



AN OVERVIEW OF NATURAL POLYSACCHARIDES AND THEIR CHEMICAL MODIFICATIONS: APPLICATION IN DRUG DELIVERY

Gouranga Nandi†, Sailee Chowdhury, Sudipta Chakraborty

BCDA College of Pharmacy & Technology, 78, Jessore Road (S), Hridayapur, Kolkata- 700127, India.

ARTICLE INFO

Short Review Article History

Received: 12 July, 2015

Accepted: 31 August, 2015

Corresponding Author:

† Gouranga Nandi

BCDA College of Pharmacy & Technology, 78, Jessore Road (S), Hridayapur, Kolkata- 700127, India.

Email: nandi.gouranga@yahoo.co.in

ABSTRACT

In recent years, worldwide extensive efforts are being paid in exploration of pharmaceutical excipients from natural origin. Various natural polysaccharides have been substantially reported as potential drug delivery carriers. These natural polymers are preferred over synthetic polymers because of their biocompatibility, low cost, free availability and biodegradability. The native forms pose certain drawbacks like variable chemical composition, variable swelling kinetic, microbial load, microbial growth and change in viscosity upon aging. These negative aspects make them less acceptable compared to commercial synthetic products. Modification of their chemical structure makes them intelligent biomaterials in controlled release applications. This article is aimed at discussing chemical modifications of natural polysaccharides like carboxy-methylation, grafting, blending, cross-linking and so on that are useful of making them suitable as potential drug carrier. The pharmaceutical applications of various natural polysaccharides and their modified forms for the development of various drug delivery systems has also been described.

Key words: natural polysaccharides, chemical modification, grafting, drug delivery

© www.albertscience.com, All Right Reserved.

1. INTRODUCTION

In recent years, worldwide extensive efforts are being paid in exploration of pharmaceutical excipients from natural origin. Various natural polysaccharides in form of gum and mucilage have been substantially reported as suitable pharmaceutical excipients [1]. These include mucuna gum [2], guar gum [3], locust bean gum [4], xanthan gum [5], carragenans [6], sodium alginate [7], gellan gum [8], gum karaya, katira gum [9], pectin [10] etc. Some of them have been used in controlled release dosage forms as rate modulating polymers [11]. These natural gums are preferred over synthetic polymers because of their biocompatibility, low cost, free availability and biodegradability. A significant number of natural gums are used in food industries and are considered as safe for human consumption [12]. The native gums pose certain drawbacks like variable chemical composition, variable swelling kinetic, microbial load, microbial growth and change in viscosity upon aging. These negative aspects make them less acceptable compared to commercial synthetic products. It can hamper the reproducibility and predictability of drug release kinetic from sustained release matrix since they are functionally related to degree of polymerization, hydration kinetic, viscosity of the hydrated boundary layer and rigidity of polymeric carrier. Therefore, they can be tailored or modified in different

ways to not only overcome their drawbacks but also modulate the site of drug release and its kinetic, and makes them parallel or superior than their synthetic counterparts. Tailoring and modification of natural polysaccharides can be done in various ways like carboxymethylation, cyanoethylation, grafting, blending, crosslinking and so on. Modification of the structure of natural polymers by graft copolymerization method makes them intelligent biomaterials in controlled release applications since native polysaccharides may not be suitable in controlled release drug delivery systems due to their substantial swelling and rapid enzymatic degradation in physiological fluids [13]. Graft copolymerization introduces hydrophobicity and steric bulkiness, which considerably protects the matrix and carbohydrate backbone to retard the drug release [14]. There are different techniques of grafting viz. grafting initiated by chemical means, grafting initiated by radiation, photochemical grafting, plasma radiation induced grafting, enzymatic grafting. Generation of free-radical sites on a polymeric backbone by direct oxidation of the backbone by certain transition metal ions such as Ce⁴⁺ is considered as very simple and easier one step method of graft copolymerization [15]. Along with free-radical initiation by redox initiator, microwave-assisted graft copolymerization has also been employed [16-18].

The microwave irradiation provides rapid transfer of fixed energy in the bulk of the reaction mixture resulting very short reaction time with significantly higher yield.

In the present review, application of natural polysaccharides and their chemically modified forms in drug delivery has been focused [18-20].

2. Natural polysaccharides used as pharmaceutical excipients

2.1. Classification on the basis of charge:

(a) Non-ionic seed gums: guar gum, locust bean, tamarind, xanthan, amylose, arabinans, cellulose and galactomannans.

(b) Anionic gums: Arabic, karaya, tragacanth, gellan, agar, algin, carrageenans, pectic acid.

