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Nanogel As A Smart Vehicle For Local Drug Delivery In Dentistry

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ABSTRACT

The nanoparticulate systems are materials having less than 100 nm at least in one dimension. Various nanoparticulate drug delivery systems include biodegradable polymeric nanoparticles, polymeric micelles, solid nanoparticles, lipid-based nanoparticles, nano liposomes, nano hydrogel, magnetic nanoparticles, quantum dots etc. As a family of nanoscale particulate materials, hydrogel nanoparticles (recently referred to as nanogels) have been the points of convergence of considerable amount of efforts devoted to the study of these systems dealing with drug delivery approaches. Interestingly, hydrogel nanoparticulate materials would demonstrate the features and characteristics hydrogels and nanoparticles separately posses, at the same time. Thus, there are many advantages of the nanoparticles including hydrophilicity, flexibility, versatility, high water absorptivity, and biocompatibility. The specific properties which help use of nanogel in medicine, especially dentistry, are the long life span of the drug and the possibility of it being directed to the desired area. Owing to the fact that the concept of nanogels in dentistry is in its infancy, the need arises to disseminate the available information so as to spurt activity in this important area. Here we review the properties, advantages, disadvantages, classification and application of nanogel in dentistry and specifically in periodontics.

Keywords: Hydrogel, Nanogels, Dentistry.

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INTRODUCTION

Nanotechnology is increasingly considered to be the technology of the future. With nanotechnology, researchers are acquiring abilities to understand and manipulate materials at the scale of atoms and molecules, having the following key properties:

Nanoparticles have at least one dimension of ~1–100 nm.

They are designed through methodologies that exhibit fundamental control over the physical and chemical properties of molecular-scale structures.

They can be combined to form larger structures.[1]

"There's plenty of room at the bottom" is the title of a lecture in 1959 by the Nobel Laureate Richard Feynman that introduced the concept of nanotechnology as an important field for future scientific researches.[2] Nanotechnology research can be developed to advances in communications, engineering, chemistry, physics, robotics, biology, and medicine. Pharmaceutical nanotechnology focuses on formulating therapeutically active agents in biocompatible nano forms such as nano particles, nano capsules, micellar systems, and conjugates.[3] A wide spectrum of nanoparticulate systems has been attempted, such as biodegradable polymeric nanoparticles, polymeric micelles, nanoparticles, which are solid or lipid-based, organic or inorganic, dendrimers, magnetic nanoparticles, ferro fluids, and quantum dots, to name a few.[4] As a family of nanoscale particulate materials, hydrogel nanoparticles (NPs) (currently referred to as nanogels), synergistically infusing the gel character at a nano level, have received much attention in recent times. Nanogels are typical formulations mainly of the size range of 1-100 nm (Figure 1), by varying solvent quality and branching the volume fraction can be altered variably to maintain a three dimensional structure. The significance of nano-sized microgel and hydrogel has arisen due to specific delivery system anticipation. Wide variety of polymer systems and the easy alteration of their physico-chemical characteristics have given advantage for versatile form of nanogel formulations.[4,5] Hence, the aim of the article is to review on the properties, advantages, disadvantages and applications of nanogels in dentistry especially in periodontics.

Properties of Nanogels

The specific properties of nanogel[6] are:

