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Inulin: A promising carrier for controlled and targeted drug delivery system

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ABSTRACT

The delivery of a drug to the preferred site of action is referred to as drug targeting. The benefits of drug targeting are a reproducible and controlled release rate of the therapeutic compound, which forestalls overdose. Due to the potential to treat colonic diseases with minimum side effects, colon targeting has become of high interest over the last decades. Inulin was investigated for its potential as encapsulation material regarding its enzymatic degradability and its drug release behaviour. Inulin is a polysaccharide with a widespread range of therapeutic uses such as a carrier in a drug delivery vehicle, as a diagnostic/analytical tool or as a dietary fibre with additional health benefits. In the main, much research has focused on inulin as a drug delivery carrier for colon-specific drug delivery. The justification for this is its potential to survive in the stomach's acidic environment. This unique stability and strength are utilized in many ways to deliver drugs safely to the colon, where they can be easily absorbed through the gut epithelium into the blood. There are also some proofs that inulin's prebiotic features also lead to health benefits, mainly for patients with inflammatory bowel disease or in the prevention of colonic cancer. Inulin based hydrodynamic research will be useful to discover the potential of inulin.

Keywords: Drug targeting, Controlled release, Inulin, Prebiotic

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1. Introduction

The delivery of a drug to the desired site of action is referred to as drug targeting. The benefits of drug targeting are a reproducible and controlled release rate of the therapeutic compound, which forestalls overdose. Moreover, the unwanted effects and toxicity of drug are minimized [1]. Now day's colon targeting has become of high interest, due to the potential to treat colon specific diseases with minimized side effects [2]. For colon specific targeting, it is essential that the therapeutic formulation bypass the stomach and the small intestine in a non-degraded form [3]. Various bio-polymers like polysaccharides have been investigated as prospective encapsulation materials for therapeutic substances [4]. Inulin is a versatile plant-derivative carbohydrate with the benefits of soluble dietary fiber [5]. Inulin is not digested or absorbed in the stomach and in the small intestine but is fermented in the colon by advantageous bacteria. Inulin functioning as a prebiotic has been linked with enhancing the gastrointestinal system and the immune system. The natural polymer inulin has numerous applications in the food and pharmaceutical industry due to its exclusive chemical and physical properties [6,7]. Inulin is non-toxic biopolymer and its β(2-1)-glycosidic-linked fructosyl units are indigestible by the upper gastrointestinal tract of humans [8]. However, inulin can be partly or totally metabolized by the colonic microbiota to acetate, propionate, lactic acid, hydrogen, and carbon dioxide [9-11]. Consequently, inulin is used as a prebiotic food element with accredited positive effects on human health.

Stevens et al. reported that ingested inulin is not altered in monosaccharides by the digestives juices. Therefore, the glycemia and the level of insulin in the blood remain steady and the inulin reaches in the large intestine where it is fermented [12]. This condition is caused by a specific bond, β(2-1) linked fructose present in the molecule of inulin [13], which confers that it cannot be processed by the human digestive system so the inulin passes through stomach, small intestine without degradation and stops in the large intestine where it produces a healthy microflora (Bifidobacterium). This shows that inulin is a natural prebiotic (an ingredient that belongs to the prebiotic family requires two stipulations: it should not be digested by the digestive enzyme, and it can only undergo fermentation in the colon. Various physiological effects implemented by inulin are summarized in Table 1.

Table 1: The physiological function of inulin in the large bowel [14]

Large Bowel	Inulin Functionality
Attenuation of faecal pH	+
Production of short chain fatty acids	+
Promote growth of *Bifidobacteria*	+
Increase stool frequency	+
Decrease intestinal transit time	-
Increase stool weight	-
Improvement of stool consistency	+

