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Review Article

A REVIEW ON GRAFTING MODIFICATION OF POLYSACCHARIDES BY MICROWAVE IRRADIATION- DISTINCTIVE PRACTICE FOR APPLICATION IN DRUG DELIVERY

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ABSTRACT

Most of the natural polysaccharides have been used as food and pharmaceutical excipients due to their biodegradability, biocompatibility, low cost and easy availability. Diverse approaches such as etherification, crosslinking and graft co-polymerization can be used for the chemical modification of natural polymers. Grafting process is a suitable method to add new properties to a natural polymer with minimum loss of the initial properties of the substrate. Water is used as a solvent in most of the polysaccharide grafting reactions, as many polysaccharides are soluble in water. This review highlights modern applications of microwave heating in the grafting modifications of polysaccharides and discusses the fundamental mechanisms of grafting.

Keywords: Polysaccharides; Microwave; Cross-linking; Grafting; Applications.

INTRODUCTION

Polysaccharides are polymers of monosaccharides. Polysaccharide are inexpensive, have wide availability and available in a variety of structures with a variety of properties.[1] 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. Problem encountered 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 amylase.[2] Most of the natural polysaccharides have been used as food and pharmaceutical excipients because of their biocompatibility, biodegradability, easy availability and low cost.

But certain drawbacks such as uncontrolled hydration, changes in viscosity during storage, pH dependent solubility, and lower shelf life, this limits their applications. These drawbacks can be overcome by **c**hemical modification of

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the natural polymers. Different approaches such as etherification, cross-linking and graft copolymerization can be used for the chemical modification of natural polymers.[3,4]

Polysaccharides are universally found in almost all living organisms. They are present in various tissues of seeds, leaves of plants stems and, body fluids of animals, shells of crustaceans and insects and also found in the cell walls and extra cellular fluids of bacteria, yeast and fungi and are thus renewable reservoirs for synthesizing high performance materials.[5,6] Seed polysaccharides from quince, psyllium, flax and guar[7] have been used in paper, textiles, cosmetics, and food and pharmaceuticals industries. Natural form of polysaccharide are used as coagulants and flocculants, e.g., starch, sodium alginate, amylopectin, guar gum, xanthan gum, chitosan and okra mucilage[8,9] while, in a modified form they are used as water super sorbent, e.g., guar-graftpoly (sodium acrylate).[10]

Polysaccharide materials can be modified through derivatization of functional groups[11,12], grafting of polymeric chains[13,14] and by oxidative[15] or hydrolytic[16] degradation.

2. 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.[17] 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.[18] 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.[19] These hot spots accelerate the solid supported reactions and make them more productive than solution phase reactions. In the earlier studies when microwaves were first used, by the using of domestic microwave ovens most of the chemical transformations were carried in which the irradiation power was generally controlled by on/off cycles of the magnetron. Due to their easy accessibility and low cost, these unmodified multimode microwave ovens were popular, their use was not much encouraged due to the safety concerns as they had insufficient control over the reaction temperature and pressure. To overcome these issues, several modifications to domestic microwave ovens were made over the past decade.[20]

3. GRAFT COPOLYMERIZATION OF POLYSACCHARIDES

Graft copolymers by definition, consists of a long sequence of one polymer with one or more branches of another polymer.[21,22] With the help of preformed polymer (polysaccharide in case of grafted polysaccharides) the synthesis of graft copolymer process will start. 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. The various methods of graft copolymer (Figure 1) synthesis actually differ in the ways of generation of the free radical sites on this preformed polymer. Conventionally, chemical free radical initiators (e.g. ceric ammonium nitrate (CAN)[23,24], high energy radiation (gamma rays or electron beam)[25,26] or UV rays in presence of photo sensitizers[27,28] are used for this purpose. Grafting process is a convenient method to add new properties to a natural polymer with minimum 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.[29] The chemistry of grafting vinyl/acryl monomers is quite different from that of grafting non-vinyl/acryl monomers. By poly-condensation process, non-vinyl/acryl graft copolymerization is possible. However this has not been widely used for preparing graft copolymers of polysaccharides usually due to susceptibility of the polysaccharide backbone to high temperature and harsh conditions of the typical poly-condensation reactions.[30]

