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POLYMER MODIFICATION FOR COLON TARGETED DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW

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ABSTRACT

When treating colon disorders, colon-targeted dose forms are more focused and efficient. Because of their many advantages, polysaccharides have drawn a lot of attention from researchers in the field of medication delivery in recent years. These materials are thought to be the finest ones for creating targeted dosage forms. They are hydrophilic, stable, and non-toxic by nature. Enzymatic activity in colon breaks them down, but they remain intact as they transit through the upper gastrointestinal tract. This characteristic can be investigated to see if the medications can use or utilizing polysaccharides in the colon. Even if there are many polymers accessible and plays vital role in colon targeted drug delivery, there are situations when they cannot meet demand due to certain constraints; therefore, modifications must be made to them. Drug targeting may benefit from the gradual substitution of modified natural polymers for native polymers. The characteristics of polymers can be changed in the variety of methods, including blending, grafting, and curing. Polysaccharides are enhanced by grafting, which also makes them a perfect drug delivery carrier. This review discusses how grafting alters polysaccharides, a naturally occurring polymer, and functions as a potent drug carrier for colon targeted drug delivery as well as various method of polymer modification like polymer grafting, cross-linking, derivative formation, polymer- polymer blending etc.

KEYWORDS: Polymer modification, grafted gum, colon targeting, drug release, natural polymers and polysaccharides.

INTRODUCTION

The need and benefits of colon targeted dose forms-which are more focused and efficient in treating conditions relating to the colon, such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBD), and inflammatory bowel disease-are well acknowledged.[1] Colon is a great location for both local as well as systemic medication administration. Compared to the colon mucosa, the small intestine has substantially higher proteolytic activity.

Therefore, the colon is the primary location of protein and peptide absorption. The colon has a longer transit time for meals, which can enhance drug absorption. Additionally, the colon contains bacterial microflora, which aids in the breakdown of several drug carriers.

When opposed to non-targeted medications, drugs that are focused to specific places offer numerous advantages, including the avoidance or eradication of side effects as well as dosage reduction. There are several therapeutic benefits for colonic drug delivery devices due to the colon's neutral pH and prolonged transit time.[2]

At the moment, colon targeting through selective oral medication delivery is receiving a lot of interest. Various methods have been developed to accomplish colon targeting.[3] Covalently binding a medication to a carrier, creating time-dependent drug delivery systems, coatings with carriers that degrade in presence of colon bacteria, pH-sensitive polymer coatings, osmotic controlled drug delivery systems, and bio adhesive systems are a few examples.

When the medicine reaches the colonic pH (7-8), the pH-dependent drug delivery systems reveal the formulation and releases the drug into the colon when the intestinal pH rises. In addition to azo cross-linked polymers, which are microbially degradable, natural polysaccharides including pectin, inulin, amylose, guar gum, and locust bean gum can also be utilized in the development of colon specific dosage forms because they stay stable in the presence of gastrointestinal enzymes. Additional strategies include pulsatile release systems, osmotically regulated systems, redox sensitive polymers, and bio-adhesive systems.[4]

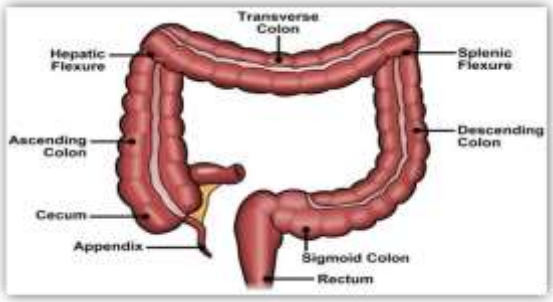


Figure 1: Anatomy of Colon.

Need of Colon Targeted Drug Delivery[5]

- The colon focused dosage form minimizes dose dumping, systemic, side effects and frequency of administration.
- Peptide and protein-based medications can be administered orally to the colon by delaying the onset of drug release.
- At the colonic location, medication release may occur locally as well as systemically.
- Colon targeting may offer more effective and dependable colorectal cancer treatment.
- It is possible to release medications into the colon precisely and efficiently, provided they are polar in character and/or susceptible to acidic or enzymatic breakdown.

Colonic Microflora

The colon has a large number of bacteria because materials pass through it more slowly. A minor number of fungi are also present; however, the majority of these isolated bacteria are anaerobic in nature. Microbial development is facilitated by the nearby areas' increased concentration of energy sources. The main nutrient source for the intestinal microbes is carbohydrates. Enzymes break down natural polysaccharides, producing fatty acids, carbon dioxide, hydrogen, methane, and hydrogen sulphide as byproducts. Because of the predominance of carbohydrate fermentation, there is a comparatively lower pH in the proximal portion of the colon and a higher pH in the distal regions due to less carbohydrate fermentation. The bacteria within the colon is predominately anaerobic having low redox potential (reducing environment).

