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A REVIEW ON MODIFICATION OF NATURAL POLYMER

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ABSTRACT
Polymers plays a vital role in each portion of lives. At present time every person depends on polymer to get various requirements. Different polymers are having different applications based on their sources. Newly, researches have been going on for the modification of natural polymer as they are easily available, non-toxic and economical nature. So they are mostly used over the synthetic polymer though we can use both of them in the Pharmaceutical field. However, it is not compulsory that all the polymers we had till now from various sources should possess all its desired properties, there might be some particular properties which can be absent in the polymers we have till now. There are some drawbacks like poor bioavailability, short half-lives, physical and chemical instability, in Pharmaceutical dosage forms. Modification of the intrinsic properties of the natural polymers can provide enhanced stability, drug release pattern and many other characteristics which are lacking in natural polymer. For these reasons development of polymer grafting is initiated. Advancement in polymer science is essential as they can improve the range of application. Polymer grafting is one of the most propitious technique for the modification of natural polymer properties and loss in the original characteristics is very less.

KEYWORDS: Polymer, natural polymer, synthetic polymer, pharmaceutical field, bioavailability, polymer science, polymer grafting.

INTRODUCTION
Polymers are composed of large number of simple molecule (i.e. Monomer) by covalent bonds in an orderly manner. The term polymer was first introduced by Jöns Jacob Berzelius d.[1] In the pharmaceutical industries polymers are widely used because of their unique properties. Pharmaceutical dosage forms faces some drawbacks like poor bioavailability, short half-lives, physical and chemical instability.[2] Moreover, by using proper polymer/s delivery of a specific concentration of drug to target site for a specific time can be effectively achieved. Polymers with required property are merged in drug delivery system due to the prolong release of merged drug, improved stability, ease of preparation, steady therapeutic concentration with a single dose. Hence, in the formulation of dosage form selection of proper polymer system is a crucial step. The stability of formulation and drug itself, mechanism, and rate of drug release is dependent on the type of polymer/s used in formulation. Over the past few years, polymers obtained from various sources like plant source, marine source, microbial source, and synthetic sources are used in various pharmaceutical applications.[3] However, it is not compulsory that all the polymers we had till now from various sources should possess all its desired properties, there might be some particular properties which can be absent in the polymers we have till now. This introduced a significant role of polymer grafting in formulation development cycle. By modifying the chemical functional groups of polymer, various desirable properties can be incorporated to polymer and undesirable one can be removed. To overcome the drawbacks and to regulate the site of drug release and it's kinetic and also to make them superior, polymer modification is required.

Natural polymer: Natural polymers are obtained from natural sources like plants and animals sources. Examples are resin, proteins, polypeptides, cellulose, and starch.

Semi-synthetic polymers: These polymers are obtained from natural polymers by subjecting them to chemical treatment to change the physical properties of natural polymers like, silicones, Starch.

Synthetic polymers: Synthetic polymers are human-made polymers. They can be synthesized in laboratory by polymerizing simple chemical molecule. Examples are synthetic rubber, nylon, Teflon, PVC etc.[4]

Advantages of natural polymer

1. Natural gums are obtained from natural sources
2. They are biodegradable and there is no adverse effects on human being or on surrounding environment.
3. They are non-toxic and biocompatible in nature.
4. Cost is low and availability is high.
5. Tolerability by the patient and public acceptance is better

Drawbacks of synthetic polymer[5-7]

1. Synthetic polymers are costly.
2. They show toxicity and poor patient compliance.
3. Synthesis of such polymers may affect environment during their synthesis.
4. Skin irritation and eye irritation can occur in workers dealing with synthesis of polymers

