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Polymer nanocomposites for tissue engineering, antimicrobials and drug delivery

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ABSTRACT

Beside common reinforced polymers like plastics, elastomers and polyblends, polymer nanocomposites represent a new very useful alternative. Polymer nanocomposites based on a macromolecular matrix and nanofillers (minerals or organic) have attracted great interrest in the last decades due to their outstanding properties. They find applications in various engineering areas like transportation, aerospace, construction, barrier materials, household items, medical field, etc. In the case of medical field polymer nanocomposites are studied in view of applications in engineering tissues for bones and skin, antimicrobials, drug release products, wound healing, etc.

Keywords: *Polymer nanocomposites, tissue engineering bone and skin, antimicrobial, drug delivery.*

1. INTRODUCTION

Polymer nanocomposites is a new class of composite materials where a filler with at least one nano size dimension is introduced at a very small amount or volume into a macromolecular matrix. Due to their superior properties it is a growing interest for their development; the polymer nanocomposites find a wide range of applications in engineering areas like aerospace, house hold items, etc. One such use of these hybrid materials is gaining importance in medicine and biomedical commodities like damaged or lost organs and tissues. Several recent reviews cover this important and actual subject [1-5].

The aim of using polymer nanocomposites in nanomedicine is to provide new and effective solutions in engineering of more biocompatible and bioactive scaffolds for tissue regeneration, antimicrobial products, delivery of therapeutic agents for cancer and other diseases treatments, in cardiovascular , neurogenerative diseases, etc. The applications of polymer nanocomposites in medicine involve diagnostic and therapeutic processes for different diseases affecting human organs.

This paper presents interesting recent contributions regarding the use of polymer nanocomposites for tissue engineering, antimicrobial products and drug carriers.

2. TISSUE ENGINEERING

Tissue engineering is a vital field which is using polymer nanocomposites for recovery of damaged or lost organs. Use of polymer nanocomposites in such application has been found due to pore shape, pore wall morphology, and interconnectivity between pores of these new materials. Such characteristics are very important for growth, cell seeding, migration, mass transportation and tissue formation.

Many synthetic polymers like poly(ε-caprolactone) (PCL), polyaniline (PANI), poly(methyl methacrylate) (PMMA), etc, and biopolymers like chitosan (CS), collagen (CL), gelatine (GEL), chitin (CH), polysaharides. alginates, etc. are used as matrices in polymer nanocomposites for tissue engineering and other medical applications.

PCL/diopside nanopowder scaffold could potentially be used to develop clinically relevant constructs for bone tissue engineering .In vivo studies have to be done to evaluate the role of the fibrous scaffolds on the new bone growth and regeneration [6]. PCL composite scaffolds obtained by electrospinning have been attracting a lot of attention because of their application in cardiac tissue engineering. The presence of 0.5% carbon nanotubes (CNTs) within the PCL nanofibres are able to improve the fatigue limit of the electrospun composites compared to common PCL scaffolds. Polydopamine coating also opened a new way to incorporate functional groups that can serve as the starting points for covalent modification with bioactive molecules [7].

Electrospinning as an electrofluidodynamic process used in many studies offers the option to form high performance bioactive systems based on polymer yarns of nanofibres or coatings of nanobeads with high surface-to-volume ratios [3]. The interconnected flexible nanofibrous structures are suitable for tissue engineering, drug delivery and wound healing. For instance PANI/PMMA electrospun fibers open the way to the use of fibrous mats as scaffolds for neuronal cells culturing [8].

Poly(lactic acid) (PLA) composite nanofibrous scaffolds containing different herbal extracts like

Equisetum arvense and nanohydroxyapatite (nHA) were developed. The findings indicated that the herbal extract has a great potential for osteogenic differentiation of adipose tissue-derived mesenchymal stem cell and can be recommended as a suitable candidate for bone tissue engineering application [9].

New non-cytotoxic and biodegradable polyurethane (PU) made of linear aliphatic hexametylene diisocyanate and poly(caprolactone diol) were designed and synthesized for tissue engineering applications. Biodegradation experiments showed that the biocomposite scaffolds exhibited progressive mass loss over 5-week period, which varied according to the composition. The loss

in mass was higher when soft segment content in PU was higher [10].

