsion between the polymer chains leading to the swelling of the matrix and at the same time de-swelling occurs if pH is less than the pK_a. (A schematic image is shown in Fig. 7.8.) While in the case of a cationic polysaccharide network (with $-NH_2$ groups), if the pH of the medium is less than the pK_b of basic functional groups, ionization occurs that results in the formation of positive charges on the polymer backbone and negative charges are movable in the fluid medium; as a result there will be an electrostatic repulsion between the polymer chains leading swelling of matrix and de-swelling occurs if the pH is greater than the pK_b [66, 67].

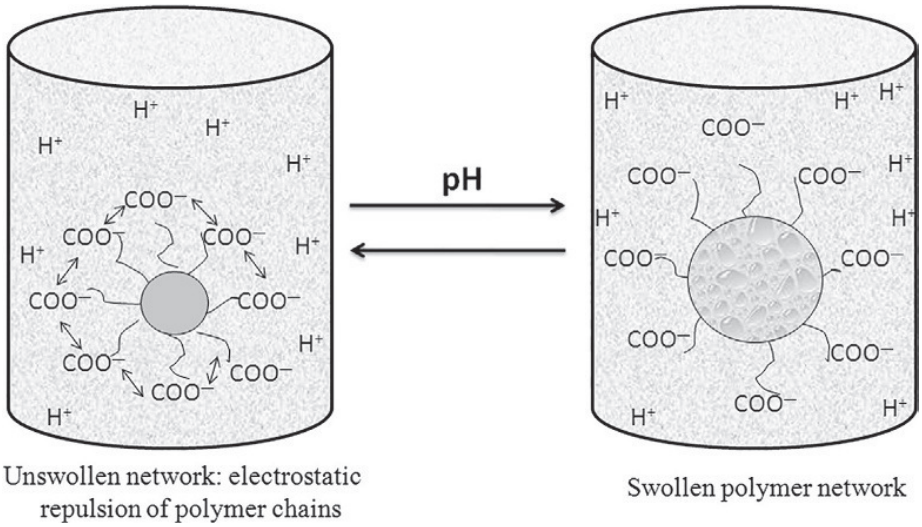


Fig. 7.8 Swelling mechanism of pH-sensitive polysaccharides.

Recently, Dharela et al., have investigated the swelling behavior of guar gum-based hydrogels at varied temperature and pH and salt sensitivity was explored using 0.9% NaCl solution. The hydrogel was prepared by grafting guar gum with acrylic acid using the gamma radiation method. The study revealed rapid swelling and stimuli-sensitiveness at the technologically significant pH or temperature. The hydrogel prepared is simple to produce, biocompatible, biodegradable, and economical. They are technologically significant with a vast potential in the drug delivery and separation processes [68].

Different ratios of guar gum and acrylamide were used to synthesize polyacrylamide-*g*-guar gum graft copolymer and then they were hydrolyzed to introduce carboxylic functional groups. Using the graft copolymer and hydrolyzed graft copolymers, the diltiazem-loaded tablets were prepared using the wet granulation method. A simulated gastric and intestinal environment was set to study the in vitro drug release which continued up to 8 and 12 h respectively for both graft and hydrolyzed copolymers. A dissolution-controlled type of drug release was found to be associated with unhydrolyzed copolymer and with hydrolyzed copolymer, initially swelling-controlled mechanism in 0.1 N HCl solution and later found to be dissolution-controlled in pH 7.4, showing the evidence of pH-sensitivity and thus is of potential to deliver drugs at the intestinal stage [69].

In another study, an enhanced film forming features and gelling characteristics was explored when the pectin-polyacrylamide graft copolymer was cross-linked with varied proportions of glutaraldehyde. The pH-dependent release of salicylic acid was noticed due to pH-dependent swelling of the cross-linked hydrogels [70].

Novel pH-sensitive polysaccharide-based polyacrylamide-grafted-sodium alginate particles were developed for controlled ketoprofen delivery by ionotropic gelation and the covalent cross-linking method. The prepared graft copolymer revealed advanced pH-sensitive behavior by releasing the drug in pH 1.2 solution in a sluggish but steady manner in comparison to buffer solution of pH 7.4. This was due to the fact that in alkaline conditions, swelling of the copolymer tends to be on the higher side. The glutaraldehyde cross-linked graft copolymer particles have demonstrated acceptable

in vitro drug release of 12% and 74% after 2 and 8 h of dissolution studies. The graft copolymer particles were successful in impeding drug release in the stomach and thereby protected the GI tract from any untoward effects such as mucosal erosion of the stomach, ulcer formation, and hemorrhage by virtue of entrapment of the drug in these pH-sensitive graft copolymer particles. This was quite evident through stomach histopathology investigation of albino rats [71].

Following the same procedure, other polysaccharide-based carboxymethylcellulose-(polyacrylamide-grafted-sodium alginate) interpenetrating network particles were prepared for the delivery of ketoprofen to the intestine. The particles which contain only ionic cross-links have developed erosion against particles containing both ionic and covalent cross-links. When the pH of the medium was changed from acidic to alkaline, the swelling of particles and drug release was significantly increased. The release of drug followed the case II mechanism in an acidic environment and the anomalous mechanism in an alkaline dissolution medium [72].