The pH of Colon

The pH of the terminal ileum is at its highest of 7.5, but it drops to 6.4, as it enters the colon. The colon exhibits a pH fluctuation, with the left colon having a pH of 7.0, and the mid colon having a pH of 6.6. The colon creates short chain fatty acids as a result of bacteria fermenting

polysaccharides, which lowers pH levels. For example, the bacteria ferment lactose to make lactic acid, which causes the pH to drop to roughly 5.0. The in vitro fermentation of polysaccharides, such as guar gum and ispaghula, by colonic bacteria, results in the similar pH drop. Its pH level is lowered by colonic illnesses.[6] The structure of colon is given in Figure 1.

Colonic Diseases

1. Colorectal Cancer

The large intestine disease known as colon cancer originates in the caecum and spreads throughout the belly until it meets the rectum. It arises from either inherited or somatic genetic changes throughout the course of a lifetime. The mucosa, or inner layer of the gut, is primarily composed of a single layer of columnar epithelial cells. This is where the early genetic alterations that may eventually cause cancer cells to spread can be found. In developed nations, it is the fourth most prevalent type of cancer.[7]

2. Ulcerative Colitis

Its chronic illness characterized by inflammation of the colon mucosa. It can refer to the entire colon, the sigmoid colon, the descending colon or rectum. Relentless colitis can occasionally become fatal. Prompt identification of colitis, together with rigorous treatment and close supervision, may enhance patient comfort as well as compliance.[8,9]

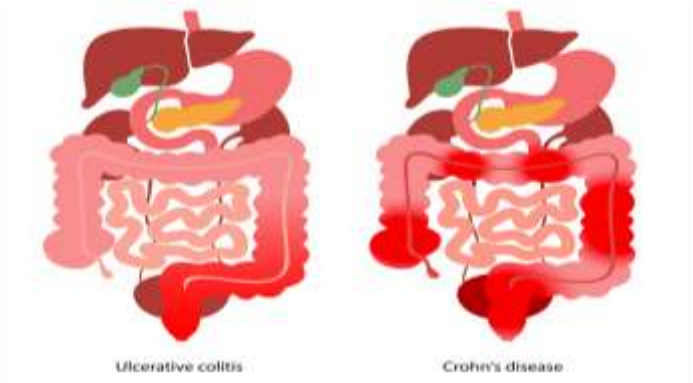


Figure 2: Inflammatory bowel disease.

3. Crohn's Disease

Relapses of bowel inflammation are the hallmark of this chronic idiopathic condition, which can affect any portion of the gastrointestinal tract, from the mouth to the anus. In addition to symptoms such abdominal pain, faecal incontinence, diarrhoea, rectal bleeding, weight loss, and exhaustion, it can result in significant morbidity.[10] The immunological imbalance

resulting in an excess of pro-inflammatory cytokines is the source of the persistent intestinal inflammation. Consequently, inhibiting inflammation can help control this condition.[11]

4. Irritable Bowel Syndrome (IBD)

It is the most common condition to be diagnosed by abdominal pain, constipation, or thin, firm, or watery stools. In wealthy nations, it affects 3–15% of the population. It is neither a life-threatening condition, nor is it the cause of Crohn's disease, ulcerative colitis, or colon cancer.[12]

General consideration for the preparation Colon Targeted Drug Delivery System

The fundamental idea behind colonic targeted drug delivery is to produce a minimum or no release in upper gastrointestinal tract and either a burst or sustained/prolonged/targeted release to the colon. One common physiological element for the creation of colon-targeted formulations is the wide range pH levels found in the GIT. According to certain findings, people with inflammatory bowel illness may have pH shifts; this may be taken into account when creating formulations specifically targeted at the colon.

Approaches for Colonic Drug Delivery System

pH Sensitive System

The foundation of this strategy is the drug's pH-dependent systemic release. Here, medication is efficiently delivered to colon by taking advantage of the pH difference between the upper and terminal portions of the GIT. It is important to remember that a variety of factors, including diet, food consumption, intestinal motility, and illness conditions, affect pH of the intestines and colon. Because of this, it becomes more difficult for the experts in this sector to create a delivery system that is resilient enough to endure changes in the gastric pH as it passes from the stomach to the small intestine. Delivery devices have been developed to administer the medication by integrating the understanding of polymers and their solubility at various pH conditions at targeted site.[13]

For colonic drug delivery, commonly utilized copolymers of methyl methacrylate and methacrylic acid have been thoroughly studied. Following an in vitro assessment of an Eudragit S and Eudragit FS, it was determined that the latter would be a better fit for the administration of medication to the ileocolonic area. Many elements, including the ratios of various polymer combinations, the media's pH, the tablets' coating thickness, and the existence of plasticizers. Some of the major factors influencing success through this route are

electrolyte concentration, transit time, and inter and intra subject variability. Despite these drawbacks, mesalamine (5 ASA) (Asacol® and Salofalk®) and budesonide (Budenofalk® and Entrocort®) are both commercially available in pH-based systems for the treatment of ulcerative colitis and Crohn's disease, respectively.[14]

Time Controlled or Time Dependant System

Time-controlled devices are helpful for delivering a medication synchronously to a patient at a pre-selected GIT location or at pre-selected times so they receive it when needed. For this reason, these systems are especially helpful when treating illnesses that are dependent on circadian rhythms. Delay-release formulations that have a time-based drug delivery delay are also known as time-controlled formulations for colonic administration. It is difficult to formulate a medication to obtain a precise drug release into colon because in these systems, the place of drug release is determined by the formulation's transit duration in the GIT.[15]

Formulations should ideally be created so that individual variations in the colon's pH, gastric emptying time, or the presence of anaerobic bacteria won't have an impact on the site of delivery, which is the colon. An oral dosage form takes approximately three hours on average to pass from the start of the colon to the length of the small intestine. In contrast to the rate of stomach emptying, the small intestine transit time is comparatively uniform.