Now a day's inulin is a promising molecule with researches and applications in medicine, pharmacology or food industry, because of its bioactivity [15]. In medicine, inulin has manifold functions, such as: maintaining the microflora of the colon, improving metabolism, maintaining gastrointestinal health [16]. A relative latest finding confirmed that pure inulin promoted Collinsella growth in the gastrointestinal tract. in addition, Smecuol et al. [17] found that inulin-type fructans contribute to the rise of Bifidobacterium infantis probiotic strains that have a positive effect on subjects with active coeliac disease, a chronic inflammation of the intestinal mucosa ensuing from an extreme immune response to dietary gluten in genetically predisposed individuals. The colonic disorder is quite hard to treat because orally administrated therapeutics are absorbed in the stomach and intestine levels and they do not reach the colon, while intravenous administrated therapeutics are eliminated from the body before reaching the colon. The fact inulin is not degraded or absorbed in the stomach or in the small intestine, but it is degraded by colonic bacteria, various inulin based pharmaceutical formulations have been developed that can be used as a promising carrier for targeting of drugs into the colon [13, 18].

2. Inulin

2.1 Origin and Identity

Rose discovered Inulin, a German scientist, in 1804 from the roots of *Inulaheleniumf*ound "a peculiar substance" from plant origin, a genus of perennial herbs of the group *Composit~e,* inhabitants of the temperate regions of Europe, Asia, and Africa [19]. The substance was named inulin but was also known by other names such ashelenin, alantin, meniantin, dahlin, sinantemin and sinisterin. In the mid of the 19th century, the biochemicalproduction was elucidated.

Inulin comes under a general class of fructose-containing polymers known as fructans. Fructans assist as storage polymers in numerous members of the Composit~e family such as *Cichoriumintybus* (chicory), *Inulahelenium* (elecampane), *Taraxacumofficinalis* (dandelion) and *Helianthus tuberosus* (Jerusalem artichoke). Inulin pulls out from chicory is a natural polydisperse carbohydrate [20]. It is a fructan which mainly comprises linear chains of 1, 2-[3-1inked d-fructofuranose units bound by an (od-132) type linkage (as in sucrose) to a terminal glucose moiety. The fructans that are found in the dicotyledons, and in some monocotyledons, are of this type. By assessment, fructans primarily composed of linear fructose units bound by a [3-(2---~6) glycosidic bond. The gross molecular formula of inulin is GF with G being a terminal glucosyl unit, F shows the fructosyl units and n demonstrating the number of fructosyl units [Fig. 1] [21].

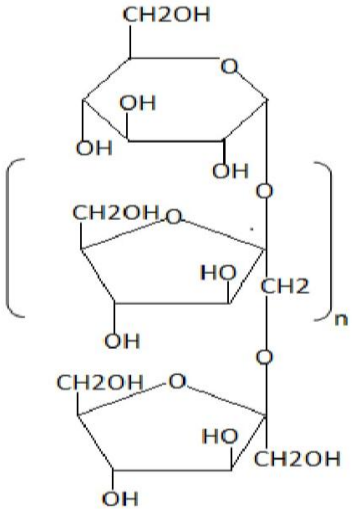

Figure 1: Basic structure of Inulin

2.2 Source and preparation

Inulin occurs in thousands of plant species, including asparagus, banana, garlic, and onion. The chicory (Cichorium intybus) root is the main commercial source where inulin constitutes 16% to 18% of the dry matter. Some inulin is also obtained from tubers of Jerusalem artichoke (Helianthus tuberosus L.). Inulin has been taken by humans since ancient times. Before the potato was introduced into Western Europe in the latter half of the 16th century, the Jerusalem artichoke tuber (14%-19% inulin) was a main source of carbohydrate. Chicory roots (and Jerusalem artichoke tubers) must be processed soon after harvesting (possibly on the same day, but not more than 7 days after harvesting) because they deteriorate quickly. The harvested roots are washed, sliced, and extracted with hot water. Colloidal materials, colored substances, and other solubles (salts, amino acids, sugars, etc.) are isolated from the extract by a purification/clarification process involving treatment with calcium hydroxide (lime) to precipitate protein, followed by treatment with CO_2 to counteract the alkaline mixture and to precipitate any calcium ions in solution as calcium carbonate, centrifugation, filtration through an adsorbent and/or activated carbon, and ion exchange, a process analogous to that used in purifying sucrose extracts. The extract is then concentrated by evaporation and spray-dried followed by ultrafiltration. The inulin may also be recovered by crystallization or precipitation. Even with extensive care, inulin extracted from chicory roots is still mainly a mixture of oligosaccharides. The commercial preparation contains 2% monosaccharides, 5% disaccharides, and 93% molecules of DP 3-60, with an average DP of 8-10. The maximum average DP of chicory root inulin is about 15, representing a comparatively high percentage of molecules of low DP. The maximum amount of inulin in chicory roots is about 18% (dry basis). [22]