2.2. Classification on the basis of source:

Marine origin/algae (seaweed) gums: agar, carrageenans, alginic acid, laminarin.

Plant origin:

1. Shrubs/tree exudates: gum arabica, gum ghatti, gum karaya, gum tragacanth, khaya and albizia gums.

2. Seed gums: guar gum, locust bean gum, starch, amylose, cellulose

3. Extract: pectin, larch gum

4. Tuber and roots: potato starch.

5. Animal origin: Chitin and chitosan, chondroitin sulphate, hyaluronic acid.

6. Microbial origin (bacterial and fungal): xanthan, dextran, curdian, pullulan, zanflo, emulsan, Baker's yeast glycan, schizophyllan, lentinan, krestin, scleroglucan.

2.3. Semi-synthetic:

1. Starch derivatives: hetastarch, starch acetate, starch phosphates.

2. Cellulose derivatives: carboxy methyl cellulose (CMC), hydroxy ethylcellulose, hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), microcrystalline cellulose (MCC) [20 - 24].

2.4. Advantages

The followings are the advantages of the natural plant based polymers [1]:

1. They are biodegradable. Natural, biodegradable polymers are produced almost by all living organisms. They are truly renewable sources and have adverse effects neither on human health nor on environmental aspects.

2. They are highly biocompatible and non-toxic in nature. They are usually carbohydrate compounds composed of sugar monomers (monosaccharide).

3. They are cheaper than any other synthetic polymer as their production cost is low.

4. They are locally available.

5. Better patient tolerance and public acceptance. There is less chance of side-effects and adverse effects with the natural materials as compared to the synthetic ones eg. povidone.

6. Most gums and mucilages are obtained from edible sources.

2.5. Disadvantages of natural polymers in pharmaceutical uses:

The disadvantages of natural gums are stated as follows [2]:

1. The main problem with the natural gums is that they are easily susceptible to microbial contamination. The equilibrium moisture content of natural gums and mucilages is generally 10% or more. Chemically they are carbohydrates and during their production they are subjected to different environmental condition; so there is a high chance for microbial contamination but this can be prevented by proper handling and proper use of preservatives.

2. Production of synthetic gums and mucilages are dependent on regional, seasonal and environmental factors whereas the synthetic gums are produced in a controlled manner using fixed amount of ingredients.

3. Uncontrolled rate of hydration. Due to differences in collection of natural gums at different times as well as from different regions, species and climatic condition there is a variation in the percentage composition of chemical constituents.

4. It has been noticed that with storage there is a decrease in viscosity. Generally the viscosity of natural gums and mucilages increase in contact with water because of their complex nature but the reverse happens on storage.

2.6. Disadvantages of synthetic polymers in pharmaceutical use:

The synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollutions during synthesis, non-renewable sources, side effects, and poor patient compliance. Acute and chronic adverse effects (skin and eye-irritation) have been observed in workers handling the related substances methyl methacrylate and poly-(methyl methacrylate) (PMMA). Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site produced by povidone. There is also evidence that povidone may accumulate in organs following intramuscular injections [16]. Acute oral toxicity studies in animals have indicated that carbomer-934P has a low oral toxicity at a dose of up to 8 g/kg. Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract. So, gloves, eye protection and dust respirator are recommended during handling [17]. Studies in rats have shown that 5% polyvinyl alcohol aqueous solution injected subcutaneously can cause anemia and can infiltrate various organs and tissues. Some disadvantages of biodegradable polymers used in tissue engineering applications are their poor biocompatibility, release of acidic degradation products, poor processing ability and rapid loss of mechanical properties during degradation. It has been shown that poly-glycolides, polylactides and their co-polymers have an acceptable biocompatibility but exhibit systemic or local reactions due to acidic degradation products. An initial mild inflammatory response has been reported when using poly-(propylene fumarate) in rat implant studies [19].

3. Chemical modification of natural polysaccharides

3.1. Grafting

A grafted co-polymer is a macromolecular chain with one or more species of block connected to the main chain as side chain(s). Thus, it can be described as, having the general structure, where the main polymer backbone, commonly referred to as the trunk polymer, has branches

of another polymeric chain emanating from different points along its length [25].

