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NOVEL POLYMER TECHNOLOGY USED IN PHARMACEUTICAL INDUSTRY

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Abstract:

Development of a new drug molecule is costly and requires a long time. Many attempts have been made to improve the safety of the effective level of "old" drugs, utilizing various ways like individualizing drug therapy, curative drug control, and dose titration.

But, recently, important efforts have been made to discover the novel drug releasing systems, which can be supplied to a target system in the human body, while controlling the level and time of delivery. Polymers, whether synthetic or natural, have great importance in pharmaceutical applications, especially in the field of drug delivery. The use of polymers in pharmaceutical applications ranges from their use as binders in tablets to viscosity and flow controlling factors in liquids, and they can be used in suspensions and emulsions; also, insome cases, they can be used as film coatings.

Moreover, they may be used as membranes implanted within the living body. Current workhighlights the importance of drug delivery systems and the role of polymers in them.

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INTRODUCTION:

Polymer is a large molecule or macromolecule, composed of repeated units called monomers that are connected onto a long chain. Because of their wide range of properties, both synthetic and natural polymers play a substantial and ubiquitous role in everyday life.

Polymers range from famous synthetic plastics like polystyrene to natural biopolymers such as DNA and proteins that are essential to biological structure and function.
Polymers can be classified based on their source into -

A- Natural polymers which are found in plants and animals, for example proteins, cellulose, nucleic acids, starch, polysaccharides, some resins and rubber;
B- Semisynthetic polymers, such as cellulose derivatives(cellulose acetate (rayon) and cellulose nitrate), etc.
C- Synthetic polymers include plastic (polythene), synthetic fibers (nylon 6,6) and synthetic rubbers (Buna - S), which are examples of man-made polymers extensively used in daily life as wellas in industry.
Polymers according to their structure as–

linear,
branched,
cross-linked, and
Network polymers.

In some polymers which are also called homopolymers, just one monomer is used to form the chains, whereas in others, two or more different monomers can be combined to have diverse structures forming copolymers of linear, branched, cross-linked, and polymeric molecular structures.

Polymers are classified according to their properties based on - Molecular forces (mechanical properties of polymers like tensile strength, toughness, elasticity) Intermolecular forces like vander Waals forces and hydrogen bonding) into thermoplastics, elastomers, fibers and thermosets.

Fibers possess high intermolecular attractive force and high tensile strength. Elastomers are polymers in which polymer chains are held up by relatively weak attractive forces. They are cross-linked polymers, and are extremely elastic; they can be lengthened or compressed to an extreme extent reversibly.

Thermoplastic polymers are polymers most in use. These polymers are linear or branched, classified by the fact that they could be soften or melted reversibly, when heated. These polymers possess intermolecular forces of attraction intermediate between elastomers and fibers. Lastly, thermosetting polymers are a network of polymers that are generally rigid, and do not soften or melt reversibly when heated.

Finally, the classification- of polymers based on the polymerization process – A. Addition polymers and B. Condensationpolymers [1-5].

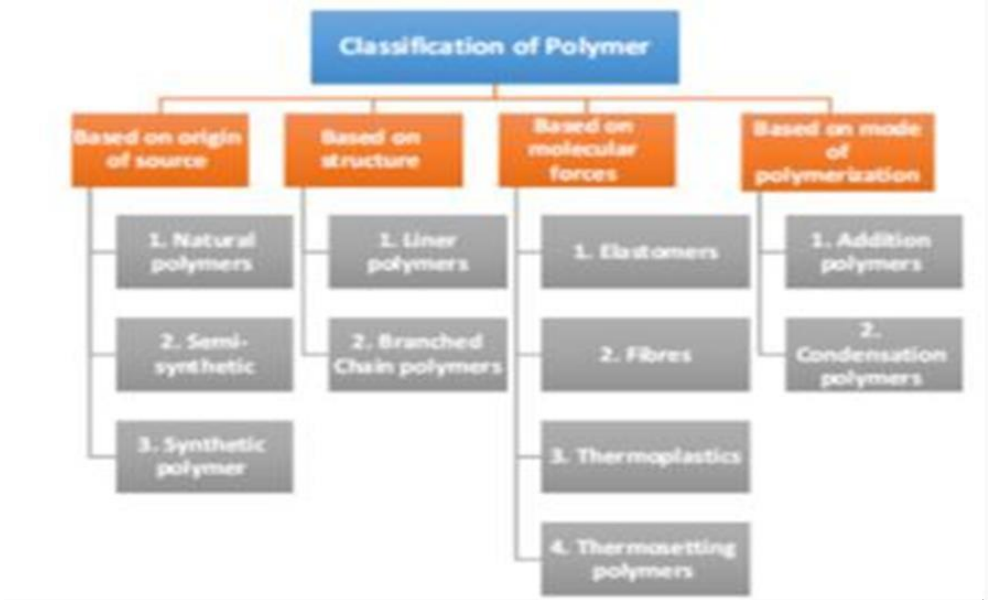

Fig. (1) illustrates the classification of polymers based on different concepts.

