



REPUBLIC OF TURKEY
MARMARA UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

**EVALUATION OF THE EFFECT OF TITANIUM DIOXIDE
NANOPARTICLES ON THE SHEAR BOND STRENGTH OF
ORTHODONTIC BONDING AGENT AND COMPOSITE
ADHESIVE**

NIMAT E. AL AKEL
MASTER THESIS

DEPARTMENT OF ORTHODONTICS

SUPERVISOR
PROF. DR. ZEYNEP AHU ACAR

2022-ISTANBUL

STATEMENT

This thesis is my own work, I have not had any unethical behavior at all stages from the planning to the writing of the thesis, I have obtained all the information in this thesis within academic and ethical rules, I have cited all the information and comments that were not obtained with this thesis study, and I have included these sources in the list of resources, Again, I declare that I have not acted in violation of patent and copyright rights during the study and writing of this thesis.



Nimat E. Al Akel

Signature:

I. ACKNOWLEDGEMENTS

“Allah be praised abundant praise sincere praise blessed praise”

First and foremost, praises and thanks to Allah for his showers of blessing throughout my studies and giving me the knowledge and patience to complete this thesis.

I would like to express my heartfelt gratitude to my amazing family especially to my parents, Essam Al Akel and Nour AlHuda Ismail. Their continuous support, guidance and love throughout my time studying abroad and especially during these difficult final months of my thesis preparation has been my driving force. I would like to express my sincere thankfulness to my second mother, Hamida Caluman, may she rest in peace, for her endless kindness and compassion. I would also like to thank my sister Nada and my brothers Wael, Mohammad, and Waleed for their support during my studies and the help that they have provided. I'm so lucky to be surrounded by a family that provides me with positivity and celebrates my success every step of the way.

I would also like to thank my best friend Ishil Shukur who was my family away from home these past three years. I will never forget the time and experiences we shared together. She added colour to our journey and made it more delightful.

I extend my gratitude to my supervisor Prof. Dr. Zeynep Ahu Acar. Without her contributions, this thesis would not be made possible. Her support allowed me to be guided on the right path.

A special thanks to Prof. Murat Beydoğan and his team from The Metallurgy and Material Engineering Department of Istanbul Technical University who shared his knowledge and facilities with me in conducting my research.

Finally, I would like to express my appreciation to my professors at Marmara University for their continued efforts to share their knowledge and expertise throughout our educational career.

II. CONTENT

1. ÖZET	1
2. SUMMARY.....	2
3. INTRODUCTION AND AIMS	3
4. LITERATURE REVIEW	6
4.1 Orthodontic Treatment	6
4.2 Orthodontic Bonding	7
4.2.1 Biological components of the orthodontic bonding process	7
4.2.1.1 Enamel structure, composition and formation.....	7
4.2.1.2 Salivary pellicle	8
4.2.1.3 Saliva properties and dental caries.....	8
4.2.2 Chemical components of orthodontic bonding.....	9
4.2.2.1 Basis of orthodontic bonding.....	9
4.2.2.2 Bonding technique	9
4.2.2.2.1 Direct bonding	9
4.2.2.2.2 Indirect bonding	10
4.2.2.3 Bonding procedure	10
4.2.2.3.1 Prophylaxis	10
4.2.2.3.2 Enamel conditioning	11
4.2.2.3.2.1 Air abrasion.....	13
4.2.2.3.2.2 Laser etching.....	14
4.2.2.3.3 Priming	14
4.2.2.3.4 Bracket adhesives.....	15

4.2.2.3.4.1 Chemically cured adhesives.....	17
4.2.2.3.4.2 Light cured adhesives	17
4.2.2.3.4.3 Dual cured adhesives.....	18
4.3 Bond Failure	18
4.4 White Spot Lesions In Orthodontic Treatment	19
4.5.2 Shear bond strength in orthodontics	20
4.6 Nanoparticles.....	21
4.6.1 Nanoparticle-based technologies	22
4.6.2 Nanoparticle applications in materials	23
4.6.3.1 Types of nanoparticles	24
4.6.3.1.1 Liposome nanoparticles.....	25
4.6.3.1.2 Polymeric nanoparticles	25
4.6.3.1.3 Metallic nanoparticles	26
4.6.3.1.5 Ceramic nanoparticles	28
4.6.3.1.6 Quantum dots.....	29
4.6.3.1.7 Carbon-based nanoparticles.....	30
4.6.5 Nanoparticles as antimicrobial agents.....	33
4.6.6 Mechanism of action of nanoparticles	35
4.6.7 Titanium dioxide and its properties	36
4.6.7.1 Titanium dioxide nanoparticles as antimicrobial agent	36
4.6.7.2 Preparation of nanostructured titanium dioxide	37
5. METHODS AND MATERIALS	39
5.2 Experimental Design Sample Size Calculation	39
5.3 Grouping	39
5.4 Teeth Preparation.....	40

