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Nanotechnology in Orthodontics- An Update

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ABSTRACT: Nanotechnology, scaling matter at nanometer level (10^{-9}) holds promise for advanced diagnostics, targeted drug delivery, and biosensors. It has conjured up speculation about a seismic shift in almost every aspect of science and engineering. Nanotechnology is expected to pervade and further revolutionize the practice of medicine and dentistry and may well have important applications spanning all aspects of disease, diagnosis, prevention and treatment. The intent of this article is to briefly discuss the enormous potential of nanotechnology and its applications in orthodontics quoting some of the latest literature available at the time.

KEY WORDS: Nanotechnology, Orthodontics, Nanorobots, Nanodentistry, Nanoparticles

I.INTRODUCTION

Nanotechnology has been entering the vocabulary of most scientific communities with increasing vigor over more than two decades now.The word "**Nano**" is derived from the Greek word meaning 'dwarf'[1]. The term 'nanotechnology' was coined by Prof. K Eric E. Drexler[2]in his 1986 book titled, 'Engines of Creation: The Coming Era of Nanotechnology'. He described Nanotechnology as the science of manipulating matter measured in one billionth of a meter or nanometer, roughly the size of 2 or 3 atoms[1].This emerging science is formed from the convergence of chemistry (classically restricted to atomic interactions) and molecular-scale physics and biology (previously restricted to the micron scale).

II.FOREFATHERS OF NANOTECHNOLOGY

The vision of nanotechnology was introduced in 1959 by late Nobel physicist Richard Feynman in his talk saying "there is plenty of room at the bottom." He proposed using machine tools to make smaller machine tools all the way down to the molecular level[3].K Eric Drexler developed the idea of using nanotechnology to build molecular assemblers that would manufacture materials with atomic precision[2]. The term 'nanotechnology' was used first by the Japanese scientists Norio Taniguchi (1912-1999) in a 1974 paper on production technology that creates objects and features on the order of a nanometer[4].Richard Smalley won the Nobel Prize in Chemistry (1996) for his discovery of the buckminsterfullerene form of carbon (aka "Buckyballs"). This discovery was the foundation of carbon-nanotube[5].

III. WHAT IS NANOTECHNOLOGY?

Nanotechnology is described as the multidisciplinary science of the creation of materials, devices, and systems at the nanoscale level. It refers to the manipulation, precise placement, measurement, modeling, or manufacture of sub-100nm scale matter. In other words, it has been described as the ability to work at atomic, molecular, and supramolecularlevels(on a scale of ~ 1-100 nm)to understand, create, and use material structures, devices, and systems with fundamentally new properties and functions resulting from their small structure.

A. The Current State[678]

The research is currently directed towards the production of a wide array of different nanoscale structures. The fabrication techniques of these structures can be divided into 5 approaches:

- Top-down approach
- Bottom-up approach
- Functional approach
- Biomimetic approaches

- Speculative approach

The 'Top-down' techniques are used to manufacture nanoscale structures by miniaturization the micron scale to enter, the nanodimension. The best example of a "top-down" approach is the photolithography technique used in the semiconductor industry to fabricate components of an integrated circuit by etching micro/nanoscale patterns on a silicon wafer.
The 'Bottom–up' approach begins by designing and synthesizing custom made molecules that have the ability to self-replicate. These molecules are then organized into higher macro-scale structures.
The 'Functional approach' is based on developing components of a desired functionality without regard to how they have been assembled. It emphasizes production of nanoparticles for a specific use.
The 'Biomimetic approach' proposes use of biomolecules for applications in nanotechnology.
The 'Speculative approach'often considers a bigger picture view of nanotechnology, with more emphasis on its societal implications than the details of how such inventions could actually be created.

B.NanoMedicine[9]

The concept of nanomedicine was first introduced by Robert A Frietas, Jr. in 1999 and was defined, as follows: "Nanomedicine is the preservation and improvement of human health using molecular tools and molecular knowledge of the human body."Prof Freitas has been credited with publishing several volumes of Nanomedicine, the first book-length technical discussion of the medical applications of nanotechnology and medical nanorobotics.
In the field of medicine, nanotechnology has been applied in diagnosis, prevention, and treatment of diseases. Nanomaterials are being applied in the field of pharmacotherapeutics toward new drug synthesis, targeted drug delivery for cancer treatment, regenerative medicine, imaging, and gene therapy.

C.NanoRobots [10,11]

Nano Robotics is the technology of creating machines or robots close to the microscopic scale of a nanometre (10^{-9} meters). Nanorobots can be defined as an artificially fabricated object able to freely diffuse into the human body and interact with specific cell at the molecular level. Nanorobots will assemble things from atomic and molecular building blocks. Nanorobots exert precise control over matter. Nanorobots will allow us to construct such crystals, molecule by molecule, as incredibly fine-grained atomic structures, following a detailed blueprint. Nano robots can be used in different application areas such as medicine and space technology. Nowadays, these Nanorobots play a crucial role in the field of Bio-Medicine, particularly for the treatment of cancer, cerebral aneurysm, removal of kidney stones, elimination of defected parts in the DNA structure, and for some other treatments that need utmost support to save human lives, not avoiding the promising role it plays in the field of dentistry as well.