Synthetic and nature-based polymers have found their ways into biomedical and pharmaceutical fields due to their unique properties [6, 7].

Pharmaceutical applications of polymers:

The pharmaceutical applications of polymers could be illustrated as follows:

Binders in tablets to viscosity and flow controlling agents in liquids, controlled release matrix systems, suspensions and emulsions, promoting drug stability, hiding the unpleasant taste of a drug. Polymers are also used in the pharmaceutical packaging industry on very large scales, and polymers play an important role in the drug delivery system [8,9]. Polymers have been widely used in the design of therapeutic agents for a number of decades.

The first work in the 1960s concentrated on using polymers as blood plasma expanders, injectable or implantable deports, and wound dressings [10]. Helmut Ringsdorf, in 1975, proposed the first pattern for pharmacologically effective polymers, as shown in Fig. (2).

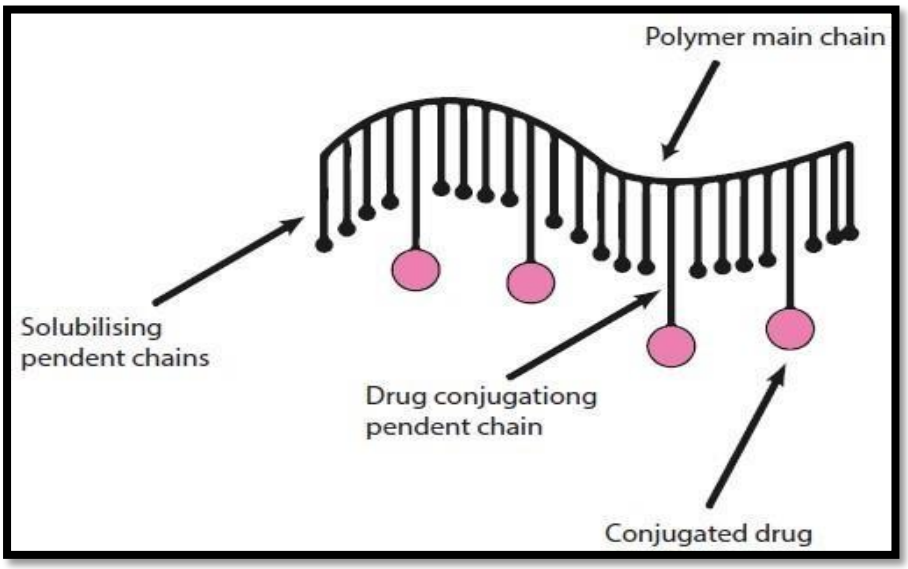

Fig No 2:

The properties of macromolecular drugs rely on the construction of the polymer used and this can be diversified over an extensive range by the conjunction of co-monomer units, through the application of polymer analogous reactions, or by structural changes.

The Helmut Ringsdorf`s model involves pharmacologically efficient polymers that incorporate the possibilityfor continued variation in

a) solubility and toxicity,
b) conformation and elimination of effective material, and
c) body distribution.

The proposed model of Helmut Ringsdorf consists fundamentally of the following ingredients:

macromolecular polymeric backbone,
drug,
spacer,
targeting moiety and
solubilizing agent [10-12].

Macromolecular carriers selected for the production of polymer therapeutics should not be poisonous, have a good solubility in water, non-immunogenicity, and also biodegradable and/or being capable to remove from the organism [13]. Lastly, the macromolecular carrier should possess convenient functional groups for linking the respective drug [14].

POLYMERIC DELIVERY SYSTEMS:

The delivery of therapeutic concentrations on an "ondemand" basis would be of great advantage for many diseases. For that, the suitable amount of the effective drug should be absorbed and transported to the place of action at the suitable time, and the rate of input can then be modified to make the desired concentrations in order to preserve the level of the influence for as long as necessary, especially when the physiological conditions of the patient change [15]. Polymeric delivery systems are fundamentally applied to fulfill either temporal or spatial control of drug delivery [16]. Basically, polymeric vehicles qualify drugs to be delivered over an extensive period of time and to the topical location of action. Polymeric delivery systems are designed to promote drug safety and efficiency, and to improve patient compliance.