Microbially Triggered System

These systems work by taking use of the unique enzymatic activity of the colon's microflora, or enterobacteria. The majority of colonic bacteria are anaerobic, and they release digestive enzymes that can break down substrates like proteins and carbohydrates that are not broken down into the upper gastrointestinal tract. The number of bacteria into the colon is substantially higher, ranging from 1011 to 1012 CFU/mL. These bacteria are primarily aerobic, comprising around 400 different species, including Bacteroides, Bifidobacterium, and Eubacterum. The two main metabolic processes that occur in the colon are hydrolysis and reduction. The colon contains the following enzymes:

- **Reducing enzymes:** Azo reductase, Nitro reductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.
- **Hydrolytic enzymes:** Amidases, Esterases, Glycosidases, Glucuronidase, sulfatase etc.

By fermenting different kinds of substrates that have been left undigested in the small intestine, such as polysaccharides, di- and tri-saccharides, etc. the vast microflora meets its

energy needs. Numerous enzymes, including glucuronidase, xylosidase, arabinosides, galactosidase, nitro reductase, azareducatase, deaminase, and urea dehydroxylase, are produced by the microflora in order to aid in this fermentation. The use of biodegradable polymers for colon-specific medication administration appears to be a more site-specific strategy than previous approaches because the biodegradable enzymes are only found in the colon.[16]

Pressure Controlled System

The stomach contracts during the digestion processes inside the GIT, and peristaltic motions are used to push food through the intestines. The word "mass peristalsis" refers to the forced peristaltic motions that occur into the large intestine to transfer contents from one section to another, such as from the ascending to the transverse colon. These powerful peristaltic waves of the colon only happen three or four times a day and have a brief duration. On the other hand, they momentarily raise the luminal pressure in the colon, which serves as the foundation for pressure-controlled system design. Because the luminal contents of colon and small intestine have different viscosities, the luminal pressure produced by peristaltic action in colon is higher.[17]

The large amount of water in the digestive juices of stomach and small intestine keeps the contents of these organs fluidic; nevertheless, reabsorption of water from lumen and the creation of faces in the colon cause the contents of these organs to become much more viscous. As far as the author is aware, there has only been one invention in relation to the creation of a colonic delivery system with pressure control. This specific delivery mechanism takes the shape of a capsule, which collapses in the large intestine due to elevated pressure but is resistant to the pressures of the upper GIT. The ethyl cellulose used to make the capsule shells allows for precise control over the length of time it takes for the capsule to collapse in the large intestine by varying the wall thickness. The ideal thickness of the capsule is about 30-60 µm.

Many more other approaches like,
CODESTM - Combined system of pH dependant and microbially triggered CTDDS.[18]
OROS-CT – Osmotically controlled system.

Polymer in Colon Targeting

Because of their many qualities, the natural polysaccharides are known as the finest options for creating solid dosage forms. By nature, they are hydrophilic, stable, and non-toxic. These polysaccharides stay intact as they transit through upper gastrointestinal tract because they are broken down by bacterial enzymatic activity found into colon. This special quality of polysaccharides can be used to direct medication toward the colon.[19] Prior to the previous several decades, it was believed that polymers were merely dosage form excipients or device components with little to no effect on drug release. However, more recent medications and drug delivery methods made of polymers have to be successful in treating a variety of illnesses and can safely transfer the gene in place of vectors.

Even though a large variety of polymers with different qualities are accessible, there are situations when these polymers are unable to meet demand due to certain constraints. It is highly difficult to get novel polymers with specified improved qualities, such as increased thermal stability, flexibility, multiphase, response, bio-compatibility and stiffness.[20] Therefore, improvement in polymer properties is necessary to meet the need of drug delivery. Drug targeting may benefit from the gradual substitution of naturally occurring polymers with modified natural polymers that have the required qualities. Polymer characteristics can be changed in a variety of ways, such as via grafting, curing, and blending. A mixture of two or more polymers and the necessary characteristics is what is produced during blending. The process of grafting involves covalently attaching monomers to the host polymer's backbone, curing is the process of oligomer mixture polymerizing to create a coating that sticks to the substrate.[21] Grafting is a commonly employed method for polymer modification among them.