IV.NANODENTISTRY

Novel Nano has opened the flood gates for major revolutions in the field of dentistry as well. Nanodentistry will make possible the maintenance of comprehensive oral health by employing nanomaterials, biotechnology including tissue engineering, and, ultimately, dental nanorobotics. Nanotechnology has the potential to revolutionise how dentists and physicians diagnose and treat diseases and injuries in future. In his aricle on nanodentistry (2000)[12], Prof Freitas elaborates on and throws light on the immense possibility of nanotechnology in dentistry. He envisioned the idea that incorporation of nanotechnology in dentistry will enable individuals to maintain near perfect oral health through the use of nanomaterials, tissue engineering and nanorobotics. Currently,numerousnanoscale dental materials, nanocharacterization methods, and nanofabrication techniques are being employed in dentistry to improve the biomaterial properties.

A. Applications by top-down approach[8]:

- Salivary diagnostics powered by nanotechnologies
- Nanocomposites
- Nanotechnology for glass ionomer cement
- Nanoceramic technology
- Nanobond
- Nanosolutions
- Dental durability and cosmetics
- Coating agents
- Nanotechnology for impression materials

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- Nanocomposite denture teeth
- Implants
- Laser plasma application for periodontia
- Nanoneedles
- Nanobone replacement materials
- Nanobonefibers
- Nanoparticles as antimicrobial agents
- Nanotechnology based root-end sealant

B. Applications by bottom-up approach[8]:

- ✓ Inducing anesthesia (local anesthesia)
- ✓ Hypersensitivity cure
- ✓ Tooth repair
- ✓ Nanorobotic dentifrice (dentifrobots)
- ✓ Orthodontic nanorobots
- ✓ Halitosis
- ✓ Nanotech floss
- ✓ Photosensitizers and carriers
- ✓ Diagnosis of oral cancer
- ✓ Treatment of oral cancer

In the following section , this review article aims to look into the applications of nanotechnology specifically in the field of Orthodontics as envisioned by Dr Freitas, at the same time going through the current evidence that exist in the literature regarding the same.

V. NANO-ORTHODONTICS

A.NANO-SCALE STUDIES ON ORTHODONTIC BRACKETS AND ARCHWIRES[13]

Orthodontic brackets and archwires are an integral part of any orthodontic therapy unless of course when someone uses clear aligners. Orthodontic brackets bonded to teeth provide the means to transfer force from the activated archwire to the teeth to facilitate tooth movement. These brackets are manufactured with different materials ranging from metallic (stainless steel,titanium, gold) to esthetic tooth colored(plastic , ceramic) materials. It's important to also know that the surface characteristics of these brackets play a crucial role in orthodontic tooth movement as well as microbial adhesion. Micro and nano scale roughness of these brackets can facilitate early bacterial adhesion. This is where nanoindentation studies come into play that is used to evaluate nano-scale surface characteristics of the bracket surfaces as well as mechanical properties like hardness, elastic modulus, yield strength, fracture toughness, scratch hardness, and wear properties , which is achieved by a nanoindenter coupled with atomic force microscope (AFM). A typical AFM can provide resolutions of the order of 1 nm laterally and 0.07 nm (sub-angstrom) vertically. AFM has been utilized to look at the nanoscale dimension of the orthodontic armamentarium and the changes taking place during the course of treatment. Orthodontic brackets and archwires can undergo changes in surface characteristics during treatment due to the effects of food and oral hygiene habits and/or calcification. Below are some AFM studies on orthodontic biomaterials. (Table 1)

Sl No.	Authors& Reference	Nanoparticle/ Nanoscale Imaging Technique Used	Parameters evaluated	Results
1.	C. Bourauel, et al.[14]	AFM	Surface roughness	Surface roughness influenced the effectiveness of sliding mechanics, corrosion behavior, and esthetics
2.	J.P. Alcock, et al.[15]	AFM with nano-	Effects of	Decontamination

		indenter	decontamination and clinical exposure on elastic modulus, hardness, and surface roughness	regimen and clinical exposure had no effect on Ni-Ti wires but did have a statistically significant effect on stainless steel wires. Decontamination of stainless steel wires significantly increased surface hardness(p=0.01) and reduced the surface roughness (p=0.02)
3.	G.J. Lee, et al.[16]	AFM	Surface roughness	2-year orthodontic treatment regime showed that self-ligating ceramic brackets had undergone less change in roughness parameters than self- ligating stainless steel brackets. Self-ligating ceramic brackets exhibited low friction and better biocompatibility than other brackets
4.	Qabel, *et al*[17]	AFM	Effect of three polishing systems on porcelain surface roughness after orthodontic bracket debonding.	Conventional use of Sof-Lex discs seems to be more cost-effective due to their lower cost.
5.	Caldeira*et al.*[18]	AFM	Effects of simulated conditions of *in vitro* cariogenic challenges on the surface roughness and topography of three orthodontic bonding materials	Fuji Ortho^{TM} LC was the material that underwent the most alteration in surface roughness and topography.

Such studies using AFM have shown that it can be utilized as an effective imaging tool to visualize and analyse the surface properties and understand the changes taking place at the nano-scale dimension of orthodontic wires or brackets during treatment.

