INTRODUCTION
Pharmaceutical and biological therapeutics are suffered from disadvantages such as short half-lives, poor bioavailability, and physical and chemical instability. Physical instability mainly includes alteration of highly ordered protein structure, leading to undesirable processes such as denaturation, aggregation, and precipitation. Chemical reactions such as oxidation, deamidation, hydrolysis, and racemization contribute to the chemical instability of drugs [1].

Furthermore, delivery of drugs to target site at a specific concentration for a specific time can be successfully achieved by the use of suitable polymer/s. The major benefits for which polymer with desired property incorporated in drug delivery systems include ease of preparation, maintenance of desired therapeutic concentration with a single dose, prolonged release of incorporated drug, and improved stability.

Therefore, selection of proper polymer system is a critical step involved in formulation of drug into dosage form. Type of polymer/s incorporated in formulation majorly decides the stability of formulation and drug itself, mechanism, and rate of drug release.

Polymers are macromolecules composed of monomers linked covalently. The term polymer was first introduced by Jöns Jacob Berzelius d [2]. In the past few years, polymers obtained from plant source, microbial source, marine source, and synthetic sources have suggested marvelous awareness owing to their varied pharmaceutical applications such as binder, diluents, disintegrates in tablets, protective colloids in suspension, gelling agent in gels, thickeners in oral liquids, and bases in suppositories [3]. However, it is not necessary the polymers we had till the date from variety of sources should possess all the desired properties, formulation scientists seeking particular properties in polymers might be absent in the polymers present. This introduced a significant role of polymer grafting in formulation development cycle.

With modification of chemical functional groups of polymer, wide range of favorable properties can be imparted to polymer and unfavorable one can be diminished.

POLYMER GRAFTING AND APPLICATIONS IN PHARMACEUTICAL DRUG DELIVERY SYSTEMS - A BRIEF REVIEW

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ABSTRACT
Selection of proper polymer system is a critical step involved in the formulation of dosage form. Type of polymer/s incorporated in pharmaceutical formulation majorly decides the stability of formulation and drug itself, mechanism, and rate of drug release. Pharmaceutical and biological therapeutics are suffered from disadvantages such as short half-lives, poor bioavailability, and physical and chemical instability. Delivery of drugs to target site at a specific concentration for a specific time can be successfully achieved by the use of suitable polymer/s. Thus, it is not necessary that available polymer till the date should have all ideal properties with respect to above. This makes a demand of tailored polymers with desired features and introduces concept of grafting for making new polymers to be used in dosage forms. Grafting can be achieved by various techniques described herein and can be analyzed by various modern analytical techniques including infrared, NMR, X-ray diffractometer, and differential scanning calorimeter. These graft copolymers offer many applications in terms of drug/biological carrying capacity, tailor-made physicochemical properties based dosage form modifications and with desired features, and also to deliver therapeutics at specific sites. Considering these advantages, a number of applications of grafted polymers developed and many patents were filed in this area till the date. This review highlights the basic concept of grafting and its various techniques and their significant pharmaceutical applications.

Keywords: Polymer grafting, Pharmaceutical formulation, Drug delivery, Grafting techniques, Analytical techniques, Patents.

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GRAFTING
The main purposes of a surface modification are improving the wettability, biocompatibility, mechanical properties, etc., of a surface polymer.

Two major types of grafting may be considered:

i. Grafting with a single monomer and

ii. Grafting with a mixture of two (or more) monomers.