The role of polymers is designed to preserve therapeutic levels of the drug, to reduce the amount of drug molecule and the dosage frequency, (iii)to decrease the side-effect profile, (iv)and to simplify the delivery of drugs with short in vivo half-lives. [17]Polymer-based drug delivery systems can be largely categorized into three forms:

Polymer-drug conjugate systems:
Reservoir-based systems

Polymer-drug conjugate systems:

Polymer-drug conjugates are a type of polymer therapeutics, where the drug is delivered in the shape of covalent conjugates with water-soluble and biodegradable polymers, and therapeutic agents are not encapsulated [18]; a clear model for polymer–drug conjugates had been proposed by Ringsdorf as mentioned in the introduction. Polymer–drug conjugates have the following major features:

a) The aqueous solubility of the hydrophobic drugs will rise.
b) Delivery of drug will be possible in an effective release method under specific conditions, like in the existence of specific enzymes or pH state.
c) Drug bioavailability will be improved, and also there will be an increase in plasma half- life.
d) Keeping drugs against degradation.
e) Biodistribution and specific accumulation in organs, tissues or cells will be changed by targeting factors or

Fig. (2). Rationale for drug delivery via polymer-drug conjugates, representation of a polymerdrug conjugate explaining the four components that include this type of therapeutic agent (Ringsdorf 1975); adapted from Godwin et al. [11]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

the familiar enhanced permeability and retention (EPR) effect [19].

Reservoir-based systems:

The reservoir-based system is considered as one of the current controlled drug delivery systems. In these systems, polymer film surrounds a drug core, and the drug release average is controlled by the following factors [20, 21]:

a) The properties of the polymer, such as molecular weight and polymer composition, etc.
b) The physicochemical properties of the surrounded drug, like solubility, molecular weight, and drug particle size, etc.
c) The thickness of the coating.

Types of polymers use in tablets:

A. Soluble polymers such as Polyethyleneglycol (PEG), Hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), and Polyvinylpyrrolidone (PVP).
B. Natural gums such as Locust bean gum, Guar gum, Karaya gum, and Xanthan gum.
C. Hydrogels polyhydroxyethylemethylacrylate (PHEMA), polyethylene oxide (PEO),

polyacrylamide (PA), cross-linked polyvinyl
D. alcohol (PVA), and crosslinked polyvinyl pyrrolidone (PVP).
E. Biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polyanhydrides, and polyorthoesters.
F. Non-biodegradable polymers such as polyethylene vinyl acetate (PVA), ethyl cellulose (EC), polyether urethane (PEU), cellulose acetate (CA), polyvinyl chloride (PVC), and polydimethylsiloxane (PDS),
G. Mucoadhesive polymers such as polycarbophil, ,polyacrylic acid, tragacanth, methyl cellulose, pectin, andsodium carboxymethyl cellulose.

Examples of pharmaceutical polymers:

Polyvinylpyrrolidone:

Polyvinylpyrrolidone (Povidone, PVP), a chain polymer of 1-vinyl-2-pyrrolidone, PVP, was patented in 1939. Polyvinylpyrrolidone is obtained by many steps of synthesis that ends with polymerization of vinylpyrrolidone in aqueous solution in the presence of hydrogen peroxide. Polyvinylpyrrolidone (Povidone), shown in Fig. (7), is a hydrophilic (nonionic) polymer that has very good aqueous solubility and it is also soluble in alcoholic solvents (such as ethanol) and chlorinated solvents, such as chloroform [58-61]. A broad range of molecular weights, from low, medium to high-molecular weight grades can be gained by controlling the degree of polymerization [62]. Soluble Polyvinylpyrrolidone was used for the first time during the second world war as a bloodplasma substitute, and PVP isused today to produce one of the most significant topical disinfectants, Povidone-iodine [63,64], which is a closely applied polymer with very good properties. Its unique combination of special physical chemical properties (biocompatibility, chemical stability, temperature-resistant, non-toxicity, affinity to complex hydrophobic and hydrophilic substances, good solubility in water and many organic solvents, pH-stablility, nonionic and colorless nature) has made it suitable as a biomaterial in numerous important medical and non-medical applications, such as pharmaceutical industry and medicine, environmental applications, etc. [65-68].