A series of nanofiber mats were produced also by electrospinning of waterborne poly (vinyl alcohol) PVA/PU solution. These mats with interconnected pores could be obtained when the amount of PVA is above 30%. Since the PVA/PU nanofibre mats are non toxic and biocompatible, the researchers consider that they would act as excellent biomaterials for many natural tissues repair [11]. It is also important to underline the fact that PU is known for its high biocompatibility, biostability and excellent blood compatibility. Beside cytocompatibility, as a dressing for skin lesions the scaffolds mast have a low cytotoxicity and adequate cell proliferation.

Poly (propylene carbonate) (PPC)/nHA composites were prepared in view of bone repair and reconstruction. The effects of reinforcement on the morphology, mechanical properties and biological performance of these polymer nanocomposites were investigated. The results demonstrated that the introduction of the nanofiller into PPC matrix provides a practical way to produce biodegradable and cost-competitive nanocomposites mimicking the osteogenic niche for bone augmentation [12].

Hyperbranched epoxy (EP)/clay/nAg nanocomposites are shown to be infection-resistant tough implantable scaffold materials. They inhibite the growth of antibiotic-resistant microbes such as Staphylococcus aureus, Escherichia coli and Candida albicaus which are mostly responsible for surgical infections. These polymer nanocomposites are highly compatible with primary liver and cardiac cell lines of wistar rat. In vivo implantation of these composites fostered wound healing in such rat [13].

Excelent combined mechanical, surface wetting and cytocompatibility properties demonstrate the potential applications of the synthetic core-shell PLA/PVA composite nanofibers in biomedical and tissue regeneration [14].

CS is a deacetylated derivative of CH, which is a naturally occuring polysaccharide found in crustaceans. Using melt-down neutralization technique,CS/nAg scaffolds have been obtained .The slow and sustained release of nAg provides long term biological characteristics and has no toxicity towards keratinocytes which support their future applications as antibacterials. The CS/nAg scaffolds prohibited cell adhesion, while at the same time supported growth of keratinocytes which is an essential characteristic for tissue engineering [15].

A CL/ nHA nanocomposite by an in situ precipitation has been produced . Porous structures were obtained by the freeze-drying technology. Cells proliferation assays confirmed that MG63 cells are able to adhere and to grow on the prepared porous scaffolds. Results suggest that such CL/nHA nanocomposite can be useful for obtaining porous scaffolds for bone tissue engineering [16].

Two bi-layered CL based nanocomposites were made to replicate the superficial and transitional zones of an articular cartilage. Aligned and random CL/PVA nanofibers were electrospun onto a freeze dried CL sponge to make the aligned and random polymer nanocomposite respectively. The research showed that the aligned composite may be more suitable for articular cartilage repair due to the higher tensile strength from aligned nanofibers on the surface that can better resist wear [17].

By the same technique GEL/nHA nanocomposites were prepared. These composites showed entranced elastic modulus value approximate to human bone. Porous GEL/nHA nanocomposites with pore size 50 and 350 μm which were prepared by freezing-drying were believed to be adequate for bone tissue engineering .In vitro MG63 cells culture indicated that these polymer nanocomposites had good cytocompatibility and could promote the proliferetion of cells. The results of this research indicated that GEL/nHA nanocomposites are promising substitutes for bone tissue engineering [18].

Another study found that GEL/CH nanofibrous mats have great potential for application as a scaffold for skin tissue engineering [19].

GEL nanofibers were in situ crosslinked with 1,4 butanediol diglycidyl ether at different concentration and incubation time-points at 37°C. Crosslinked GEL meshes show no toxicity towards fibroblasts, stimulating their adhesion , proliferation and synthesis of new extracellular matrix, thereby indicating the potential of this strategy for skin tissue engineering [20].

Poly (3-hydroxybutilate-co-3-hydroxyvaleriate)/silk fibroin blend nanofibrous scaffolds were produced. At equal amounts of components it possessed enhanced hydrophilicity and partially good biocompatibility, indicating its potential application for skin tissue engineering and wound dressing [21].

β-CH/nanodiopside/nHA composite scaffolds were also produced. The study of cell attachment and mouse preosteoblast cell proved the cytocompatibile nature of the scaffolds with improved cell adhesion. The research illustrated that such nanocomposite could be a candidate for bone tissue engineering application [22].