Furthermore, grafting copolymers can be obtained mainly by two mechanisms known as grafting from and grafting to. To several process-related parameters such as the type and concentration of initiator, monomer concentration, reaction temperature, and time influences grafting parameters such as grafting percentage and grafting efficiency. The properties of the resulting graft copolymers are widely controlled by the characteristics of the side chains including molecular structure, length, and number [5]. Following are the different techniques of grafting:

1. Chemical grafting
   a. Free radical grafting
   b. Ionic grafting
2. Grafting through living polymerization
3. Photochemical grafting
Chemical grafting

In the chemical grafting, the role of initiator is very important as it determines the path of the grafting process. It is further classified as free radical grafting and ionization grafting.

a. Free radical grafting

Free radicals are produced from the initiators and transferred to the substrate to react with monomer to form the graft copolymers. Initiator systems used in free radical initiated grafting are as follows [5]:
- FAS: Ferrous ammonium sulfate
- CAN: Ceric ammonium nitrate
- PDC: Potassium diiodoplatinate (III)
- PPS: Potassium persulfate
- TCPB: Thiocarbonationpotassium bromate
- APS: Ammonium persulfate.

b. Ionic grafting

Grafting can be triggered in ionic conditions proceeding mainly through ionic mode. Grafting can proceed through an anionic mechanism where alkoxide of alkali metals used as initiators (such as sodium methoxide) or by cationic mechanism where alkali metal salts are used such as alkyl aluminum (R3Al) [4].

Anionic grafting: Hossein Hosseinzadeh modified a polysaccharide, sodium hyaluronate, through graft copolymerization of acrylic acid. This graft copolymerization was initiated using anionic initiator ammonium persulfate. Increase in the molecular mass of sodium hyaluronate, after extraction of homopolymer, was considered as the end point of grafting, and also the basis for the determination of the grafting parameters. In this study, effect of concentration of acrylic acid, sodium hyaluronate, and ammonium persulfate as well as grafting temperature on grafting process was evaluated [7].

Cationic grafting: Yoshikawa et al. grafted chitosan with cationic living polymers such as poly(isobutyl vinyl ether) and poly(2-methyl-2-oxazoline). In this study, analysis of the effect of molecular weight of living polymer cation on the mole number of grafted polymer was done. With the grafting process, viscosity of the resulting polymer was found to increase with the increasing percentage of grafting. This grafted polymer was also found to be soluble in water [9].

Grafting through living polymerization

Szavarc et al. define the living polymerization as “living polymer” is “that retains their ability to propagate for a long time and grow to a desired maximum size while their degree of termination or chain transfer is still negligible.” [9]

Controlled free radical polymerizations combine features of conventional free-radical and ionic polymerizations. In case of a living polymerization, it provides living polymers with regulated molecular weights and low polydispersities [4].

A conventional radical polymerization suffers from disadvantage that it does not possess control over the molecular weight, molecular weight distribution, and architecture of the polymer, making its macroscopic properties very difficult to be tailored. While living ionic polymerizations can provide a methodology for preparation of copolymers with well-defined structures, such as controlled molecular weights and narrow molecular weight distribution, defined copolymer compositions, branching, and end-group functionalities.

a. Stable free radical polymerization (SFRP) - reversible homolytic cleavage of a dormant chain end to form a stable free radical as well as an active radical site was applied to the polymerization. SFRP mainly applied for styrenics, acrylates, and acrylamides, still major attention in literature was on styrenic monomers [10].

b. Reversible addition-fragmentation chain transfer (RAFT) is achieved by performing a free radical polymerization in the presence of dithio compounds, which act as efficient RAFT agents [11].

c. Atom transfer radical addition (ATRP) - dormant chains are capped by halogen atoms, which are reversibly transferred to metal complexes in the lower oxidation state. This generates the transient growing radicals and complexes in the higher oxidation state. The key reaction of ATRP is the activation-deactivation dynamic equilibrium process [11].

Sonmez et al. reported acrylamide grafting by ATRP; the initiation appears to take place through radical formation in a redox reaction of N-chlorosulfonamide groups with CuBr [12].

Each of these methods relies on the establishment of a rapid dynamic equilibrium between a low concentration of active propagating chains and a predominant amount of dormant chains that are unable to propagate or terminate and is more tolerant toward functional groups and impurities [13].