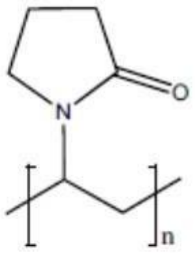

Fig. (7). The structure formula of polyvinylpyrrolidone.

Many remarkable aspects, which make PVP a perfect choice for pharmaceutical industry, are binding and adhesive power solubility, its ability to form film, itsaffinity to hydrophilic and hydrophobic surfaces, suitability for preventinggathering of nanoparticles after freeze-drying due to its properties such as cryo-protectant and lyo-protectant, it acting as inhibitor of recrystallization, and its availability in different molecular weights [66, 69-71]. Polyvinylpyrrolidone is mostly used as a binder in the production of tablets and granules, and also there are other applications such as

a. polymer coating for granules and tablets,
b. solubiliser in oral and parenteral formulations, and
c. viscosity-modifying agent in a diversity of topical formulations [72].

Many studies support the role of polyvinylpyrrolidone in drug delivery systems [73, 74]; for example, a novel supersaturable self-emulsifying drug delivery system (S-SEDDS) was designed by adding PVP polymer (30 mg) as a precipitation inhibitor to a conventional SEDDS system to provide a high concentration–time profile of cyclosporine A (cyclosporine A is a poorly water-soluble immunosuppressant) with reduced use of the vehicle. In an in vitro dialysistrial in a biorelevant environment, PVP polymer efficiently slowed drug precipitation. This study provides a good comparison in the case of conventional studies where SEDDS was prepared with two times more oil, surfactant, and co-solvent [75, 76].

Hydroxypropyl Methylcellulose:

Hypromellose is the short name for hydroxypropyl methylcellulose (HPMC), shown in Fig. (8). HPMC is considered as one of the best known cellulosic polymers, which is applied in the development of controlled released drug delivery.It can be obtained by treating alkali cellulose with chloromethane and propylene oxide. It is a non-ionic cellulose ether,which appears as a white powder, and is odorless and tasteless. It shows good solubility in water, most polar organic solvents, and has the suitable ratio of propanol /water, ethanol/water and dichloroethane, but it does not dissolve in acetone, anhydrous alcohol, and diethyl ether [7779].

HPMC is extensively used in controlled drug delivery system because it shows unique properties that other polymershave not been observed to possess so far [80, 81]:

Hydroxypropylmethyl cellulose behaves as a chemical inert material because its solution does not hold ionic charge and does not interact with metal salts or ionic organics (it is considered as a type of non-ionic cellulose ether).

Hydroxypropylmethyl cellulose is comparatively stable in acid and alkali; it provides a perfect viscosity stability between pH 3 to pH 11 during storage for a long time. Aqueous solutions have enzymeresistance relatively. These have a good quality and stability compared to traditional materials such as starch, dextrin, etc.

i. Hydroxypropyl methyl cellulose is considered as a safe medicinal production substance because it isnot absorbed and metabolized in the body.
ii. Hydroxypropylmethylcellulose is safe in general; it is considered as a nontoxic and non-irritating material, and because the levels consumed by the drug no longer pose a health hazard, the World Health Organization has not determined its daily intake.
iii. Viscosity of hydroxypropyl methyl cellulose can be regulatory, where its viscosity can be modifiedaccording to particular principles.
iv. Hydroxypropyl methyl cellulose is soluble in cold water under 40 or 70% ethanol.

Hydroxypropyl methyl cellulose has many applications in pharmaceutical preparation, which are defined as follows:

As binder and disintegrant [81].
As inhibitor of self-microemulsifying drug delivery system (SMEDDS) [82].
As suspending agent [83].
As topical gel [84].
As capsule wall material [85].
As biological adhesive [86].
As retardant, controlled release agent and channel agent [87].
As thickening agent and protective colloid [88].
As film-coating and film-forming material [89].

Poly(ethylene oxide):

Poly(ethylene oxide) (PEO) is also known as polyethylene glycol (PEG). PEO is a synthetic polymer with the same chemical structure like PEG but higher molecular weights (–O–CH2–CH2–)nOH. Poly(ethylene oxide) is synthesized depending on the catalytic polymerization of ethylene oxide in the presence of metallic catalyst systems; it perfectly dissolves in both cold and hot water. Poly(ethylene oxide) is used as a controlled release excipient to adjustdrug release and dissolution from matrix tablets due to its desired properties.

It is also a promising bioadhesive material [90].