Polysaccharide-based Drug Delivery Systems

Polysaccharides are plentiful, widely, accessible, reasonably priced monosaccharide-(sugar) polymers with a diverse variety of properties and topologies. These have the ability of undergo chemical and biological changes and are hydrophilic, gel-forming, non-toxic, very stable, and biodegradable, all of which point to their application in OCTDDS. Several polysaccharides have been investigated as colon-specific medication transporters, including chitosan, locust bean gum, pectin, chondroitin, sulphate, dextran, locust bean gum, inulin, pectin, cyclodextrins, guar gum and amylose TABLE 1. The Table lists the several polysaccharides that are used to make OCTDDSs, along with some of their advantages and

disadvantages. The enzymatic activity of the colonic bacteria on polysaccharides on the basis of the most defining colon-specific medication delivery methods.[22]

Table 1: Polysaccharides In Ctdds.

Polysaccharide	Description	Advantages	Disadvantages
Chitosan	Source: Chitin Structural unit: β-(1,4)-linked D-glucosamine and N-acetyl-D-glucosamine units	Chitosan causes the drug's colonic enzymes to degrade while shielding the medication from the harsh conditions of the upper gastrointestinal tract. Chitosan possesses ucoadhesive properties, is enzymatically degradable, and is non-toxic.	It is soluble at low pH, and it may lead to premature drug release in the stomach and small intestine
Dextran	Source: Microbial origin Structural unit: a-(1,6)-linked D-glucose units with some degree of branching via a-(1/2), a-(1/3) and/or a-(1/4) linkages.	It is biocompatible, biodegradable, low cytotoxic, and has anticoagulant properties.	Early drug release
Pectin	Source: Dried citrus peel Structural unit: (1,4)-linked a-D-galacturonic acid	Both enzymatically degradable in the colon and gastric resistant. Pectin has the ability to stabilize, adsorb, gel, thicken, and produce bulk.	Higher water solubility and Early drug release
Guar gum	Source: Seeds of Cyamopsis tetragonolobus Structural unit: (1-4) β-D manopyranosyl units with α-D galactopyranosyl units attached by (1-6) linkages	improved qualities for swelling and gelling. delay the release of the medication in the upper gastrointestinal tract and make it more prone to enzymatic breakdown in the colon	Premature drug release.
Inulin	Source: Polysaccharide obtained from family Compositae Structural unit: fructosyl groups linked by β 2,1 glycosidic bond	Preserve the medication from the stomach's acidic environment and deliver the probiotic benefit when gut microbiota is present.	Indigestible in humans
Alginate	Source: Brown seaweeds Structural unit: β D-mannuronic acid and α L-guluronic acid linked with 1,4 glycosidic bonds	biodegradable, biocompatible, and bio adhesive. utilized while creating hydrogels	Higher aqueous solubility
Locust Bean Gum	Source: Carob- or Locust Bean Gum-is processed from the seeds of leguminous tree known as eratonia Siliqua, family Leguminosae. This tree is widely cultivated in the Mediterranean area and, to a smaller extent, in California.	Solubility enhancement of a poorly water-soluble drugs, Therapeutic purpose, Viscosity development.	Premature drug release.

Because biodegradable polymers are safe, non-toxic, affordable and compatible with the other excipients of the formulation, interest in them is growing daily. The several kinds of biodegradable polysaccharides that have already been employed in the first methods of colon-specific medication administration have been discussed in this article. Polysaccharides have favourable characteristics that make them ideal for creating colonic delivery systems. Excellent microflora that can be exploited to target drug release to colon is abundant in the colon.[23] The microbially degradable polymer-containing formulation exits on upper gastro-intestinal tract undamaged. As well as release the drug in the colon. Heance, polysaccharides appear to be promising agents for obtaining of the colon-specific drug delivery systems *figure 03.*

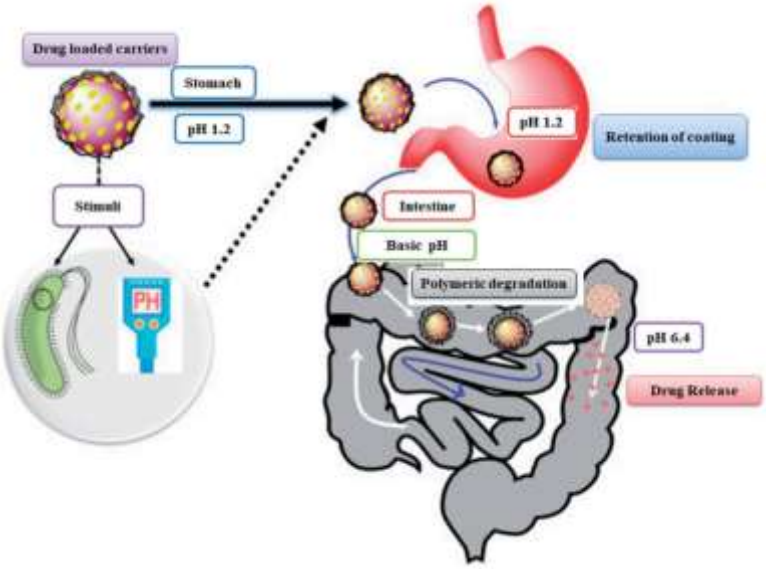


Figure 3: Drug Release Pattern From Ph Sensitive Polymeric Beads.