Freeze-drying technique Carrageenan – hyaluronic acid/nHA/microcrystalline cellulose nanocomposite scaffold with various amount of cellulose (0-60 wt%) were prepared . The study showed its highly porous micro structure, improved mechanical properties, and good in vitro cytocompatibility. Such composite materials may have promising application as bone product in low loading bone tissue engineering applications [23].

3. ANTIMICROBIALS

Microbial contamination is a severe issue in the healthcare field; it is a world health problem. Because of this situation the need for effective treatments and prevention is increasing. Synthetic and biopolymers are investigated as components of antimicrobial nanocomposites and many studies regarding the nanofillers show that among nanometal fillers like Cu, Zn, ZnO, Ti, TiO_2, Mg, Au, the Ag nanoparticles show the highest antimicrobial efficacy.

Eggshell membrane protein – assisted adsorption of nAg is a viable approach to improve the introduction of this nanometal

and thus the antibacterial activity of PCL electrospun fiber mat. The antibacterial rates of these products can be over 99% against both gram-negative Escherichia coli and gram-positive Bacillus subtilis which is an important requirement for applications in the biomedical field. CL can also assist adsorption of nAg on a PCL film mat [24].

The efficacy of gentamicin-loaded PCL/nTiO2 nanocomposite electrospun membranes against a wound isolate of methicillin-resistant Staphylococcus aureus has been evaluated. The study demonstrated that PCL/nTiO2 nanocomposite membranes can synergistically act with glutamicin to inhibit the growth of methicillin-resistant Staphylococcus aureus (25). PCL/nAg/Montmorillonite (MMT) nanocomposites with a strong antibacterial activity were obtained mainly for active packaging use [26, 27].

Post modified poly (acrylonitrile) (PAN) micro/nanofibers was produced by a rapid and green technique of microwave irradiation and electrospinning. The fibers were endowed with antibacterial activity due to Ag ions which were embedded in the polymer by nitrile click chemistry with microwave irradiation; they were then electrospun into neat and smooth microfibers/nanofibers. These fibers exhibited powerful and long lasting antibacterial properties against Staphylococcus aureus [28].

PVA/CS/nAg nanocomposite membranes were synthesized by using γ-radiation. These membranes showed good antimicrobial activity and were found to cause significant reduction in microbial growth .They exhibited also non-thrombogenicity effect and slightly haemolitic potential, suggesting their promising use in biomedical applications [29].

nAg impregnated crosslinked beaded polystyrene (PS)/polyamidoxime interpenetrating networks were also produced . Their size was found to be less than 5 nm. The desinfaction potential was evaluated using different antibacterial experiments. A bactericidal test revealed the promising antibacterial efficiency with complete microbacterial inhibition within 4-6 h. The reusability for industrial applications of the above mentioned beads was also tested [30].

The addition of ethanolic extract of propolis to the poly(lactic acid) PLA/cellulose nanofiber films significantlly increases the antibacterial effect against gram-positive bacteria such as Bacillus anthracis, Staphylococcus aureus and Salmonella euteric. No effect was observed on gram-negative bacteria [31].

Via radical polymerization, polymer nanocomposites were prepared through a blend solution of PLA and poly (N-isopropylacrylamide)-co-acrylamide. Tests were performed to evaluate the drug release and antibacterial activity against Escherichia coli. The results suggested that the obtained nanocomposite hydrogels can be used as a promising candidate for dual functions in biomedical application [32].

PS microsphere was grafted on pure multi walled carbon nanotube (P-MWCNT) and amine multi walled carbon nanotube (A-MWCNT) with nAg decorated on MWCNT. Antibacterial activity of the nanocomposites were investigated against respiratory track demolishing Staplylococcus aureus , Escherichia coli and Pseudomonas aeruginosa. nAg was found responsible to potential death rate of microbes [33].

Poly (acrylic acid) (PAA)/nAg nanocomposites possed antimicrobial activity with long-term use without exposure to infections [34].

Poly (vinyl acetate) (PVAc)/nAg nanocomposites were investigated as antimicrobial agents against pathogenic bacteria, i.e.Staphylococcus aureus and Escherichia coli. These nanocomposites could be used as promising products for enhanced and continuous as antibacterial coating and packaging materials [35].

