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A Short Review on Presence of Pharmaceuticals in Water Bodies and the Potential of Chitosan and Chitosan Derivatives for Elimination of Pharmaceuticals

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Abstract

Pharmaceutical products are being increasingly detected in the environment. However, conventional treatment systems do not provide an adequate treatment for pharmaceutical drug elimination and still there is not a regulated standard for their limitation in water. Adsorption is one of the most effective and practical techniques to remove pollutants from water. Nowadays, considerable focus is on development of natural wastes to be utilized as adsorbent in wastewater treatment plants. Among bio waste materials, chitosan has many applications in various fields based on its chemical and physical properties together with being abundant and cheap. Chitosan has removal capabilities for certain pollutants from water such as dyes, metal ions, phenol and different anions. Moreover it is widely used as carrier for pharmaceutical components in drug delivery. Based on the properties and applications that are already known for chitosan, using it to remove pharmaceuticals could resolve costly and inefficient techniques that are currently employed in wastewater treatments. In this paper the potential of chitosan and its derivatives for removal of pharmaceutical has been discussed.

Keywords: Chiosan; Cross-linking; Pharmaceutical; Pollution; Wastewater

Introduction

Existence of pharmaceuticals in the aquatic environment has been of great concern in many countries. Pharmaceuticals are bioactive compounds and they are able to cause potential effects on living systems [1]. Different classes of pharmaceuticals have found their way to the environment after being used or excreted through wastewater and sewage treatment systems [2]. In some analysis accomplished in Austria, Brazil, Canada, Croatia, England, Germany, Greece, Italy, Spain, Switzerland, the Netherlands, and the U.S., more than 80 compounds, pharmaceuticals and drug metabolites, have been detected in the aquatic environment. Moreover the data on the aquatic ecosystems resulting from long-term low-dose exposure to pharmaceuticals are still limited [3].

Researchers have discovered evidence that even very low dosage of pharmaceutical can be possibly a serious threat to aquatic species in water [4]. Meanwhile, some studies on human cells reported the cell failure growth when exposed to trace amount of certain drugs. Few contaminated packaging and drug waste are incinerated, but mainly they are disposed to the environment [3]. Based on the precaution principle, the European Union Water Framework Directive, currently there are no legally regulated maximum permitted concentrations of pharmaceuticals in the environment [5].

Scientists' objective is mainly giving a clear image of the behavior and toxicity of pharmaceutical compounds in the environment in order to safeguard living organisms from any adverse health effect caused by them. In 2002, 150 pharmaceutical compounds have been monitored in the environment, mainly in aqueous samples [6] which the wastewater treatment enables to remove these pharmaceuticals partially. The amounts of various pharmaceuticals detected in inlet and outlet water of various wastewater treatment plants (WWTPs) confirmed that many of these substances are not effectively removed by former treatments. Thus, conventional treatment systems are unable to totally remove a large amount of the pharmaceutical micro pollutants present in urban wastewaters. More effective and particular treatments are required to reduce the potential impact of these pollutants [7].

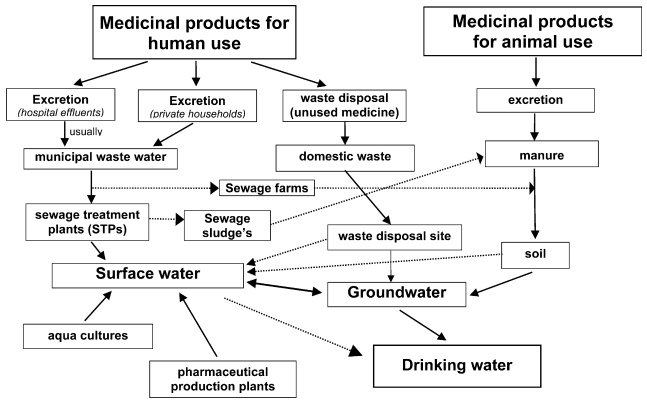

Figure 1: Possible sources and pathways for the occurrence of pharmaceutical residues in the aquatic environment [8].

Figure 1 briefly shows possible sources and pathways for the occurrence of pharmaceutical residues in the aquatic environment. As presented in the figure there are multiple sources for pharmaceuticals

present in the environment which finally end up in surface water, ground water and even drinking water [8].

