IJPSR (2017), Vol. 8, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 August, 2016; received in revised form, 22 October, 2016; accepted, 06 December, 2016; published 01 February, 2017

A REVIEW ON MICROWAVE ASSISTED GRAFTING OF POLYMERS

Loveleenpreet Kaur * and G. D. Gupta

Department of Pharmaceutics, ASBASJSM College of Pharmacy, Bela, Ropar, IKGPTU, Jalandhar, Punjab, India.

Keywords:

Microwave irradiation, Grafting, Polysaccharides

Correspondence to Author:
Loveleenpreet Kaur

Department of Pharmaceutics, ASBASJSM College of Pharmacy, Bela, Ropar, Ikgptu, Jalandhar, Punjab, India.

E-mail: Loveleen585@gmail.com

ABSTRACT: The use of microwave irradiation in grafting of synthetic polymers onto natural polysaccharides is a popular method. It reduces all the limitations of conventional method of grafting like use of toxic solvents as well reduces reaction time for grafting methods. Microwave irradiation also increases the yield of grafting. Also the microwave grafted polymer has better properties as compared to polymer grafted by conventional method. The purpose of this review is to highlight the various recent modifications of grafting and its further applications in pharmaceutical formulations.

INTRODUCTION: Polysaccharides are universally found in almost all living organisms. They are present in various tissues of seeds, stems and leaves of plants, body fluids of animals, shells of crustaceans and insects. They are renewable reservoir for synthesizing high yielded materials, also found in the cell walls and extra cellular fluids of bacteria, yeast and fungi [1, 2] . In their natural forms polysaccharides are used as coagulants and flocculants, e.g., starch, sodium alginate, amylopectin, guar gum, xanthan gum, chitosan and okra mucilage [3, 4], while, in a modified form they are used as water super sorbent, e.g., guar-graft-poly(sodium acrylate [5]). Modification of polysaccharide materials is often carried out through derivatization of functional groups [6, 7], grafting of polymeric chains [8, 9] and by oxidative [10] or hydrolytic [11] degradation.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(2).422-26

Article can be accessed online on: www.ijpsr.com

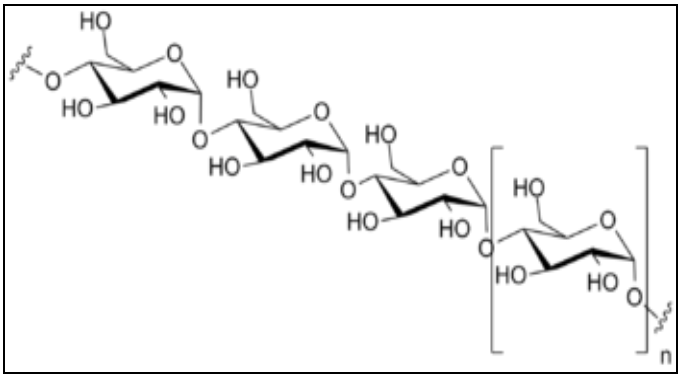
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (2).422-26

Polysaccharides are polymers of monosaccharides. Polysaccharide are inexpensive, and found in a variety of structures with a variety of properties and have large availability [12]. They can be easily modified and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition biodegradable, so used as targeted drug delivery systems. Main Problem occurs with the use of polysaccharides is their high water solubility. An ideal approach is to modify the solubility while still retaining their biodegradability. Most of the polysaccharides have already been used as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrins, dextrans, guar gum, inulin, pectin, locust bean gum and amylose [13].

Many of the natural polysaccharides have been used as food and pharmaceutical excipients due to their biocompatibility, biodegradability, easy availability and low cost. But certain drawbacks occurs such as uncontrolled hydration, changes in viscosity during storage, pH-dependent solubility, and lower shelf life, this limits their applications. By chemical modification of natural polymers these drawbacks can be overcome.

In Chemical modification of natural polymers different approaches such as etherification, cross-linking and graft copolymerization can be used [14].