According to the tests done, some mechanical properties and antibacterial activity of low density polyethylene (LDPE) were significantly increased by adding $nTiO_2$ [36].

Through solvent casting technique micropore composite films of poly(ethylenetherphtalate)(PET) were prepared. The addition of poly (ethylene glycol) (PEG) and nAg particles to PET significantly increases some important physical properties. When 1% nAg were added to PEG/PET (10/90) film, good antibacterial activity was achieved [37].

The experiments carried out to evaluate the antibacterial activity showed that the EP polymer nanocomposites with 3% Cu^2 -MMT exhibited an inhibition action higher than 96% against Escherichia coli and Staphylococcus aureus [38].

Poly (glycidyl methacrylate – co - ethyleneglycol dimethacrylate) nanoporous copolymer with nAg was prepared. Preliminary antimicrobial efficiency measurements using laboratory flow setup indicated potential applicability for waste water treatment [39].

Xanthate madiated block copolymers of butyl acrylate with varying concentration of glycidyl methacrylate by using reversible addition fragmentation chain transfer polymerization was synthesized. The copolymers were modified by introducing imine functionality and dispersed nano ZnO. It was observed that with the increase of these two factors the antimicrobial activity becomes more pronounced in case of bacteria Escherichia coli compared with Bacillus Subtilis [40].

Indole-3-acetic acid -based / nAg nanocomposites were produced by in situ polymerization. The obtained nanocomposites have antibacterial, antifungal, antioxidant properties, are tuned pH-responsive and thermally stable; they can be widely applied in wound healing and burn dressing, treatment of topical fungal infections and in other biomedical applications. They showed excellent antimicrobial activities in opposition to Bacillus.aureus, Staphylococcus aureus and Escherichia coli [41].

Poly (4-vinyl pyridine)/grafted graphene oxide nanocomposite obtained by in situ atom transfer radical polymerization are biocompatible and antimicrobial and can act as a drug delivery vehicle [42].

Polypropylene /$nTiO_2$ (nanotubes) nanocomposite exposed to black light bulb illumination showed a biocidal behavior, reducing 81% a colony of Escherichia coli [43].

Polyamide 6 containing glass microparticles doped with ionic Zn presents better antibacterial action against Salmonella typhimurium and Staphylocopccus aureus than polyamide 6 containing nZnO particles [44].

Polyindole/nTiO2 nanocomposite shows maximum antibiotic activity against Staphylococcus aureus and Bacillus subtilis as compared to Escherichia coli. The polymer nanocomposite was synthesized jn situ polymerization of indole ,

in water, under ultrasonic condition using ammonium persulfate as an oxidant [45].

The antibacterial activity of water dispensible PU nano colloids was studied on Staphilococcus aureus and Eschericia coli. They displayed significanbly higher zone of inhibition in both cases indicating the potential use of these nano colloids on antibacterial coating [46].

Polyacrylamide/saponite/nAg nanocomposite showed strong antibacterial effect [47].

Poly(p-phenylene ethylene) and poly[(2-methacryloyloxy) ethyl trimethylammonium chloride)] graft copolymers were tested against a range of clinically and industrially relevant bacteries and results showed many of these conjugated polyelectrolytes to be active [48].

A biopolymer exopolysaharide was used to produce with Fe_3O_4 magnetic nanoparticles a polymer nanocomposite. It was found that this composite has antimicrobial activity against both Escherichia coli and Staphylococcus aureus [49].

A survey shows that cellulose derivatives such as cellulose acetate appear as basic elements in the production of materials with excellent biodegradability, biocompatibility or antimicrobial activity applicable in food packaging and biomedical areas [50].

Cellulose/nAg aerogel showed strong antibacterial activities for both Escherichia coli and Staphylococcus aureus .It is expected to be used for various biomedical applications, as a green heat-resistant high-performance antibacterial biopolymer nanocomposite [51]. Cassia alata leaf extract infused wet cellulose films were dipped in different concentrated aqueous $CuSO_4$ solutions and allowed for in situ generation of Cu nanoparticles inside the matrix. The conclusion of the research is that cellulose/nCu polymer nanocomposite films are suitable for antibacterial wrapping and medical purposes [52].