Photocatalytic grafting

To initiate the grafting process, photochemical radiations are used; these radiations cause dissociation of a chromophore into reactive free radicals using. The grafting process by a photochemical technique can proceed in two ways: With or without a sensitizer.

The mechanism without sensitizer involves the generation of free radicals on the backbone, which react with the monomer free radical to form the grafted copolymer. On the other hand, in the mechanism “with sensitizer,” the sensitizer forms free radicals, which can undergo diffusion so that they abstract hydrogen atoms from the base polymer, producing the radical sites required for grafting.

Liu and Xu photochemically grafted a hydrophilic polymer, poly(N-vinyl-2-pyrrolidone), onto the surface of polypropylene microfiltration membrane (PPMM) using ultraviolet and γ-radiations. Grafting resulted in an enhanced hydrophilicity for the modified membrane. Evaluation of the biocompatibility of poly(N-vinyl-2-pyrrolidone)-modified PPMM had shown positive result in their research [14].

Enzymatic grafting

It is based on the principle that an enzyme can be used to initiate the chemical/electrochemical grafting reaction [15]. Application of enzyme can offer a green approach in grafting techniques by eliminating the use of reactive reagents with respect to safety, efficacy, and economy. Furthermore, enzymes specificity may offer the potential for precisely tailoring macromolecular properties to desired ones.

Chen et al. studied tyrosinase initiated the grafting of peptides onto the amine-containing polysaccharide chitosan [15].

Plasma radiation-induced grafting

Slow discharge plasma radiations offer about the same grafting probabilities as with ionizing radiation. The main events in plasma radiation-induced grafting are electron-induced excitation, ionization, and dissociation. Thus, the high-energy accelerated electrons from the plasma used to induce cleavage of the chemical bonds in the polymeric structure, which subsequently form macromolecule radicals and initiates graft copolymerization [16].

Acrylic acid grafted polyethylene terephthalate used successfully to reduce antithrombogenic property of polymer polyethylene terephthalate, and heparin immobilized over grafted polymer was found to be blood compatible [17].

Radiation grafting

High energy radiation exposure over the polymeric backbone to form active sites (free radicals) serving as the site of grafting for propagation to form side-chain grafts. These radicals easily react with appropriate...
functional monomers to form covalent bonds and, as a consequence, growth of macromolecular chains, and all of this without the use of chemical initiators [18,19]. Singh and Roy studied radiation grafting of chitosan with N,N-dimethyl amionomethacrylate. Radiation parameters such as radiation dose rate and total dose/time were found to affect the rate of grafting and homopolymerization. In this study, it was found that a desired level of grafting was achieved by appropriate selection of these radiation parameters in grafting conditions [20].

a. Free radical grafting
The irradiation of macromolecules can cause homolytic fission and thus forms free radicals on the polymer. In the radiation technique, the presence of an initiator is not essential. The medium is important in this case, e.g., if irradiation is carried out in air, peroxides may be formed on the polymer. The lifetime of the free radical depends on the nature of the backbone polymer. Grafting proceeds in three different ways: (a) Pre-irradiation, (b) peroxidation, and (c) mutual irradiation technique [18].

b. Radiation grafting can also proceed through an ionic mode
With the ions formed through high-energy irradiation, ionic grafting may be of two different types: cationic or anionic. The polymer is irradiated to form the polymeric ion and then reacted with the monomer to form the grafted copolymer. The potential advantage of the ionic grafting is high reaction rate [4].

**ANALYTICAL TECHNIQUES UTILIZED IN CHARACTERIZATION OF GRAFTED POLYMERS**

Following are analytical techniques used to characterize and evaluate grafted polymeric materials: Fourier transmission infrared (FTIR), NMR, X-ray diffractometer (XRD), differential scanning calorimeter, **ELEMENTAL ANALYSIS**, and **MW ANALYSIS** explained in following Table 1 [21].