Chemical Structure of Polysaccharides: [15]



Graft copolymerization: The synthesis of graft copolymer process will start consists of a long sequence of one polymer with one or more branches of another polymer, with the help of preformed polymer i.e. polysaccharide in case of grafted polysaccharides [16-17]. The free radical sites will create on this preformed polymer with the help of external agent. The agent should be effective enough to create the required free radical sites, at the same time should not be too drastic to rupture the structural integrity of the preformed polymer chain. Once the free radical sites are formed on the polymer backbone, the monomer can get added up through the chain propagation step, leading to the formation of grafted chains. Grafting process is a advantageous method to add new properties to a natural polymer without much more loss of the initial properties of the substrate. Natural polysaccharides used as starting materials for the synthesis of graft copolymers because of their structural diversity and water solubility. Most of the copolymers are prepared through graft polymerization of vinyl or acryl monomers onto the biopolymer backbone [18].

Microwaves: In organic synthesis the use of microwave irradiation has become popular within the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development. By taking advantage of microwave irradiation, compound libraries for lead generation and optimization of compound can be assembled in a fraction of the time required by classical thermal methods [19].

Microwaves generate electromagnetic radiation in the frequency range of 300 MHz to 300 GHz. On exposure to microwaves, the polar or charge particles tend to align themselves with electric field component of the microwaves which reverses its direction e.g. at the rate of 2.4 × 109/s at 2.45 GHz microwave frequency. As the charged or polar particles in a reaction medium fail to align themselves as fast as the direction of the electric field of microwaves changes, friction is created, which heated the medium [20].

Microwave reactions have been done both in solution as well as in dry medium. Since in the dry medium reactions the mixing of reactants is not feasible, in homogeneous electric field of microwaves is created to produce localized superheating zones called hotspots measuring about 900–1000 m and having temperatures higher(∼100–200 K) than the bulk temperature [21]. These hot spots accelerate the solid supported reactions and make them more productive than solution phase reactions [22].

Synthesis of graft copolymer:-Three methods:

1. Conventional grafting
2. Microwave initiated grafting
3. Microwave assisted grafting

Conventional grafting: Polymer chains are grafted on polysaccharides through three main strategies [23]: the ‘grafting through’, the ‘grafting on’ and the ‘grafting from’ processes. The ‘grafting through’ technique involves copolymerizing pre-made vinyl functionalized polysaccharide material with comonomers. Besides the conventional free radical processes, the ‘grafting from’ technique involving the growth of grafts directly from the polysaccharide backbones is the most extensively studied and used technique. Conventional grafting procedures may lead to polysaccharide backbone degradation and are not susceptible to block copolymer formation. Their use may often be harmful for some applications as they have limited control over graft molecular weight distribution. These problems have been addressed through the use of controlled/living radical polymerizations to obtain graft-functionalized polysaccharide based macromolecular materials [23].

Microwave assisted grafting: In this class of grafting reactions, external redox initiators are added to the reaction mixture, which produces ions and their presence enhance the ability of the aqueous reaction mixture to convert the microwave energy to heat energy [24, 25, 26, 27]. Under the influence of microwave dielectric heating, the generation of free radicals from the initiators facilitates the grafting reactions [28].

Microwave initiated grafting: In microwave initiated grafting reactions no initiators are added. A free radical mechanism for grafting under microwave irradiation has been postulated as the presence of a small amount of radical inhibitor such as hydroquinone was sufficient to inhibit the grafting reactions, though presence of free radicals in the reaction mixture has not been confirmed by modern instrumentation like ESR.

Advantages of Microwave method over Conventional method are: [29]

1. Heating rate fast in MW as compared to conventional.
2. Overheating above the boiling point of the solvent of up to (i) 100°C in closed-vessel reactions and (ii) 40 °C in open-vessel reactions in MW and in conventional there is limited reaction temperature.
3. Reaction time short in MW methods while in conventional methods longer reaction time.
4. High pressure reaction are no more dangerous in conventional these are more dangerous due to longer reaction time.
5. High yield of product obtained in MW heating while in conventional low yield obtained.
6. Easy to conduct in solvent free condition in MW methods and in conventional method not possible without solvent.
7. Reproducibility high in microwave methods and low in conventional methods. [30]
8. MW reactions possible without initiator/catalyst while in conventional methods not possible without initiator/catalyst [30].
9. %G and %E higher in MW methods while it is lower in conventional methods [30]

Free radical polymerization: The linear free radical polymerization comprises two steps:

1. The generation of free radicals derived from primary alcohol groups and
2. The reaction of the free radical with monomers bearing allyl groups.