A research presents a new, simple and “green” technique for producing nAg in aqueous medium using natural and biodegradable polymers like alginate and GEL The use of such biopolymers opens up possibilities of applying the nano formulations in wound dressing, active packaging and several other biomedical applications [53].

3-amino-2 phenyl-4(3H)-quinazolinone was prepared and loaded on polypirrole/ CH core-shell nanoparticles. The synthesized polymer nanocomposite exhibits antibacterial activity against gram-negative as well as gram-positive bacteria [54].

Novel cryogel/nAg composites base on CH and PEG were synthesized by in situ chemical reduction. The inhibition zone test and antibacterial ratio experiment suggested that good antibacterial ability against Escherichia coli could be achieved with a high inhibition ratio of 95% by introducing nAg into cryogel matrix, and meanwhile the biomimetic composition, the excellent swelling ability of the cryogel made it recommended for use in biomedical field as antibacterial product [55].

Chitosan/nAu and zein/nAu blank films have been also evaluated by inhibition zone test and spectrophometric growth inhibition for antibacterial activity [56].

Pectin/germanium oxide biopolymer nanocomposite is also a promising candidate for antibacterial activity [57].

Glyoxal-crosslinked Iota carrageenan/PVA film loaded with nAg showed fair antimicrobial activity against Escherichia coli [58].

4. DRUG RELEASE

Studies show that polymer nanocomposites or even nanopolymers can release the necessary drugs at the target site upon triggering by a stimulus.

A copolymer of functionalized MCM-41 (a mesoporous product from the families of silicates and alumosilicates) and methacrylic acid was synthesized via in situ copolymerization.

To produce nanocapsule MCM-41 was removed by treating the copolymer with hydrofluoric acid. The drug Naproxen was entraped into these drug carriers and the in vitro release profiles were established separately in both enzyme -free simulated gastric (SGF, pH 1) and simulated colonic fluids (SCF pH 7,4). The release rates of SCF were higher than that of SGF [59].

A PS latex templating technique for obtaining core-shell silica nanoparticles with porous shell was developed via biomineralization in the presence of poly [2-(methacryloxy) ethyl] trimethylammonium chloride modified latex. The results in vitro aspirin release study demonstrated that the $HSiO_2$ with high loading capacity had a sustained release characteristic [60].

Another study used 3 methyl-1-[2(2-methyl-acryloxy)-ethyl]-imidazolium chloride, an ionic liquid monomer intercalated into MMT layers and subsequently copolymerized with methacrylic acid. Naproxen was entrapped in these pH-sensitive positively charged polymer nanocomposite carriers and the in vitro release profiles were established separately in both enzyme free simulated gastric (SGF pH 1) and intestinal (SIF pH 7,4) respectively. It was established that the drug release percentages in SIF were higher; hence the prepared nanocomposite could be considered as a suitable carrier for colon specific drug delivery [61].

For the release control of 5-Fluorouracil, the objective of a research was to propose dual responsive beads based on sodium alginate, methylcellulose and magnetic iron oxide nanoparticles. The characterization results showed that the drug molecules and the iron oxide were well dispersed in the polymer matrix and the drug release was confirmed [62].

The CS/β-cyclodextrin /magnetic nanoparticles demonstrated the magnetic tumor targeting and that the nanocomposite may have a potential as a photodegradable and hydrophobic drug delivery carrier [63].

Curcumin obtained from the spice turmeric is knowen for its anticancer activity; its use as a viable drug is impeded by its low solubility in water. Amphiphilic poly (2-alkyl-2-oxazoline) blockcopolymers able of self assembling in aqueous media were synthesized and the feasibility of employing these polymer nanoparticles to encapsulate curcumin was demonstrated [64].

Polylisine coated tamoxifen loaded poly (lactic-co-glycolic acid) nanoparticles were prepared; non-covalently surface functionalization have been done in order to improve nanoparticle-cell interaction and hence tamoxifen therapeutic effect. The nanoparticles were characterized in vitro performance against human brest adenocarcinoma cells. The successful incorporation of tamoxifen was evidenced by a high loading efficiency (86%) [65].

It was confirmed that the incorporation of 5-amino salicilic acid-loaded hallosite nanotubes within the thermoplastic starch makes it possible to delay a drug release. The swelling behavior of the nanocomposites does not depend on pH and thus starch is able of transporting drugs adapted to the acidic environment of the stomach to the colon [66].