THEORY OF GRAFTING

There are various ways to modify the properties of polymer with the help of some techniques like blending, grafting and curing. Physical mixture of two or more polymers are used to get desired properties in blending technique. Grafting involves covalent bonding of monomers on polymer chain and in curing oligomer mixtures are polymerized to get a coating which adheres to substrate by physical forces followed by a soft finish by filling in the dell in surface. The main aim of modification are to enhance the mechanical properties, wettability, biocompatibility, etc. of a polymer. Grafting can be accomplished either by 'grafting to' or 'grafting from' approach. In case of 'grafting to' approach, reaction of functionalized monomers with the backbone polymer provides in the grafted polymer. On the other hand 'grafting from' immobilized initiators are formed followed by polymerization by reacting the substrate with appropriate method.[8]

Grafting can be done in two ways

1. Grafting with a single monomer and
2. Grafting with a mixture of two (or more) monomers.

First one is a single step process and second one may occur either with simultaneous or chronological use of the two monomers.

GRAFTING TECHNIQUES

Grafting initiated by chemical means

Grafting can be done by chemical means via two methods such as ionic and free radical. Initiator plays a vital role in chemical process, because it decides the fortune of grafting process. Apart from common free-radical mechanism, grafting in the melt and atom transfer radical polymerization (ATRP) are alluring techniques for grafting.[9-11]

Grafting through living polymerization

In current years, 'Living Polymerization' has urbanized to supply a possibility for grafting. According to Szwarc et al., most reasonable meaning of a living polymer is one which holds its ability to proliferate for extended time and grow to preferred highest size while their degree of extinction or chain transfer is still insignificant. Features of both the conventional free-radical and ionic polymerizations combine to express controlled free-radical polymerizations.[10] In case of conventional free-radical polymerization, there is a requirement of constant initiation, with annihilation of growing chain radicals in coupling or disproportionate reactions, leading to unreactive polymers called dead polymers and basically time invariant degrees of polymerization and large molecular weight allocation. In living polymerization, it supplies living polymers with synchronized molecular weights and low polydispersities.[11-18]

Photochemical grafting

When chromophore on macromolecule absorbs light and undergoes in excitation it will form reactive free radicals as a result grafting can be initiated. State to form reactive free radical. If the absorption of light only is not sufficient, the process may be encouraged by addition of photo sensitizers like benzoin ethyl ether, dyes like Na-2, 7 anthraquinonesulphonate or acrylatedazo dye. So it can be stated that in photochemical grafting there are two approaches two approaches which are: with or without a sensitizer. In Without sensitizer approach grafted polymer formed due to the production of free radicals on backbone polymer which will further reacts with monomer free radical. While, in 'with sensitizer' approach, sensitizer will produce the radical sites which are required for grafting and forms free radicals and to abstract hydrogen atoms from the polymer base diffusion of free radicals takes place.[19-21]

Enzymatic grafting

Enzymatic grafting is a novel technique in which, chemical or electrochemical grafting reaction begins because of the enzyme. For example, phenol converts into reactive oquinone due to tyrosinase, and after that it will undergo successive non-enzymatic reaction with chitosan.[22]

Plasma-radiation induced grafting

In plasma-radiation induced grafting technique, plasma conditions achieved through slow release bring up the same potential as with ionizing radiation.[23, 24] Electron-induced excitation, ionization and dissociation are the main processes in plasmas. Accelerated electrons from plasma ruptures chemical bonds in polymeric structures to form macromolecule radicals, results graft co-polymerization.

Grafting initiated by radiation technique

Free-radical grafting

Irradiation of macromolecules will form free radicals on polymer and for this homolytic fission will occur. The medium is more important than the initiator used in radiation technique. For example, peroxides can form on polymer if irradiation is executed on air.[26-28] The life span of free radicals depends on the nature of polymer

backbone. Radiation technique of grafting generally occurs in three different ways:
1. Pre-irradiation
2. Peroxidation
3. Mutual irradiation

In pre-irradiation approach, in presence of inert gas or polymer backbone irradiation free radicals can be generated followed by treating monomer with polymer substrate, in vapor state or in liquid or as a solution in a suitable solvent. In peroxidation approach, to form hydro peroxides or diperoxides in the presence of air or oxygen trunk polymer is subjected to high-energy radiation, based on the nature of polymeric backbone and irradiation circumstances. To initiate grafting, stable peroxy products are treated with monomer and decomposition of peroxides occurs at higher temperature.[25-29] These intermediary peroxy products can be stored up prior to grafting for long periods.