They further investigated preparation of pH sensitive interpenetrating network hydrogel beads utilizing polyacrylamide-*g*-xanthan gum and carboxymethyl cellulose sodium loaded with an antiinflammatory drug, ketoprofen. An electron microscopic study reveals that a porous matrix structure is acquired in the alkaline pH, and in acidic pH the beads acquire a nonporous matrix structure. As the pH varied between 1.2 and 7.4, an enhanced drug release and swelling was observed and it was assumed that ionization of carboxyl functional group of the hydrogel occurs at higher pH values that tend to augment osmotic pressure of beads resulting in greater swelling and drug release [73].

In a similar manner, pH-sensitive ketoprofen-loaded hydrolyzed polyacrylamide-*g*-xanthan microbeads were formulated by an ionotropic gelation technique using aluminum chloride. The drug release pattern from pristine xanthan beads was greater and almost discharged the drug completely in 5 h as compared to beads prepared using graft copolymer, where release was much slower and a maximum of 92.6% was released after 8 h. The graft copolymer beads were successful in impeding release of drug in the stomach and thereby protected the stomach from any untoward effects such as ulcer formation, hemorrhages, and gastric erosion by virtue of entrapment of drug in polyacrylamide-*g*-xanthan gum beads, which was evident through stomach histopathology investigation of albino rats [74].

pH-sensitive graft copolymers of *N*-octyl-*N*-(2-carboxyl-cyclohexamethenyl) chitosan were synthesized and characterization was carried out using FTIR, ^{1}H-NMR and elemental analysis. The critical micelle concentration of modified chitosan was determined using fluorescence spectroscopy and was found to be between 11 to 72 g/mL. A drug loading was found to be between 30.47% and 48.10% and entrapment efficiency was between 42.22% and 59.24%, Further, the pH-sensitivity and drug release pattern demonstrated that at normal physiological pH of 7.4, micelles remain plausibly stable and tend to be very sensitive in a mild acidic environment of pH 5.5. Thus a potential antitumor drug delivery system for cancer chemotherapy can be possible with grafted chitosan micelles [75].

Newer approaches have been reported by employing poly (NIPAAm)/chitosan nanoparticles with pH-sensitive distinctiveness to target the tumors. The drug release

pattern of the graft copolymer was studied. The encapsulation efficiency of 85.7% and loading efficiency of 9.6% was reported. The collective drug release pattern was profoundly improved below pH 6.8 and reduced swiftly above pH 6.9. The drug release was enhanced in the vicinity of the tumor against the normal condition, where the release tends to be slower as evident through MIT assay and fluorescence microscopic study. There was a profound tumor regression effect seen and a complete tumor regression observed was more than 50% of treated mice. The study also reveals that a diminutive reduction in the body weight and enhanced life expectancy in the tumor-afflicted mice administered with drug loaded nanoparticles was observed. Thus these carriers might be an excellent antitumor drug delivery system [76].

The nifedipine loaded pH-sensitive microspheres were developed using sodium alginate-*g*-poly(itaconic acid). The resultant graft copolymer microspheres demonstrated pH-responsive characteristics. At pH 1.2 solution, the drug release pattern for the grafted microsphere was found to be slow compared to that of pH 7.4 buffer solution. It was evident that the increased concentration of drug, graft copolymer, and cross-linking agent has retarded drug release from the microspheres, whereas an increase in graft yield tends to enhance drug release [77].

Further, pH-sensitive semiinterpenetrating network microspheres of chitosan and acrylamide-*g*-hydroxyethylcellulose were developed using glutaraldehyde as a cross-linker (GA) by the emulsion cross-linking method. An effective encapsulation of diclofenac sodium into microspheres was carried out using a varied ratio of polymers. The drug encapsulation was found to be 83% and the mean particle size was in the range of 188–310 μm. The diffusion coefficients of microspheres for water transportation were determined by means of an empirical equation. A buffer solution of pH 1.2 and 7.4 were employed to study the in vitro drug release [78].

Recently, pH-sensitive microspheres were prepared using partially hydrolyzed polyacrylamide-graft-gum karaya by spray dried method containing an anticancer drug, capecitabine for colon-specific drug delivery. The pH-sensitive graft copolymer was developed and characterized successfully using free radical polymerization followed by alkaline hydrolysis. The prepared microspheres were of the desired spherical nature with the drug entrapment efficiency ranging from 77.30% to 88.74%. The graft copolymer shows substantial pH-sensitivity as demonstrated by pulsatile swelling characteristics. The in vitro assessment of drug release for the microspheres prepared using ungrafted karaya gum were not competent to hold back the release of drug in the environment of the stomach and intestine within the first 5 h, whereas the microspheres prepared by means of pH-sensitive graft copolymer having cross-links were able to retard the release of drug considerably within the first 5 h, and able to release a greater amount of drug in a controlled fashion up to 24 h. The cross-linking technique utilizing glutaraldehyde was evident to demonstrate the slow release of drug in the upper GI tract and later delivered the maximum quantity of drug in the lower part of the intestine specifically at colon level. A swift and enhanced drug release was evident in rat caecal content medium owing to colonic bacterial action on the graft copolymer [79].