B.NANOCOATINGS ON ORTHODONTIC ARCHWIRES[13]

Orthodontic archwires are used to generate mechanical forces that are transmitted through brackets to bring about tooth movement in the correction of a malocclusion. They are also used for retentive purposes, i.e., to maintain teeth in their current position. Currently orthodontic arch wires are fabricated from base metal alloys such as stainless steel, Ni-Ti, and beta-titanium alloys as well as from esthetic materials. When employing sliding mechanics, friction between the wire and the bracket is one of the primary factors influencing tooth movement. When one moving object contacts another, friction is introduced at the interface, which results in resistance to tooth movement. This frictional force is proportional to the force with which the contacting surfaces are pressed together and is governed by the surface characteristics at the interface (smooth/rough, chemically reactive/passive, or modified by lubricants). Minimizing the frictional forces between the orthodontic wire and brackets has the potential to increase the velocity of desired tooth movement and therefore result in less treatment time. The use of nano-particles to reduce friction has resulted in development of dry lubricants. Dry lubricants are solid phase materials that are able to reduce friction between two surfaces sliding against each other without the need for a liquid media. Biocompatible nanoparticles have been coated on orthodontic stainless steel wires to reduce friction. Few of the recent studies on the use of nano-coatings on orthodontic archwires as a method of reducing friction have been enlisted in Table 2.

Sl No.	Authors	Nanomaterial/tech employed	Parameters evaluated	Results
1	M. Redlich, *et al.*[19,20]	Ni-P filmimpregnated with IF-WS2 nanoparticles	(i) Frictional forces measured on coated and uncoated wires (ii) Friction coefficient	(i) Reduced to 54% on coated wires (ii) Friction coefficient reduced one-third from 0.25 to 0.08
2	G.R. Samorodnitzky-Naveh, et al.[21]	Cobalt andIF-WS2 nanoparticles	Friction coefficient	66% reduction in coated substrates
3	Venkatesan K & group[22]	(TiO2) nano-coating	Effect of titanium dioxide (TiO2) nano-coating on surface roughness (Ra) of nickel-titanium (NiTi) archwires and its influence on *Streptococcus mutans* adhesion and enamel mineralization	TiO2 nanoparticle coating on NiTi archwires causes an initial reduction in roughness but the benefit was lost by the end of 1 month. They also found out that *S. mutans*adhesion was lesser on the coated wires,
4	Kachoei M *et al.*[23]	ZnO nanoparticles	Fabrication of a friction reducing and antibacterial coating with zinc oxide (ZnO) nanoparticles on nickel-titanium (NiTi) wire.	The coated wires presented up to 21% reduction in the frictional forces and antibacterial activity against*Streptococcus mutans*.

C.USE OF NANOTECHNOLOGY IN ORTHODONTIC ADHESIVES

Since the time when orthodontic brackets were first tried to be directly bonded on to tooth surfaces (Newman and Miura in mid1960s) [24, 25] many adhesives have been tried and tested. Composite materials and glass ionomer cements (GIC) have been primarily used in orthodontics as adhesive agents for securing orthodontic brackets and bands to the surface of the teeth. The largest application of nanoparticles has been in dental composite materials, where they have been used to enhance the long-term optical properties by virtue of their small size, and at the same time provide superior mechanical strength and wear resistance. The chief components of composite adhesive include resin matrix, filler particles and coupling agents. Bowen in 1963 introduced a silica-reinforced polmer for dental restorations.[26]
Filler particlesimprovethemechanicalpropertiesofthecompositematerial.Thefillerusedby Bowen in1963 , consisted of milled quartz articles with average size ranging from 8to12 μm (8000-2,000nm).Due to the estheti climitation s of macro filled composites (lack of surface gloss),the minifilled composite was introduced in the 1970s.Improvement in properties such as tensile and compressive strength(CS),modulus of elasticity,abrasion resistance,radiopacity, esthetics, and handling was noted with higher filler load. The filler material used was silica particles of average diameter of 400nm allowing a maximum filler loading of 55wt%,with better polish ability,but with a significantly lower mechanical strength.[27]It was not until the1980sand 1990s that mixtures of filler material s were tested.These hybrid fillers (600-2000 nm)were commercialized as hybrid, microhybrid, and condensable composites.[27]There was an

improvement in mechanical strength; however, the polishability was still a limitation. Microfilled composites(10-100 nm)were not suitable for high stress bearing areas (e.g.,ClassI,II,andIVrestorations)of the dentition.The particle sizes of the sehybrid composites were not similar to the size of thehydroxyapatite crystal, dentinaltubule,and enamelrod.There was also a potential for compromise in adhesion between the macro scopicrestorativematerial and the nanoscopic (1-10 nminsize) tooth structure. So nano filled composite materials were introduced. There are two distinct types of dental nano composites currently available:nanofills and nanohybrids.[28, 29]Nanofills contain nanometer-sized particles (1-100 nm)throughout the resin matrix, with no other large primary particles included.Nanohybrid sconsist of larger particles (400-5000 nm) with added nanometer-sized particles. The use of nanoparticles addresses the a forementioned difficulty by combining high mechanical strength with long-term polishretentioninone material.