Polymer Modification Methods

To form the necessary polymers, one can choose from a variety of polymer modification techniques. A general overview is provided in the figure below. Three basic methodologies can used to characterize the interaction between monomers and polymers: "physio sorption," "grafting," and "crosslinking." Figure 4.

The word "physio sorption" refers to the polymerization that is accomplished with the use of physical attracting forces. End-functionalized polymers are able to physiosorbed, a reversible process, onto the solid surface of polymeric surfactants. When "grafting" occurs, covalent bonds are irreversibly attached. The joining of polymers by a chemical bond is called

crosslinking. Most crosslinking processes are irreversible and can occur between or inside molecules.[24]

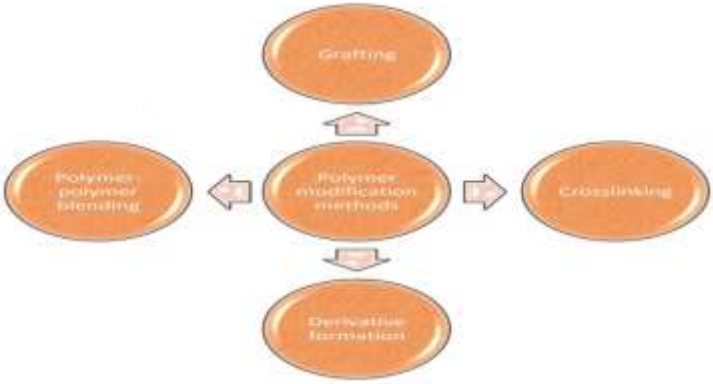


Figure 4: Polymer Modification Methods.

This article primarily focuses on the chemical reaction and microwave irradiation method of polymer modification. As previously mentioned, grafting is the irreversible connection of covalent bonds.

There are essentially two forms of grafting: one that involves the use single monomer and concludes in a single step, and the other that involves the use of a mixture of two or more monomers and requires the use of the two monomers in either sequential or simultaneous manner. The binary monomers are subjected to mosaic grafting.

Grafting

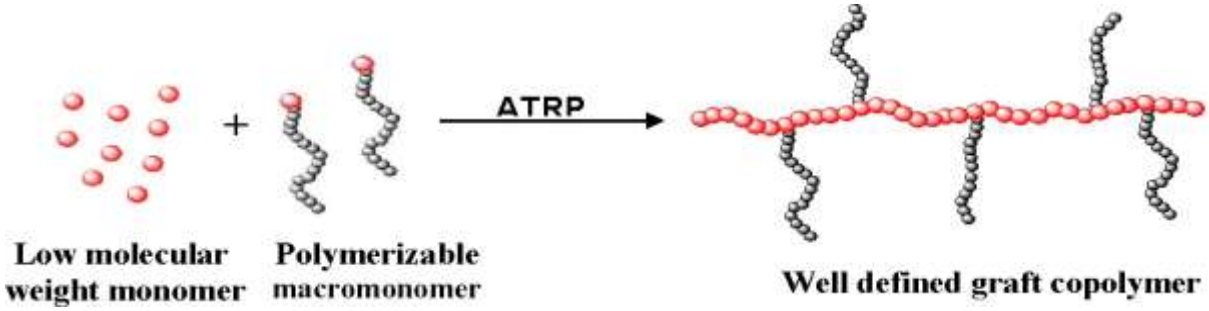


Figure 5: Graft Copolymerization.

The process known as "grafting" involves covalently bonding (modifying) monomers onto the polymer chain. Graft copolymers, as shown in FIG. 5, are segmented copolymers including a primary polymer chain or backbone covalently attached to one or more side chains, and a randomly dispersed branching of another composition.

Brief Introduction of Grafting

- Monomers are repeating tiny molecules that can be combined to produce polymers, which are larger, more complicated compounds. A polymer is a macromolecule that can be either manufactured or natural, consisting of repeating units of a smaller molecule called monomers. Although the terms "plastic" and "polymer" are sometimes used synonymously, polymers are a considerably broader class of molecules that includes many different materials in addition to plastics, including cellulose, amber, and natural rubber.[25]

- Grafted co-polymer: A grafted co-polymer is a macromolecular chain that has one or more block species attached as side chains to the main chain. It can therefore be defined as having the general structure, with branches of another polymeric chain emerging from various locations along the length of main polymer backbone, also known as the trunk polymer. One of the most effective methods for using polysaccharides for controlled release delivery is through graft copolymerization of synthetic polymers onto polysaccharide backbone.[26] Due to their significant swelling and quick enzymatic degradation, native polysaccharides may not be appropriate for controlled and sustained release drug delivery systems. Graft copolymerization, on another way, is a simple way to change the structure of natural polymers, making them appealing biomaterials in these applications.[27]

- In the era of polymers, it is critical to alter a polymer's characteristics in accordance with custom requirements created for intended uses. Polymer characteristics can be altered using a variety of techniques, including grafting, curing, and blending. "Blending" refers to the physical blending of two or more polymers for achieve the desired characteristics. Figure 6. Into the process of "grafting," monomers are covalently attached (modified) onto the polymer chain; in curing, however, an oligomer mixture is polymerized to create a coating that is physically linked to the substrate. Curing fills in the surface's indentations, resulting in a smooth finish. This is not the same as when rubber is vulcanized, which creates chemical cross-links between loosely.