3. Controlled and targeted drug release by Inulin complexes

Inulin offers controlled release of therapeutics to the colon because it provides protection against the acidic environment in the stomach for the encapsulated drug as well as allowing degradation in the colon in the presence of the colonic microbiota [23]. The potential of inulin, as a coating system, with its effectiveness in controlled drug released was tested by [24] swelling tests, water vapour transmission tests and drug permeability in colonic media was evaluated using

polymethacrylates (eudragit) with and without inulin. In the absence of inulin polymers, drug release was controlled by the pH of the media. The swelling behaviour and permeation of drug were observed more with inulin dependent system as compared to the pH-dependent polymers (24). Drugs with low water solubility have low bioavailability due to partial solubility and thus present a dilemma in successful drug delivery [25]. Irbesartan tablet was prepared by mixing it with inulin and poly (acrylic acid) grafted inulin. The flower-like platelets of inulin, surrounding the drug were observed that consequently increased the drug dissolution. Increasing inulin concentration increased the drug solubility [26]. Quality of inulin to form aggregates in different solutions like water, DMSO and CnTAB (cetyl trimethylammonium bromides) and CHAPS (3-[(3-cholamidopropyl) dimethylammonio]-1-propanesulfonate) can be useful for the solubilisation and encapsulation of drugs [27]. The physicochemical interaction with cationic amphiphilic surfactants CnTAB of varied alkyl chain length was studied at a variable concentration of CnTAB and inulin. Increasing concentration of alkyl group was reported to strengthen the inulin aggregates up to a moderate concentration of the amphiphile. At very high concentrations the amphiphile formed free micelles [28]. Inulin incorporation in a three-layer coating system has also been reported by Ravi et al. A tablet made up of the drug Diltiazem HCl matrixed with chitosan and guar gum was used. This tablet was bounded by inulin (inner) and shellac (outer) layer. The outer and inner coats were intended to provide protection against gastric and intestinal environments, respectively. The drug was then released in the colon with the degradation of the other two polysaccharides [29, 30].

Due to its resistance to the gastric fluid and degradation in the distal intestine inulin was used as a promising carrier to deliver butyrate to its site of action. The study was conducted in order to recognize the apoptotic potential against colonic cancerous cells and showed that the use of inulin provided secure targeting of butyrate to its site of action [31].

3.1 Hydrogels of Inulin

A range of inulin hydrogels has been developed to be used as potential carriers for the targeting of drugs with variable composition into the colon [32]. Appropriate degradation rate, bioadhesive nature, mechanical and hydrolytic resistance are the desirable characters imposed by polysaccharide-poly amino acid gels that can be helpful for the successful delivery of drug to its targeted site [33]. For example, cross-linking of Inulin with Methacrylic Anhydride and Succinic Anhydride (INU-MA-SA) resulted in the production of a derivative that is reluctant to degradation in the stomach and is compatible to intestinal degradation [34]. This inulin derivative (INU-MA-SA) has also been tested using Differential Scanning Calorimetry (DSC) for delivery of Non-Steroidal Anti Inflammatory Drugs (NSAIDs). These drugs have the potential to irritate gastric mucosae [35]. Diflunisal was the NSAID (the drug used to treat early morning angina) used exclusively for this study at pH 4.0 and 7.4. Use of inulin provided defence from the acidic environment in the stomach to the drug and was found to be more useful to avoid any side effects caused as a result of NSAIDs in the stomach. Degradation of inulin occurred in the colon in the presence of the enzyme inulinase [23].