Water treatments for pharmaceutical compounds have been centered on ozonation [9], photo oxidation [10], electro oxidation [11] and activated carbon adsorption/bioadsorption so far [12]. Post-treatment techniques such as ozonation, membrane filtration and sorption on activated carbon may be effective for completing the removal of the most pharmaceutical and personal care products (PPCPs). Meanwhile most of these treatments such as ozonation and using activated carbon are costly or not effective enough [9,13]. Even a study on removing few pharmaceutical with membrane bioreactor (MBR) proved that membrane technology would not completely stop discharge of micropollutants [14,15]. Another conventional treatment for disinfecting drinking waters is use of chlorine which reacts which some pharmaceuticals like Acetaminophen and form toxic compounds [16]. In general, WWTPs comprise a primary system of physicochemical treatments and a secondary system that consists of a biological reactor formed by activated sludge. These conventional plants have a limited capacity to remove pharmaceutical products from urban wastewaters, since most of the compounds cannot be metabolized by microorganisms as source of carbon and may even inhibit the activity of the microorganisms or produce their bioaccumulation in the food chain [17].

Although further research is required on this issue, it is known that conventional wastewater treatment plants do not remove all pharmaceuticals from wastewaters. Therefore, they remain in effluents and contaminate surface and ground waters, which are the main source of drinking water [18,19]. In fact, it is vital to search for efficient and economically feasible procedures to remove pharmaceuticals from wastewater before they enter the environment [20]. Since decades before, pharmaceuticals have been in water but only recently their levels in the environment have been recognized and quantified as potentially hazardous to ecosystems. Due to the increasing global usage of pharmaceuticals and the fact that there are currently no legally regulated maximum permitted concentrations of pharmaceuticals in the environment, it is essential to remove pharmaceuticals before they enter the environment. However, there are not much of studies conducted on removal of pharmaceuticals, especially in trace amounts from wastewater. In the company of all the treatments utilized for wastewater, adsorption is the most popular method for the removal of trace amount of pollutants. Other techniques such as reverse osmosis and membrane filtration are used for post-treatment of drinking water and is not applicable everywhere due to high cost [15]. Among adsorbents, there are a few reports available on activated carbon been used as an adsorbent in removing some pharmaceuticals. Nevertheless, high production and maintenance costs plus not being friendly through environment make it vital to look for more appropriate and convenient adsorbents to remove pharmaceuticals [21]. In particular, the costly conventional adsorbents certainly make bio-waste materials one of the most appealing sorbents for wastewater treatment [22].

Since few years ago, considerable focus has been given on development of polysaccharide derivatives as the basic materials for new applications [23]. Polysaccharide-based materials such as chitosan which are abundant, renewable and biodegradable have demonstrated outstanding removal capabilities for certain pollutants such as dyes, metal ions, phenol and different anions as compared to other low cost sorbents and commercial activated carbons. Chitosan is extracted from Chitin, considered as the second biopolymer in nature after cellulose. Chitosan is a naturally abundant bio adsorbent for many pollutants from water and it has a capacity to associate by physical and chemical interactions with a wide variety of molecules [24]. Meanwhile chitosan has wide ranges of application in the fields of drug delivery and is a well-known carrier for many drugs in pharmaceutical industries [25-28]. Based on the properties and applications that are already known for chitosan, using it to remove pharmaceutical could resolve costly and inefficient techniques that are currently employed in wastewater treatments. Since in drug delivery, the concentration of pharmaceutical is higher than the amount in wastewater, there is more affinity between chitosan as carrier and the drug. This review paper initially discusses different methods of pharmaceutical removal from water bodies and after that the focus will be on adsorption of different pharmaceuticals by chitosan and its derivatives which have been reported so far.