Self-assembled nanoparticles obtained from CH/oleic acid have shown antibacterial activity and potential application as a carrier for hydrophobic anti cancer drugs [67].

The reversibility behavior at pH of 1.0 and 9.0 indicated great potential of a hidrogel made by grafting the binary mixture of methacrylic acid and sodium-2-acrylamido-2-2-methyl-1-propane sulfate onto sodium alginate with NN'-methylenebisacrylamide and amonium persulfate (crosslinker and initiator) as a candidate system for controlled drug delivery [68].

A study reports development of carboximethylcellulose / PVA / graphene polymer nanocomposite for the control of drug release applications [69].

Fatty acid-conjugated PEG-block-PEL nanoparticles hold considerable promise in drug delivery to the brain and their potential applications for disorders of the central nervous system should be explored [70].

Copoly (2-acrylamide-2-methylpropane sulfonic acid /acrylamide) nanohydrogels can serve as a promising product for the sustained release of 5-fluorouracil in stomach and colon [71].

Its biocompatibility and non-toxicity beside other characteristics make PVA a good choice to be used for drug delivery. Vitro tests showed that the core/shell structure of PVA/sodium alginate nanofibers could be regarded as a suitable carrier for the controlled release delivery of dexpanthenol [72].

Beside polymer nanocomposites,polymer nanoparticles also play an important role in delivering chemotherapeutic agents in a controlled manner; they gained a growing interest recently as carriers for anticancer drugs. For instance, the antiproliferative effect of doxorubicin slowly released from nanodegradable starch/cellulose acetate-co-acrylate illustrated growth inhibition potency toward human colon and liver cancer cell lines LoVo and HEPG2 [73].

PU bearing active functional groups have been exploited to prepare surface functionalized nanoparticles for active targeting cancer cells. Herceptin, a monoclonal antibody, has been coupled to the surface of nanoparticles and its activity towards target cells has been preserved [74].

A recent review is focused on the chemical design and synthesis of polymer-based drug delivery system (amphiphilic block copolymers including polyether-polyester and polyether-polyanhydride) in particular with stimuli-responsive nanoplatforms for cancer treatment [75].

Resveratrol exhibits many biological properties that can influence bone osteogenesis. Uniform defect free electrospun nanofibers of PC and PLA loading resveratrol were obtained and characterized. In vitro assay was demonstrated that the two membranes were able to release drug in a tunable and sustained manner but with different kinetic [76].

5. REMARKS

Biopolymers and synthetic polymers could be used for obtaining new composite materials.

Beside engineering areas like automative, aerospace, barrier materials, food packaging, construction, environment, etc, polymer nanocomposites are intensively studied for applications in biomedical fields for bone and skin tissue engineering, antimicrobials, drug release, biomedicine, pharmaceutics, bioenergie, health care applications, wound healing, medical equipments.

This review is presenting the contribution of the new group of polymer composites in a few medical areas like tissue engineering, antimicrobials and drug release.

The use of polymer nanocomposites in medicine contributes to saving lives and improving the life of sick people.

Nanopolymers are now being studied for possible application in some medical areas.

6. ABBREVIATIONS

CH - Chitin
CL - Collagen
CNT - Carbon nano tube
CS - Chitosan
EP - Epoxy polymer
GEL - Gellatine
HEPG2 - liver hepatocellular carcinoma cell
LDPE - Low density polyethylene
LoVo - epithelial colon cell
MCM-41 - A mesoporous product from the families of silicates and alumosilicates
MG63 - Cell line human bone.
MMT - Montmorillonite.
nHA - Nano hydroxyapatite
Nmmt - Nano montmorillonite
PAA - poly(lactic acid)
PAN - Poly(acrylo nitrile)
PANI - Polyaniline
PEG - Poly(ethylene glycole)
PET - Poly(ethylenetherephtalate)
PLA - Poly(lactic acid)
PMMA - Poly(methylmethacrylate)
PPC - Poly(propylene carbonate)
PS - Polystyrene
PU - Polyurethane
PVA - Poly(vynil alcohol)
PVAC - Poly(vynil acetate)
SGF - Free simulated gastric enzime
SIF - Free simulated intestinal enzime

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