The colon targeted tablets of salbutamol sulphate were prepared utilizing the graft copolymers of starch-*g*-polymethylmethacrylate and acetylated starch-*g*-polymethylmethacrylate. Drug release from these tablets was pH-dependent and there

was a decreased drug release pattern in an acidic environment as compared to alkaline pH. In comparison to pristine starch and acetylated starch tablets, the pharmacokinetic parameters of graft copolymer tablets have demonstrated noteworthy decrease in C_{max} with an enhanced t_{max}. The gastro-intestinal transit of the tablets was examined by gamma scintigraphy in healthy rabbits. In the stomach condition, the radioactive tracer release was very small from the labeled tablets, but it increased when the tablets reached the large intestine [80].

In another report, polyacrylamide-*g*-carboxymethylcellulose sodium pH-sensitive spray dried microspheres were developed to deliver an anticancer drug—capecitabine—to the colon. The swelling study indicated that the grafted copolymer has considerable pH-sensitive behavior. (A schematic image is shown in Fig. 7.9). The in vitro drug release pattern of microspheres developed using ungrafted carboxymethylcellulose sodium failed to impede drug release in the stomach and small intestine; but those developed using pH-sensitive grafted copolymer were efficient to target the drug to the colon since they reduced release of drug in the upper part of the GIT. Surprisingly, rapid boost in release of drug release was observed in the caecal contents of rats owing to the colonic bacterial effect [81].

Graft copolymer hydrogels of chitosan and acrylic acid were synthesized utilizing *N*,*N*′-methylene-bis-(acrylamide) cross-linker for colon-targeted drug delivery. The swelling pattern in buffer solutions of different pH and colonic enzymatic degradability were analyzed. The hydrogels showed excellent pH-sensitivity and avoided drug release in stomach pH. The gels were degraded by colonic enzymes and a direct correlation between the degradation of the matrix and the swelling of gels was observed; this triggered drug release in the colon [82].

A recent study was reported where a chitosan was grafted with polymethacrylic acid and the matrix was integrated with graphene oxide to develop graft copolymer. This drug delivery tool was efficient to establish drug loading capacity of 93.8% and encapsulation proficiency of 78.6% for doxorubicin. The drug release pattern indicated pH-responsive characteristics. The study reveals that graft copolymer formulations offered a larger drug release at pH 4 and a small amount of drug release at pH 7.4. A 48-h study by MTT assay on MCF7 breast cancer cells showed cytotoxicity

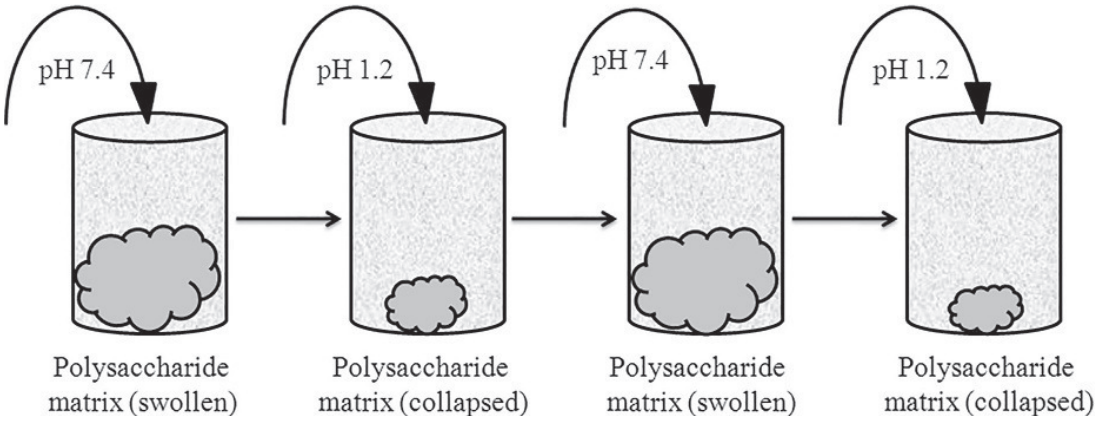


Fig. 7.9 Schematic pH-responsive pulsatile swelling of polysaccharide-based microspheres.

of the developed formulations, which revealed a greater toxicity of free drug against the developed formulations. Therefore, the developed drug delivery tool could be of significant use to optimize or minimize the adverse effects of doxorubicin to improve efficacy during therapeutic payload alterations [83].

7.10 Temperature sensitive polysaccharides

Temperature responsive polymers, a class of environmental sensitive polymers, have been extensively explored owing to their highly promising relevance in the biomedical field. Temperature responsive polymers display a critical solution temperature. At this juncture, the polymer phase and the solution are separated according to their composition. Upper critical solution temperature (UCST) is usually demonstrated by certain polymers as they show one phase above a certain temperature and a phase separation below that temperature. Whereas, lower critical solution temperature (LCST) is usually shown by certain polymer solutions as they tend to appear monophasic below a particular temperature and biphasic above it. An example of poly(*N*-isopropylacrylamide) at temperature of 32°C in water appears to exhibit LCST and the polymer tends to get soluble because of hydrogen bonding below that temperature. A phase separation precipitates owing to predomination of hydrophobic interaction above LCST i.e., cloud point [84].