Graft copolymerization of synthetic polymers onto polysaccharide backbone offers one of the best ways to use polysaccharides for controlled release delivery. Graft copolymerization is an easy method to modify the structure of natural polymers and thus makes them attractive biomaterials in controlled release applications since native polysaccharides may not be suitable in controlled release drug delivery systems due to their substantial swelling and rapid enzymatic degradation in the biological fluids [26]. In the polymeric age, it is essential to modify the properties of a polymer according to tailor-made specifications designed for target applications. There are several means to modify polymers properties, viz. blending, grafting, and curing. 'Blending' is the physical mixture of two (or more) polymers to obtain the requisite properties. 'Grafting' is a method wherein monomers are covalently bonded (modified) onto the polymer chain, whereas in curing, the polymerization of an oligomer mixture forms a coating which adheres to the substrate by physical forces. Curing gives a smooth finish by filling in the valleys in the surface. This is somewhat different from the curing (or vulcanization) of rubber which produces chemical cross-links between loosely coiled polymeric chains, producing elasticity as the chains stretch under a stress, and retract on release of the stress.

3.1.1. Techniques of grafting

The techniques of grafting of different monomers onto natural polysaccharides backbone include chemical, radiation, photochemical, plasma-induced and enzymatic grafting.

3.1.1.1. Chemical induced grafting

Grafting initiated by chemicals can emanate along either of two major paths, viz. free radical and ionic, which is determined by the initiator [27].

Free radical grafting

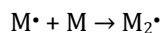
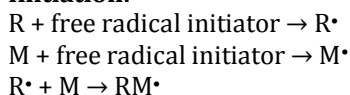
This includes three steps [28]:

Initiation: In this process, initiators produce free radicals and transfer to the substrate polymer to initiate the reaction with monomer. The monomer attached directly to the polymer backbone is then converted into a free radical.

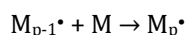
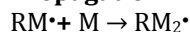
Propagation: Following initiation another monomer molecule gets attached to the monomer-free-radical which is previously attached to the polymeric backbone and is converted into free radical. This process goes on and the length of the grafted chain propagates.

Termination: Finally, chain-propagation is terminated by coupling between two propagating polymeric free radicals, propagating polymeric free radical and single monomeric free radicals, or propagating polymeric free radical and propagating homopolymeric (composed with only grafting monomer molecules) free radical resulting grafted copolymer. Homopolymer formation results from the coupling between two propagating homopolymeric free radicals. The general scheme of the three steps is as follow [28]:

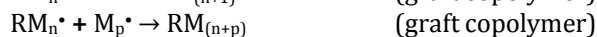
Initiation:



Propagation:



Termination:

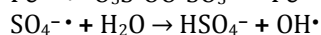
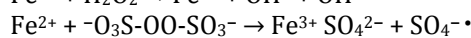
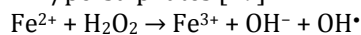


(R = polymeric backbone; M = grafting monomer)

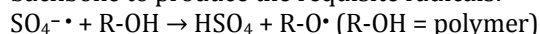
Free radical generators produce free radicals on the polymeric backbone by direct and indirect methods:

Indirect free radical generation:

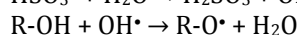
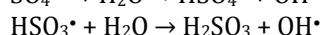
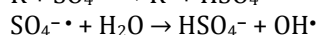
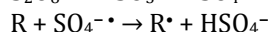
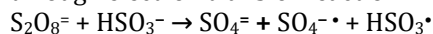
An example of such indirect method of free radical production through redox reaction, viz. M^{n+}/H_2O_2 or $M^{n+}/\text{persulphates}$ [29]:



$OH\cdot$ subsequently produces free radicals onto polymeric backbone. $SO_4^{\cdot-}$ may react directly with the polymeric backbone to produce the requisite radicals:



Combination of organic peroxide, persulphate, Fe^{3+} , Cu^{2+} , etc. together with a reducing agent such as sodium bisulphate, thiosulphate or Ag^+ produces free radicals through electron transfer reaction:



The most widely used method of chemical initiation for graft copolymerization onto polysaccharides has been with ceric salts like ceric ammonium nitrate (CAN) or ceric ammonium sulphate (CAS) [30].

Microwave assisted free radical initiated grafting

Sen *et al* [25] reported microwave assisted free radical initiated graft copolymerization of acrylamide onto carboxymethyl starch. Various grades of the grafted polymer were synthesized by varying the irradiation time and the monomer (acrylamide) concentration. It is evident that the grafting is optimized at monomer concentration of 0.14 moles and at irradiation time of 3 min, when the microwave power is maintained at 900 W. When small polar molecules like water are irradiated with microwave, it results in rotation of the molecules, leading to generation of heat. However, no free radical is produced as such. But, if bigger molecules or macromolecules are present, rotation of the entire molecule is not possible. In that case, the microwave is absorbed by the polar groups present (e.g. -OH groups attached to CMS molecule) which then behave as if they were anchored to an immobile raft and its immobile localized rotations will occur in the microwave region, which eventually leads to the severing