- coiled polymeric chains, which yield elasticity as they stretch and retract in response to stress.

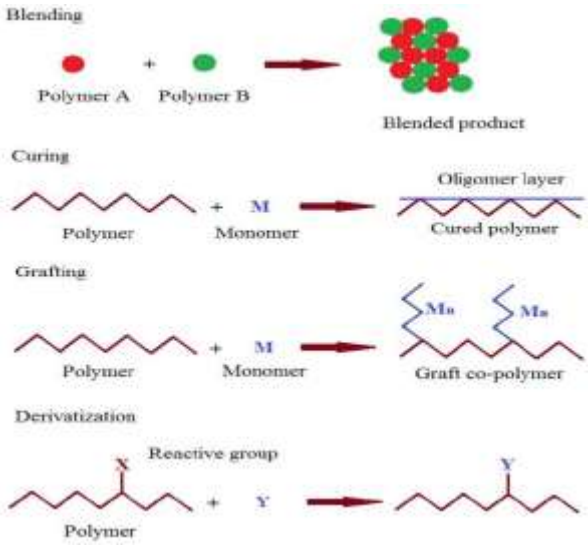


Figure 6: The Procedures of Blending, Grafting and Curing.

Types of Grafting

Grafting can be divided into two main categories

(1) grafting using a single monomer,

(2) grafting using a combination of the two or more monomers.

While the second type can happen when the two monomers are used either simultaneously or sequentially, the first type often happens in a single step. This mosaic grafting has drawn a lot attention for binary monomer grafting. Two different monomers are grafted side by side to obtain the requisite property. This is the main origin of bipolar membranes. The first part of the review discusses the different techniques of grafting and the primary factors, which control the Grafting. Two applications - the science of membrane separation and conducting polymers-are then covered. Chemical, radiation, photochemical, plasma-induced, and enzymatic grafting are among the several grafting methods.

Graft Copolymerization

Natural polymers gain a new property and are endowed with improved properties by grafting. Because natural polymers are non-toxic, inexpensive, readily available, and biodegradable, they are frequently used for grafting over synthetic polymers. One further advantage of the given grafted copolymer is that it may be converted to an ionic form by hydrolysing the amide groups, resulting in a pH-sensitive copolymer. Drugs that target the colon or other lower region of the GIT can be administered using such copolymers.

The most promising technique of polymer modification is grafting synthetic polymer into natural polymer, as the resulting copolymer will have features not found in the substrate. Owing to their beneficial characteristics, such as their water solubility and biodegradability, natural polysaccharides appear to be a good choice for a starting material into the synthesis of graft copolymers. Grafting polymerization of vinyl as well as acryl monomers on to the backbone of different natural polysaccharides is the method used to create the majority of graft copolymers. Chemically, vinyl/acryl monomer grafting is different from non-vinyl/acryl monomer grafting. The process of polycondensation can be used for graft non-vinyl/acryl monomers; however, the polysaccharide backbone is not compatible with the severe circumstances of conventional polycondensation reactions, such as high temperatures.

The Synthesis of a grafted polymers can be done by two ways;

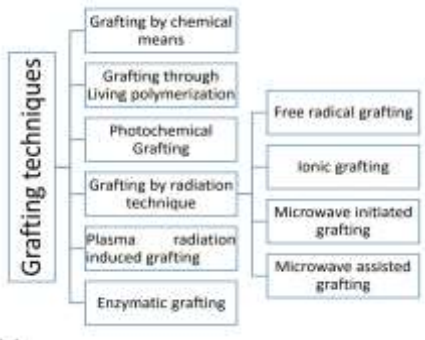
- Microwave Irradiation technique
- Conventional technique.

The conventional technique may lead to the degradation of polysaccharide and not amenable for the formation of the block copolymer. While microwave assisted technique is cleaner, straight forward, simple, reproducible and eco-friendly. The differences between both the techniques are described in given table.

Table 2: Methods of Grafting.

CONVENTIONAL METHOD OF GRAFTING	MICROWAVE METHOD OF GRAFTING
The Inert atmosphere is necessary	Atmospheric conditions require
Initiator or catalysts are required	Reaction can be possible without Initiator or catalysts
Reaction time is long (in hours)	Reaction time is short (in minutes)
Reaction is required in solution or suspension form	Reaction is possible in dry medium as well
It shows Lower grafting efficiency	It shows Higher grafting efficiency

Techniques of Grafting



➢ **GRAFTING BY CHEMICAL MEANS**

The favoured conventional chemical method for polymer grafting is the use of the redox initiators. The creation of free radicals is the fundamental idea underlying this technique. Redox reagents come into variety of forms that can be employed to aid the polymer's free radical sites form.[28]

