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CARBOHYDRATES: AS PHARMACEUTICAL MOLECULES

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ABSTRACT
A large number of carbohydrates and carbohydrate-derivatives are used as production of (Therapeutic or in diagnostics) pharmaceuticals. Carbohydrates are the most abundant biomolecules and essential components of many natural products known for great pharmaceutical importance. They are monosaccharide's, oligosaccharides, polysaccharides and as essential components of glycoconjugates, including glycolipids, glycoprotein, and glycosylated natural products (Asano,N. ,2001). A good drug is a target-specific drug; its users can expert high efficiency and few, if any, side effects. Target specificity also means recognition, and this is where carbohydrates come in. While many drugs contain carbohydrates as part of their molecules, other drugs-lacking carbohydrates covalently bound to their molecules can be guided them. Carbohydrates, value is that they provide a guidance mechanism for sick cells, enabling drugs to arrive there with precision and act properly. On the other hand, carbohydrates can provide a defence mechanism to sick or deadly cells, preventing a drug to act properly. The carbohydrates moieties can increase drug water solubility, decrease toxicity, and contribute to the bioactivity of the drug (natural products). This review provides a short summary of diverse carbohydrates containing drugs their potential application in pharmaceutical chemistry.

INTRODUCTION

Carbohydrates are important constituents of all living organisms and have a variety of different functions. They make up more than 50% of the dry weight of the Earths biomass. Carbohydrates are the most abundant biomolecules. Thus the knowledge of biomolecules and mechanisms under going for the maintenance of living beings become essential for a person practicing pharmaceuticals. The classical example of a carbohydrate containing drug dates back to 1705 when the effect of digitoxin as a treatment in heart failure was first recorded. This drug has been subject to extensive modification to circumvent its narrow therapeutic index without gaining major success. Probably the largest individual group of carbohydrate-based therapeutics is the antibiotics (Park, J., Cho, J. Y. ,2009) . The classical example is that of streptomycin which started a wave of successful research in aminoglycoside antibiotics eventually giving the kanamycins, gentamycin and neomycins. Another important group of carbohydrate-based drugs is the cytostatics including examples as daunorubicin, mithramycin and bleomycin. Sucralfate, a aluminium complex of per sulfated sucrose, constitutes a new and interesting principle for treatment of ulcers including, inter alia, mechanical protection of the necrotic mucus and induction of bicarbonate secretion. A few high molecular weight carbohydrates have had a major impact in human medicine. Probably the three most important are dextrin, heparin and hyaluronan. The original idea of using partially hydrolyzed dextran as a plasma substitute dates back to 1942 when B. Ingelman and A. Groenvall studied sugar beet juice. For the first time in 1947 a 6% solution of a dextran fraction was approved for clinical use in Sweden. By continued studies and development dextran-baesd products have kept their position as an important plasma substitute with several interesting additional therapeutic benefits, e. q., and antithrombotic activity.

Starting from the technology base of dextran some other interesting pharmaceuticals have been developed. The most important is probably debris an,

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a wound agent, prepared by cross-linking of dextran. The product acts by absorbing wound exudates in secreting wounds and shortens the healing time. The clinical effects of heparin in therapeutic and prophylactic treatment of thrombosis have been documented for several decades. Heparin has, however, some well-known and serious side-effects such as risk of bleeding, impairment of the thrombocyte function and influence of the lipolytic activity in the plasma. During the 1990s, new understanding formed a new basis for heparin products. One critical observation was that various factors generated by nitrous acid degradation. Form this and other observation it was possible to develop a new therapeutic, Fragmin, reduced side-effects and simplified routines for administration. Since the use of artificial implants and devices are increasing rapidly in modern medicine it is of considerable importance to be able to prepare bio-compatible surfaces (Oyston, P. C. F., Fox, M. A., Richards, S. J., Clark, G. C.,2009) . A method based on covalent binding of heparin fragments generated by nitrous acid degradation to a polyethylenimine covered surface has proved to give a particular stable and bio-compatible surface. This has been explored for intra-ocular lenses, oxygenators and other devices. Hyaluronan displays extraordinary reological properties. In the late 1970s development of the concept of viscosurgery had revolutionized ophthalmic surgery, in particular cataract surgery. Here a high molecular weight non inflammatory fraction of hyaluronan (Healona) is instilled in the eye by a syringe prior to lens extraction and implantation of the new intra-ocular lens. It facilitates the eye surgery because it maintains space, protects tissues and makes it possible to gently maneuver tissues.