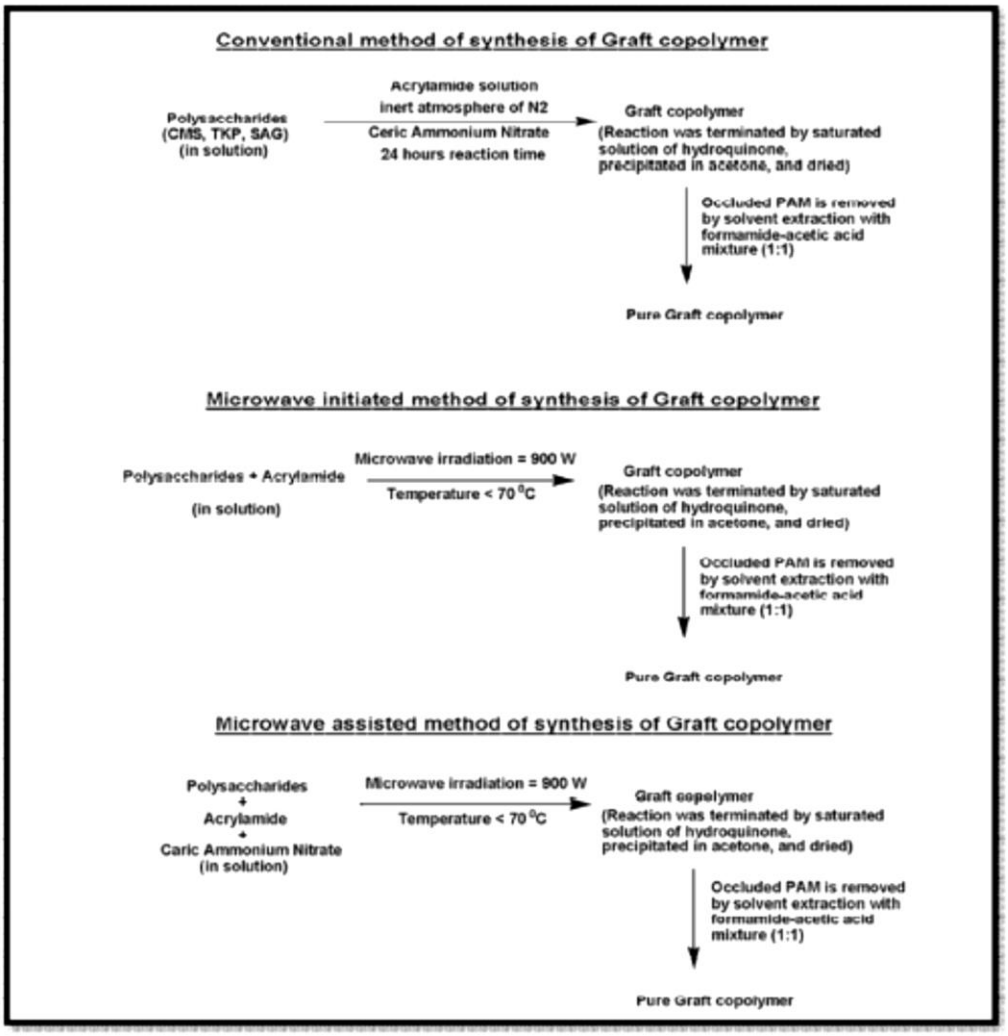

Figure 1: Schematic representation for the synthesis graft copolymer using conventional, microwave initiated and microwave assisted method

3.1. Vinylic/Acrylic Graft Copolymerization

Grafting onto the polysaccharides by polyvinylic and polyacrylic synthetic materials are mainly achieved by radical polymerization. The Grafting is achieved by first generating free radicals on the biopolymer backbone and then these radicals to serve as macro initiators for the vinyl or acrylic monomer. The chemical and radiation initiating systems are employed to graft copolymerize these monomers onto polysaccharides.[31]