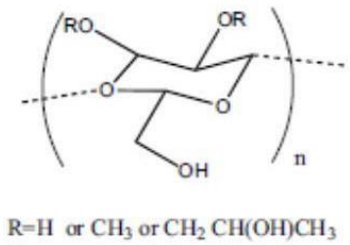

Fig. (8). The structural formula of hydroxypropyl methylcellulose

Polyaniline:

Polyaniline (PANI) is one of the most studied conducting polymers because of its chemical and physical properties (Fig. 8). It is synthesized by the chemical or electrochemical polymerization of aniline in the presence of dopants. Depending on the synthesis method; the temperature and time regimes; the types of oxidant, dopant, and solvent; the voltage applied on the electrode; etc., polyaniline featuring different properties namely, the structure, morphology, and redox state may be prepared [91]. PANI can present in several forms relying on the pH of the medium, and hasability to exhibit high thermal and chemical stability in the conductive form and its facile nature can be altered with organic and inorganic acids [92].

Polyaniline has wide usage in pharmaceutical applications; published studies have proven this, for example, Sixiang Li et al. [93] synthesized a pH-electroactivehydrogel of bacterial cellulose (BC) and polyaniline (PAni) by chemical oxidation polymerization, in order to improve a controlled drug release system. An ionic drug berberine hydrochloride (BH) (5,6-Dihydro9,10-dimethoxybenzo[g]1,3benzodioxolo[5,6-a]quinolizinium, the major constituent of the Chinese medicinal herbs Rhizomacoptidis and Cortex phellodendri), was loaded on the BC/PAni hydrogel, and its capability to stimulate drug release under various pH conditions and electrical stimulation (as it is poorly absorbed by oral administration and it is forbidden via intravenous injection) was estimated. The electrochemical property of the developed composite hydrogel was good. The pH-electro sensitive hydrogel showed fast release in neutral and alkalineenvironments and slow drug release in case of acid environments.

Kaveeta Pergas Jotiran et al. [94] studied the antibacterial action of polyniline while they prepared conducting polyaniline nano-fibers combined with mupirocin (also called pseudomonic acid A; it is an antibiotic effective against
Staphylococci, Streptococci, and certain gram-negative bacteria such as Haemophilusinfluenzae [95]) through a selfassembly method. The antibacterial properties of the prepared polymer were tested against several gram negative and gram positive bacteria like Escherichiacoli, Staphylococcusepidermidis, Streptococcuspyogenes, and Staphylococcusaureus. The results of this study showed that increased concentration of polyaniline (PANI) and polyaniline combined with mupirocin (PANI- mupirocin) leads to an increase in the antimicrobial action, and this maybe useful in the near future, to estimate the possible use of nanostructured polyaniline incorporated with antibacterial agents as a preventive use against bacterial skin infections, as also suggested by the researchers.

Polyvinyl Alcohol:

Polyvinyl alcohol (PVA), as displayed in Fig. (9), was prepared for the first time in 1924 by Hermann and Haehnel through hydrolyzing polyvinyl acetate in ethanol with potassium hydroxide [96]. PVA is readily degradable via biological organisms due to the presence of hydroxyl groups on the carbon atoms that enhance its degradability. Furthermore, PVA is water-soluble and possesses a hydrophilic nature [97, 98].

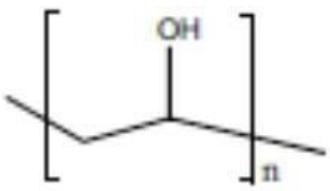

Fig. (9). The structure formula of polyvinyl alcohol.

The physical and chemical properties of polyvinyl alcohol might differ depending on the proportion of hydrolysis, which defines the grade of polyvinyl alcohol and its molecular weight [99]. The surface properties of PVA fillers are mainly dependent on the standard of PVA fillers [100]. PVA itself has good tensile strength, extra flexibility, hardness, and aroma barrier characteristics [101]. Polyvinyl alcohol like proteinshave good solubility in water; its solubility in water and physical properties are extremely influenced by molecular weight, its crystal precipitation, and the degree of hydrolysis [102]. Polyvinyl alcohol is characterized as chemical resistant, water soluble and biodegradable, and these physical properties make PVA harmonious with human tissues. Biocompatible PVA possesses a structure which can absorb protein molecules and it has no toxic effects; due to this, membranes of polyvinyl alcohol have been excessively developed for biomedical use [103]. PVAs are very popular polymers [104] due to their extraordinary physical and chemical properties [105-107], such as consistency in temperature alteration, biocompatibility, and non-toxicity [108, 109].