This brief review has focused on some classical as well as some newer developments in carbohydrate-based pharmaceuticals. In the future we will certainly see several interesting opportunities in the area of glycoconjugates where advances during the recent past have been initiated. This basic research opens up avenues in such diverse areas, for example, tumor markers for diagnostics, drug targeting and metabolic modulation of drug action. However, any practically important success will depend on close co-operation between scientists in several areas of structural studies, functional studies, synthetic chemistry and applied goal and customer oriented development.

CARBOHYDRATE PHARMACEUTICALS: A large number of Carbohydrates and carbohydrate-derivatives are used as therapeutics or in diagnostics. Examples are found in important areas as antibiotics and anticoagulants. These drugs can be divided into five categories, as monosaccharide conjugates, disaccharides and disaccharide conjugates, oligosaccharides and polysaccharide,trisaccharides and macrolides.

1. Monosaccharide conjugates: monosaccharide conjugates include, in turn, four groups of prescription drugs: (**a) Anthracycline antibiotics and agents:** This group is represented by cytotoxic anthracycline antibiotics of microbial origin (Doxorubicin and Daunorubicin) or their semi-synthetic derivatives (Epirubicin and Idarubicin). All of these drugs are potent neoclassic agents consisting of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amine sugar,daunosamine. All of them bind to nucleic acid, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix, between nucleotide base pairs, with consequent inhibit topoisomerase ll activity by stabilizing the DNA-topoisomerase ll complex, blocking the ligation-religation reaction. All of these drugs show the cytotoxic effect on malignant cells and-as side effects-on various organs. Intercalation inhibits nucleotide replication and action of DNA and RND polymerases. All of them induce apoptosis, which may be an integral component of the cellular action related to antitumor therapeutic effects as well as toxicities**. (b)Nucleotides and Nucleosides and their Analogs:** This group of drugs is represented by an assortment of nucleotides and nucleosides and their synthetic analogs. Among them are: **(I)** potent neoplastic agent, such as Fludarabine Phosphate (fluorinated arabinofuranosyladenine 5′ monophosphate) whose metabolic products inhibits DNA synthesis. This drug is indicated for the treatment of patients with B-cell chronic lymphocytic leukemia, while another such agent Gemcitabine (2-deoxy-2,2-difluorocytidine), is a

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nucleoside analogue that inhibits DNA synthesis and exhibits antitumor activity.(II)-Drugs active against the human immunodeficiency virus (HIV) such as Stavudine, a synthetic thymidine nucleoside analog. This drug is a derivative of deoxythymidine, which inhibits the replication of HIV in human cells**.(III)** An antiarrhythmic drug adenosine (6-amino-9- b-D-ribofuranosyl-9-H-purine),which presents in all cells of the body and apparently activates purine receptors (cell-surface adenosine receptors). These molecules in turn activate relaxation of vascular smooth muscle through a number of biochemical events, and they are therefore indicated in patients with paroxysmal supraventricular tachycardia.(**IV**) The first synthetic non-interferon type antiviral drug Ribavirin (ribofuranosyl-triazole derivative), a nucleoside analog, which is particularly active against respiratory syncytial virus(RSV) **.(V)**A cardioprotective agent Acadesine, a ribofuranosyl-imidazole derivative and a purine nucleoside analog, which is employed in particular in coronary artery bypass graft surgery (Hong,Z. Y., Liu, L., Sugiyama, M., Fu, Y., Wong, C. H. ,2009) **.(c) polyenes:** This group, polyenes, is exemplified by Amphotericin B, which is an antifungal antibiotic of microbial origin. Amphotericin B is a 3-Amino-3,6-dideoxy- B-D- mannopyranosyl derivative of an octahydroxypolyene containing seven carbon-carbon double bonds in a macrocyclic 38-member ring. The drug changes the permeability of the cell membrane of susceptible fungi by binding to sterols in the membrane (Nagao, T, Adachi, K., Sakai, M., Nishijima, M., Sano, H.,2001) . This binding causes leakage of intracellular content and as a consequence, cell death. **(d) Other Agents:** This group of monosaccharide drugs contains a number of assorted compounds, such as (**I**) The cancer chemotherapeutic agent Etoposide, a semi-synthetic B-Dglucopyranoside derivative of podophyllotixin.(**II**) An antibacterial antibiotic of microbial origin Lincomycin, which is a derivative of 1-thio-D-galacto-octopyranoside. **(III)** A semisynthetic antibiotic, Clindamycin, which is a derivative of 1-thio-L-thero-alpha-D-galacto-octopyranoside and produced from Lincomycin. Clindamycin is indicated in the treatment of infections caused by susceptible anaerobic bacteria, streptococci, pneumococci, and staphylococci.(**IV**) An antitumor drug, Pentostain, that inhibits RNA and DNA synthesis by being a direct inhibitor of enzymes adenosine deaminase and ribonucleotide reductase, particularly in cells of the lymphoid system.