Microwave-enhanced chemistry is based on the efficiency of the interaction of molecules in a reaction mixture (substrates, catalyst and solvents) with electromagnetic waves generated by a "microwave dielectric effect" depending upon the specific polarity of the molecules.[32] Due to homopolymerization reaction in conventional thermal grafting reaction lowering the grafting yield but under microwaves, copolymerization is the favoured reaction.[33,34] By different heating rates under the two conditions, microwave or thermal, different product selectivity is achieved. Water is used as a solvent in most of the polysaccharide grafting reactions, as many polysaccharides are soluble in water. Water being polar in nature, has a good potential to absorb microwaves and convert them to heat energy.

Therefore, faster the reaction in the case of aqueous grafting reactions then those done under conventional grafting reactions[35] and this accounts for the high yield in the microwave grafting reactions. It is well known in the presence of salts water can be rapidly heated to high temperatures when exposed to microwaves and because of the very high heat capacity of water, there is a certain control on the reaction temperature[36]. The reaction time can be reducing significantly by the use of microwaves besides eliminating the requirement of radical initiators and/or catalyst.[37] While, No grafting takes place under thermal conditions without an initiator, under microwave conditions it takes place without the addition of an initiator. oxygen acts as an inhibitor in conventional grafting reactions and has to be expelled before performing the grafting reaction, In most grafting studies, a domestic microwave oven has been used where in the temperature of the reaction mixture measured immediately after the completion of the reaction is reported to be <100°C, but this does not prove that the temperature during the reaction in the microwave cavity did not exceed 100°C.[38]

3.2. Grafting in Aqueous Solution

Most of the polysaccharide grafting reactions are carried out in water, in which the polysaccharide is in the solution and other reactants such as monomers, catalyst initiators and may be miscible or immiscible in the polysaccharide solutions, depending upon their type.[39]

Irradiating a reaction mixture in an aqueous medium by microwaves involves two key mechanisms:

1. Dipolar polarization of water molecules

2. Ionic conduction

The dielectric heating that ensues from the tendency of dipoles to follow the inversion of alternating electric field induces energy dissipation in the form of heat through molecular friction and dielectric loss. This allows more regular repartition in reaction temperatures compared to conventional heating.[36]

For grafting in aqueous solution, mainly two approaches have been used:

1. Microwave assisted grafting

2. Microwave initiated grafting

3.2.1. Microwave Assisted Grafting

In this process, the ions will produced by addition of external redox initiators to the reaction mixture, and their presence enhance the ability of the aqueous reaction mixture to convert the microwave energy to heat energy.[40-43] Under the influence of microwave dielectric heating, the generation of free radicals from the initiators facilitates the grafting reactions[44,45] shown in Figure 2.

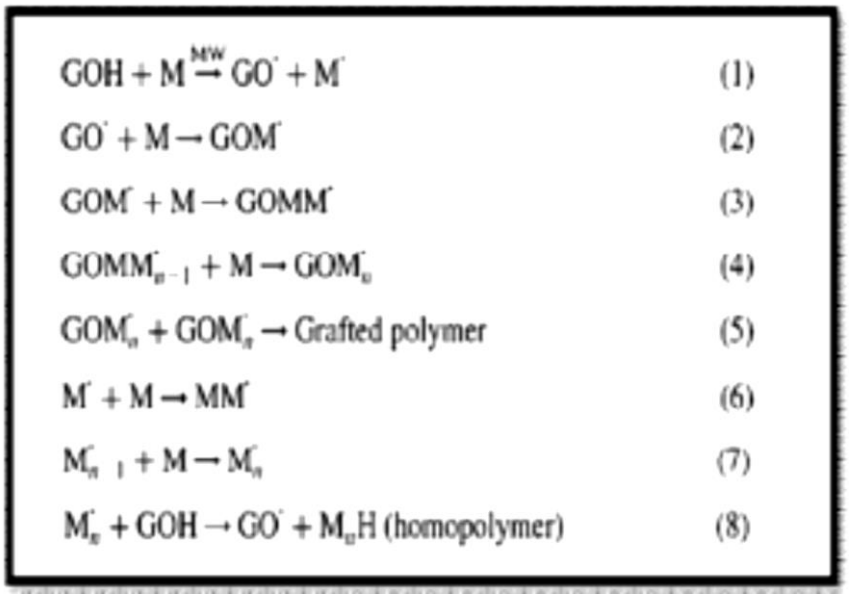

Figure 2: Mechanism proposed for the MW-assisted grafting of acrylamide on guar templates