Another study has reported INU-MA-SA hydrogels to be used in conjunction with a ß-poly[N-(2-hydroxyethyl)-D, Laspartamide]. This polysaccharide/poly (amino acid) UV induced hydrogel system was used to deliver protein and peptide-based drugs to the colon. Immunoglobulin G (IgG) was selected as a model drug. These hydrogels were inulinase degradable, compatible with epithelial cells and the released protein reserved their biological activity. [33] Inulin a-ß-polyaspartylhydrazide gels (INUPAH) were made from a-ßpolyaspartylhydrazide (PAHy), a synthetic and biocompatible amino acid. The gel was loaded with two therapeutic peptides, glutathione and oxytocin, respectively. The gel was apposite for intestinal delivery of these peptides for the management of inflammatory bowel disease [36]. Another hydrogel of inulin was obtained by cross-linking inulin derivatives (inulin with divinyl sulfone and succinic anhydride) with trimethylolpropane tris (3-mercaptopropionate). The anti-cancerous drug, 2-Methoxyestradiol was complexed with this hydrogel and found to be apoptopic against Caco-2-cell lines. Also, this gel was reported to be appropriate for colon drug delivery because of its degradation by inulinase and esterase [37].

3.2 Solid dispersion

The solid dispersion technology is another method utilised for introducing therapeutics. Here, the therapeutics is dispersed in a hydrophilic matrix [38]. In this study by Visser, an inulin matrix (Mw: 4kDa) was observed to improve solubility and drug release rates for weakly water-soluble drug TMC240 along with an increase in drug loading threshold (38). Inulin and its derivatives are suitable candidates for solid dispersion drug delivery for a heavy load of lipophilic drugs. Inulin (Mw: 2.3kDa), Inulin derivative Inutec SP1 (inulin back bone with covalently linked lipophilic alkyl side chains), and polyvinylpyrrolidone were spray dried to form a solid dispersion in which the drug was loaded. The drug encapsulation was reported using DSC. All three formulations gave excellent physical stability with Inutec SP1 with utmost dissolution rate owing to its surface-active nature [39].

Inulin has also been used as a solid dispersion to give stability to highly unstable, easily degradable and lipophilic Δ9- tetrahydrocannabinol (THC). A blend of THC and inulin in a solution of water and tertiary butyl alcohol was lyophilised to make a solid dispersion and stored for 7 days at 20°C at 45% relative humidity. This exposure led to total degradation of unprotected THC in 40 days while solid dispersed THC showed only 20% degradation even after 300 days. The high aqueous dissolution rate of the tablets prepared from THC incorporated in inulin matrix was recommended to improve bioavailability in sublingual administration [40].

In another study based on the stabilizing capability of inulin, it was found that inulin is a better stabiliser than trehalose. The research was targeted to formulate an orally ingestible tablet that can be used to eradicate endotoxins released during sepsis. The compaction behaviour of inulin and trehalose and their effect on the loaded bovine isolated alkaline phosphate (BIAP) was observed. Trehalose tends to crystallize upon compaction and had moisture in it while inulin had low friability, was stable at high relative humidities and offered good tabletting strength. Thus, inulin had a benefit over trehalose as a stabiliser of BIAP in the form of a tablet [41].

4. Conclusion

Inulin is versatile polysaccharide that can be used as a drug delivery vehicle, as a diagnostic tool or as a dietary fibre with widespread health benefits. In this review study, the drug targeting potential of inulin has been reviewed. Inulin's chemical structure makes that it is not degraded by the upper gastrointestinal tract. Gut micro-biota, however, are able to metabolize inulin. This unique stability and strength are utilized in a number of ways to deliver drugs safely to the colon where they can be easily absorbed through the gut

epithelium into the blood. There are some proofs that inulin's prebiotic features also lead to health benefits, mainly for patients with inflammatory bowel disease or in the prevention of colonic cancer. Inulin based hydrodynamic research will be valuable to find out inulin potential. In addition, more and more research is being made with chemically tailored inulins, making it likely that more applications will be established for this versatile polysaccharide.

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