of these bonds, leading to formation of free radical sites. Further, the microwave energy absorbed by the water molecules is quickly transferred to the acrylamide molecules, causing 'dielectric heating' which results in severing of their double bond; thus producing another set of free radicals. The microwave is also known for lowering Gibbs energy of activation of the reaction [31]. These free radicals generated by these effects (on the polar -OH groups of the CMS backbone and on the monomer); then recombined with each other through initiation, propagation and termination steps to produce the graft copolymer. Effect of microwave exposure time was that increase in exposure time (1-4 min), the percentage grafting increases up to 3 min (which was optimum) after which it decreases. This may be because of the fact that, beyond exposure time of 3 min; the prolonged exposure of microwave irradiation may have degraded the polysaccharide backbone, thereby decreasing the percentage of grafting and intrinsic viscosity. Grafting ratio increased on increasing the monomer concentration from 0.07 to 0.14 moles. The increase in percentage grafting may be due to availability of extra monomer for grafting. But percentage grafting decreased with increase in monomer concentration beyond 0.14 moles may be because of the more homopolymer formation through competing side reaction [30].

Purification of the graft copolymer by solvent extraction method

Any occluded polyacrylamide (PAM) formed by competing homopolymer formation reaction was removed from the grafted polymers synthesized as above (by both conventional as well as microwave initiated method), by solvent extraction using a mixture of formamide and acetic acid (1:1 by volume).

Effect of initiator concentration

A low concentration of catalyst should initiate a few grafting sites, which results in longer polyacrylamide chain, compared to a high concentration of catalyst, which will initiate a larger number of grafting sites. This will make the average polyacrylamide chains shorter for the same acrylamide concentration. So while grafting polyacrylamide onto CMS, two possibilities are there; one can either have a small number of long polyacrylamide chains or a large number of short polyacrylamide chains in the graft copolymer [30].

Effect of monomer concentration

Sen et al [25] reported grafting of acrylamide onto carboxymethyl starch where increase in concentration of acrylamide (from 0.14-0.28 moles), results increase in percentage grafting continuously and achieves the maximum when the concentration of acrylamide is 0.21 moles, followed by decrease in the percentage grafting. They explained this behavior by the fact that an increase in monomer concentration leads to the accumulation of monomer molecules in close proximity to the CMS backbone. The decrease in the percentage grafting after optimization could be associated with the reduction in the active sites on the CMS backbone as graft copolymerization proceeds. It can also be accounted that once the graft copolymer radical has formed, the excess monomer will shield the graft copolymer, which may decrease the rate of graft copolymerization. In addition to this, with excess

monomer concentration, the competing homopolymer formation reaction becomes significant, leading to depletion in percentage grafting as well as viscosity.

3.2. Interpenetrating polymeric network Cross-linking by glutaraldehyde:

Semi-IPN microspheres of AAm-g-Dex and CS were prepared by emulsion-crosslinking method. Briefly, AAm-g-Dex and CS were dissolved in 2% aqueous acetic acid with continuous stirring until a homogeneous solution was obtained. A required amount of drug was directly dissolved in polymer solution and allowed to stir for overnight. This solution was added slowly to the light liquid paraffin (100 g) containing 1% (w/w) Span -80 under constant stirring at 400 rpm for 10 min. To this w/o emulsion, the required amount of GA was added slowly and stirring was continued for 2 h. However, % encapsulation efficiency showed a dependence on % drug-loading, polymer composition and extent of crosslinking. The % encapsulation efficiency was found to be greater in formulations containing higher drug loadings. This is due to the limited water solubility of the drug thereby, leading to the retention of more of drug particles while preparing the microspheres. As the amount of crosslinking is increased, there is a slight increase in % encapsulation efficiency due to the formation of a rigid network structure, which reduces the possibility of leaching out of the drug during the microsphere preparation. By increasing the content of graft copolymer, a slight decrease in % encapsulation efficiency was observed, which is attributed to greater swelling of the matrix, which will allow leaching out of drug particles during the preparation of microsphere. Also, the particle size varied depending upon the drug loading into the microspheres. For instance, formulation F4 exhibits a higher particle size than F1. Similarly, F5 and F6 have higher particle sizes than F2 and F3 formulations. This is due to the accumulation of slightly water-soluble drug crystals in the polymer matrix at higher drug loadings. [32].

Interpenetrating polymer network (IPN) hydrogel microspheres of xanthan gum (XG) based superabsorbent polymer (SAP) and poly(vinyl alcohol) (PVA) were prepared by water-in-oil (w/o) emulsion crosslinking method for sustained release of ciprofloxacin hydrochloride (CIPRO).