When a polymer solution endures phase separation at a given critical temperature from a single phase (isotropic state) to two phases (anisotropic state) it is termed LCST. The hydrogen bonding between water and polymer tends to be the cause for polymer solubility below LCST. A hydrophobic reaction ensues if the temperature is raised above LCST; these hydrophobic interactions dictate the precipitation of the polymers. The integration of hydrophilic or hydrophobic groups can alter the LCST of polymers in water solutions. The polymer tends to be in an expanded state and swell at equilibrium hydration degree below the transition temperature and de-swells and tends to be in a collapsed state above the transition temperature [85]. The mechanism is usually reversible and can be implied to demonstrate a pulsatile mannerism of the polymer to act as an "on-off" system whenever the stimuli are applied or removed (see Fig. 7.10).

A controlled release drug delivery tool for 5-fluorouracil was developed by means of thermo-sensitive ionically cross-linked hollow nanospheres from self-assembly of chitosan-graft-poly(*N*-isopropylacrylamide) copolymer. At a temperature above LCST, integration of graft copolymer as core-shell micelles was aggregated by collapsed poly(*N*-isopropylacrylamide) as the core and chitosan as the shell. Altering the environmental temperature and varying the pH resulted in the manipulation of the size of hollow spheres. These hollow spheres demonstrated abundance of internal cavities which enhanced the drug loading efficiency as a result of polymer-drug interactions. At a temperature above LCST, a paid drug release pattern was observed for 5-fluorouracil nanoparticles, possibly due to obliteration of polymer-drug interactions and particle size reduction. The pH alteration and diminutive ionic strength

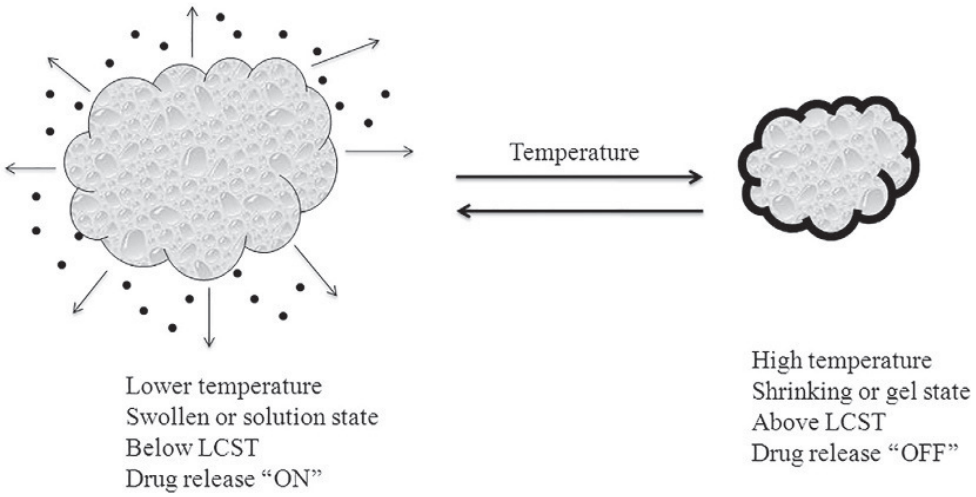


Fig. 7.10 Schematic image of drug release from temperature-sensitive polysaccharides.

disintegrated the hollow sphere structure leading to a greater release of the drug. The developed hallow nanoparticles with environment responsive characteristics have greater potential to be employed in smart drug delivery [86].

An effort was made to develop temperature-sensitive pullulan-grafted-poly(*N*-isopropylacrylamide-*co*-acrylamide) copolymer-based microspheres. The graft copolymer microspheres were more hydrophilic as compared to those prepared from ungrafted pullulan. The thermo-sensitivity of carboxylated microspheres depends on the number and the ionization form of carboxylic groups. Both microspheres acquire a phase transition in isotonic phosphate buffer of pH 7.4 and near human body temperature. Lysozyme drug loading and release patterns were investigated from these microspheres [87].

The turn of the 21st century witnessed a curiosity to develop devices and biomaterials for the delivery of bioactive compounds under external control stimuli. One such study investigates the development of temperature-sensitive beads of indomethacin for colonic delivery. Under microwave radiation, a graft copolymer of sodium alginate and *N*-isopropylacrylamide was synthesized and thoroughly characterized. This study reveals the reduced drug release from the beads if the ratio of graft polymer/drug and cross-linking degree were increased. The study also showed that the beads possess temperature-responsiveness, as the drug release pattern tends to be enhanced at a temperature of 37°C as compared to 25°C [88].

Reversible addition fragmentation chain transfer (RAFT) polymerization of *N*-isopropylacrylamide with tosylic acid-chitosan complex was employed to develop thermo-sensitive chitosan graft copolymers. A controlled polymerization reaction was carried out where chitosan amino group was deprotected using 15% Tris solution, aldehyde vanillin and amino group of chitosan-*g*-PNIPAM copolymer were conjugated through schiff base bond having a loading efficiency of 77.6 mg/g, which can control the drug release with temperature-responsiveness. These characteristics endorse the chitosan graft copolymer as a "smart" drug delivery system [89].