Due to the simple structure of polyvinyl alcohol and its unique properties like biocompatibility, safety, noncarcinogenicity, adhesiveness, film-forming strength, and swelling, polyvinyl alcohol polymers have many applications in various industries, especially in pharmaceutical.

Starch:

Starch is the main component of the carbohydrate ammunition in green plants [112]. It exists, in its natural shape, as a semi-crystalline molecule called grain or granule. The reason for the use of starch (native or modified) inpharmaceutical applications, in different drug delivery technologies and formulations, is itsphysicochemical and functional properties. Chemically, starch consists of amylose and amylopectin, and both of them consist of a single carbohydrate repeating unit of D-glucose, as shown in Fig. (10) [113]. It is a dry, odorless and soft powder, and its color differs according to the botanical source, from white to slightly creamy.

A number commercially used kinds of starch are often undergone to particular physical treatments to promote elegance and adjust some physical properties like moisture content and whiteness, without changing its essential properties [113, 114]. It is insoluble in cold water and most organic solvents like alcohols, acetone and ether, but it canbe made soluble in water if heated up to a specific critical temperature called the gelatinization temperature [113].

Starch has many pharmaceutical applications, such as its use as an excipient; it is used as an excipient in modern drug delivery systems for nasal, oral, periodontal, and other locationspecific delivery systems [115]. Starch isused as a binder in solid oral dosage forms to bind the active pharmaceutical material with inactive materials together in a coherent mixture [116].

Starch is considered one of the most ordinarily utilized tablet disintegrates at concentrations of 3– 15% w/w [117]. Starch is also used as a diluent, a filler used to enhance the size of a tablet or capsule by integrating a diluent with the effective pharmaceutical materials [117].

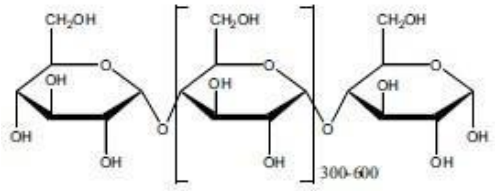

Fig. (10). Chemical structures of D-glucose units showing amylose

Major attention has recently been paid to nano-crystal and nano-particle starch derivatives applications as drug delivery systems because of their biocompatibility, improved mechanical characteristics, thermal characteristics, barrier characteristics, absorption characteristics, and capability to be amended for particular functional characteristics. Starch nano-crystals of diverse shapes and sizes have become possible to be obtained depending on the starch source and the method of isolation [118]. Xu et al. [119] found that the structure and morphology of obtained nano-crystals are affected by many factors, like the kind of crystal used, amylopectin, amylose relative portion, morphology of starch granule, and botanical origin. As an example of applications of starch nanocrystals, HajaBavaBakrudeen et al. [120] prepared starch nanocrystals as a drug carrier to form hydrogels using several polymers for transdermal drug delivery system.

Buccal gels containing miconazole nitrate are usually used to treatconditions such as oral candidiasis. They must be applied several times a day. In order to increase the buccal residence time of miconazole, a bioadhesive buccal tablet with slow-release properties can be used. The main advantages of this delivery system are reduction in the frequency and amount of drug administered, which might improve patient compliance. The bio-adhesive tablet formulation contains pregelatinised waxy maize starch. The salivary miconazole nitrate concentrations after administration of the bioadhesive tablet and of oral gels have been compared [121].

Chitosan:

Chitosan is a natural linear bio-poly aminosaccharide, shown in Fig. (11), which is obtained through deacetylation process of chitin in the presence of alkaline. It is inexpensive, not poisonous to mammals and biodegradable; these properties make it usable in several industries such as the food industry (as an additive), cosmetics industry (as a hydrating factor), and recently in the pharmaceutical industry (as an antimicrobial factor in clinical application and as a pharmaceutical factor to prepare biomedicine). It is considered as a weak base insoluble in water and organic solvent, but it is soluble in dilute aqueous acidic media (pH < 6.5) [122]. It is considered the only saccharide that has a high density positive net charge, which causes it to react with an enormous scope of anionic polymers and biological molecules [123].

Chemical properties of chitosan can be illustrated as follows [122, 124]:

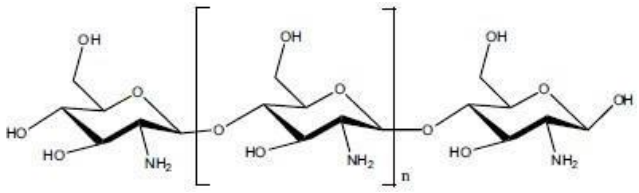

Fig. (11). Chemical structure of chitosan.