5.5 Preparation of Bonding Agent- NPs Mix.....	40
5.6 Preparation of Transbond Composite Adhesive- NPs Mix.....	42
5.7 Bonding Procedures.....	43
5.8 Thermocycling Process	44
5.9 Shear Bond Strength (SBS) Test	45
6. RESULTS.....	48
6.1 Sample's Description.....	48
6.2 Shapiro-Wilk's Test.....	48
6.3 Shear Bond Strength in Study Groups	49
6.4 One-Way ANOVA Test.....	49
6.5 Shear Bond Strength Comparisons Between Groups	50
7. DISCUSSION AND CONCLUSION	52
8. REFERENCES	57
9. ENCLOSURES	Error! Bookmark not defined.
10. CURRICULUM VITAE	Error! Bookmark not defined.

III. ABBREVIATIONS

AgNP: Silver Nanoparticles
ANOVA: Analysis Of Variance
ASTM: American Society for Testing and Materials
Au: Gold
AuNP: Gold Nanoparticle
B subtilis: Bacillus subtilis
Bis-GMA: Bisphenol A- Glycidal methacrylate
C: Carbon
CaP: Calcium Phosphate
CdSe: Cadmium Selenium
CeO₂: Cerium Dioxide / Ceria
Cm: centi meter
CNT: Carbon Nanotube
CuO: Cupper Oxide
E value: Expected value
E. coli: Escherichia coli
EDS: Energy Dispersive Spectroscopy
Fe₃O₄: Iron Oxide
FTIR: Fourier Transform Infrared spectroscopy
G power: Gravitational power
HAP: Hydroxyapetite
HCl: Hydrogen Chloride
ICON: Caries infiltration concept
InAs: Indium Arsenate InP:
Indium Phosphate
ISO: International Organization of Standardization
K: Kelvin

K. pneumoniae: Klebsiella
pneumoniae kHz: kilo Hertz LED:
Light- Emitting Diode
M: Mega
M. luteus: Micrococcus luteus
MIP: Moisture Intensive
Primer ml: milli liter mol:
moles MPa: Mega Pascal
MRP: Multi- Drug Resistance Proteins
MSN: Mesoporous Silica Nanoparticles
MWCNT: Multi-walled Carbon Nanotube
N: Newton
NAA: Nanoporous Anodic
Alumina NIR: Near Infrared
Radiation nm: nanometer NP:
Nanoparticles
NT: Nanotubes
NZVI: Nanoscale Zero-Valent Iron
P. aeruginosa: Pseudomonas aeruginosa
PCB: Polychlorinated
Biphenyls PEG: Polyethylene
Glycol pH: potential of
Hydrogen PLA: Polylactides
PMMA: Polymethyl Methacrylate pSi:
porous Silica
PSPMA: Poly 3-sulfopropyl Methacrylate Potassium
PTT: Photothermal Treatment Transducer
PVK: Poly N-vinylcarbazole
QD: Quantum Dots
QY: Quantum Yield
S. mutans: Streptococcus mutans

S.aureus: Staphylococcus aureus SBS:
Shear Bond Strength
SEM: Scanning Electronic Microscope
SiO₂: Silicone Dioxide / Silica
SWCNT: Single-walled Carbon Nanotube
TCP: Tricalcium Phosphate
TEGDMA: Triethylene glycol dimethacrylate
TiO₂: Titanium dioxide
TiO₂: Titanium Dioxide / Titania
TMOS: Tetramethyl Orthosilicate
TNT: Titanium Nanotubes
UV: Ultra Violet
W: Watts
WS₂: Tungsten Disulfide
WSL: White Spot Lesion
XPS: , X-ray Photoelectron Spectroscopy
ZnO: Zinc Oxide
ZnOCuO: Zinc Oxide Cupper Oxide
ZnS: Zinc Sulfide ZrO₂: Zirconium
Dioxide / Zirconia β: Beta μm:
micrometer / micron
(ζ: Zeta
%: Percent
°C: Degrees Celsius