Polymers with temperature responsiveness have been explored as smart drug delivery tools. The chitosan-graft-poly(*N*-isopropylacrylamide) copolymer was made into

nanofibers through electro-spinning using poly(ethylene oxide). The prepared hyrogel nanofibers were investigated for drug release behavior in varied temperature and cytotoxic evaluation by MIT technique using L929 cell lines. The study reveals that the hydrogel nanofibers acquire a temperature-dependent phase transition and LCST at 32°C in aqueous solutions. Altering of environmental temperature can adjust the drug release rate. Further, hydrogel nanofibers were found to have appropriate cytocompatibility indicating the significance of these nanofibers as smart material for drug delivery and tissue engineering [90].

A study was carried out to develop thermo-sensitive chitosan-*g*-poly(*N*-isopropylacrylamide) copolymeric nanoparticles with high drug loading efficiency to deliver the oxaliplatin at the target tumor site. A surfactant-free dispersion copolymerization technique was employed to prepare graft copolymer. This study reveals that the increase in concentration of chitosan resulted in increased percent drug loading and also enhanced release of drug at above LSCT and slower drug release at below LSCT. This demonstrates the thermo-sensitivity characteristics of synthesized copolymer in drug delivery [91].

7.11 Conclusions

The need-based supply of medicines to the body (chronotherapy) is said to be expensive initially, but it will be cost effective in the near future. Administration of drugs at the required amount, at the required time, and at the requited site in the body reduces the systemic side effects, dosage, and enhances therapeutic efficacy and patient comfort. The stimuli-sensitive polymers play a vital role in chronotherapy and they can be prepared by grafting reaction to blend in some desired characteristics on the backbone of the host polymer, which in turn offer many applications in drug delivery. The literature survey has witnessed that there is increased research activity on the synthesis of stimuli-sensitive polymers as carriers for "smart or intelligent" drug delivery systems to treat diseases that follow a circadian pattern of symptom appearance and show timely variation in pathophysiology, symptom intensity, and lethal events.

Regardless of the fact that stimuli-sensitive polymers have wide applications in drug delivery, there are still challenges for the development of effective drug delivery systems which can work properly in the preferred manner under the acidic and basic environment of the body by maintaining the mechanical strength and integrity of dosage forms. Hence, there is an urgent need of a multidisciplinary research approach and combined efforts from biomedical, pharmaceutical, and polymer scientists to get effective drug delivery systems onto the market.

References

[1] Zohuriaan-Mehr MJ. Advances in chitin and chitosan modification through graft copolymerization: a comprehensive review. Iran Polym J 2005;14:235–65.

[2] Yadav G, Sharma N, Bansal M, Thakur N. Application of natural polysaccharide for delivery of biopharmaceuticals. Int J Pharm Life sci 2013;4:2756–65.

[3] Deshmukh AS, Setty CM, Badiger AM, Muralikrishna KS. Gum ghatti: a promising polysaccharide for pharmaceutical applications. Carbohydr Polym 2012;87:980–6.
[4] Parmar NS, Shivprakash B. Biopharmaceutical and pharmacokinetic considerations. In: Jain NK, editor. Controlled and novel drug delivery. 1st ed. New Delhi: CBS Publishers and Distributors; 1997. p. 1–2.
[5] Bhardwaj TR, Kanwar M, Lal R, Gupta A. Natural gums and modified natural gums as sustained-release carriers. Drug Dev Ind Pharm 2000;26:1025–38.
[6] Badwan AA, Abumalooh A, Sallam E, Abukalaf A, Jawan OA. Sustained release drug delivery systems using calcium alginate beads. Drug Dev Ind Pharm 1985;11:239–56.
[7] Arıca B, Çal S, Ka HS, Sargon MF, Hincal AA. 5-Fluorouracil encapsulated alginate beads for the treatment of breast cancer. Int J Pharm 2002;242:267–9.
[8] Halder A, Mukherjee S, Sa B. Development and evaluation of polyethyleneimine-treated calcium alginate beads for sustained release of diltiazem. J Microencapsul 2005;22:67–80.
[9] Sarmento B, Ferreira D, Veiga F, Ribeiro A. Characterization of insulin-loaded alginate nanoparticles produced by ionotropic pre-gelation through DSC and FTIR studies. Carbohydr Polym 2006;66:1–7.
[10] Ahmad Z, Pandey R, Sharma S, Khuller GK. Alginate nanoparticles as antituberculosis drug carriers: formulation development, pharmacokinetics and therapeutic potential. Indian J Chest Dis Allied Sci 2006;48:171–6.
[11] Sezer AD, Akbuga J. Release characteristics of chitosan treated alginate beads: II. Sustained release of a low molecular drug from chitosan treated alginate beads. J Microencapsul 1999;16:687–96.
[12] Janes KA, Alonso MJ. Depolymerized chitosan nanoparticles for protein delivery: preparation and characterization. J Appl Polym Sci 2003;88:2769–76.
[13] Yassin AEB, Alsarra IA, Al-Mohizea AM. Chitosan beads as a new gastroretentive system of verapamil. Sci Pharm 2006;74:175–88.
[14] Srinatha A, Pandit JK, Singh S. Ionic crosslinked chitosan beads for extended release of ciprofloxacin: in vitro characterization. Indian J Pharm Sci 2008;70:16–21.
[15] Badawi AA, El-Laithy HM, El Qidra RK, El Mofty H, El dally M. Chitosan based nanocarriers for indomethacin ocular delivery. Arch Pharm Res 2008;31:1040–9.
[16] Thimma RT, Tammishetti S. Barium chloride crosslinked carboxymethyl guar gum beads for gastrointestinal drug delivery. J Appl Polym Sci 2001;82:3084–90.
[17] Reddy T, Tammishetti S. Gastric resistant microbeads of metal ion cross-linked carboxymethyl guar gum for oral drug delivery. J Microencapsul 2002;19:311–8.
[18] Al-Saidan SM, Krishnaiah YS, Patro SS, Satyanaryana V. In vitro and in vivo evaluation of guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. AAPS PharmSciTech 2005;6:E14–21.
[19] Talukdar MM, Kinget R. Swelling and drug release behaviour of xanthan gum matrix tablets. Int J Pharm 1995;120:63–72.
[20] Yeole PG, Galgatte UC, Babla IB, Nakhat PD. Design and evaluation of xanthan gum-based sustained release matrix tablets of diclofenac sodium. Indian J Pharm Sci 2006;68:185–9.
[21] Maiti S, Ray S, Mandal B, Sarkar S, Sa B. Carboxymethyl xanthan microparticles as a carrier for protein delivery. J Microencapsul 2007;24:743–56.
[22] Jain S, Yadav SK, Patil UK. Preparation and evaluation of sustained release matrix tablet of furosemide using natural polymers. Research J Pharm Tech 2008;1:374–6.
[23] Aydin Z, Akbug J. Preparation and evaluation of pectin beads. Int J Pharm 1996;137:133–6.
[24] Sriamornsak P, Nunthanid J. Calcium pectinate gel beads for controlled release drug delivery: I. Preparation and in vitro release studies. Int J Pharm 1998;160:207–12.