2. Disaccharides and disaccharides conjugate: This group of carbohydrate drugs, disaccharides and their conjugates is represented by the following medications: **(I)** an antipeptic and antiulcerative drug, Sucralfate, which is a B-D- fructofuranosyl-alpha-D-glucopyranoside basic aluminium sucrose sulfate complex. It accelerates healing of duodenal ulcers, in part by inhibiting pepsin activity in gastric juice**.(II)** A synthetic colonic acidifier Lactulose, 4-O -B-D-galactosyl-D-fructose, which promotes laxation**.(III)** A microbial amphoteric glycopeptides antibiotic, Vancomycin, which inhibits cell-wall biosynthesis. Vancomycin is active against staphylococci, streptococci, enterococci, and diphtheroids, and it is indicated for treatment of systemic infections (Bellostas, N., Sorensen, A. D.Sorensen, J. C., Sorensen, H., 2007) .

3. Trisaccharides: This group of carbohydrate, trisaccharides and their conjugates, is represented by the antibacterial aminoglycoside antibiotic origin, Tobramycin, which is a derivative of an aminoglucopyranosyl-ribohexopyranosyl-L-streptamine. The drug acts primarily by disrupting protein systhesis through altering cell membrane permeability; thereby breaching the cell envelope and causing eventual cell death. It is indicated for the management of cystic fibrosis patients. A cardiac glycoside, Digoxin, that belongs to a closely related group of drugs of plant origin and that contains a sugar and a cardenolide, the sugar part consists of (O-2,6-dideoxy-B-D-ribo-hexapyranosyl)3. Digoxin inhibits sodium- potassium ATPase that in turn leads to an increase in the intracellular concentration of sodium and calcium (Cheng,Y. Shen, L. H., Zhang, J. T.,2005) . This results in a chain of biochemical events that have multiple effects on cardiac muscle and the cardiovascular system in general.

4. Oligosaccharides and polysaccharides: This group of carbohydrate drugs made of oligosaccharides and polysaccharides include two groups **(I)** Heparin and Heparin-like saccharides: This group is represented by

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heparin and a series of its low-molecular weight fragments and analogs, all of them being antithrombotic agents. Heparin is a heterogeneous group of glycosaminoglycans, straight-chain anionic mucopolysaccharides that have anticoagulant activity, in particular they inhibit formation of fibrin clots in blood. These drugs variably sulfated polysaccharide chains are composed of repeating units of D-glucosamine and L-iduronic or D-glucuronic acids. Enoxaparin, Tinzaparin and Dalteparin are all prepared by controlled depolymerization of Heparin or its derivatives. This is accomplished by alkaline degradation, enzymatic hydrolysis, and nitrous acid fragmentation, respectively. Danaparoid is a complex glycosaminoglycuronan whose active components are heparin sulfate, dermatan sulfate, and chondroitin sulfate. Finaly, Pentosan polysulfate is a semi-synthetic sulfated heparin- like oligomer. Composed of B-D –xylopyranose residues, it shows anticoagulant and fibrinolytic effects (Kennedy, D. O., Scholey, A. B. ,2003) **.(II)** Complex oligosaccharides: The group of complex oligosaccharides contains two fundamentally different kinds of prescription drugs. The first are bactericidal aminoglycoside antibiotics of microbial origin, Streptomycin and Neomycin, which act by interfering with normal protein synthesis. Streptomycin is usually available as the sulfate(2:3) salt. The second kind of complex oligosaccharide Acarbose, also of microbial origin, inhibits alpha-glucosidase and delays the digestion of ingested carbohydrates, making the drug beneficial for the management of type 2 diabetes mellitus.