The biological properties of chitosan can be illustrated as [122, 125]:

a) biodegradability
b) biocompatibility
c) Its ability to act as haemostatic Having an analgesic effect
d) It has bacteriostatic and fungistatic effect.
e) Its antitumor effect.
f) Its permeation enhancing impact.
g) Its anticholesterolemic effect
h) Its antimicrobial activity
i) Its antioxidant activity.

Because of the polymeric nature of chitosan, it has been largely investigated for a diversity of micro-particulate pharmaceutical forms. Chitosan is as well a candidate for possible applications in the delivery of radiopharmaceuticals,genes and peptides [126].

As mentioned above, chitosan has a good solubility at low pH, so it is possible to use it in applications for colon drug delivery systems, but this application requires that it must be coated with intestinal coating or modified intestinal coating using other natural polymers that would protect it in the stomach environment. Chitosan has been chosen for colon-specific drug delivery system fundamentally in the style of a capsule forming material. The prepared entericcoated chitosan capsules had shown an ability to accelerate the recovery effect of R68070, which is a new thromboxane synthase inhibitor, against 2,4,6-trinitrobenzenesulfonic acid sodium salt (TNBS)-induced ulcerative colitis (inflammation of the lining of the colon) in rats [127-129].

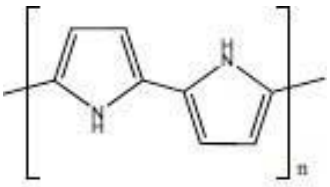

Fig. (12). Chemical structure of polypyrrole.

Polypyrrole:

Polypyrrole (PPy) is an inherently conducting polymer that has attractive electrical properties; it was discovered and reported for the first time at the beginning of 1960s, and is shown in Fig. (12). Polypyrrole (PPy) can be created through several easy methods, including electrochemical and oxidatively chemical polymerization of the monomers of pyrrole [130132].

PPy has many applications in electronic devices, chemical sensors, and can provide an efficient way for pharmaceutical drug release; furthermore, polypyrrole has shown big promise for biomedical applications within the nervous system [133-135]. For example, KyöstiKontturi et al. studied the potency of utilizing polypyrrole as an ion gate membrane for the controlled release of anionic drugs utilizing three model materials with therapeutic efficiency: salicylate, naproxen and nicoside. The result of this study showed that the stability of the membrane doped with the suitable drug towards chloride exchange (in a 0.1 M NaCl solution) was perfect [136]. The biocompatibility of polypyrrole–based drug delivery systems was found to be better than all conjugated polymers drug delivery systems [137]. Jean-Michel Pernaut and John R. Reynolds tested the properties of polypyrrole and its electro-active membrane pattern; this polymer/drug pattern indicated that it is possible to structure a controlled release system based on a conductive electroactive polymer in a number of different configurations. The amount of adenosine triphosphate (ATP) could be released utilizing this methodology extending from nanogram to milligram, via regulating the constitutional and geometric parameters of the effective membrane [138]. Alshammary et al. [135] provided much important information about using polypyrrole and conducting polymers in general in the drug delivery system; it could be illustrated as follows:

1 - Drug delivery systems may have a great benefit from rising concentration of pyrrole monomers since this prohibits the electrochemical effective drugs to undergo polymerization.
2- Conducting polymers are generally not biodegradable and a procedure isneeded to remove them, raising the hazard of infection and reducing the patient's healing process but this problem could be solved by grafting the monomers with a biodegradable side group like glycineethyl ester.

Alginate:

Alginates are natural polysaccharide polymers. They have good biological properties such as immunogenicity, bioadhesion, biocompatibility and non-toxicity. Alginates typically are isolated from brown seaweed (Phaeophyceae), including Laminariahyperborea, Laminaria japonica, Laminariadigitata, Macrocystispyrifera, and Ascophyllumnodosu through treating with aqueous alkali solutions, generally with NaOH [139,140]. The alginate is composed of mixed salts with varied cations found in seawater including Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, and Na^{+}, and the native kinds are ordinarily found as unsolvable Ca^{2+}cross-linked gels [141]. Alginate also might be supplied by bacterial biosynthesis [142].