GIC is yet another popular adhesive widely used in orthodontic band cementation. GIC is translucent and adhesive to tooth structure and has unique properties such as biocompatibility, anticariogenic action (due to fluoride release), and adhesion to moist tooth structure. In addition, the coefficient of thermal expansion for GIC is low and close to the values of tooth structure. Besides its advantages, GIC has some disadvantages such as brittleness and inferior mechanical strength. The use of GIC in orthodontics became popular during the late 1980s due to its fluoride-releasing potential which made it highly attractive for orthodontic band cementation. Compared with glass ionomer cements (GICs) that offer a relatively lower bond strength with teeth when used for bracket bonding , resin-modified glassionomer cements (RMGICs) present with stronger bond strength while maintaining some ability to release fluoride.[30]

Modifying conventional as well as resin modified GICs with nanoparticles has shown promising results in terms of physical and mechanical properties as well as fluoride release and antibacterial properties.

Table 3 enumerates some studies on the incorporation of nanoparticles in orthodontic adhesives.

Sl No.	Authors& Reference	Nanomaterial/tech employed	Parameters evaluated	Results
1.	*Asiry et al*[31]	Yttrium (III) Fluoride nanopowder	Adhesion strength and antibacterial effect	Yttrium fluoride nanoparticles, blended with a conventional resin at 1% concentration, demonstrated significant antibacterial effect and did not compromise adhesion strength.
2.	M. Poosti*et al*[32]	TiO2 nanoparticles	Shear bond strength (SBS) and antibacterial effects of an orthodontic composite	Adding TiO2 nanoparticles to orthodontic composite enhances its antibacterial effects without compromising the SBS.
3.	Sodagar A *et al*[33]	Propolis nanoparticles (prpNPs)	Antimicrobial property and shear bond strength (SBS) of orthodontic composite	Nano propolis has a significant antimicrobial effect at 2% and 5% concentrations, and the SBS is maintained within the acceptable clinical range.

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Table 4 enumerates some of the commercially available nanocomposites and nanoionomers

Sl No.	Brand name	Type	Filler composition, vol% (wt%)	Manufacturer
1.	Filtek Supreme	Nanofilled	Nanomers and nanoclusters58%–60% by volume and 78.5% by weight	3M ESPE, St. Paul, MN, USA
2.	Premise	Nanohybrid	Nonagglomerated "discrete" silica nanoparticles, pre polymerized fillers (PPF), and barium glass fillers 69% by volume and 84% by weight	Kerr/Sybron, Orange, CA, USA
3.	Ceram-X	Nanohybridormocer-based, nanoceramic composite	Glass fillers (1.1–1.5µm)Methacrylate modified silicon-dioxide-containing nanofiller (10nm) 57% by volume and 76% by weight	DentsplyDeTrey, Konstanz, Germany
	Nanoionomer			
1.	Ketac N 100	Light cure resin modified GIC	Fluroaluminosilicate glass, nanofillers, nanoclusters	(3M, ESPE, St. Paul, MN, USA)

D.NANOPARTICLES IN ORTHODONTIC ELASTICS

Fixed orthodontic appliance treatment significantly increases the risk of enamel decalcification and white spot lesions. These are caused due to prolonged accumulation and retention of bacterial plaque on the enamel surface adjacent to the attachments, of which elastomeric ligatures are a main culprit.These ligatures are required to secure the archwire in the bracket slots during the treatment process. Earlier, it was reported that the ligation with elastomeric rings was associated with increased microbial load compared to ligation using steel wires.[34] Nowadays newer methods of ligation like self-ligating brackets are available , but studies point that these innovations are also not riskfree.[35] The advent of nanotechnology hasn't spared research in this field as well where these elastomeric ligatures can serve as a carrier scaffold for delivery of nanoparticles that can be anticariogenic, antiinflammatory, and/or antibiotic drug molecules embedded in the elastomeric matrix. Studies indicate that incorporation of nanoparticles in elastics has considerable scope in reducing enamel decalcification and oral biofilm accumulation during orthodontic therapy.

Table 5 summarises some of the latest studies on the same.

Sl No.	Authors & Reference	Nanomaterial/tech employed	Parameters evaluated	Results
1.	Hernández-Gómora*et al*[36]	silver nanoparticles(AgNPs)	Antibacterial and physical properties of orthodontic elastic ligatures	AgNPs demonstrated higher physical properties such as maximum strength, tension and displacementcompared to conventional modules as well as good antibacterial properties as well
2.	Subramani K *et al*[37]	Chlorhexidine (CHX) hexametaphosphate (HMP) nanoparticles	Antibacterial activity and force decay	Use of nanoparticle coating on orthodontic elastomeric chains(OECs) can exhibit antibacterial

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				effect and reduction of biofilm buildup and prevent white spot lesions as well as did not alter the force decay

E.SHAPE-MEMORY POLMERS

Over the past decade, there has been an increased interest in producing esthetic orthodontic wires to complement tooth colored brackets.Shape-memory esthetic polymer is an area of potential research. Shape memory polymers (SMPs) are materials that have the ability to "memorize" a macroscopic ("'permanent') shape, be manipulated and "fixed to a temporary or dormant shape under specific conditions of temperature and stress, and then later relax to the original, stress-free condition under several external stimuli such as temperature, magnetism, electricity, specific wavelength, moisture, pH and some specific chemicals. Once inside the mouth, these polymers are activated by the body's temperature or photoactive nanoparticles activated by light.[38]This relaxation is associated with elastic deformation stored during prior manipulation.[39] Various types of polymers exhibiting shape memory includes polyacrylate copolymers , polynorbornene , segmented polyurethanes , segmented polyurethane ionomers , epoxy-based polymers , thiolene-basedpolymers , crosslinkedpolycyclooctene , crosslinked ethylene-vinyl acetate copolymer , styrene-based polymers and many more .In a recent systematic review and patent landscape report on shape memory polymers used in dentistryshowed that more patents on SMPs were registered in the field of orthodontics (51%) compared to other fields of dentistry,ranging from archwires, clear aligners to elastic modules [40] and orthodontic bands.[41]