The microspheres were prepared with various ratios of hydrolyzed SAP to PVA and extent of crosslinking density. The prepared microspheres with loose and rigid surfaces were evidenced by scanning electron microscope (SEM). Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD) analysis confirmed the IPN formation. Differential scanning calorimetry (DSC) study was performed to understand the dispersion nature of drug after encapsulation. The *in vitro* drug release study was extensively evaluated depending on the process variables in both acidic and alkaline media. All the formulations exhibited satisfactory physicochemical and *in vitro* release characteristics. Release data indicated a non-Fickian trend of drug release from the formulations. Based on the results, this study suggest that CIPRO loaded IPN microspheres were suitable for sustained release application. They firstly prepared

modified bentonite by drying an aqueous composite dispersion of bentonite and xanthan gum [33].

Ca⁺⁺ ion induced Cross-linking

Interpenetrating network (IPN) matrix tablets of diltiazem-HCl (DTZ) was prepared by wet granulation method using polyacrylamide-grafted-sodium alginate (PAam-g-SAL) co-polymer and sodium alginate (SAL) for sustained release of the drug. Formulation of IPN structure was examined using FTIR spectroscopy, and compatibility of the drug with the polymers was evaluated through FTIR, DSC, and XRD analyses. The effect of co-polymer/SAL ratios, drug load, and total polymer/calcium gluconate (CG) ratios on drug release in acidic and phosphate buffer solutions was investigated. The release of drug was controlled by the relative magnitude of swelling capacity of IPN matrix and viscosity of the gel formed following dissolution of the polymers. The swelling capacity of the matrix was governed by the formation of calcium alginate gel structure and the rigidity imparted by the co-polymer. The results indicated that IPN matrix tablets of PAam-g-SAL and SAL could be used for sustained release of DTZ [34].

Application in drug delivery

Interpenetrating polymeric microspheres

Rokhade *et al* [35] reported acyclovir loaded semi-interpenetrating polymeric microspheres composed of polyacrylamide-grafted-dextran and chitosan where emulsion-crosslinked method was employed using gluteraldehyde as crosslinker. The microspheres were then characterized by FTIR, particle size analysis, DSC, XRD, encapsulation efficiency, % drug loading, *in vitro* drug release study. This work demonstrates the usefulness of semi-IPN microspheres in size ranges of 265–388 μm in the controlled release of acyclovir. It was found that the drug encapsulated microspheres (maximum encapsulation efficiency 79.6%) prepared by water-in-oil emulsion method could successfully extend the release of acyclovir up to 12 h with a cumulative release of up to 80%. However, % cumulative release rates showed to be function of degree and the nature of the crosslinking in the formulated product. The % encapsulation efficiency up to 80% was observed depending upon the nature of the matrix. Diffusion coefficient and diffusional exponents calculated from the empirical equations have indicated the non-Fickian nature of transport of drug through the matrices developed.

IPN matrix tablet

Mandal *et al* reported preparation of inter-penetrating polymeric network matrix tablet for sustained release of diltiazem hydrochloride. Ca²⁺ crosslinked polyacrylamide grafted sodium alginate and native sodium alginate matrix tablets showed an overall sustained drug release over a period of 12 h following Fickian transport except when the ratios of total polymer to sodium alginate were varied from 1:0.5 to 1:1.5, the values of release exponent *n* were found to vary within 0.76–0.52 indicating that the release deviated from Fickian to anomalous transport [36].

Grafted gums

Natural gums have been modified to defeat specific downsides including unrestrained hydration rate, fall in viscosity while storage, thickening and microbial

contamination. As the execution of polymeric materials in the field of pharmaceutical technology, many efforts have been made to alter physical and chemical properties of polymeric materials, and hence, their potential applicability in drug delivery. Many researchers in recent years have done research works with respect to grafting modification.

Literature reviews, especially abstracts of some research works based on grafting modification of natural gums are discussed below:

Deogade, U. M. *et al.* mentioned grafting of natural gums to prepare tailor-made advanced polymers and their importance and applications. [30].

Tamarind seed gum (TS) with methyl methacrylate (MMA) was grafted by Shailaja, T. *et al.* Chemical method of grafting by ascorbic acid redox pair and potassium per sulphate has been selected for grafting. Physical characterization showed no fall of viscosity on storage, and controlled rate of hydration of grafted tamarind seed polysaccharide (GTS) [31].