Removal Strategies for Pharmaceuticals in Water Treatment

Standard water treatment plants are not equipped to remove pharmaceuticals from water. According to a recent study in Australia some drugs may become more dangerous during conventional treatment. Pharmaceuticals may change due to an enzyme reaction or interaction with bacteria [29]. If the pharmaceuticals have an organic carbon base, then disinfection by chlorine could potentially create dangerous byproducts [30]. The degree of removal and biodegradation of pharmaceutical compounds during wastewater treatment (WWT) varies considerably. As methods in the elimination of pharmaceuticals in water treatment systems are different. In most cases the technologies that have been used are membrane filtration, adsorption on activated carbons and advanced oxidation processes (AOPs) that employ ozone, ultraviolet radiation, gamma radiation and electro-oxidation [31]. Micropollutants that resist conventional processes can be removed by membrane filtration, nanofiltration, reverse osmosis or adsorption on activated carbon. However, the retention capacity of these methods can be reduced through blockage by natural organic matter in water [32]. The most common techniques applied in water treatment plants and their effects on pharmaceutical removal are briefly explained below.

Membrane filtration

Microfiltration (MF) or Ultrafiltration (UF) membranes are utilized for a high-quality final effluent exit. Passing the wastewater through this type of membranes ensures an efficient elimination of suspended contaminants, but it is generally not able to remove Pharmaceuticals pollutants. The majority of pharmaceuticals were not rejected when passing through an UF system [31]. Although the technical feasibility of membranes has been proven, high investment and operational costs keep their application very limited [33]. Currently membrane filtration, nanofiltration (NF) and reverse osmosis (RO) are almost exclusively applied in drinking water treatment facilities, whereas their application during wastewater treatment is scarce. In addition, the combination of MF or UF with RO as secondary effluent post-treatment seems to be efficient for the removal of pharmaceuticals [34]. In Singapore and few cities in Australia a combination of MF or UF with RO is to perform the biological treatment in a Membrane bioreactor (MBR) followed by a RO system at full scale, which has been operated at pilot scale first by Snyder et al. in 2007 [35]. Some studies report that membrane bioreactors do a better job of removing medicines from water since the plant cannot determine which pharmaceuticals it removes [30].

Ozonation and advanced oxidation process (AOP)

During ozonation in wastewater, micropollutants can be directly oxidized by O_3 or by the hydroxyl radicals (HO•) which are formed during ozone decay. Those pharmaceutical compounds that react rapidly with O_3 will be oxidized by direct reactions, whereas the rest will be oxidized by the HO• formed. When there are ozone resistant contaminants, ozone is transformed to HO radicals and the ozonation modifies to advanced oxidation process (AOP). The purpose of AOP design is to use HO• as a strong oxidant. The common way to transform a conventional ozonation process into an AOP is to add H_2O_2 or UV irradiation [9]. The advantage of ozonation as a post-treatment is to disinfect the final effluent before discharge. However in most treatment plants, where disinfection of final effluent is required, it is preferable to apply chlorination or UV irradiation instead as they demand lower oxidation capacities. AOPs are very effective in the oxidation of numerous organic and inorganic compounds. However, these procedures are occasionally not capable of degrading pollutants to the levels required and there has been little investigation of its use against pharmaceuticals. Only a limited number of STPs apply ozonation for post-treatment to their secondary effluents [36]. Advanced oxidation is not in widespread use due to inadequate knowledge of its performance and the necessary safety conditions [32]. The main disadvantage of ozonation is related to the by-products, which can have toxic properties [37].

Electro-oxidation

The most common electrochemical technique for wastewater remediation is the electrochemical oxidation which also named anodic oxidation (AO) when no chloride solutions are treated [11]. This procedure provides the oxidation of pollutants in an electrolytic cell by first transferring electron to the anode and then indirect oxidation with radicals such as OH or active oxygen at the anode. In wastewater treatment, high cell voltages are required to obtain the oxidation of pollutants and water maintaining the anode activity at the same time. The main disadvantage of electro chemical oxidation is its high operating costs. Moreover applying this technology is efficient when the effluent is conducting and not many waste streams have sufficient conductance. Furthermore electrode fouling could occur as a result of deposition of material on the electrode surface [38].

Adsorption

Adsorption is a surface phenomenon defined as the increase in concentration of a particular component at the surface or interface between two phases. Pollutant that adheres to the solid surface is adsorbate and the solid surface is known as adsorbent. Adsorption is affected by the nature of the adsorbate and adsorbent, pH, concentration of pollutants, contact time, particle size of the adsorbent, temperature, the presence of other pollutants and experimental conditions [39].