IV. FIGURE LIST

Figure 1: A diagram showing the types of nanoparticles and their main biomedical applications	31
Figure 2: Extracted intact premolars collected	40
Figure 3: Vortex and IKA® T25 digital ULTRA-TURRAX® machine	42
Figure 4: 3M Transbond™ XT Light Cure Adhesive and Transbond™ MIP bonding agent used	43
Figure 5: Group A - 20 specimens with TiO ₂ nanoparticles incorporated in the bonding agent	44
Figure 6: Group B - 20 specimens with TiO ₂ nanoparticles incorporated in the composite adhesive	44
Figure 7: Group C - 20 specimens with conventional bonding agent and composite adhesive (no nanoparticles).	45
Figure 8: The specimens during the thermocycling process	46
Figure 9: Instron Universal Testing Machine (SHIMADZU)	47
Figure 10: 0.6-mm metal blade attachment used for bracket contact	48
Figure 11: Specimens distribution among study groups.	49
Figure 12: Box plot of SBS in study groups	51
Figure 13: SBS mean and standard deviation in study groups	52

V. TABLE LIST

Table 1: Specimens distribution among study groups	49
Table 2: Shapiro-Wilk's test for normal distribution	49
Table 3: Descriptive statistics of SBS in study groups	50
Table 4: One-Way ANOVA test to study the difference in SBS between groups	50
Table 5: Pairwise comparisons of SBS between groups	51



1. ÖZET

Titanyum Dioksit Nanopartiküllerin Ortodontik Bonding Ajanları ve Kompozit Adezivlerin Makaslama Dayanımı Üzerindeki Etkisinin Değerlendirilmesi

Öğrencinin ismi: Dt. Nimat E. Al Akel

Danışman: Dr. Zeynep Ahu Acar

Anabilim Dalı: Ortodonti Anabilim Dalı

Amaç: Bu araştırmanın amacı, TiO₂-NP ortodontik bonding ajanı ve kompozit yapıştırıcının makaslama bağlanma kuvveti üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Bu çalışmada, ortodontik bonding ajanı ve TiO₂-NP ile entegre ortodontik kompozit yapıştırıcının makaslama bağlanma kuvvetini değerlendirmek amacıyla Marmara Üniversitesi Diş Hekimliği Fakültesi Cerrahi Anabilim Dalı'ndan 60 adet çekilmiş sağlam premolar diş kullanılmıştır. Grup A'da, braket uygulaması için bonding ajanına TiO₂-NP ilave edilmiştir. Grup B'de, braket uygulaması için kompozit yapıştırıcıya TiO₂-NP ilave edilmiştir. Grup C, normal bonding ajanı ve adeziv kompozit ile braket uygulaması yapılan dişleri içermiştir. Deney sonrası, tüm grupların makaslama bağlanma kuvveti, Evrensel Çekme Dayanımı test cihazı kullanılarak ölçülmüştür.

Bulgular: bonding ajanına TiO₂-NP eklenmesinin braket-diş arayüzünün kesme bağlanma mukavemeti üzerinde önemli bir etkisinin olmadığı bulundu. Ayrıca, ortodontik kompozit adeziv içine TiO₂-NP'nin dahil edilmesinin, kesme bağlanma mukavemeti üzerinde minimum etkiye sahip olduğu bulundu.

Sonuç: TiO₂-NP'ler, ortodontik tedavi sırasında braket yapışmasının kesme bağlanma mukavemetinden ödün vermeden WSL'ler umut verici bir antibakteriyel ajandır.

Anahtar Kelimeler: Makaslama bağlanma dayanımı; Nanopartiküller, Titanyum dioksit; Ortodontik tedavi.