➢ **GRAFTING THROUGH LIVING POLYMERIZATION**

The living polymerization technique provides an access to polymers

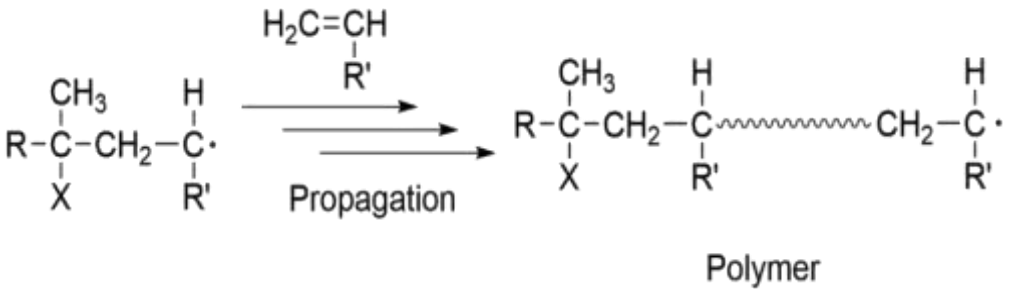
(Poisson molecular weight distribution) of controllable size, functional polymer, block copolymers as well as star and comb-shaped polymers. Living polymers are that again receive their ability to propagate and grow to a desired size while their degree of termination as well as chain transfer is still negligible.[29]

➢ **PLASMA RADIATION GRAFTING**

Plasma modification of polymers is an extremely useful for way of tailoring a polymer in desired material by selective creation of the chemistry and molecular structure on the surface.[30]

➢ **FREE RADICAL GRAFTING**

Through the substrate, the radicals created by the initiators are transmitted to the polymer or monomer in free radical grafting, where they react to form graft copolymer. One can generate radicals by direct or indirect methods. For example, the formation of a free radicals by an indirect process involves the redox reaction of Mn+/H2O2 and per-sulphates.[31]



➢ **IONIC & ANIONIC GRAFTING**

An ionic mode is another way that grafting can proceed. Sodium naphthylamide, organ metallic complexes, and alkali metal suspension into a Lewis base liquid are helpful initiators for this. Copolymerization results from the interaction of alkyl aluminium and the backbone

of polymer in its halide form (ACl), which forms carbonium ions with the polymer chain. The cationic mechanism drives the reaction forward.

Factor that Influences Grafting

There are various factors which affect the process of grafting,

- **TIME**

When microwave technology is used instead of traditional methods, which take about five hours to finish and roughly twenty-four hours to fully produce the grafted polymer, the time needed to complete the grafting process is greatly reduced. (US 2012/0027690 A1) is the patent. However, the new microwave approach requires. maximum time of 10 mins. for completely getting the process done.

- **TEMPRATURE**

The kinetics of polymer grafting are significantly influenced by temperature. Temperature variations have impact on both the grafting yield and the grafting process itself. After looking into the temperature effect, it was discovered that a rise in temperature increases grafting efficiency with the least amount of contact angle forming between the monomer and substrate. Ahmad S. et al. used Benzoyl per oxide initiator to study the effects of temperature on alginate grafted methyl methacrylate. They discovered that at a relatively high temperature of 80oC, with a grafting percentage of 78.90%, graft copolymerization was preferred.[32]

- **NATURE OF SOLVENT**

In grafting, solvents are very important because they dissolve all of the process's constituents. Every molecule of the reactants that are present into the solvent interacts with them all. For instance, the type of solvent used determines both the solubility of the initiator and the monomer. The solvent also serves as a transporter of moieties to the monomer chain. Solvents are therefore crucial to the grafting process. Because of the substrate's partitioning between the solvent and the monomer, Zhao et al. claim that raising the solvent concentration maximizes the absorbance.

- **MONOMER**

Monomers are one of the most crucial components for grafting is monomers, since they determine both the percentage yield and the grafting effectiveness. As the number of binding sites grows, so does the grafting yield when the amount of monomer increases.

- **INITIATOR**

The initiator is the portion of the grafting process that speeds up the process by generating free radicals and serving as a connector to finish the grafting process. It's important to consider the type of initiator used to determine whether electropositive or electronegative radicals are produced. Graft polymerization of a vinyl monomers on the starch has been achieved using a variety of initiators, including the Ce4+ system, persulphate, Fe2+/H2O2, manganic pyrophosphate, etc.[33]

pH Sensitive Graft Copolymers used in Colon Targeted Drug Delivery

The sol-gel approach was used to create methacrylic acid (MAA) or perlite composites (APC) that were intended to administer 5-aminosalicylic acid colonially. 2,2-azo-bis-isobutyronitrile (AIBN) was used as a reaction initiator in an experiment to test the free radical grafting of a methacrylic acid (MAA) on perlite particles. FTIR spectroscopy was used to analyze the copolymers, and an equilibrium swelling research was carried out using simulated intestinal and gastric fluids. The in-vitro drug release study was shown that whereas drug release into the buffer solutions rose with increasing silica content, drug release decreased with increasing concentration of 3 (trimethoxysilyl) propyl methacrylate also called as (TSPA) and a coupling agent.[34] Another work used cross-linking to create pH-sensitive hydrogels based on konjac glucomannan and the acrylic acid, for the administration of 5-aminosalicylic acid using N, N-methylene-bis-(acrylamide). After 36 hours, the drug release had reached 95.19%.[35]