5. Macrolides: This and final subcategory of prescription carbohydrate drugs is represented by macrolide group of antibiotics, of which there are four. The first, Erythromycin, is of microbial origin, it appears to inhibits potein synthesis in susceptible organisms by binding to ribosomal subunits and thereby inhibiting translocation of aminoacyl transfer- RNA. The other three-Dirithromycin, Clarithromycin and Azithromycin-are semi-synthetic macrolide antibiotics derived of Erythromycin. Dirithromycin is a pro-drug that is transformed during intestinal absorption into an anti-bacterial active form, Erythromycylamine. Clarithromycin is 6-o-methylerythromycin. Azithromycin is N-methyl-11-aza-10-deoxo-10-dihydroerythromycin. An essential component of these drugs, as well of all other carbohydrate drugs described in sugar moiety. On other hand, addition of a certain sugar moiety sometimes enhances the recognized potential of the drug at the target level.

Some of the carbohydrates are very importance for manufacturing of drug suchas mannitol,sorbitol,sucrose,glucose, lactose, starch and cellulose described as: **Mannitol -** mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10-90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formations because of its sweetness.It has also been used to prevent thickening in aqueous antacid suspensions of aluminium hydroxide (<7% w/v**). Sorbitol-** It is used as a diluents in tablet formulations prepared by either wet granulation ordirect compression. It is particularly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation. In capsule formulations it is used as a plasticizer for gelatin. Inliquid preparations sorbitol is used as a vehicle in sugar free formulations and as a stabilizer for drug, vitamin and antacid suspensions. In syrups it is effective in preventing crystallization around the cap of bottles.Sorbitol is therapeutically used as an osmotic laxative, it may also be used analytically as a marker for assessing liver blood flow(Sparg, S. G., Light, M.E., Van Staden, J. ,2004) . Sorbitol has been used as a plasticizer in different cosmetics and toothpaste**. Glucose-** Glucose is the most abundant carbohydrate, found both in plants and animals. It is a basic energy source for many of the body's operations .Liquid glucose is used as a base in oral solutions and syrups and also as a granulating and coating agent in tablet manufacture. It is also used as sweetener in confectionery products. **Lactose-** Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture- sensitive drugs due to its low moisture content. **Sucrose-** sucrose is used as

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sweetener in chewable tablets. It is used as binding agent for wet granulation. Sucrose syrups are used as tablet coating agent at concentrations 50% and 67% w/w. Sucrose syrups are also widely used as vehicles in oral liquid dosage forms to increase viscosity. **Starch-** Starch is a polysaccharide carbohydrate consisting of a large number of glucose units joined together by glycosidic bonds. It is used as an excipient primarily in oral solid- dosage formulations where it is utilized as a binder, diluents, and disintegrant. As a diluents, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-fill capsule formulations for volume adjustment of the fill matrix. In tablet formulations, freshly prepared starch paste is used at a concentration of 5-25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate. Starch is one of the most commonly used tablet disintegrants at concentrations of 3-15% w/w. **Cellulose-** Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes. In addition to its use as a binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that it useful in tableting. Powdered cellulose is used as tablet diluents and hard gelatin capsule filler. In soft gelatin capsules, powdered cellulose may be used to reduce the sedimentation rate of oily suspension fills. It is also used as the power base material of power dosage forms, and as a suspending agent in aqueous suspensions for per oral delivery. It may also be used to reduces sedimentation during the manufacture of suppositories. Carboxy methyl cellulose sodium is additionally one of the main ingredients of self adhesive wound care and dermatological patches, where it is used as a muco-adhesive and to absorb wound exudates (Dewick,P.M., Medicinal natural products,2001), . This mucoadhesive property is used in products designed to prevent post-surgical tissue adhesions and to localize and modify the release kinetics of active ingredients applied to mucous membranes. Carboxy methyl cellulose sodium is also used in cosmetics, toiletries, surgical prosthetics, personal hygiene, and food products. In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film coating, and extended-release matrix former. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer. Hydroxy propyl methyl cellulose is used as polymer for preparation of sustained release dosage form.

CONCLUSION

This review has focused on some classical as well as some newer development in carbohydrate based pharmaceuticals. Finding drugable carbohydrate-containing natural products remains an ongoing process. With the increasing interests in the field of carbohydrates and the rapid advance of the powerful tools including chemical synthetic strategies cheomenzymatic methods, and glycodiversification strategies, it is now possible to expand the existing repertoire of carbohydrate- containing natural products to find new drugs that can be used to protect human health and to combat and treat diseases. Nevertheless, developing more efficient and more economic synthetic approaches for synthesizing carbohydrate-containing natural products remains to be a great challenge and thus an active area of research for years to come. However, any practically important success will depend on close co-operation between scientists in several areas of structural studies, functional studies, synthetic chemistry and applied goal and customer oriented development.

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