2. SUMMARY

Evaluation of the Effect of Titanium Dioxide Nanoparticles on the Shear Bond Strength of Orthodontic Bonding Agent and Composite Adhesive

Student Name: Nimat E. AL Akel

Name of Supervisor: Prof. Dr. Zeynep Ahu Acar Department:

Department of Orthodontics

Aim: Evaluation of the shear bond strength of orthodontic bonding agent and orthodontic composite adhesive upon the incorporation of TiO₂-NP.

Materials and Methods: A total of 60 intact extracted premolar teeth were gathered from Marmara University, Department of Oral and Maxillofacial Surgery, to evaluate the SBS of orthodontic bonding agent and orthodontic composite adhesive integrated with TiO₂-NP. The teeth were divided into 3 groups, Group A, B, and C. In Group A, TiO₂-NP was incorporated to the bonding agent used for orthodontic bracket application. In Group B, TiO₂-NP were incorporated to the composite adhesive. Group C would contain teeth that underwent orthodontic bracket application with normal bonding agent and adhesive composite. Post- experimentation, the SBS of all groups were measured using the Universal Tensile Strength tester.

Results: According to the findings, the incorporation of TiO₂-NP into orthodontic bonding agent had no significant effect on the shear bond strength of the bracket- tooth interface. It was also found that incorporating the TiO₂-NP into the orthodontic composite adhesive had minimal effect on the shear bond strength.

Conclusion: TiO₂-NPs is a promising antibacterial agent preventing WSLs during orthodontic treatment without compromising the shear bond strength of the bracket adhesion.

Keywords: Shear bond strength, Nanoparticles, Orthodontic Titanium Dioxide, Orthodontic Treatment.

3. INTRODUCTION AND AIMS

The definition of orthodontic treatment is the way of aligning or improving the appearance of teeth and mastication. Orthodontic treatment not only improves aesthetics of both the face and the teeth but also improves oral hygiene, prevents periodontal diseases, and reduces abnormal excessive stress on both the teeth and the temporomandibular joint aiding in prevention and treatment of temporomandibular joint disorders. Orthodontic treatment avails in prevention of dentoalveolar trauma, management of speech problems, enhancement of social well-being, and generally the quality of life (Benson et al. 2015). The 2 main categories of orthodontic treatment modalities are simple removable appliance techniques and fixed appliance techniques (Horridge et al. 2012).

In fixed orthodontic techniques, the standard clinical practice in bonding orthodontic brackets to etched enamel is the use of light-cure adhesive systems. Light-cure adhesives are popular because they have adequate working time to allow the orthodontist to place the brackets on the patient's teeth and generate strong early bond strength after polymerization. Bis-GMA and inorganic fillers are the most common ingredients in light-cure adhesives. The bracket bond strength of an adhesive is affected by a number of factors. First and foremost, the composition and features of the adhesive material itself, as well as the complex interactions among the various components at the various interfaces (tooth-adhesive-bracket), are directly related to bond strength conduct (PARK, S.-B et al. 2009).

Nanoparticles have been recently introduced into scientific research as they have been shown to have antimicrobial properties that are beneficial in medicine, cosmetics and food packaging. Nanoparticles are particulate dispersions or solid particles having a diameter of 10 to 1000 nanometers. Nanoparticles, nanospheres, or nanocapsules can be obtained depending on the technique of preparation. Nanoparticles have been used abundantly nowadays in dentistry specifically in dental materials (Mohanraj et al. 2007). The oral cavity is rich in microorganisms known as the bacterial flora. Plaque, a bacteria- produced biofilm, is the major cause of dental caries, gingivitis,

periodontitis, and other dental diseases. Major supremacy of nanoparticles used in dentistry is their antimicrobial effects. This is due to their ultra-small sizes thus large surface area-to-mass ratio, and their spectacular physicochemical properties. Metal and organic nanoparticles have been applied in several areas of dentistry because of their broad-spectrum bactericidal properties (Song et al. 2019). During orthodontic treatment and the placement of orthodontic appliances, the accumulation of dental plaque occurs. When there is a greater accumulation of dental plaque, the pH levels decrease, making it a preferable environment for the formation of dental caries and the demineralization of enamel, commonly known as white spot lesions. There are numerous methods to treat white spot lesions that include cooperation from the patient. Latterly, it has been confirmed that antimicrobial nanoparticles can be incorporated in the prevention and treatment of these lesions. Studies have been performed to exhibit the combination of nanoparticles with orthodontic bonding agents, composite adhesives, or glass ionomer cements, and it has been shown that there would be a hinderance in the accumulation of plaque as well as bacterial adhesion (Song et al. 2019).