3.2.2. Microwave Initiated Grafting

No initiators are used in microwave initiated grafting reactions. Hydroquinone was used as a radical inhibitor for inhibit the grafting reactions, though existence of free radicals in the reaction mixture has not been confirmed by modern instrumentation like ESR. Under microwave conditions, the heating results from the dipolar relaxation of solvent (water) and due to localized rotation polar functional groups of polysaccharides.[33,34,46]

3.3. Grafting on Solid Support

Most of the reactions have been carried out between sup-ported reagents on solid mineral supports in “dry media” by impregnation of reactants on solid supports. In microwave synthesis under such solvent-free (dry media) conditions, the reagents are reacted neat or are preadsorbed on a more or less microwave transparent support (silica, alumina, or clay) or on a strongly absorbing (graphite) inorganic support that additionally can be doped with a catalyst or reagent. Such reactions are of interest as they allow the safe use of domestic household microwave ovens and standard openvessel usage leading to a clean, efficient and economical technology with simplified work-up.[47,48]

4. GOOD SOLVENTS FOR MICROWAVE HEATING

Solvent have a major effect on the grafting process when used in microwave heating. Solvents used should not give any toxic effects on the polymer. Also should give good results with microwave heating. Table 1 comprises of various good solvents which can be used for microwave heating without giving any major hazardous effects.[49]

Table 1: Good solvents for MW heating

Solvent	Boiling Point	Temperature	Pressure
N,N Dimethyl formamide (DMF)	153	250	5
Water	100	220	16
Methanol	65	107	17
Ethanol	78	180	16
Acetone	56	150	5
Acetonitrile	86	200	10
Xylene	137	150	2
Toluene	110	170	4
Pyridine	115	220	8
Dimethyl sulfoxide (DMSO)	189	250	5
Diethyl ether	35	135	4

5. 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.[31] Metronidazole tablets using various polysaccharides or indigenously 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. Uncoated tablets containing xanthan gum or mixture of xanthan gum with methacrylic acid-g-guar gum showed 30-40% drug release during the initial 4-5h, whereas 70% drug release for tablets containing guar gum with the graft copolymer. Using Eudragit-L 100 (for enteric coating), the release of metronidazole was drastically reduced to 18-24%.

Since the cost of synthesizing a new polymeric substance and testing for its safety is enormous, polymeric physical blends are frequently used as excipients in controlled drug delivery systems due to their versatility.[50]

In the preparation of polyacrylamide-g-guar gum (pAAm-g-GG) three different ratios of guar gum to acrylamide (1:2, 1:3.5 and 1:5) was taken and were hydrolysed to induce carboxylic functional groups. Diltiazem tablets were prepared with these graft copolymers and hydrolysed copolymers. 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. With

hydrolyzed copolymers, drug release was swelling-controlled initially in 0.1 N HCl solution, but at later stage, it became dissolution-controlled in pH 7.4. Hydrolyzed graft copolymers were pH sensitive and can be used for intestinal drug delivery.[51] Cross linkage 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.[52]

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.[53]

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.[54]

6. CONCLUSION

The grafting approach as a tool to manipulate natural polysaccharides, with the precise control over the graft polymer, under microwave irradiation can be a powerful strategy for the development of valuable derivatives with tailor made properties. The properties of microwave synthesized graft polysaccharides are normally superior to the derivatives synthesized conventionally. Overall, it may be concluded that the current advancements in the area of polysaccharide grafting under microwaves have generated awareness on obtaining higher performance materials through such processes. Without having to compromise on efficiency or yield, the microwave methodology works towards achieving the goal of cleaner technologies as it is much simpler, cheaper, quicker and safer than the prevailing traditional methods.

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