Polymer and monomers are irradiated at the same time to form free radicals and successive addition in mutual irradiation approach.[30-36] In preirradiation approach, monomers are not exposed to radiation, the method is almost free from generation of homopolymer and this is the distinct advantage of this approach. Conversely, certain drawback of preirradiation approach is scission of base polymer because of its direct irradiation which may result in formation of block co-polymers.[32-34]

Ionic grafting
Grafting as well can proceed through an ionic mode. Some useful initiators in this purpose include alkali metal suspensions in a Lewis base liquid, organ metallic compounds and sodium naphthalenide. For example, Alkyl aluminium (R3Al) and backbone polymer in halide form (ACl) act together forming carbonium ions along the polymer chain, leading to copolymerization. The reaction proceeds through cationic mechanism.

$ACl + R3Al \rightarrow A^+R3Cl^-$

$A^+ + M \rightarrow AM^+-M \rightarrow$ graft co-polymer

Cationic catalyst BF3 can be implemented for this purpose. An anionic mechanism also involved in the grafting process. For example, sodium ammonia or methoxide of alkali metals form alkoxide of polymer (PO^-, Na^+) which reacts with monomer to form graft co-polymer.[37-41]

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

$PO^- + M \rightarrow POM^{\cdot}-M \rightarrow$ graft co-polymer

Microwave initiated grafting
In this technique, no initiators are used. Hydroquinones are used as a radical inhibitor to slow down the reactions of grafting, while survival of free radicals in reaction mixture has not been confirmed by current instrumentation like electron spin resonance (ESR). Under microwave settings, heating results from the dipolar relaxation of solvent; especially water and because of localized rotation polar functional groups of polysaccharides.[42]

Microwave assisted grafting
In this technique, initiators are used and by addition of initiators to reaction mixture, ions are produced which improve the skill of aqueous reaction mixture to change microwave energy into heat energy. Grafting reactions are facilitated by the production of free radicals from initiators under control of microwave dielectric heating.[42]

FACTORS AFFECTING GRAFTING

Nature of polymer backbone
The nature of polymer backbone i.e. physical nature and chemical composition have important role in the process of grafting involving covalent connection between monomer and pre-formed polymeric backbone. Ng et al. have found that cellulose does not support grafting reactions in water due to its insolubility. Because of the vast size of polymeric chain bonding between amino residues in wool, cysteine linkages and intra-molecular H-bonding may be accountable for determining and setting characteristics. In the presence of UV light, oxidative reactions are initiated and free radicals formed, leading finally to grafting if monomers are present.[43]

Effect of monomer
The reactivity of the monomer is vital in grafting such as the nature of polymer backbone. Reactivity of monomers depends on various factors like polar and steric nature, swellability of backbone in the presence of monomers and concentration of monomers.[43]

Effect of solvent
The solvent is the carrier through which monomers are passed to the surrounding area of backbone in grafting mechanism. The criteria for assortment of suitable solvent relies on numerous parameters such as solubility of monomer in the solvent, swelling properties of backbone, miscibility of the solvents (if more than one is used) and generation of free radical in presence of solvent. Nature of solvent plays important role in solubility of monomer and polymer. For example, alcohols are helpful solvents for grafting of styrene as they can swell the backbone proficiently and can dissolve styrene so the monomer can simply diffuse in cellulosic structure. The degree of grafting reduces gradually with alcohol change from methanol to ethanol to isopropanol and then to t-butanol, owing to the slowly decreased swelling properties of alcohol, recognized to be corroborated by largeness of the alcohol molecules.[44-46]