Though, thus far, silver has been the most commonly investigated nanoparticle in the scope of dentistry, Titanium Dioxide nanoparticles, too, have recently been incorporated more abundantly into industries pertaining to pharmaceuticals and food commerce due to their size and distinctive photocatalytic activity. These properties facilitate titanium dioxide nanoparticles to be antimicrobial in nature. The nanoparticles small size attribute to its facile penetration through the membranes of microorganisms (Weinberger et al. 1934).

Shear bond strength is the main factor, which has to be concerned in the evolution of bonding materials. Shear bond strength is defined as the amount of force required to break the connection between a bonded object and the tooth surface with the failure occurring in or near the adhesive/adherents interface (Ziental et al. 2020). The bonding of metal and ceramic orthodontic brackets is based on a mechanical lock between the adhesive and the attachment (orthodontic bracket). The bond strength of orthodontic brackets bonded to teeth should be sufficient to withstand orthodontic forces applied

during treatment. The ideal orthodontic adhesive should have adequate bond strength. Bond strength determines the amount of force that can be delivered and also has an effect on the treatment duration. Shear bond strength depends on various factors including the adhesive properties of the bonding materials, the attachment at the different interphases such as the tooth to composite interphase and the composite to bracket interphase, as well as the polymerization of the composite bonding material.

This study aims to investigate the effect of incorporating titanium dioxide nanoparticles with bonding agent and composite adhesive on the shear bond strength of orthodontic bracket adhesion. Titanium dioxide has a strong oxidizing power when it is illuminated with UV light, it generates active free radicals to achieve its antibacterial effect and it provides disinfecting solutions for the prevention of biofilm formation. The continual study and use of nanoparticles as a preventive measure in the field of dentistry can benefit both the operator as well as the health of the patients and the structural integrity of their oral cavity.

Therefore, this thesis aims to answer the following questions:

1. Is there significant difference in the shear bond strength between orthodontic brackets bonded to teeth incorporated with titanium dioxide nanoparticles in the bonding agent compared to brackets bonded without nanoparticles addition?
2. Is there significant difference in the shear bond strength between orthodontic brackets bonded to teeth incorporated with titanium dioxide nanoparticles in the composite adhesive resin in comparison to brackets bonded with plain conventional composite adhesive?

4. LITERATURE REVIEW

4.1 Orthodontic Treatment

Until recently, "health" was primarily defined as the absence of sickness disease or disability. For many years, orthodontics has been at odds with a more scientifically acceptable view of "orthodontics and malocclusion" that corresponded to this definition of health. In recent years, the definition of health has been broadened to encompass a complete condition of physical, mental, and social well-being. This transformation in our perception of medicine and dentistry has resulted from the emergence of the concept of health. It has given rise to a new health viewpoint that places a greater emphasis on improving one's quality of life (Liao et al., 2020). The foundation of orthodontic therapy is the application of sufficient forces to move teeth through the alveolar bone without causing permanent damage to the teeth or their attachments to the bone. Various movements, such as tipping, rotational, physical, torque, and vertical movement, can occur during orthodontic treatment. There are two types of orthodontic appliances: detachable appliances and fixed appliances. They provide a controlled force to achieve the correct tooth movement (Mirhashemi & Jazi, 2021).

Fixed appliances have attachments that are directly attached to the teeth, whereas removable appliances have components attached to a framework that retains the appliance in place. Fixed appliances have several advantages over removable appliances: they do not become dislodged in the mouth, shortening treatment time, requiring less patient competence to handle, and allowing for more tooth movements (Pourhajibagher & Bahador, 2021). The attachments are an important part of the success of fixed appliances. During orthodontic treatment, bands and brackets are firmly fastened to the teeth to avoid loosening (Nanda et al., 2021).