F.NANOELECTROMECHANICAL SYSTEMS(NEMS)

Orthodontic patients frequently complain about the long duration of their treatment (2.5–3.0 years). Increasing the speed of tooth movement can solve this dilemma. Many chemical and physical agents are useful as adjuncts to the mechanical forces in accelerating orthodontic tooth movement. Many studies suggest that orthodontic tooth movement might be accelerated by the use of force in conjunction with electrical currents, specifically in range of 10–20 microamperes.[42, 43]

The main clinical problem with this concept is the source of electricity for intraoral use. In 2009, J. Kolahi*et al* proposed the concept of biocatalytic fuel cells (enzyme batteries) that could generate the required electricity within the oral environment to accelerate tooth movement.[44]

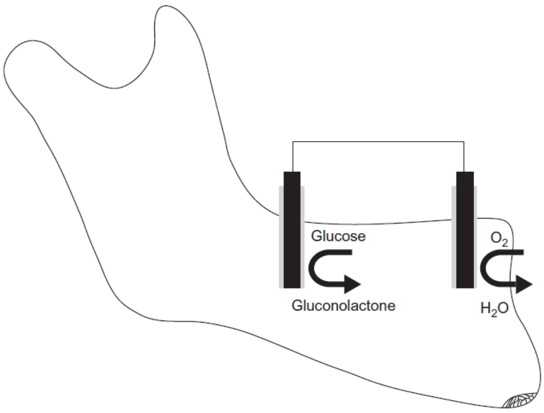

Fig. 1 Example of a biocatalytic cell circuit given by *J. Kolahiet al(2009)*[44]

An enzymatic micro-battery, would be an implantable device which is placed on the gingiva near the alveolar bone, that uses glucose or any other suitable metabolic substrate as the fuel source and these devices would be noninvasive and non-osseointegrated. In this way, a combined force–electric treatment may provide a powerfuland practical technique for enhancing the velocity of orthodontic tooth movement, regardless the type of the orthodontic appliance. But there are some valid questions that arises. Is a microfabricated enzyme battery tolerated by the oral tissues? Is there a risk of tissue damage? What is the effect of foods with different range of temperatures and pH on the output of the

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enzyme battery? The use of microenzyme batteries has issues like enzyme stability, electron transfer rate, and enzyme loading which result in shorter lifetime and poor power density.
This is where novel nano comes into play.Recent progress in nanobiocatalysis increases the likelihood of improving these aspects of the system. Many nanostructured materials, such as mesoporous media, nanoparticles, nanofibers, and nanotubes, have been demonstrated as efficient hosts of enzyme immobilization. It is evident that, when nanostructure of conductive materials is used, the large surface area of these nanomaterials can increase the enzyme loading and facilitate reaction kinetics, and thus improve the power density of the biofuel cells. In addition, research efforts have also been made to improve the activity and stability of immobilized enzymes by using nanostructures. It thus appears reasonable to expect that progress in nanostructured biocatalysts will play a critical role in overcoming the major obstacles in the development of powerful biofuel cells. It is expected that the NEMS based system will be applied over the next few years to develop biocompatible powerful biofuel cells, which can be safely implanted in the alveolus of the maxilla or mandible or in the palate to enhance orthodontic tooth movement or rapid maxillary expansion.[13]

G.NANOTECHNOLOGY IN THE FIELD OF LOCAL ANAESTHESIA

In 2000, Robert A Freitas Jr. idea about the use of nanotechnology to induce local anaesthesia in the field of dentistry was as follows: 'A colloidal suspension containing millions of active analgesic micron-size nanorobots will be instilled on the patient's gingivae. The ambulating nanorobots reach the pulp via the gingival sulcus, lamina propria and dentinal tubules. Once installed in the pulp, the analgesic dental robots may be commanded by the dentist to shut down all sensitivity in any particular tooth that requires treatment. After oral procedures are completed, the dentist orders the nanorobots to restore all sensation.'[12]

As histrionic as it sounds, when we look into the literature , we see promising leads in the use of nanoparticles in local anaesthesia.
Conventional L.A agents have few limitations in terms of duration of action, potential systemic toxicity (CVS and CNS) that restrict its application and raise the urgency to counterbalance the side effects and prolonged analgesia.[45]The uses of nanotechnology with respect to LA agents are targeted towards 3 main aspects:

1.) Extended release LA agents
2.) Targeted drug delivery
3.) Controlled drug release

Compared to macro-scaled drug delivery systems (DDSs), nano-scaled DDS with state –of- the- art manufacturing techniques is more compatible to nano structured human biological environment that has precedence over conventional agents in terms of [46]

- cellular penetration,
- better bioavailability,
- longer retention time
- improved loading
- efficiency,
- better biocompatibility (acceptable local Inflammation such as myotoxicity and neurotoxicity),
- and biodegradability

In order to prolong LAs' analgesic effect while preventing adverse events, many efforts have been put into the development of extended-release LAs. Of the most popular are the liposomal and polymeric formulations of extended release LA agents, both of which are nanotechnology-designed formulations for drug delivery.
EXPAREL™ (Pacira Pharmaceuticals, Parsippany, New Jersey, USA) is the only extended-release liposomal LA which is approved by American Food and Drug Administration (FDA).