Ring opening polymerization (ROP): This grafting mechanism depends on the use of polysaccharide initiators, inherently displaying various –OH initiation sites for the ROP of lactones such as CL. Since the initiator is multifunctional, for similar monomer/initiator weight ratios the length of the poly(ester) blocks produced is shorter than that of PCL copolymers synthesized with mono or bifunctional initiators (e.g., PEG). In addition, the final products are more hydrophilic [32]. As with linear ROP (see above), the main drawback of thermal reactions is that they may require several hours. Liu et al. used chitosan templates to polymerize CL using SnOct as catalyst under mild conditions [210]. Amphoteric chitosan-g-PCL copolymers with high grafting percentage (up to 232%) were obtained in remarkably short times (~15 min). Amine groups were initially protected with phthaloyl moieties, generating phthaloyl-protected chitosan (PHCS) and constraining the initiation step only to the –OH groups. The amine groups were then regenerated after the ROP with hydrazine monohydrate in water at 100 ^{0}C. The grafting percentage increased with irradiation time up to a maxima after 12.5 min (at 450W) [33].

Applications of grafted polysaccharides in drug delivery: In recent years, a wide variety of grafted polysaccharides have been used to fabricate different types of drug delivery system. Among these, colon targeted drug delivery systems have attracted many researchers because of distinct advantages they present such as near neutral pH, longer transit time and reduced enzymatic activity. In recent studies, colon specific drug delivery systems are gaining importance for use in the systemic delivery of protein and peptide drugs and treatment of local pathologies of the colon. [34]

Metronidazole tablets using various polysaccharides or intrinsic developed graft copolymer of methacrylic acid with guar gum for colon targeted drug delivery. Drug release studies were performed in simulated gastric fluid at pH 1.2 for 2 hr. and intestinal fluid at pH 7.4.

Using Eudragit-L 100 (for enteric coating), the release of metronidazole was drastically reduced to 18-24% [35].

Diltiazem tablets were prepared by three different ratios of guar gum to acrylamide (1:2, 1:3.5 and 1:5) and were hydrolyzed to induce carboxylic functional groups in the preparation of polyacrylamide-gguar gum (pAAm-g-GG*). In vitro* drug release was carried out in pH 1.2 and pH 7.4. The drug release continued up to 8 and 12h, respectively, for graft copolymers and hydrolysed graft copolymers. In the case of unhydrolyzed copolymer drug release was found to be dissolution-controlled. Hydrolyzed graft copolymers were pH sensitive and can be used for intestinal drug delivery [36].

Crosslinkage of polyacrylamide grafted pectin with varying amount of glutaraldehyde and it was noticed that the cross-linked product showed better film forming property and gelling property than pectin. The pH dependent release of salicylic acid was observed due to pH dependent swelling of the crosslinked hydrogel [37].

The microspheres of acrylamide grafted on dextran (AAm-g-Dex) and chitosan were prepared by emulsion-crosslinking method using glutaraldehyde as a crosslinker. Acyclovir, an antiviral drug with limited water solubility, was successfully encapsulated into the microspheres by varying the ratio of AAm-g-Dex and chitosan, percentage drug loading and amount of glutaraldehyde. Encapsulation of acyclovir in the microspheres (265-388 μm) was up to 79.6%. In vitro release studies indicated the dependence of drug release rates on both the extent of crosslinking and amount of AAm-g-Dex used in preparing microspheres; the slow release was extended up to 12h [38]. Six graft copolymers of hydroxypropyl guar gum were synthesized with variation in the number and length of grafted polyacrylamide chains. Flocculation jar tests were carried out in 0.25 wt % kaolin, iron ore, and silica Suspensions. Among the series of graft copolymers, the one with fewest but longest polyacrylamide chains showed the better performance [39].

CONCLUSION: The microwave assisted method of grafting is superior to conventional grafting method. The grafted polymers are used in various formulations and microwave approach can be further used to improve the grafting efficiency by improving properties of natural polymers.

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How to cite this article:
Kaur L and Gupta GD: A review on microwave assisted grafting of polymers. Int J Pharm Sci Res 2017; 8(2): 422-26.doi: 10.13040/IJPSR.0975-8232.8(2).422-26.