4.2 Orthodontic Bonding

4.2.1 Biological components of the orthodontic bonding process

4.2.1.1 Enamel structure, composition and formation

Dental bonding comprises both enamel and dentin bonding for the effective attachment of dental components during restorative treatment. Because of the physical variations between enamel and dentin, the bonding process changes significantly. Orthodontic brackets, on the other hand, are virtually solely adhered to the enamel surface during treatment, obviating the need for dentin bonding (Jasso-Ruiz et al., 2019). Enamel is the strongest and most mineralized substance in the human body when compared to the rest of the body. Enamel production, size and shape, susceptibility to cavities, and shade vary from person to person. The enamel structure is made up of 96 percent minerals, 3 percent water, and 1 percent organic matter by weight. The majority of the mineral content in enamel is comprised of calcium salt in carbonated hydroxyapatite crystals (Gomez et al., 2021).

These highly orientated crystals have a volume over 1000 times that of comparable crystals in the bone, dentin, and cementum. The crystals are arranged into prisms, each measuring around 4 μ m in diameter and extending from the dentin (Eldebany et al., 2020). Amelogenins and enamelines are two types of enzymes found in the 1 percent of organic materials. During amelogenesis, these enzymes aid in the formation of the enamel frame for mineral deposition (Kotta et al., 2020). The development of the dentinoenamel junction for dentin and enamel kicks off amelogenesis. On the enamel side, crystal nuclei stretch into long, evenly spaced ribbons that increase in size to become ameloblasts begin to produce enamel proteins into the extracellular matrix (Wu & Tang, 2018). This matrix contains many hasps by the formation of the ameloblasts. Over time, the hasps become mineralized. If this process is disrupted, the enamel crystals that follow are likely to be exceedingly thin and hypoplastic. Proteinases are released after the crystals reach a certain length, halting their growth and allowing the mineralization process to begin. As minerals are deposited, the

enamel crystals expand in width and thickness, and they begin to solidify. This period lasts approximately three to four years. The enamel that forms if this process is disrupted may be pathologically soft or porous (Behnaz et al., 2018). The tooth is ready to erupt after the development phase has been completed. The enamel surface becomes encased by a salivary pellicle, among other things, when exposed to the oral cavity during eruption (Carrouel et al., 2020).

4.2.1.2 Salivary pellicle

Saliva is used for several things, including lubrication, protection, and digesting. Saliva acts as an acid barrier, adding strength and diminishing the effectiveness of potentially harmful substances, and allowing poisonous substances to be eliminated by salivary flow. Saliva also contains a high quantity of proteins, including as glycoproteins and proline-rich proteins, that help create the oral salivary pellicle (Kotta et al., 2020). Further research has revealed that the enamel absorbs certain salivary biopolymers, and that this dynamic biofilm is what regulates all interactions between teeth and the oral cavity. After being in contact with saliva, the pellicle forms on the tooth surface and grows in less than an hour. This film appears to be a complex network with a homogeneous density throughout its structure when examined under a scanning electron microscope (SEM). The pellicle obtained from the buccal surface of the teeth is thicker than the pellicle obtained from the lingual surface of the teeth, according to the orthodontist. Once fully developed, the film lubricates the teeth with which it comes into contact, minimizing abrasion and attrition while also protecting the teeth from acidic attack (Yin et al., 2020).

4.2.1.3 Saliva properties and dental caries

Saliva is a key component in maintaining the oral cavity's balance. Saliva aids speech, mastication, cleansing, digestion, antimicrobial activity, and the capacity to carry ions that aid in remineralization (Pinget et al., 2019).

4.2.2 Chemical Components of Orthodontic Bonding

4.2.2.1 Basis of orthodontic bonding

The notion of orthodontic bonding is based on the mechanical locking of an adhesive to etched tooth enamel surface, as well as mechanical locks designed at the base of the orthodontic attachment. As a result of this notion, proper orthodontic bonding needs careful consideration of three system components: the tooth surface and its preparation, the nature of the attachment base, and the bonding substance used (Asiry et al., 2019).

4.2.2.2 Bonding technique

All orthodontists have the same goal in mind while treating patients professionally: to achieve great results. Treatment success is reliant on accurate bracket placement during bonding, which will improve subsequent periods of orthodontic treatment and increase predictability of results, no matter how difficult it is (Garcia et al., 2019).