**PHARMACEUTICAL UTILITIES OF GRAFTED POLYMERS**

To alter drug of biological carrying capacity
Dailey et al. improved biomolecules carrying capacity of PLGA was by its grafting with PVA polymer. The PVA backbone can be modified conveniently to create negatively or positively charged surface properties using sulfobutyl or amine functional groups tethering. This grafting process increased hydrophilicity which in turn enhanced biomolecule carrying capacity, especially sensitive biomolecules such as proteins, peptides, and DNA [22].

**Jung et al.** developed the application of grafted polymer sulfobutylated poly(vinyl alcohol)-graft-poly(lactide-co-glycolide) with association of tetanus toxoid in combination with cholera toxin enabled the use of tetanus toxoid as oral and nasal vaccination [23].

**Omer et al.** prepared and characterized pH sensitive polyelectrolyte complex hydrogel microcapsules for the oral delivery of proteins. In this research, the **Omer et al.** prepared chitosan (CS) grafted alginate hydrogel using “grafting to” technique, using P-Benzquinone as the coupling agent later by click grafting of chitosan chains through NH$_2$ groups [24].

To achieve tailored physicochemical properties by grafting of polymers
Although chitosan is an effective flocculating agent only in acidic media, the derivatives having side chain carboxyl groups showed zwitterionic characteristics with high flocculation abilities in both acidic and basic media [5]. Hydrogels based on poly(N-isopropylacrylamide) (PNIPAAm)-grafted chitosan were developed by Cai et al., by applying irradiation. The swelling behavior of these chitosan-g-PNIPAAm hydrogels increased with the increase in the amount of the grafted branches, i.e. grafting percentage [25].

Many applications of acrylic acid grafts of chitosan as possible means of creating hydrophilic and mucoadhesive polymers have been reported recently. Such as CS - poly(acrylic acid) (PAA) graft proved to be a promising vehicle for the administration of hydrophilic drugs, proteins, and peptides in the work of Hu et al., where they used silk peptide as a model drug [26].

Modified psyllium exhibiting altered pH-sensitivity, swellability, biodegradability, and ultimately drug release mechanism produced by chemical grafting of psyllium with N-hydroxymethylacrylamide, mixtures of acrylamide and 2-acrylamido-2-methylpropane sulfonic acid, and succinic acid treatment [27].

Thermosystem generated by Vibhola et al. through stabilization of thermally responsive particles by grafting of thermosensitive polymers poly (N-vinylcaprolactam) (PVC) with poly (ethylene oxide) to produce PVC-graft-C11EO42. These new polymeric materials provide hydrogel particles with more thermostable system can be used for controlling drug release [28].

To achieve desired dosage form characteristics
Pistel et al. grafted poly (lactic-co-glycolic acid), PLGA, onto water-soluble poly (vinyl alcohol) (PVAl) backbones. Biodegradable polyesters generated had considerable potential for parenteral drug delivery systems with lower burst effects and controlled release profiles based on the structure and molecular weight of the copolymer [29].

Kulkarni and Sa developed pH-sensitive controlled drug delivery systems of ketoprofen using pH-sensitive interpenetrating polymer network (IPN) beads of PAAm-g-XG and NaCMC. The grafting of acrylamide on the backbone of Xanthan Gum (XG) and IPN of PAAm-g-XG- NaCMC was used for this purpose [30].

Patil S A et al. developed transdermal films using modified XG, which obtained by grafting acrylamide onto XG. Successful controlled release of atenolol was obtained by these modified XG films [31].

Conteras-garcia et al. grafted N,N-dimethylacrylamide and N-isopropylacrylamide on polypropylene film these functionalized PP films have desirable bioproperties along with sustained release of norfloxacin [18].

Sraj et al. blended PVAl and with a natural polymer, methylcellulose (MC) and incorporated with 6-thioguanine. As a result of this blending, Interpenetrating polymer network microsphere so generated which effectively controlled release of drug in the in vivo study [32].