Effect of initiator
The nature of initiator has a deep impact on the grafting process. Except radiation technique, all other chemical grafting techniques need an initiator and hence, its nature, concentration, solubility and function should be considered. There are some initiators like

azobisisobutyronitrile (AIBN) and potassium persulfate (K2S2O8). In the grafting of 2-hydroxy methacrylate (HEMA) on cellulose, azobisisobutyronitrile (AIBN) provides reduced grafting and potassium persulfate (K2S2O8) is not suitable as an initiator, as it degrades cellulose chain.[47]

Effect of temperature

Temperature is the key factor that controls the kinetics of graft co-polymerization. With increasing temperature, grafting yield also increases until a limit is achieved. This may be attributed to faster monomeric diffusion in backbone which increases with the rising temperature and makes the progress of grafting smooth. Sun et al. reported such behavior to produce free radicals on base polymer with increasing temperature by increased thermal decomposition rate of initiator and the initiator efficiency resulting in increased polymer macro radical's concentration leading to enhanced graft polymerization. Rising temperature, at first enhances the grafting yield and helps the decomposition of peroxide. On the other hand, as reported by Maldas, in case of acrylamide grafting on cellulose acetate, grafting yield decreases gradually with the increase in temperature. The initial rise in grafting is the result of decomposition of peroxides formed due to irradiation of base polymer in air, making the necessary radicals accessible for grafting, and the following decrease is observed because of the increased molecular motion with rising temperature, ensuing in increased radical decay.[48]

Effect of additives on grafting

The presence of additives like metal ions, acids, and inorganic salts affects the extent of graft co-polymerization or grafting yield. Hence, the reaction amongst the monomer and backbone has to fight with any reactions amongst monomer and additives. Even if few additives may improve the monomer/backbone reaction to increase the grafting effectiveness, the reverse will be factual if reaction between monomer and additive is overriding.[49,50]

CHARACTERIZATION TECHNIQUES FOR GRAFTED GUMS

There are various analytical techniques used to characterize and evaluate grafted polymeric materials. These are Fourier transmission infrared (FTIR), NMR, X-ray diffractometer (XRD), differential scanning calorimeter, elemental analysis, and MW analysis.

Fourier transform infrared spectroscopy (FTIR)

The occurrence of specific functional groups in compounds can be examined by Fourier transform infrared spectroscopy (FTIR). For characterization, 0.5-1 mm thick films of natural gum and all graft copolymers can be prepared and analyzed by ATR-FTIR by means of transmittance mode.[51]

Solid state 13C NMR spectroscopy

13C solid state NMR analysis of natural gum and grafted gum can be done by NMR spectrophotometer operating at 75 MHz. Around 300 mg of sample is required to insert in ceramic rotor of NMR spectrophotometer for its characterization[51,52]

Scanning electron microscopy (SEM)

SEM system is used to characterize the morphology of material. Natural gum and its grafted form can be characterized by SEM analysis. To increase the conductivity of electron beam, samples can be gold coated.[51]

Powder X-ray diffraction

X-ray diffractometer is used to record X-ray powder diffractometry (PXRD) of sample. The native gum and grafted gum can be studied. The X-ray source is generally Cu, with wavelength 1.5406° A and Si (Li) PSD detector. The diffractometer basically run at a scanning speed of 2° /min, a chart speed of 2° / 2 cm per 2 θ and an angular range fixed between 3° and 80°.[51]

Differential scanning calorimetry (DSC)

DSC instrument is used to obtain DSC thermograms of compounds. 3-5 mg samples are heated from 10 °C to 300 °C under nitrogen purge (50 ml/min) at a heating rate of 10°C/min.[52]

Elemental analysis

PCHN 2400 microanalyser is used for the elemental analysis. The samples of native gum and all the graft copolymer can be examined for contents. The carbon, hydrogen and nitrogen contents can be calculated.[51,52]