1. Biocompatibility and degradability.
2. Swelling property in aqueous media.
3. Higher drug loading capacity.

4. Particle size.
5. Solubility.
6. Electromobility.
7. Colloidal stability.
8. Non-immunologic response.
9. Others.

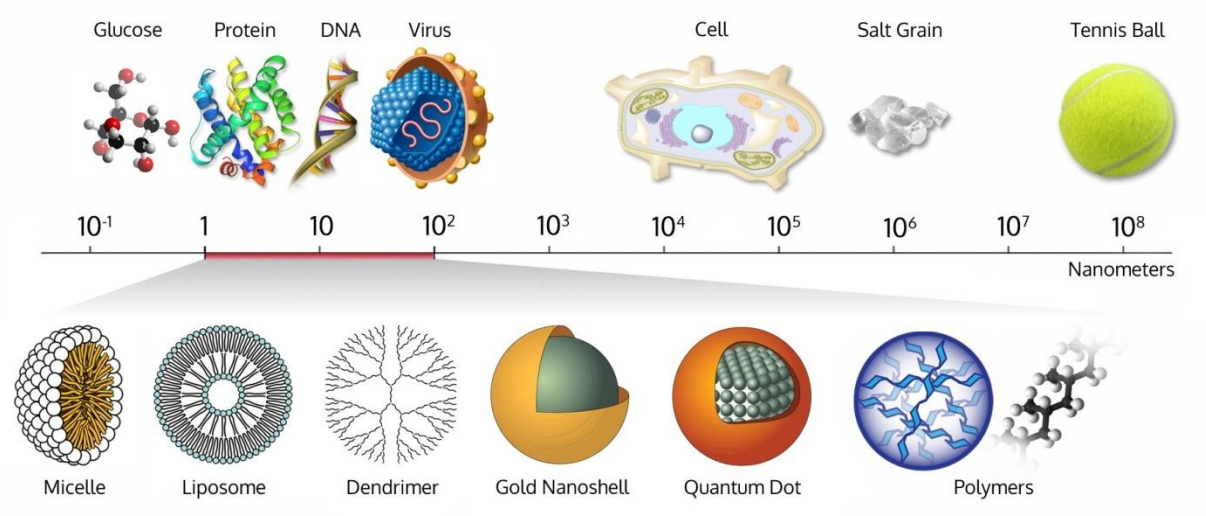

Figure 1: Schematic representation of the size of objects from the nano to the macrocosm world. In this article we are concerned with particles in the range of 1-100 nm shown in the lower panel.

Mechanism of Drug Release from Nanogels

The drug can be released from the nanogels due to:

1. Diffusion.[5,7]
2. Nanogel degradation.[8]
3. Displacement by ions present in the environment.[9]
4. Photochemical internalization and photoisomerisation.[6]

Classification of nanogels.

Nanogels can be classified into two ways.[6]

Based on their responsive behaviour,

stimuli-responsive

stimuli-non-responsive.

Based on the type of linkages present in the network chains of gel structure, they are subdivided into two main categories:

Physical cross-linked gels.

Chemically cross-linked gels.

Advantages and disadvantages of nanogels.

The advantages of nanogel drug delivery system are: [6,10]

1. Highly dispersible in aqueous medium
2. Uniform distribution of the active agent over an extended period of time
3. Controlled release of the drug
4. Reduces frequency of administration
5. Increased stability
6. Penetrate regions inaccessible to other delivery systems

Just as other drug delivery system nanogel systems have certain disadvantages such as 1. Expensive technique

Surfactant or monomer traces may remain and lead to toxicity.

Despite these noted disadvantages the overwhelming advantages as noted above have made the nanogel systems to emerge as the preferred vehicle of local drug delivery.

Application of Nanogels

Nanogels have been transforming the field of curative medicines. In the short duration since the appearance of the concept, these non-conventional drug delivery systems have served as potential candidates for wide spectrum of applications (Figure 2), a representative list of which is given below.

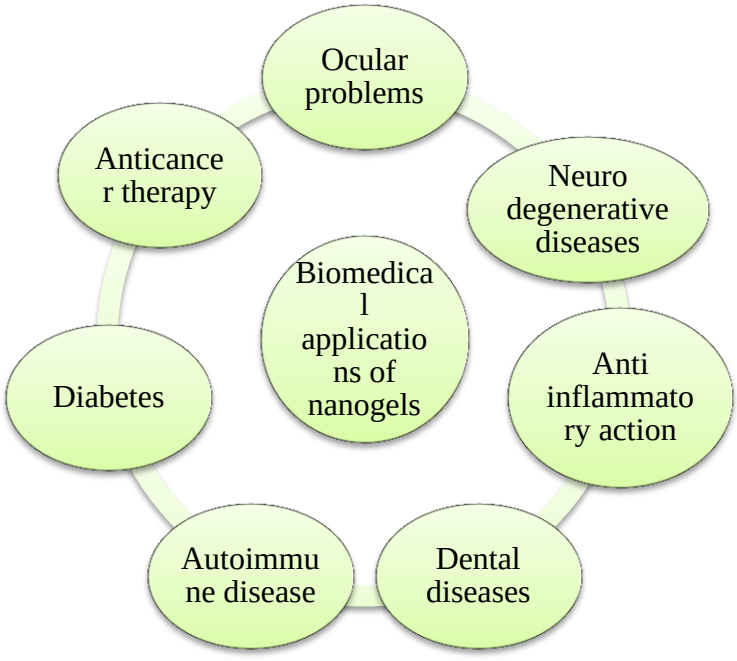

Figure 2: Application of nanogels

1. Anticancer therapy[11]

Many polymeric nanogels have been employed for cancer therapy. Incorporating chemotherapeutic drugs into the nanogel not only increases the bioavailability but also enhanced permeability and retention. One of the polymeric nanogels for use in patients with breast cancer, which has received FDA approval also, is Genexol-PM.

2. Autoimmune disease[12]

A study conducted in 2013 designed and tested a novel nanogel drug delivery vehicle for the immunosuppressant mycophenolic acid (MPA). The results of this study concluded that there is a better efficacy of nanogel based local drug delivery for lupus erythematosus as it targets antigen-presenting cells.

3. Ocular problems[13]

An in vitro release study conducted in 2013 revealed a relatively long sustained release of pilocarpine from the prepared polyvinylpyrrolidone-poly(acrylic acid) nanogel particles if compared with pilocarpine in solution.