The commonly used nano-formulations for LA agents under research have been summarised in Table 6.[47]

Nano-materials	Formulations
Nanorod	Gold nanorod-liposomes-tetrodotoxin
Micro-particles	PLGA-micro-particle-LDC
Nanospheres or nanocapsules	nanosphere-poly(D,L-lactic acid)-LDC, poly(e-Caprolactone)-nanospheres-LDC,

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	poly(ethylene-glycol)-poly(e-caprolactone)-nanosphere-LDC nanocapsules-poly(L- lactide) compared to benzocaine-loaded PNs
Hydrogel	Poloxamer-407 hydrogels-mebeverine, Genipin cross-linked catechol-chitosan hydrogel-LDC
Nanoparticles	Lipid–polymer hybrid nanoparticles-LDC, nanoparticles-PCL-LDC
Cyclodextrin	β-CD-LDC

H. USE OF NANOTECHNOLOGY IN TEMPORARY ANCHORAGE DEVICES (TADS)

While TADs have become increasingly utilized by orthodontic professionals to assist in the process of moving teeth, commercially available TADs exhibit a success rate of 60-75%.[48, 49] Currently, TADs are manufactured with smooth titanium surfaces (Ti6Al4V) because completeosseointegration is a disadvantage that complicates their removal. On the other hand, lack of osseointegration is also one of the factors for the failure of TADs.

The success of TADs also depends on other factors like proper initial mechanical stability and loading quality and quantity. Clinically there are difficulties encountered in the removal of TADs due to increased osseointegration even on the smoother surface TADs. Therefore, it is postulated that the balance lies in the fabrication of an ideal surface that could stimulate initial osseointegration and facilitate its removal once the TAD is no longer needed. Biocompatible coatings like titanium nanotubes should be studied to evaluate if the nanotubular layer can enhance initial osseointegration and can serve as an interfacial layer between the newly formed bone and the TAD.[13]
A study conducted by Wen You Zhou & associates(2010) hypothesized that primary stability and partial osseointegration of TADs could be achieved by the synergistic effects from nanoclay reinforced E-tricalcium phosphate (TCP) nanocoating on titanium miniscrews.[50]The nanocoated Ti samples were characterized by SEM (scanning electron microscope), TF-XRD (Thin-film X-ray diffraction)and nano-scratch test. MC3T3-E1 osteoblast-like cells were cultured on nanocoated Ti and cell viability and morphological observations were performed.They concluded that ananoemulsion coating could be developed to coat nanoclay reinforced magnesium substituted E-TCP on titanium surface for enhancement the stability of orthodontic miniscrews by imparting nanoporosity and nanoroughness features on titanium surface.

I.USE OF NANOTECHNOLOGY IN BIO-IMAGING

Since the discovery of X-rays by Roentgen in1895, biomedical imaging techniques have evolved dramatically. Nowadays conventional radiographs as diagnostic tools arelargely being replaced by CBCT and MRI in orthodontics, if not entirely but essentially for the following applications: [51]

- Evaluation of Impacted Teeth and Oral Anomalies
- Evaluation of the Airway and Sinus
- Evaluation of the Alveolar Bone Height and Volume
- TMJ Evaluation
- Three-dimensional Display of Dentition
- Orthognathic Surgical Applications
- Evaluation of Asymmetries
- Evaluation of Cleft Lip and Palate and Alveolar Bone Grafts
- Facial Analyses
- Cephalograms Obtained from CBCT

Recently, nanomaterials have stimulated efforts in improving biomedical detection and imaging due to unique passive, active and physical targeting properties. Applications include

- nanoparticle fluorescence imaging

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- nanometerscale contrast agents for MRI scans
- nanosized CT contrast agents
- nanoparticle ultrasound contrast agents

Compared to conventional contrast agents, nanoparticles have demonstrated improved signal intensity, targeting ability and longer circulation time both in vitro and in animal disease models.Currently, most nano-contrast agents are still in the experimental stage. Despite the impressive progress that has been made, very few nano-contrast agents have been evaluated in humans.
In the field of digital radiography, development of nanophosphor scintillators not only has decreased the radiation dosage but also has enhanced the quality of images obtained.[52]