Viscosity measurement

A well programmed Brookfield viscometer is used to record the viscosity. 2% w/v aqueous solution of native gum and graft copolymer is sufficient for the viscosity study. Temperature can be maintained at 32.7^{o}C. The samples are generally dissolved in water for native gum and heated at 80°C. The spindle, usually spindle no. S-01 is rotated at varying rpm and corresponding shear rate, shear stress and viscosities can be recorded.[52]

Molecular weight analysis

Gel permeation chromatography technique is used for the molecular weight analysis of sample by a refractive index detector. A PL aqua gel-OH mixed column (7.5 mm × 300mm; 8 µm) is used with mobile phase containing 0.1 % w/w sodium azide dissolved in de-ionized water. The flow rate of mobile phase and column temperature is kept at 0.5 ml/min and 30 °C respectively. Dextrans with molecular weights of 150,000, 410,000, 670,000, 1,400,000 and 2,000,000 Daltons are used as standards. 1 mg/ml of standard or sample solution is filtered through a cellulose nitrate membrane (pore diameter = 0.45 µm) before analysis. At least triplicates should be carried out for each batch of sample and the average results reported.[52,53]

Swelling study

Two different media can be used for equilibrium swelling measurements of both native gun and different grades of grafted ones. A small, formerly weighed amount of the material (W1) is immersed in 50 ml buffer (pH 1.2 and pH 6.8) and left to swell for 2 h. Afterward, the swollen quantity is recovered and excess water is removed vigilantly with tissue paper and reweighed (W2) to an accuracy of ± 0.01 mg on electronic microbalance.[52] The swelling characteristics of sample can be measured by using following equation:

$$\text{Swelling index} = W2 - W1 / W1 \times 100$$

Where, W2 and W1 are the swollen and dry weights of the native gum/grafted gum, respectively.

Acute oral toxicity study

Acute oral toxicity study of grafted gum can be performed as per Organization of Economic Co-operation and Development (OECD) guideline. 5 nulliparous and nonpregnant five weeks old female mice (Swiss albino strain) are required for this study. Mice are required to house in polycarbonate cage with food and deionized reverse osmosis water at 20-25 °C and 40-70 % relative humidity in a 12 h light/dark series. A single dose of 2000 mg/kg body weight of grafted gum is administered by gavages using a stomach tube in the first animal. The same dose is administered in the remaining four animals after survival of first animal. The animals should be kept under constant examination up to 4 h subsequent to dosing. The examination must continue up to 14 days. The mortality rate can be evaluated by visible inspection and reported consequently. Serum biochemical studies on 30th min, 4th h, 1st, 3rd, 7th and 14th day should be performed. The animals should then forfeit on the 15th day and histopathological studies on liver, kidney, lung and stomach should be performed.[52,53]

Biodegradability study

Sample films of grafted gums (5 % gum solution casted on Petri dish and dried) are inoculated with Aspergillus niger on a medium and incubated at ambient temperature of 25-37 °C for 21 days. Afterward, the films are then observed for confirmation of colony development.[52]

APPLICATIONS OF GRAFTED GUMS

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

Deogade et al. mentioned grafting of natural gums to prepare tailor-made advanced polymers and their importance and applications.Tamarind seed gum (TS) with methyl methacrylate (MMA) was grafted by Shailaja 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). [53] Tamarind seed polysaccharide (TSP) from tamarind kernel powder was isolated by Ganesan 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.[54]

Graft copolymerization of acrylic acid on guar gum which is initiated by vanadium (V)-mercaptosuccinic acid redox pair was performed by Pandey et al. The most favorable reaction conditions giving maximum grafting ratio, efficiency and conversion have been studied. Osemeahon 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. Varshosaz 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).[30]

Da Silva et al. have grafted acrylamide onto cashew gum. The radical polymerization 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.[30]

Mundargi 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.[31]

Vijan 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 anti-diabetic drug, metformin hydrochloride in grafted gum along with excipients.[29]

Kaity et al. have synthesized acrylamide grafted locust bean gum (LBG) by microwave irradiation in which ceric ammonium nitrate w-as 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).[27]

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