[25] Patil S, Sharma S, Nimbalkar A, Pawar A. Study of formulation variables on properties of drug-gellan beads by factorial design. Drug Dev Ind Pharm 2006;32:315–26.
[26] Parauvathanahalli S, Mishra RB. Preparation and in vitro characterization of gellan based floating beads of acetohydroxamic acid for eradication of H. pylori. Acta Pharma 2007;57:413–27.
[27] Fares MM, El-faqeeh AS, Osman ME. Graft copolymerization onto starch—I. Synthesis and optimization of starch grafted with N-tert-butylacrylamide copolymer and its hydrogels. J Polym Res 2003;10:119–25.
[28] Moreira ACE, Oliveira MG, Soares BG. Thermal degradation studies of poly (EVAL-gmethylmethacrylate). Polym Degrad Stab 1997;58:181–5.
[29] Kaith BS, Kalia S. A study of crystallinity of graft copolymers of flax fiber with binary vinyl monomers. E-Polymers 2008;2:1–6.
[30] Meshram MW, Patil VV, Mhaske ST, Thorat BN. Graft copolymers of starch and its application in textiles. Carbohydr Polym 2009;75:71–8.
[31] Kaith BS, Singha AS, Kumar S, Kalia S. Mercerization of flax fiber improves the mechanical properties of fiber-reinforced composites. Int J Polym Mater 2008;57:54–72.
[32] Dhiman PK, Kaur I, Mahajan RK. Synthesis of a cellulose-grafted polymeric support and its application in the reductions of some carbonyl compounds. J Appl Polym Sci 2008;108:99–111.
[33] El-Sherbiny IM. Synthesis, characterization and metal uptake capacity of a new carboxymethyl chitosan derivative. Eur Polym J 2009;45:199–210.
[34] Wibowo AC, Desai SM, Mohanty AK, Drzal LT, Misra M. A solvent free graft copolymerization of maleic anhydride onto cellulose acetate butyrate bioplastic by reactive extrusion. Macromol Mater Eng 2006;291:90–5.
[35] Kalia S, Kaith BS, Sharma S, Bhardwaj B. Mechanical properties of flax-g-poly(methyl acrylate) reinforced phenolic composites. Fibers Polym 2008;9:416–22.
[36] Stannett V. Grafting. Radiat Phys Chem 1981;18:215–22.
[37] Athawale VD, Rathi SC. Graft polymerization: starch as a model substrate. J Macromol Sci Rev Macromol Chem Phys 1999;C39:445–80.
[38] Fernandez MJ, Casinos I, Guzman GM. On the graft copolymerization: effect of the way of addition of reactants in the graft copolymerization of a vinyl acetate methyl acrylate mixture onto cellulose. J Polym Sci A Polym Chem 1990;28:2275–92.
[39] Hsu ST, Pan TC. Adsorption of paraquat using methacrylic acid-modified rice husk. Bioresour Technol 2007;98:3617–21.
[40] Cho CG, Lee K. Preparation of starch graft copolymer by emulsion polymerization. Carbohydr Polym 2002;48:125–30.
[41] Misra BN, Dogra R. Grafting onto starch. IV. Graft copolymerization of methylmethacrylate by use of AIBN as radical initiator. J Macromol Sci Chem A 1980;14:763–70.
[42] Chiang HC. The improvements in flame retardance and mechanical properties of polypropylene/Fr. blends by acrylic acid graft copolymerization. Eur Polym J 1996;32:385–90.
[43] Zahran MK, Mahmoud RI. Peroxydiphosphate metal ion cellulose thiocarbonate redox system-induced graft copolymerization of vinyl monomers onto cotton fabric. J Appl Polym Sci 2003;87:1879–89.
[44] Kaith BS, Kalia S. Preparation of microwave radiation induced graft copolymers and their applications as reinforcing material in phenolic composites. Polym Compos 2008;29:791–7.
[45] Khan MA, Shehrzade S, Sarwar M, Chowdhury U, Rahman MM. Effect of pretreatment with UV radiation on physical and mechanical properties of photocured jute yarn with 1,6-hexanediol diacrylate (HDDA). J Polym Environ 2001;9:115–24.