Adsorption considered as an efficient treatment for the removal of most emerging compounds from water. The possibility to reach high removal percentage of the contaminant is more than other water treatment techniques [13]. Meanwhile being a physical process, does not imply by-products formation, which could be more toxic than parent compounds. This means adsorption could be a friendly method through environment. The most common adsorbents in wastewater treatment are activated carbon, clays, zeolite, agricultural wastes considered as low cost adsorbents and industrial wastes like sludge, fly ash and red mud.

Activated carbon is the most popular and widely used adsorbent in wastewater treatment throughout the world. Powdered and granular activated carbon (PAC and GAC) have been used for sorption of organic micropollutants such as pesticides or taste and odor compounds [40]. The main advantage of activated carbon processes is that no by-products are generated. The use of activated carbon to adsorb aromatic contaminants including few pharmaceuticals has been studied so far. The main advantage of using activated carbon to remove pharmaceuticals is that it does not generate toxic or pharmacologically active products [12]. Meanwhile activated carbons generally demonstrate a high capacity to adsorb pharmaceuticals which depend on the activated carbon type, pharmaceutical composition, and solution chemistry [41].

Despite the effectiveness of activated carbon, there are major drawbacks for its application. Since the activation stage requires very high temperature, a lot of energy is required to provide sufficient heat for such high temperature. As a result, the production cost will be very high due to high utility cost. Thus, the price of commercial activated carbon is also high [42]. Furthermore the production of activated carbon is also non-environmental friendly, as activated carbon dust might be emitted to the environment during production and the chemicals used will contaminate the water source and affect the aqua ecosystem [43]. Therefore, a great attention is given to more environmental friendly and low cost adsorbent as a potential sorbent to replace activated carbon [44].

Adsorption by chitosan

Adsorption process in water treatment is capable of removing both inorganic and organic pollutants. Therefore it is often considered the most appropriate method in removing pollutants from water [45]. Recently more attention is given to utilizing natural polymers and their derivatives to remove pollutants from water. Natural polymers are abundant, cheap, mostly nontoxic, and biodegradable. Chitosan is one of these materials which is produced by the N-deacetylation of chitin. It is one of the most naturally biopolymers after cellulose which is cationic and hydrophilic. Chitosan and its derivatives have been potent biosorbents for removing metal ions from wastewater [46].

Chitosan is produced commercially by deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans (such as crabs and shrimp) and cell walls of fungi. The chemical structure of Chitosan is demonstrated in Figure 2 [47]. Chitosan as it is shown is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit) [48].

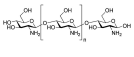

Figure 2: Chitosan chemical composition [47].

The mechanism of metal adsorption on chitin and chitosan-derivatives is mostly formation of ion pairs in acidic media (ion exchange) [49]. Chitosan has been prepared in form of membranes, microspheres, gel beads and films and utilized to remove different pollutants from wastewater. Ionic charge of the adsorbent, solution pH and the chemistry of the pollutant are the main parameters impact in

chitosan reaction [50,51]. Chitin and chitosan derivatives have gained wide attention as effective biosorbents due to low cost and high contents of amino and hydroxyl functional groups which show significant adsorption potential for the removal of various aquatic pollutants. Results have proven that chitin and chitosan-derivatives are capable of removing metal cations and metal anions, dyes, phenol and substituted phenols, and different anions [52].

The removal of metal anions by chitosan and chitosan-derivatives has been examined by many researchers. Chitosan was found very efficient for the removal and recovery of precious metals such as gold Au(III). Moreover chitosan beads were used to remove As(III) and As(V) from water in both batch and continuous operations while the mechanism of metal adsorption on chitosan has been mainly electrostatic interactions in acidic media (ion exchange) [53].

Chitosan as pharmaceutical carrier in drug delivery

Chitosan is biodegradable and metabolized by certain enzymes in human being. Due to these properties, chitosan and its derivatives have been used for drug delivery in the recent years [27,54]. Moreover chitosan is capable of interacting with negatively charged polymers, macromolecules and anions in aqueous environments since it is hydrophilic and positively charged. These properties make chitosan a proper option to be a drug carrier [27]. In medical and pharmaceutical applications, chitosan is used as a component in hydrogels [55].