For colon-specific administration, metronidazole-loaded tablets were made utilizing a grafted polymer of guar gum as well as methacrylic acid. In the first four to five hours, 30–40% of the medicine was released from uncoated xanthan gum tablets or tablets containing a combination of xanthan gum and guar gum. In contrast, 70% drug was released from tablets made with guar gum as well as graft copolymer. The medication content has drastically decreased to between 18 and 24 percent when tablets are coated with Eudragit-L100.[36] Physical blends of a polymers were utilized into the controlled drug release applications due to their utility, as the synthesis and assessment of novel polymers is an expensive process. The physical mixtures of copolymers grafted with starch had shown better targeted or controlled release of drugs as well as proteins for colon targeted delivery.[37]

Salbutamol sulfate tablets intended for the intestines and colon were made with grafted copolymers starch (St-g-PMMA) as well as acetylated starch (Ast-g-PMMA). The

medication and excipients' compatibility was verified by FTIR. Drug release was dependent on pH; in acidic versus alkaline pH environments, drug release get reduces. The pharmacokinetic characteristics of tablet prepared by graft copolymer have shown a considerable decrease in Cmax and increase in tmax when compared to pristine both starch as well as acetylated starch tablets.[38] Gamma scintigraphy on healthy rabbits was used to ascertain the pills' gastrointestinal transit. The radioactive tracer was release from the tagged tablets was relatively tiny in stomach condition, but it increased as the pills reached the intestine.[39]

It showed that the inflammatory colon tissue had the largest drug accumulation. According to Laroui et al., TNFαsiRNA was loaded into poly (lactic acid), poly (ethylene glycol) and block copolymer (PLA–PEG) nanoparticles, and then a surface graft of a macrophage-specific ligand (the Fab′ component of the F4/80 Ab—Fab'-bearing) was made. Following oral dosage, TNFα-siRNA-loaded nanoparticles have demonstrated an improvement in colitis.

In a different study, pH-sensitive spray-dried polyacrylamide-g-carboxymethylcellulose sodium microspheres were created to distribute capecitabine colonically. After undergoing free radical polymerization in an inert atmosphere, alkaline hydrolysis was applied to the PAAm-g-NaCMC. 1H NMR, viscosity measurement, chemical analysis, neutralization equivalent, thermogravimetric analysis FTIR techniques were used to characterize it. According to the swelling investigation, PAAm-g-NaCMC exhibits significant pH sensitivity. Microspheres prepared with the pH sensitive PAAm-g-NaCMC copolymer is suitable for colon targeting because it reduced the drug release in the upper part of the gastrointestinal tract (GIT). In vitro drug release shows the failure of microspheres prepared using native NaCMC, which are unable to impede drug release in the stomach as well as small intestine. Surprisingly, the rat caecal drug release increased quickly.[40]

N, N′-methylene-bis-(acrylamide) cross-linker was used to create graft copolymer and hydrogels of chitosan and acrylamide for colon-targeted medication administration. An analysis was conducted on the swelling pattern in buffer solutions with varying pH levels as well as colonic enzymatic degradability. The hydrogels avoid the drug release in the pH of the stomach and shown exceptional pH sensitivity. Colonic enzymes broke down the gels, it was found that there was a direct link between the matrix's breakdown and the gels' swelling, which caused the drug to leak into the colon.

Poly-acrylamide grafted katira gum was used to make colon-targeted matrix tablets for Ibuprofen. The transport mechanism for medication release in case-II. Whereas other tablets crumbled in a pH 1.2 buffer in less than two hours, indicating that ibuprofen is targeting the colon, the tablets containing 0.3 g of acrylamide have maintained their integrity in stomach, small intestinal, and colonic fluids. Thermogravimetric as well as swelling analysis were used to assess the gum Ghati or methacrylic acid or aniline based conductive hydrogels, which were created using gamma radiation as well as cross linked with N, N′-methylene-bis-acrylamide. Methacrylic acid is graft copolymerized into gum Ghati using γ-rays. The hydrogels that were made had a higher degrading efficiency when compared to Gg-cl-poly (MAA). The drug loading and amoxicillin trihydrate release capabilities of these hydrogels were investigated at various pH levels.[41]

Glimepiride-targeted colon pellets were made with locust bean gum grafted with polyacrylamide. This work uses locust bean gum, a naturally occurring polymer, which is modified using acrylamide and a free radical polymerization reaction to create PAam-g-LBG, a pH-sensitive polymer. It is evident from drug release data that release of the drug increases as the capsules approach into colonic pH.[42]

CONCLUSION

In recent years, grafting natural polysaccharides onto polymers has been given special consideration in order to create carriers that are specifically tailored. Polysaccharide graft copolymers can be produced using microwave-assisted synthesis or free radical polymerization. These modified grafted copolymers are seems essential for applications involving medication targeting and controlled drug delivery. Although colon drug targeting has advanced thanks to modified graft copolymers, there are still a lot of natural polysaccharide graft copolymers that need to be investigated for colon targeting applications. Therefore, it is necessary for polymer chemists, pharmacists and physicians to collaborate.

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