[46] Singh V, Tiwari A, Tripathi DN, Sanghi R. Microwave enhanced synthesis of chitosan graft-polyacrylamide. Polymer 2006;47:254–60.
[47] Singh V, Kumar P, Sanghi R. Use of microwave irradiation in the grafting modification of the polysaccharides: a review. Prog Polym Sci 2012;37:340–64.
[48] Kumar G, Smith PJ, Payne GF. Enzymatic grafting of a natural product onto chitosan to confer water solubility under basic conditions. Biotechnol Bioeng 1999;63:154–65.
[49] Wenzel A, Yamgishita H, Kitamoto D, Endo A, Haraya K, Nakane T, Hanai N, Matsuda H, Kamuswetz H, Paul D. Effect of preparation condition of photoinduced graft filling polymerized membranes on pervaporation performance. J Membr Sci 2000;179:69–77.
[50] Yamaguchi T, Yamahara S, Nakao S, Kimura S. Preparation of pervaporation membranes for removal of dissolved organics from water by plasma-graft filling polymerization. J Membr Sci 1994;95:39–49.
[51] Bhattacharyaa A, Misra BN. Grafting: a versatile means to modify polymers techniques, factors and applications. Prog Polym Sci 2004;29:767–814.
[52] Kale KH, Desai AN. Atmospheric pressure plasma treatment of textiles using nonpolymerizing gases. Indian J Fibre Text Res 2011;36:289–99.
[53] Stubble BG, Smedt SC, Demester J. Programmed polymeric devices for pulsed drug delivery. Pharm Res 2004;21:512–8.
[54] Hilt JZ, Peppas NA. Microfabricated drug delivery devices. Int J Pharm 2005;306:15–23.
[55] Kost J, Langer R. Responsive polymeric delivery systems. Adv Drug Deliv Rev 2001;46:125–48.
[56] Wichterle O, Lim D. Hydrophilic gels for biological use. Nature 1960;185:117–8.
[57] Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev 2001;53:321–39.
[58] Kulkarni RV, Sa B. Electrically responsive smart hydrogels in drug delivery: a review. J Appl Biomater Biomech 2007;5:125–39.
[59] Kulkarni RV, Setty CM, Sa B. Polyacrylamide-g-alginate-based electrically responsive hydrogel for drug delivery application: synthesis, characterization, and formulation development. J Appl Polym Sci 2010;115:1180–8.
[60] Kulkarni RV, Sa B. Electroresponsive polyacrylamide-grafted-xanthan hydrogels for drug delivery. J Bioact Compat Polym 2009;24:368–84.
[61] Siegel RA, Falamarzian M, Firestone BA, Moxley BC. pH-controlled release from hydrophobic/polyelectrolyte co-polymer hydrogels. J Control Release 1988;8:179–82.
[62] Firestone BA, Siegel RA. Kinetics and mechanisms of water sorption in hydrophobic ionizable copolymer gels. J Appl Polym Sci 1991;43:901–14.
[63] Ferreira L, Vidal MM, Gil MH. Evaluation of poly(2-hydroxyethyl methacrylate) gels as drug delivery systems at different pH values. Int J Pharm 2000;194:169–80.
[64] Gutowska A, Bae YH, Feijen J, Kim SW. Heparin release from thermosensitive hydrogels. J Control Release 1992;22:95–104.
[65] Ullah F, Othman MBH, Javed F, Ahmad Z, Akil HM. Classification, processing and application of hydrogels: a review. Mater Sci Eng C 2015;57:414–33.
[66] Buenger D, Topuz F, Groll J. Hydrogels in sensing applications. Prog Polym Sci 2012;37:1678–719.
[67] Gupta P, Vermani K, Garg S. Hydrogels: from controlled release to pH-responsive drug delivery. Drug Discov Today 2002;7:569–79.
[68] Dharela R, Raj L, Chauhan GS. Synthesis, characterization, and swelling studies of guar gum-based pH, temperature and salt responsive hydrogels. J Appl Polym Sci 2012;126:E260–5.