4. Diabetics[14]

In vivo experiments conducted in diabetic rats in 2012 revealed that insulin-loaded nanogels decreased the blood glucose levels by 51% from the baseline level for almost 2 hours. Significantly, when compared with free insulin the insulin-loaded nanogels could keep blood glucose levels stable and avoided blood sugar variations.

5. Neurodegenerative diseases[15]

For treatment of neurodegenerative disorders systemic delivery of oligonucleotides (ODN) to the central nervous system is needed. Macromolecules injected in blood are poorly transported across the blood-brain barrier (BBB) and rapidly cleared from circulation. An in vivo study conducted in 2004 using mouse model for bio distribution showed that 1 hour after intravenous injection of nanogel and phosphorothioate ODN increases accumulation in the brain by over 15 fold while in liver and spleen decreases by 2-fold compared to the free ODN. Overall, this study suggests that nanogel is a promising system for delivery of ODN to the brain.

6. In arresting bleeding[16]

A nanogel composed of a biodegradable gel with self assembled protein molecules has been used to stop bleeding.

7. Anti-inflammatory action[17]

In a specific study Poly-(lactide-co-glycolic acid) and chitosan were used to prepare bilayered nanoparticles and the surface was modified with oleic acid. Hydroxypropyl methyl cellulose

(HPMC) and Carbopol with the desired viscosity were utilized to prepare the nanogels. The result of this study showed that nanogel increases potential for the percutaneous delivery of spantide II and ketoprofen to the deeper skin layers for treatment of various skin inflammatory disorders.

Application of Nanogel in Dentistry

The unprecedented growth of nanosciences in every walk of life has created lots of optimism in nano applications for medicine and the field of dentistry is not lagging behind.

Dental Diseases

Dental diseases are a major health problem in all parts of the world, common in all age groups, races and genders. The percentage of dental diseases has grown to a large extent in recent years. Around 70% of dental diseases population suffers from dental problems. The human population is affected by major of oral diseases like periodontal infections, dental caries.[18,19] According to estimates by Government of India-World Health Organization collaborative programme, more than 90% of adults are having periodontal diseases. Periodontal disease is a collective term that includes several pathological conditions characterized by degeneration and inflammation of the tissues surrounding and supporting of the teeth. The relationship between the subgingival plaque and the development of periodontal disease is well established. There are various stages of periodontal disease such as: Gingivitis, Periodontitis. Gingivitis is the inflammation of the gum tissue. It is a non-destructive periodontal disease. It is a reversible condition with good oral hygiene. However in the absence of treatment gingivitis can progress to periodontitis. The signs of periodontitis are inflammation of the gingiva, bleeding, alveolar bone resorption, formation of periodontal pocket[20-22]. Apart from the conventional methodologies known for the treatment of dental diseases nanogel drug delivery system are being considered as potential candidates for effective treatment.

Some of the areas in dentistry where nanogel is being explored include:

1. For local anaesthesia
2. For restorations
3. As a tooth paste
4. As local drug delivery in periodontitis

For local anaesthesia

Pain control is one of the top priorities in therapeutics in dental treatment. Improvement of regional administration of local anaesthetics could be achieved by incorporating them into drug delivery systems. Nanogels are probably one of the best candidates due to longer blood circulation time. In a study conducted to develop and evaluate thermo-reversible *in situ* gelling

drug delivery system for periodontal anaesthesia.[23] It was found that Pluronic gel proved to be a promising carrier for effective release of mepivacaine hydrochloride throughout the dental procedure.

Nanogel-Modified Resins for Restorations

Due to the various disadvantages the placement of resin-bonded composite materials, there is need to revise and replace these restorations, and thus is a clear need for materials with improved clinical performance. Composite restoration not only has an esthetic advantage over dental amalgams, but they offer a means to adhesively bond the restoration to dentin and enamel. But these composite restorations have higher amount of shrinkage and increased amount of breakage of these restorations. Thus application of nanogel-modified resins helps in improving polymeric dental materials.[24] A study conducted in 2012 introduced nanogel-modified adhesives in a way to control the material's hydrophobic character without changing the basic monomer formulation. The results of the study concluded short-term micro-tensile bond strengths to acid-etched and primed dentin were significantly enhanced by nanogel inclusion in the adhesive resins.[25]

Hydroxyapatite nanogel toothpaste

An *in vitro* study conducted in 2011[26] compared two toothpastes containing nanohydroxyapatite and amine fluoride. The results revealed higher remineralizing effects with nanohydroxyapatite toothpaste when compared to amine fluoride toothpastes with bovine dentine, and comparable trends were obtained for enamel. The nanohydrogel hydroxyapatite toothpaste is marketed as CTx4 Gel 5000 (by CARI FREE ®).