The alginate polymers possess an extensive possibility in drug formulation consequent of their large usage as food additives and their known loss of toxicity. This set of polymers has a number of properties that make it useful as a formulation aid, both as a traditional excipient and more particularly as an agent in polymeric-controlled drug delivery [143]. Algenet is applied in oral dosage forms (tablets and capsules). Conventionally, sodium alginate is utilized as a tablet binding factor, whereas alginic acid is utilized as a tablet disintegrant in pressed tablets prepared for instantaneousdrug release.

Alginate has the ability to compose two kinds of gels according to pH, such as an acid gel and an ionotropic gel, and this ability provides the polymer with significant properties compared to neutral macromolecules [143]. Nikhil K Sachan et al. illustrated the characteristics of alginates which have enabled them to be utilized as a most agreeable matrix for controlled drug delivery [144]:

1. Alginates are easily obtainable and they are not relatively expensive.

2. Alginates include ingredients that are accepted as food additives.
3. Alginates are non-toxic when taken orally and exert a preventive influence on the mucous membranes of the upper gastrointestinal tract.
4. Alginates are hemocompatible and do not gather in any human organ.
5. Alginates are biodegradable, thus there is no requirement to remove them by surgery after the drugis exhausted.
6. Algenates can form hydrogels under moderate conditions.
7. Algenates are water soluble, thus they exclude utilization of deleterious solvents through processing, and so toxicological and environmental problems associated with solvents can be reduced.
8. Algenates form gels at ambient temperature, thus minimizing the opportunity of destroyed efficiency of sensible drugs at high temperatures.
9. Soluble sodium alginate cross-linked with a diversity of cross-linking factors forms an insoluble gel, which is utilized to delay the release of some drugs.
10. Beads formed are mechanically powerful, thus they may be coated with enteric polymers to form enteric drug delivery systems.
11. Adopted by European Pharmacopoeia, which is the highest possible classification of food additives, the accepted daily intake for alginates is not specified.

Hence, alginates can be an appropriate matrix for sustained releasing of several drugs, such as amoxicillin [145], chloramphenicol [146], ibuprofen [147], vitamin C [148], etc. As mentioned above, there are several advantagesof polymer in drug systems, but there are some major challenges in using polymers as drug delivery vehicles that need to be addressed. For example, all kind of polymers have some level of heterogeneity. Each polymer-drug conjugate molecule differs in terms of molecular weight, drug loading and subsequent conformation. Also, the complexities in synthesis and characterization increase as the conjugates become more complex (i.e., multifunctional nanomedicines).Hence it is crucial that the disparities in such properties should be minimized in order to fulfill stringent regulatory criteria and the polymeric conjugates must be synthesized in a reproducible manner. The validated methods for physiochemical characterization must also be established to certify the quality of the reproducible product. The amount of drug release is directly proportional to the efficacy and safety of polymer drug conjugates; therefore, novel approaches such as the design of better linker chemistries will be helpful in facilitating further improvement of polymer- drug conjugates [149].

Recent advances in polymeric drug delivery systems:

Natural polymers such as arginine, chitosan, dextrin, polysaccharides, poly (glycolic acid), poly (lactic acid), and hyaluronic acid have been treated for polymeric drug delivery systems. Synthetic polymers such as poly (2- hydroxyethyl methacrylate), poly(N-isopropyl acrylamide)s, poly(ethylenimine)s, dendritic polymers, biodegradable and bio-absorbable polymers have been also discussed for polymeric drug delivery. Targeting polymeric drug delivery, biomimetic and bio-related polymeric systems, and drug-free macromolecular therapeutics have also treated for polymeric drug delivery.. The systems of non-virial vectors for gene delivery are polyethylenimine derivatives, polyethylenimine copolymers, and polyethylenimine conjugated bio-reducible polymers, and the systems of virial vectors are DNA conjugates and RNA conjugates for gene delivery.

CONCLUSION:

The delivery of drugs in a controllable pattern is an object of intensive research, whether it is academic or applied, due to its influence on healthcare. Drug release can be carried out via different routes with alterations in temperature, pH or electrical potential; however, each separate route has shortcomings and the most efficient route could be the integration of all the individual routes. Continuous researches have shown that polymers, whether syntheticor natural, have a significant and important role in delivering drugs due to:

- Drug delivery systems based on polymers could be used locally to supply the in-demand concentration for long-term, without repeated doses at different periods of time.

- These systems have the ability to decrease drug toxicity and drug side effects, ensuring protection of the drugstill they reach the specific target, and this leads to improvement in the absorption rates of the drug.

Finally, it could be stated that there is no doubt that natural and synthetic polymers may play an important role in Pharmaceutical Industries and especially in the field of drug delivery.

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