[69] Toti US, Aminabhavi TM. Modified guar gum matrix tablet for controlled release of diltiazem hydrochloride. J Control Release 2004;95:567–77.
[70] Sutar PB, Mishra RK, Pal K, Banthia AK. Development of pH sensitive polyacrylamide grafted pectin hydrogel for controlled drug delivery system. J Mater Sci Mater Med 2008;19:2247–53.
[71] Kulkarni RV, Sa B. Polyacrylamide-graftedalginate-based pH-sensitive hydrogel beads for delivery of ketoprofen to the intestine: in vitro and in vivo evaluation. J Biomater Sci Polym Ed 2009;20:235–51.
[72] Kulkarni RV, Sa B. Novel pH-sensitive interpenetrating network hydrogel beads of carboxymethylcellulose-(polyacrylamide-graftedalginate) for controlled release of ketoprofen: preparation and characterization. Curr Drug Deliv 2008;5:256–64.
[73] Kulkarni RV, Sa B. Evaluation of pH-sensitivity and drug release characteristics of (polyacrylamide-grafted-xanthan)-carboxymethyl cellulose-based pH-sensitive interpenetrating network hydrogel beads. Drug Dev Ind Pharm 2008;34:1406–14.
[74] Kulkarni RV, Sa B. Enteric delivery of ketoprofen through functionally modified poly(acrylamide-grafted-xanthan)-based pH-sensitive hydrogel beads: preparation, in vitro and in vivo evaluation. J Drug Target 2008;16:167–77.
[75] Liua J, Li H, Jiang X, Zhang C, Pinga Q. Novel pH-sensitive chitosan-derived micelles loaded with paclitaxel. Carbohydr Polym 2010;82:432–9.
[76] Li F, Wu H, Zhang H, Li F, Gu C, Yang Q. Antitumor drug paclitaxel-loaded pH-sensitive nanoparticles targeting tumor extracellular pH. Carbohydr Polym 2009;77:773–8.
[77] Nuran I, Murat I, Kurs F, Ercan G. pH-responsive itaconic acid grafted alginate microspheres for the controlled release of nifedipine. Carbohydr Polym 2011;84:933–43.
[78] Al-Kahtani Ahmed A, Bhojya Naik HS, Sherigara BS. Synthesis and characterization of chitosan-based pH-sensitive semi-interpenetrating network microspheres for controlled release of diclofenac sodium. Carbohydr Res 2009;344:699–706.
[79] Alange VV, Birajdar RP, Kulkarni RV. Functionally modified polyacrylamide-graft-gum karaya pH-sensitivespray dried microspheres for colon targeting of an anti-cancer drug. Int J Biol Macromol 2017;102:829–39.
[80] Kumar P, Ganure AL, Subudhi BB, Shukla S. Design and comparative evaluation of in-vitro drug release, pharmacokinetics and gamma scintigraphic analysis of controlled release tablets using novel pH-sensitive starch and modified starch-acrylate graft copolymer matrices. Iran J Pharm Res 2015;14:677–91.
[81] Alange VV, Birajdar RP, Kulkarni RV. Novel spray dried pH-sensitive polyacrylamide-grafted-carboxymethylcellulose sodium copolymer microspheres for colon targeted delivery of an anti-cancer drug. J Biomat Sci Polym Edn 2019;28:139–61.
[82] Gong S, Tu H, Zheng H, Xu H, Yin Y. Chitosan-g-PAA hydrogels for colon-specific drug delivery: preparation, swelling behavior and in vitro degradability. J Wuhan Univ Technol Mater Sci Educ 2010;25:248–51.
[83] Abbasian M, Rodi MM, Mahmoodzadeh F, Eskandani M, Jaymand M. Chitosan-grafted-poly(methacrylic acid)/graphene oxide nanocomposite as a pH-responsive de novo cancer chemotherapy nanosystem. Int J Biol Macromol 2018;118:1871–9.
[84] Schild HG. Poly(N-isopropylacrylamide): experiment, theory and application. Prog Polym Sci 1992;17:163–249.
[85] Hoffman AS, Stayton PS, Bulmus V. Really smart bioconjugates of smart polymers and receptor proteins. J Biomed Mater Res 2000;52:577–86.
[86] Li G, Guo L, Wen Q, Zhang T. Thermo-and pH-sensitive ionic-crosslinked hollow spheres from chitosan-based graft copolymer for 5-fluorouracil release. Int J Biol Macromol 2013;55:69–74.

[87] Fundueanu G, Constantin M, Ascenzi P. Preparation and characterization of pH-and temperature-sensitive pullulan microspheres for controlled release of drugs. Biomaterials 2008;29:2767–75.
[88] Nuran I, Kucukbalc G. Microwave-induced synthesis of alginate-graft-poly(N-isopropylacrylamide) and drug release properties of dual pH-and temperature-responsive beads. Eur J Pharm Biopharm 2012;82:316–31.
[89] Jiang J, Pan X, Cao J, Jiang J, Hua D, Zhu X. Synthesis and property of chitosan graft copolymer by RAFT polymerization with tosylic acid-chitosan complex. Int J Biol Macromol 2012;50:586–90.
[90] Yuan H, Li B, Liang K, Lou X, Zhang Y. Regulating drug release from pH-and temperature-responsive electrospun CTS-g-PNIPAAm/poly(ethylene oxide) hydrogel nanofibers. Biomed Mater 2014;9:055001. https://doi.org/10.1088/1748-6041/9/5/055001.
[91] Patil AS, Gadad AP. Development and evaluation of high oxaliplatin loaded CS-g-PNIPAAm co-polymeric nanoparticles for thermo and pH-responsive delivery. Indian J Pharm Edu Res 2018;52:62–70.