In some drug delivery application of chitosan, examination of the electron micrographs proved that the drug and the chitosan as carrier were mixed uniformly in physical mixture and the drug was homogenously distributed in chitosan. This shows that chitosan which has been successfully applied as a carrier for pharmaceutical compounds in drug delivery, is also capable of adsorbing drugs from other aqueous environments. As an example chitosan is reported to be Acetaminophen carrier in drug delivery [25,26].

Figure 3 shows possible interaction between carbonyl group of Acetaminophen and amide group of Chitosan which shaped the hydrogen bond and in drug delivery formed the solid dispersion. Acetaminophen formed solid dispersions with chitosan when the mixtures of the drug and the carrier were spray dried. Acetaminophen became amorphous as the result of the formation of solid dispersions. The carbonyl group of Act and the amino group of Chitosan carried out the hydrogen bond, and formed the solid dispersion. The interaction between Acetaminophen and chitosan was also studied with FT-IR analysis which showed the hydrogen bond joined them together [25]. Based on the reports, alkaline conditions (pH=10) were optimum for the adsorption process of chitosan, while acidic conditions (pH=2) were suitable for desorption. The functional parameters in adsorption are initial pharmaceutical concentration, pH, temperature, contact time and regeneration (desorption pH, cycles reuse) which should be carefully investigated [56].

In spite of the chitosan advantages there are some limiting factors in its utilization such as poor solubility, low surface area, and porosity. Its solubility is limited at a pH higher than 6.5 where chitosan starts to lose its cationic nature. Chitosan membrane is swollen in water while the amino groups may be protonated and leave the hydroxide ions free in water [57]. Chitosan can be modified by grafting or cross-linking or other methods based on the application. Chitosan-based adsorbents are micron-sized and need large internal porosities to provide adequate surface area for adsorption. This results in limiting the particles diffusion and decrease in adsorption rate and capacity.

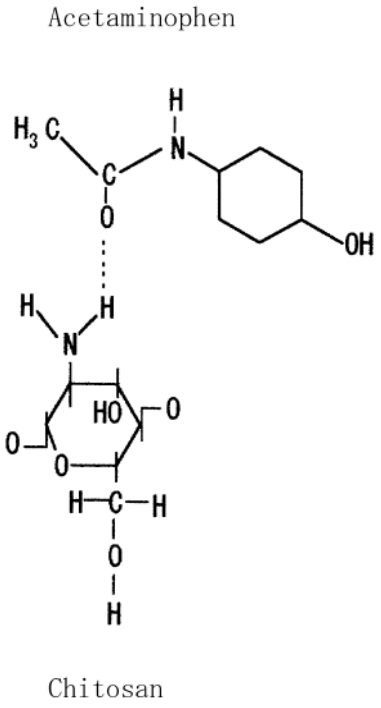

Figure 3: Interaction between carbonyl group of Acetaminophen and amide group of Chitosan [25].

Modification of chitosan adsorbent

In adsorption, chitosan need to be grafted or cross-linked with compounds that increase its interaction with pharmaceuticals and immobilize chitosan at the same time. Magnetic compounds has been an option as magnetic adsorbents can be manipulated by an external magnetic field and hence facilitate phase separation [58]. In fact, the application of magnetic adsorbent technology to solve environmental problems has received considerable attention in recent years and it has been proven that Chitosan could be immobilized on the surface of Fe_3O_4 particles. Due to the presence of magnetic particles with an external magnetic field, the adsorbent can be separated from the aqueous solution [59].

Another suitable compound is cyclodextrin. Recently, immobilization of cyclodextrin (CD) in cross-linked chitosan has received considerable attention. In few studies grafted chitosan with ß-cyclodextrin was used in adsorption from aqueous solutions. Cyclodextrin has the capability of incorporation with different compounds like aromatic compounds with a series of weak intermolecular forces. The hydrophobicity of cyclodextrin can raise the adsorption potential of chitosan [28]. The chitosan grafted with CD derivatives can configure complexes with a variety of other fitting compounds, to develop sorbent materials. The chemical structure of β-cyclodextrin could be seen in Figure 4 [60].