Tamarind seed polysaccharide (TSP) from tamarind kernel powder was isolated by Ganesan, K. *et al.* and investigated for sustained release of tablet granules of salicylic acid by means of two dissimilar grades of TSP, cross linked TSP and embedded with chemically synthesized ZnS nanocrystals. Formulation containing TSP and cross linked released drug in sustained manner and there were no noteworthy changes in drug content and physical parameters [32].

Graft copolymerization of acrylic acid on guar gum which is initiated by vanadium (V)-mercaptosuccinic acid redox pair was performed by Pandey, P. K. *et al.* The most favorable reaction conditions giving maximum grafting ratio, efficiency and conversion have been studied [33].

Osemeahon, S. A. *et al.* have developed sodium alginate and konkoli gum grafted polyacrylamide blend membrane. It was observed that grafting parameters such as acrylamide, ceric ammonium nitrate, konkoli gum, temperature and reaction time had notable influence on percent graft yield of the graft copolymer. Results showed the optimum grafting conditions required for copolymerization of acrylamide onto konkoli gum [34].

Varshosaz, J. *et al.* have developed sustained release matrix tablets of extremely water soluble tramadol HCl by using xanthan gum and guar gum as nontoxic, easily available, cheap and suitable hydrophilic matrix systems against broadly investigated hydrophilic matrices (i.e., hydroxypropyl methylcellulose or carboxymethyl cellulose) [35].

Durcilene A da Silva *et al.* have grafted acrylamide onto cashew gum. The radical polymerisation technique was used for synthesis of cashew gum grafted polyacrylamide by using potassium persulphate as redox initiator under N₂ environment. Acrylamide concentration was varied whereas concentration of initiator and polysaccharide was kept constant to prepare series of graft copolymers. Comparison between grafting parameters of reaction of variety of natural polysaccharides with polyacrylamide was done. High percentage of acrylamide conversion (% C) and grafting efficiency (% E) were obtained for cashew gum (CG), also with a low acrylamide/cashew gum ratio [36].

Mundargi, R. C. *et al.* have prepared controlled release matrix tablets for antihypertensive drugs such as atenolol (ATL) and carvedilol (CDL) by using acrylamide grafted xanthan gum. Tablets were manufactured by using plain xanthan gum, grafted xanthan gum and other excipients. With increasing grafting ratio, release time increased and swelling pointed out that xanthan gum showed highest swelling compared to graft copolymers. The drug release via matrix tablets followed the non-Fickian (anomalous) trend [37].

Vijan, V. *et al.* have synthesized acrylamide grafted gellan gum in microwave assisted free radical polymerization method by using ceric ammonium nitrate as initiator. By varying in amount of acrylamide, ceric ammonium nitrate and microwave irradiation time, a series of graft copolymers was prepared. Comparison of grafting parameters like grafting efficiency, percent grafting and percent conversion was done. Three independent process variables were used to optimize synthetic parameters including amount of ceric ammonium nitrate, amount of acrylamide and microwave irradiation time. Elevated level of all these three variables had given higher grafting efficiency (*GE %*) of grafted gum. Tablets were prepared by incorporating metformin hydrochloride (anti-diabetic drug) in grafted gum along with excipients [38].

Kaity, S. *et al.* have synthesized acrylamide grafted locust bean gum (LBG) by microwave irradiation in which ceric ammonium nitrate was used as initiator. It was later used to formulate controlled release matrix tablets of buflomedil hydrochloride. *In vitro* release profile of tablet showed that rate controlling property of acrylamide grafted locust bean gum was parallel to that of hydroxypropyl methylcellulose (HPMC-K15M) [39].

CONCLUSION

Natural polysaccharides and their modified forms have been emerging in last few years as most widely used drug delivery excipients. In recent times, immense inquisitive has been compensated to the modification of natural polymers to obtain new smart biomaterials. Modified polymers can be used in design of a range of controlled and sustained drug release systems. Most of the exploration on natural polymers in various novel drug delivery systems plays around polysaccharides. Natural gums can also be modified to eliminate the disadvantages of synthetic polymers to get tailor-made products for designing much better drug delivery systems. In not-too-distant future, it could be further exploited as ground-breaking modified natural polymers for development of various drug delivery systems. The abundance of gums, their economic cost and biodegradability have compelled formulation scientists to design approaches for making them suitable for modifying the drug release of dosage forms. This review should be helpful to researchers in exploration and exploitation of smart biodegradable and biocompatible efficient carrier for the delivery of newer generation biotechnology based drugs especially macromolecular drugs.

Conflict of interest

The authors report no conflicts of interest.