J. USE OF NANOTECHNOLOGY IN GENE THERAPY

Gene therapy is a type a therapeutic approach that seeks to modify the expression of certain genesin order to alter certain biological properties, which has gained significant amount of interest in recent years. Successful gene therapy depends on two important aspects. (1) Efficient and safe delivery of genes to the target cell in vitro and *in vivo*. To achieve this goal, it is necessary to improve transduction efficiency, viral titre when using viral gene therapy, or transfection efficiency when using nucleic acids. (2) Effective monitoring of modified cells or modifying agents by non-invasive imaging techniques. This will allow tracking of gene delivery and gene expression.
These aspects and others are being addressed in new approaches, one of which involves magnetic nanoparticles. In gene delivery, the nanoparticles used in MRI present important advantages over other imaging techniques, such as fluorescence, luminescence, or PET, which have been also used in gene therapy.
In the last few years, many groups have reported the use of nanoparticles to complex and deliver viral vectors (e.g., adenoviruses, retroviruses) and nucleic acids, leading to the emergence of new approaches known as magnetofection and theranostics. Magnetofection is a viral and non-viral approach that uses superparamagnetic nanoparticles to improve gene delivery under a magnetic field. Theranostics combines therapeutics with diagnostics and covers several fields, including personalized medicine, pharmacogenomics, and molecular imaging to develop efficient new targeted therapies with an adequate risk/benefit ratio. Furthermore, theranostics aims to monitor the response to treatment and to increase efficacy and safety.[53]
Cationic PEG-PLA(Polyethylene glycol- polylactic acid) nanoparticles is used as a major delivery system to deliver small interference RNA (siRNA) . PEG-PLA nanoparticles encapsulating siRNA can enter the cells toperform gene-specific knockdown. However, challenges still remain for these biodegradablenanoparticle-assisted anti-cancer therapies to come to realization in the clinics. CALAA-01, an anti-solidtumor nanoparticle containing siRNA, showed great potential in its phase I clinical trial ,was terminated after phase Ib as two of the five patients enrolled had experienced dose-limiting toxicities . CRLX101, another anti-tumor targeted nanoparticle for various cancers, continuesto show promising. In 2019, the first ever siRNAnanodrug for hereditary amyloidosis, Onpattro, was approved by the FDA .Onpattro encapsulates the therapeutic siRNA moiety into a lipid nanoparticle, and deliversit directly to the liver to prevent the body from producing the disease-causing amyloid proteins .Similarly, research on stem cell therapy utilizing nanoparticles is also on the rise. Because of thesmall size and target specificity of the nanoparticles, scientists are aiming to treat some neurologicaldiseases using this strategy.[54]
Mandibular underdevelopment has been attributed to a variable interaction ofgenetic and environmental factors, which is believed to be difficult to manipulateor stimulate. Bite-jumping appliances, also known as functional appliances (FAs),have long been claimed and used to enhance mandibular growth in cases withdeficient mandibles (mandibular retrognathism). A recent study systematicallyreviewed reports on the effectiveness of FAs and concluded that the analysis ofthe effect of treatment with FAs versus an untreated control group showed skeletalchanges that were statistically significant in the short term, but unlikely to beclinically significant.Regardless of its successful use, nanobiotechnology is still at an early stage of development and its use in treatment of diseases otherthan cancer could be especially challenging.[55]

K. NANOFABRICATED ULTRASOUND DEVICES

Accelerating orthodontic tooth movement has been in the research front since many decades now. Even though successful research on invasive and minimally invasive techniques has come out, search for non-invasive techniques is on the rise. Therefore, recent studies[56] have focused on exploring the potential use of non-invasive physical methods to

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achieve faster orthodontic tooth movement.One of the potential physical approaches suggested in these studies is low-intensity pulsed ultrasound (LIPUS).

A study was conducted on the application of LIPUS to stimulate mandibular growth in humans with hemifacialmicrosomia by El- Baily et al.[57]The results showed that after one year of treatment, significant improvement of the underdeveloped side of patients' faces and mandibles was recognized both clinically and radiographically. But the patients (young adults) needed to hold the LIPUS transducers (applicators) to their mandibular condyles for 20 minutes every day for at least 1 year.

Another study by El- Baily & group showed that LIPUS application to orthodontically moving teeth can minimize root resorption.[58]The patients have to hold the LIPUS transducers tightly against the gingiva of the corresponding tooth/ teeth for 20 minutes per day for at least 4 weeks in order to achieve a clinically noticeable decrease in EARR concurrent with orthodontic treatment. We can clearly see compliance issues with the above applications .In order to minimize errors in LIPUS application and maximize consistency in treatment, a noncompliant LIPUS application is in high demand. In order to build an intraoral LIPUS device that is independent of power supply or patient compliance, a nanocircuit design as well as a nano-battery is required in a nanoscale intraoral LIPUS device. This is a potential area of research.

L. NANOMECHANICAL SENSORS FOR ORTHODONTIC FORCES AND MOMENTS MEASUREMENT- 'SMART BRACKETS'[59, 60]

In order to apply biologically tolerable forces and moments to the teeth to efficiently move teeth with minimal adverse effects, such as EARR, depending on the individual's intrinsic susceptibility, researchers have been working to develop brackets that can carry three-dimensional mechanical sensors in the bracket bases to measure in three dimensions the real-time forces and moments applied to the teeth. This would facilitate the orthodontist adjusting these forces should they exceed biologically acceptable limits. In order to achieve this, microsensors are being tested in orthodontic appliances to come up with 'smart brackets.'Development of a nanosystem chip that can be encapsulated into small low-profile contemporary bracket systems with reduced mesio-distal and occlusogingival dimensions will allow clinical testing of the utilization of this technology.

In 2007, Lapatki& Paul reported on the introduction of a "smart bracket" for multidimensional force and moment measurement. They worked on the concept of developing a smart bracket with an integrated sensor system for 3D force and moment measurement, using finite-element (FE) simulation and came up with promising results. They believed that quantification of real time forces exerted by the orthodontic mechanisms could help clinicians in optimization of the applied mechanical stimulus to predict the course of tooth movement as well as reduction of traumatic side effects such as orthodontic pain and EARR.