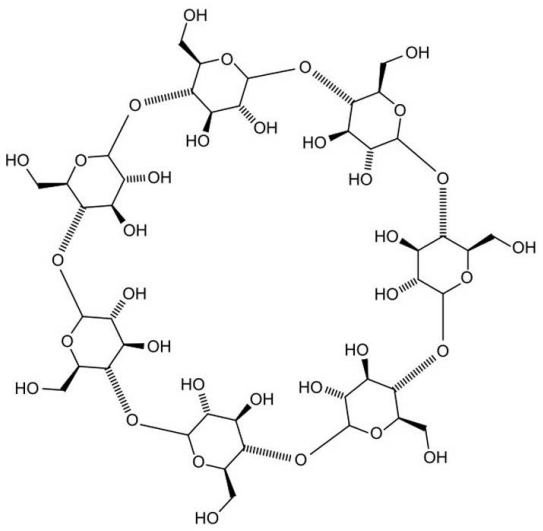

Figure 4: Chemical structure of β-Cyclodextrin [60].

Cross-linked chitosan in pharmaceutical application

The other group of chitosan modifiers could be cross-linkers. Cross-linkers are molecules with at least two reactive functional groups that form bridges between polymeric chains. Depending on the nature of the cross-linker, the dominant interactions forming are ionic bonds or covalent. Some of the covalent cross-linkers are recognized as toxic compounds, or their fate in the human body is unspecified such as gulutaraldehyde ($C_5H_8O_2$). Cross-linkers are molecules of MW much smaller than the MW of the chains between two consecutive cross-links. The properties of cross-linked hydrogels depend mainly on their cross-linking density. To date, the most common cross-linkers used with chitosan are dialdehydes such as glyoxal and in particular glutaraldehyde. Their reaction with chitosan is well-documented.

For chitosan, ionically cross-linked hydrogels are more feasible in drug delivery systems compared to covalently cross-linked ones. Ionically cross-linkers can be used for controlled release both in acidic and basic media. Adsorption performance in chitosan can be enhanced by cross-linking with glutaraldehyde, tripolyphosphate salts ($Na_5P_3O_{10}$), epichlorohydrin (C_3H_5ClO), ethylene glycol ($C_2H_6O_2$) or diglycidyl ether ($C_6H_{10}O_3$). Notably, these cross-linkers stabilize chitosan in acid solutions and improve its mechanical properties [61]. However, their main disadvantages are the possible lack of mechanical stability and the risk of dissolution of the system, due to a highly pH-sensitive swelling [55,62]. On the contrary, networks containing covalently cross-linked chitosan are considered as porous with higher mechanical stability, this pores could be filled with free water or bound water to hydrophilic groups.

If the pH increases, the protonation of chitosan decreases and induces a decrease of the cross-linking density, allowing swelling. If the pH becomes too high, amino groups of chitosan are neutralised and ionic cross-linking is inhibited. When the cross-linking density becomes too small, interactions are no longer strong enough to avoid dissolution and the ionic cross-linker is then released. Tripolyphosphate, sulfate (SO_4^{-2}), citrate ($C_6H_5O_7^{3-}$) can be used as ionic cross-linkers for chitosan in form of beads as they do not need other additional polymer. Among covalent cross-linkers, Genipin ($C_{11}H_{14}O_5$) is not toxic and degradable which is used as chitosan cross-linker in blood substitutes and wound dressing. Genipin cross-linked with chitosan form a porous compound which is mechanically stable in different pH.

Another technique to improve chitosan sorption capacity is to protect the amino group which causes protonation. This method has been used for sorption of some heavy metals [63]. Solfunate derivatives such as benzyl disulfonate ($C_6H_4(SO_3K)_2$ could be an example. Benzene sulfonic groups are classified among strong cation exchangers and showed good performances in acidic media.

Conclusion

There have been studies on modification of chitosan using different techniques. Nevertheless the selectivity and performance of it on pharmaceuticals has not been discovered much. Furthermore, since chitosan is a carrier for drugs, it is capable of releasing the adsorbed drug as well which means the adsorbed pharmaceuticals from wastewater could be separated from chitosan and regenerated in a process. However, Chitosan by itself might not be suitable for adsorption of certain pharmaceuticals from water. Therefore, there might be a need to modify chitosan with particular compounds to improve chitosan interaction with pharmaceuticals and subsequently the adsorption capacity.

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