Acknowledgements

We, the authors are very much thankful to the authors of the reference articles and the authority of BCDA College of Pharmacy & Technology for their support.

REFERENCES

1. Prajapati VD, Jani GK, Moradiya NG, Randeria NP. Pharmaceutical application of various natural gums, mucilages and their modified forms, Carbohydrate Polymers, 2013, 92:1685-1699.
2. Anthony AA, & Obichukwu JN. Mucuna gum microspheres for oral delivery of glibenclamide: *In vitro* evaluation, Acta Pharmaceutica, 2007, 57:161-171.
3. Chourasia MK & Jain SK. Potential of guar gum microspheres for target specific drug release to colon, Journal of Drug Targeting, 2004, 12:435-442.
4. Deshmukh VN, Sakarkar DM, Wakade RB. Formulation and evaluation of controlled release alginate microspheres using locust bean gum, Journal of Pharmacy Research, 2009, 2(3): 458-461.
5. Vendruscolo C W, Andrezza IF, Ganter JL. Xanthan and galactomannan (from M. Scabrella) matrix tablets for oral controlled delivery of theophylline, International journal of pharmaceutics, 2005, 296(1-2): 1-11.
6. Bonferoni MC, Rossi R, Tamayo M. On the employment of L-carrageenan in a matrix system. I. Sensitivity to dissolution medium and comparison with Nacaroxy methyl cellulose and xanthan gum, Journal of Controlled Release, 1993, 26:119-127.
7. Alison CH, John RM, Martyn CD. Structure and behavior in hydrophilic matrix sustained release dosage forms: The influence of pH on the sustained release performance and internal gel structure of sodium alginate matrices, Journal of controlled release, 1995, 33(1):143-152.
8. Coviello T, Dentini M, Rambone G. A novel cocross linked polysaccharides: studies for a controlled delivery matrix, Journal of controlled release, 1998, 55:57-66.
9. Bharaniraja B, Kumar KJ, Prasad CM, Sen AK. Modified katira gum for colon targeted drug delivery, Journal of Applied Polymer Science, 2011, 119:2644 - 2651.
10. Giunchedi P, Conte U, Chetoni P. Pectin microspheres as ophthalmic carriers for piroxicam: Evaluation *in vitro* and *in vivo* in albino rabbits, European Journal of Pharmaceutical Science, 1999, 9:1-7.
11. Efentakis M & Kouttis A. Release of furosemide from multiple unit and single unit preparations containing different viscosity grade of sodium alginate, Pharmaceutical Development and Technology, 2001, 6: 91-98.
12. Jani GK, Shah DP, Prajapati VD, Jain VC. (2009). Gums and mucilages: versatile excipients for pharmaceutical formulations, Asian journal of pharmaceutical sciences, 2009, 4:308-322.
13. Kottke KM, Edward MR. Tablet Dosage Forms. In: Banker GS, Rhodes CT, ed. Modern Pharmaceutics. New York: Marcel Dekker, Inc; 2002: pp287-333.
14. Aslam A & Parrott E. Effect of aging on some physical properties of hydrochlorothiazide tablets,. J. Pharm. Sci., 1971, 60: 263-266.