As local drug delivery for treatment of periodontitis

Periodontitis is treated invariably by mechanical debridement of the tooth surface and a proper maintenance of oral hygiene.[20-22] Comprehensive mechanical debridement of sites, particularly with deep periodontal pockets is difficult to achieve. The chief difficulty arises due to problems associated with elimination of pathogenic micro flora embedded deep within the gingival tissues, and the consequent inaccessibility to periodontal instrumentation.[27] As an adjunctive approach, systemic or local administration of antibiotics is being increasingly recommended because of the microbial etiology of periodontitis. However, two well known drawbacks of systemic administration of antibiotics are: (i) Repeated intakes over a prolonged period of time required to achieve an effective concentration of the drug, and (ii) risk of inducing bacterial resistance and distortion of commensal flora while employing broad spectrum antibiotics.[27] This dichotomy obviously demands a more effective approach with an emphasis being placed on delivering the drug directly into the pocket under consideration, and more importantly in a controlled fashion.

The specific addressing of the target sites, which eliminates systemic uptake, has the huge advantage of minimizing harmful side effects and can attain 1000-fold higher concentrations of the agent in subgingival sites compared with a systemic drug regimen[28]. Over the years, a number of devices have been proposed for local drug delivery (LDD), including conventional ones like fibres, strips, films, gels, sponges, micro particles and recently, nanoparticles. Some of the nanogels used in treatment in periodontitis are:

Chitosan loaded-Tripolypeptide (TPP):

A study proposed a drug delivery system based on a series of formulations with chitosan (3-4%) nanogels, designed for local, intra-pocket treatment of periodontal disease, containing two drugs (an antibiotic tetracycline hydrochloride and a chemotherapeutic antimicrobial agent metronidazole benzoate). The aim of the study were to outline the rheological profiles of these formulations and also to evaluate the drug release[29]. All formulations exhibited pseudoplastic and thixotropic behaviour. The drug kinetic profiles and the release mechanisms followed Peppas equation. Based on the experimental data, an optimum concentration of chitosan in gel (3%) for useful modulation of drug loading, as a success factor in local therapy of periodontitis, was proposed.[29]

Pluronic Nanogel

Pluronic has been employed in a micellar type as a pharmaceutical nanocarrier, consisting of a hydrophobic core and a hydrated outer shell. The hydrophilic Polyethylene glycol (PEO) outer shell enhances the stability in blood stream by avoiding the reticuloendothelial system (RES) and other clearance and defensive mechanisms.[30]. However, recent reviews of Pluronic micelles elucidate that Pluronic has advantages in pharmaceutical applications because of its biological as well as inert nature. The biological activities are attributed to the particular abilities to intervene various cellular functions including mitochondrial respiration, ATP synthesis, apoptotic signal transduction, and gene expression, resulting in overcoming the multi-drug resistance (MDR) to various anticancer drugs through complicated mechanisms.[31]. A study was conducted to develop a biocompatible and biodegradable syringeable *in situ* gel having controlled release characteristics for direct placement into the periodontal pocket. The formulation contained Ornidazole with Poloxamer 407 (Pluronic F-127). *In vitro* drug release showed that the formulation containing 20% Pluronic F-127 released the drug completely within 8 hours. The results of study indicate that, Pluronic F-127 is a promising polymer to develop *in situ* gel formulation for periodontal disease.[32]. A study was conducted to formulate satranidazole-containing mucoadhesive gel for the treatment of periodontitis. Different mucoadhesive gels

were prepared, using various gelling agents like sodium carboxymethylcellulose (SCMC), Pluronic F-127, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and the mucoadhesive polymer Carbopol 934P. The selected formulations were studied for different mechanical properties, such as mucoadhesive strength, hardness, compressibility, adhesiveness, and cohesiveness through Texture Profile Analyzer. *In vitro* satranidazole release from the prepared formulations was also determined and compared with the marketed preparation of metronidazole (Metrogyl® gel). At the end of the 42 days of clinical studies, all formulations were found to significantly reduce the probing depth, Plaque Index, gingival index, calculus criteria, and bleeding index.[33]. In another study tetracycline-containing formulations were developed for the treatment of periodontitis by direct periodontal intra-pocket administration.[34] The analysis indicated that when applied subgingivally tetracycline-containing Pluronic gels produce a significantly improved outcome in moderate to deep pockets in adjunct with scaling and root planing periodontal pockets.

CONCLUSION

Recent developments in nanomaterials and nanotechnology have provided a bright insight into the commercial applications of nanomaterials in the management of dental disease. It can be supposed that the nanogel technology has an immense opportunity for designing a novel, low dose, and effective treatment method for different dental problems. Although many works have been published concerning nanocomposites, it will become of increasing importance to specifically develop commercially available nanocomposites as local drug delivery to manage various dental diseases.

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