To achieve site specific delivery by grafting of polymers
Kumar et al. prepared microspheres of polyacrylamide-grafted-chitosan crosslinked with glutaraldehyde to encapsulate indomethacin, for treatment of arthritis. The initial release of indomethacin from these microspheres occurs by polymer chain relaxation process, while at

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**Table 1: Analytical technique and property being characterized**

| Analytical technique | Characterization |
|----------------------|------------------|
| FTIR | Specific functional groups added to blend as a result of grafting |
| 13C-solid state | Hydrocarbon backbone characterization |
| NMR | Polymorphism of polymers |
| XRD | Purity and melting point of polymers |
| DSC | Elemental composition such as C, H, N content |
| Elemental analysis | Gain in molecular weight after grafting characterized |
| MW analysis | |

FTIR: Fourier transmission infrared, DSC: Differential scanning calorimeter, XRD: X-ray diffractometer.
longer times, the release occurs mainly from the fully swollen polymer by controlled molecular diffusion [33].

To achieve site-specific drug deliveries, certain other polymeric graft systems were evaluated such as microspheres of grafted chitosan crosslinked with glutaraldehyde were prepared to encapsulate nifedipine, an antihypertensive drug [34], and N-lauryl carboxymethyl chitosan with both hydrophobic and hydrophilic groups was studied in connection with the delivery of taxol to cancerous tissues [5].

Intracellular delivery for gene therapy using N-dodecylated chitosan-based materials was developed by Liu et al. The complex also found to protect DNA from DNA nuclease and enhanced activity [35].

Nam et al. developed grafted-chitosan polymeric micelles carrying two drugs. The chitosan derivative O-carboxymethyl chitosan was conjugated first with α-tocopherol, forming α-tocopherol O-carboxymethyl (TOC), then ligated with doxorubicin and an anti-human epidermal growth factor receptor 2 (HER2) target peptide, producing the final construct, HP-TOC-DOX polymeric micelles. An in vivo study carried out by attached showed that the anti-HER targeting peptide enhanced not only cellular uptake but also therapeutic efficacy [36].

RECENTLY FILED PATENTS IN AREA OF POLYMER GRAFTING

Fast dissolving films for oral administration of drugs

- US 20040402933 A1
  A dosage form prepared using two polymers where a first polymer; a deposit, including an active ingredient; and a cover layer comprising a second polymer, a polyvinyl alcohol-polyethylene glycol graft copolymer (PVA-PEG) [37].

Process for producing solid dosage forms

- US 7419685 B2
  Here, a water-swellable graft copolymer or a mixture of graft copolymers is employed as polymeric binder to prepare solid dosage forms [38].

Fast dissolving films for oral administration of drugs

- WO 2013040654 A2
  A dosage unit comprises set of polymers including several layers and involved graft polymers such as PVA-PEG and PVA-PEG [39].

Solid dispersion of poorly soluble drugs in graft copolymers

- WO 2007115381 A2
  It involved the formulation of solid dispersions of low aqueous solubility and dissolution rate bioactive compound using PVA-PEG copolymer, such as Kollicoat IR and more particularly to a system and method for improving the solubility and dissolution rate of drugs with low aqueous solubility and dissolution rate bioactive compound, such as a BCS Class II or Class IV drug compounds [40].

CONCLUSION

Using grafting technique tailored properties obtained in polymer, this made polymer grafting a new technique in dosage form design. Polymer grafting makes polymer superior to their synthetic and natural counterpart. To achieve the tailored properties of the polymer by grafting various methods utilized such as conventional one chemical grafting, enzyme grafting, living polymerization, radiation-induced and recently introduced plasma radiation grafting. These grafted polymers efficiently characterized and analyzed by modern analytical techniques such as FTIR, NMR, and XRD. There are a number of recently filed patents in the area of polymer grafting. The industrialist should have to show great interest in the field of polymer grafting. In the future, the polymer grafting has wide scope in the drug delivery system.

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