15. Chang RK, Shukla AJ. Polymethacrylates. In: Raymond CR, Paul JS, Paul JW, ed. Handbook of Pharmaceutical Excipients, The Pharmaceutical Press and The American Pharmaceutical Association, 2003, 462-468.
16. Hizawa K, Otsuka H, Inaba H. Subcutaneous pseudosarcomatous PVP granuloma, Am. J. Surg. Path., 1984, 8: 393-398.
17. Kolen JJ, McGinity JW, Wilber WR. Carbomer-934P, In: Raymond CR, Paul JS, Paul JW, ed. Handbook of Pharmaceutical Excipients, The Pharmaceutical Press and The American Pharmaceutical Association; 2003: 89-92.
18. Weller PJ, Owen SC. Polyvinyl alcohol. In: Raymond CR, Paul JS, Paul JW, ed. Handbook of Pharmaceutical Excipients, The Pharmaceutical Press and The American Pharmaceutical Association, 2003: 491-492.
19. Khaled AT, Jagdish S. Recent patents on drug delivery and formulation, 2007, 1: 65-67.
20. Zohuriaan-Mehr MJ, Advances in chitin and chitosan modification through graft copolymerization: A comprehensive review, Iranian Polymer Journal, 2005, 14: 235-265.
21. Soppimath KS, Aminabhavi TM, Dave AM, Kumbar AG, Rudzinski WE. Stimulus responsive smart hydrogels as novel drug delivery systems, 2002 28(8):957-74.
22. Bhattacharya A, Misra BN. Grafting: a versatile means to modify polymers; techniques, factors and applications, Prog. Polym. Sci., 2004, 29:767-814.
23. Nandi G, Patra P, Priyadarshini R, Kaity S, Ghosh LK. Synthesis, characterization and evaluation of methacrylamide grafted gellan as sustained release tablet matrix, International Journal of Biological macromolecules, 2015, 72: 965-974.
24. Mishra BN, Mehta IK, Khetrpal RC. Grafting onto cellulose. VIII. Graft copolymerization of poly (ethylacrylate) onto cellulose by use of redox initiators. Comparison of initiator reactivities. J Polym Sci Polym Chem, 1984, 22: 2767-2775.
25. Sen. G., Kumar. R., Ghosh. S., & Pal. S. (2009). A novel polymeric flocculant based on polyacrylamide grafted carboxymethyl starch. Carbohydrate polymers, 77, 822-831.
26. Singh, V., Tripathy, D. N., Tiwari, A., & Sanghi, R. (2006). Microwave synthesized chitosan-graft-poly(methylmethacrylate): An efficient Zn²⁺ ion binder. Carbohydrate Polymers, 65, 35-41).
27. Rokhade AP, Patil SA, Aminabhavi TM. Synthesis and characterization of semi-interpenetrating polymer network microspheres of acrylamide grafted dextran and chitosan for controlled release of acyclovir, Carbohydrate polymers, 2007, 67, 605-613.
28. Bhattacharya SS, Mazahir F, Banerjee S, Verma A, Ghosh A. Preparation and *in vitro* evaluation of xanthan gum facilitated superabsorbent polymeric microspheres. Carbohydrate polymers, 2013, 98:64-72.
29. Mandal S, Basu SK, Sa B. Ca²⁺ ion crosslinked interpenetrating network matrix tablet of polyacrylamide-grafted-sodium alginate and sodium alginate for sustained release of diltiazem hydrochloride, Carbohydrate Polymers, 2010, 82: 867-873.
30. Deogade, UM, Deshmukh VN, Sakarkar DM. Natural gums and mucilage in NDDS: Application and recent approaches, Int. J. PharmTech Res., 2012, 4(2): 799-814.
31. Shailaja T, Latha K, Sasibhushan P, Alkabab AM, Uhumwangho UM. A novel bioadhesive polymer: grafting of tamarind seed polysaccharide and evaluation of its use in buccal delivery of metoprolol succinate, Der Pharmacia Lettre, 2012, 4(2):487-508.
32. Ganesan K, Rajaram SK, Chinnathambi A, Murugesan V, Muruganatham K, Amanullah TR, Barthelomai IS, Chinnasamy S. A sustained release of tablet granules associated with ZnS nanocrystals using Tamarind seed polysaccharide, J. Appl. Pharm. Sci., 2013, 3(4):S44-S47.
33. Pandey PK, Srivastava A, Tripathy J, Behari K. Graft copolymerization of acrylic acid on to guar gum initiated by vanadium (V)-mercapto succinic acid redox pair, Carbohydr. Polym., 2006, 65:414-420.
34. Osemeahon SA, Barminas TJ, Aliyu BA, Nkafamiya II. Development of sodium alginate and konkoli gum grafted polyacrylamide blend membrane: optimization of grafting condition, Afr. J. Biotech., 2008, 7(9): 1309-1313.
35. Varshosaz J, Tavakoli N, Kheirolahi F. Use of Hydrophilic Natural Gums in Formulation of Sustained-release Matrix Tablets of Tramadol Hydrochloride, AAPS PharmSciTech., 2006, 7(1):E168-E174.
36. Durcilene A da Silva, Regina CM, Judith PA. Graft copolymerisation of acrylamide onto cashew gum, Eur. Polym. J., 2007, 43:2620-2629.
37. Mundargi RC, Patil SA, Aminabhavi TM. Evaluation of acrylamide-grafted-xanthan gum copolymer matrix tablets for oral controlled delivery of antihypertensive drugs, Carbohydr. Polym., 2007, 69:130-141.
38. Vijan V, Kaity S, Biswas S, Isaac J, Ghosh A. Microwave assisted synthesis and characterization of acrylamide grafted gellan, application in drug delivery, Carbohydr. Polym., 2012, 90:496-506.
39. Kaity S, Isaac J, Mahesh Kumar P, Bose A, Wong TW, Ghosh A. Microwave assisted synthesis of acrylamide grafted locust bean gum and its application in drug delivery, Carbohydr. Polym., 2013, 98:1083-1094.