In 2013, M. Kuhl*et al* came up with a prototype bracket with a wireless stress mapping chip that achieves a maximum stress resolution of 11 kPa with a power consumption of 1.75 Mw for the stress evaluation.The stress mapping chip was fabricated in a 0.35µ m process and a micro coil produced by gold electroplating in a photoresist mask. Twenty-four transistor-based stress sensors for measuring either in-plane shear stress or the difference of in-plane normal stresses are strategically distributed over the chip area. They concluded that the system paves the way towards the implementation of smart brackets in orthodontic therapy, providing the clinician with direct sensory feedback on the forces and moments applied to individual teeth, which could increase treatment effectiveness and reduce negative therapeutic side effects such as irreversible root resorption due to overloading of teeth.

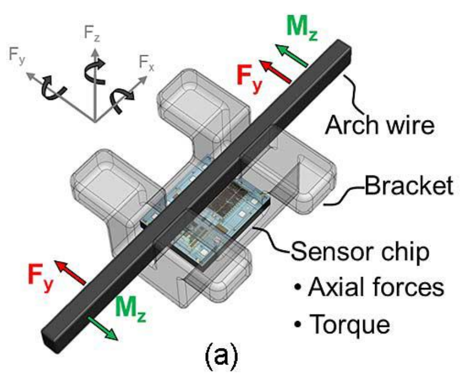

Fig 2. A prototype Smart Bracket

VI.SAFETY OF ENGINEERED NANOMATERIALS(ENMs) [61]

A.THE SAFETY OF PATIENTS:

Risk is a function of exposure and hazard (toxicity), and both aspects are considered in risk assessments for ENMs. For patients, the exposure is defined by the intended treatment, the physical form, and concentrations of the ENMs in the therapeutic agent or medical device.

There are several theoretical routes of exposure for dental patients. These include: (i) accidental or incidental ingestion of the nano-containing dental material during or after treatment; (ii) the generation of aerosols during dental treatment that might present a respiratory hazard to the patient (*e.g.*, aerosols from drilling into a nano-composite during a dental repair); (iii) systemic toxicity from any ingested or inhaled ENMs; (iv) direct toxicity to the cells/tissue of the oral cavity.

The ingestion and subsequent systemic hazard from oral exposure to ENMs has been studied in rodents (TiO2[62, 63]; Cu NPs[64];Ag NPs[65]) and other animals as well as *in vitro* using the Caco-2 intestinal cell line[66] or isolated perfused intestines[67]. Most oral toxicity studies in animal models have used gut gavage, and there is some concern that ENMs introduced to the gut *via* salines may have a higher bioavailability than those in a food or dental material matrix.*In vivo* studies on rodents show that at least total metal concentrations in the internal organs from exposure to metal-containing ENMs can increase, and this may also lead to organ pathology.For example, Wang *et al*. found pathology in liver and kidney of mice after single oral gavage of TiO2 NPs (25 or 80 nm).[63] There is also at least one report of argyria in humans after chronic ingestion of colloidal silver solution, indicating that silver from nano-silver can be absorbed.[68]

The toxicity data in the public domain on ENMs used specifically in dental applications is sparse, with no information on oral toxicity from dental materials, biomaterials or implants containing ENMs in animal models or patients. As a rule, dental materials for permanent restorations are designed to be inert and chemically stable in the oral environment. However, there has always been a concern that leaching of toxic compounds may occur either as a result of material instability or degradation, or due to inappropriate application or preparation of the dental material by the clinician. However, similar information for dental materials containing ENMs is lacking.

There is a concern that some ENMs are immunogenic[69] and would induce a hypersensitivity reaction or inflammation in a vulnerable patient. This risk may be present with traditional medicines and medical devices, and whether the risk would be greater for an ENM in the oral cavity is unknown.

B.OCCUPATION EXPOSURE OF THE PRACTITIONER:

The occupational health of the practitioner should also be considered in the context of routes of exposure. For health and safety in the workplace, safe systems of work are aimed at preventing exposure so that there is a negligible risk. This approach also applies to ENMs, [70, 71] although in practice employers do show some uncertainty about what might be nano-specific in the governance of health and safety. Potential exposure of the practitioner could arise from incidental ingestion or dermal contact. However, the clinical practice of wearing surgical gloves, and not eating or drinking while treating patients should minimise these exposure routes as they would with other substances.

However, distance from the point source of the exposure is also critical, and in dentistry the practitioner is inevitably very close to the patient. Clearly, further research is needed on workplace exposure to ENMs in dentistry.

VII. CONCLUSION

The scope of nanotechnology in the field of orthodontics is boundless especially with new state-of-the-art fabrications techniques within one's easy reach. As we skim through the latest available literature , we observe the areas where nanotechnology is providing promising results in the field of orthodontics ranging from improvements in biomaterials, acceleration techniques for orthodontic tooth movement to even future possible applications in gene therapy which ultimately could make treatment of a malocclusion effortless for the clinician and at the same time affordable for patients. Biosafety of engineered nanomaterials does raise questions of concern that calls for more studies to ascertain their toxicology in the oral environment. Nevertheless as its always said about novel nano, 'small is the next big thing'.

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