4.2.2.2.1 Direct bonding

Direct bonding is the process of placing brackets directly on the tooth surface without the use of a transfer tray. When brackets are being positioned intraorally, this technique can be used effectively in a clinical routine. When opposed to indirect bonding, one of the main disadvantages of this procedure is that the orthodontist must be able to properly and swiftly determine the optimal attachment position and transfer it to the bonding position. As a result, the possibilities of getting accurate measurements or good bracket position are low. Direct bonding is considered as not providing the same level of bracket placement accuracy as indirect bonding. Direct bonding, on the other hand, has the following benefits: it is simpler, faster (especially if only a few teeth are to be bonded), and less expensive because laboratory manufacturing processes are not necessary (Aguilar et al., 2020).

4.2.2.2 Indirect bonding

In indirect bonding, brackets are positioned and prepared for placement in a laboratory setting and a transfer tray is produced for clinical delivery of the brackets . This method allows for a better three-dimensional depiction of tooth placement and, as a result, more accuracy when fitting brackets because it is accomplished in the laboratory and then transferred to the patient's mouth using custom-made trays (Mobeen et al., 2021). Indirect bonding over direct bonding lowers bracket placement faults in one of three perceptual aspects: height, mesiodistal position, and angulation, according to Hodge et al (2004). Furthermore, indirect bonding has the following benefits: 1) less chair time, 2) fewer compensation bends, 3) less physical and emotional stress due to the therapeutic process being simpler than direct bonding, and higher patient satisfaction (Siddiqui et al., 2019).

4.2.2.3 Bonding procedure

4.2.2.3.1 Prophylaxis

An organic pellicle coats the tooth surface, consisting of a protein film produced from saliva that adheres to the enamel surface through selective glycoprotein binding. This coating has been shown to lower the strength of the bond between the bracket base, the tooth, and the adhesive resin. As a result, cleaning the tooth surface before performing chemical etching is preferable. When dealing with orthodontic brackets, conventional brushing is insufficient to eliminate this organic layer (Gea et al., 2019). Prophylaxis begins with the use of non-fluoride pastes and polishing brushes or rubber cups with a low-speed handpiece ((Mirhashemi et al., 2021). Enamel loss is to be expected during prophylaxis. Initial rubber cup prophylaxis has been seen to remove 10-15 μm from the enamel, whilst the bristle brush only removes about 10 μm (Al Azzawi et al., 2021).

Based on the findings of previous experiments, this process can be clinically avoided using typical acid-etch methods. As a result of these tests, it has been determined that prophylaxis is not required for effective connection with common acid etching

systems. Pre-traditional composite or resin modified glass ionomer etching showed no direct bonding impact on the in vivo bond failure rate, according to Kielan-Grabowska et al., (2021).

The use of air abrasion (micro-etching) in the preparation of enamel surfaces is a relatively new procedure. Subramani et al. (2020) performed an in vivo split mouth investigation with acid-etched and micro-etched teeth in each patient. For a six-month period, the bracket failure rate was not statistically different, according to the findings. Several in vitro investigations have yielded similar results (Moradpoor et al., 2021). Ozone has also been used to prepare enamel without causing an increase in SBS levels (Zhu et al., 2018).

In regard to enamel pre-preparation, fluoride has been used in a variety of ways. Fluoride paste (Souza et al., 2018) and fluoride varnish as a pre-preparation have been demonstrated to enhance bracket failure in prospective split mouth studies (Yu et al., 2020).

4.2.2.3.2 Enamel conditioning

To make a tooth more adhesion-friendly, phosphoric acid etches according to the enamel etch pattern; a powerful acid is required. The acid removes minute antiprismatic enamel, resulting in a porous surface that improves the overall bonding surface while also allowing adhesion promoters to permeate the enamel pores, providing safe micromechanical retention (Papp et al., 2020).

To show his conceptual evidence, Buonocore began using an 85 percent phosphoric acid etch solution that was applied to the enamel for 30 seconds in 1955. Since then, the acid type and concentration, as well as the duration of acid contact with the enamel, have all been investigated (El-Gazzar & Ismail, 2020).

Kanniyappan et al. (2015) found that dicalcium phosphate dihydrate was an insoluble by-product at concentrations less than 27%, while monocalcium phosphate

monohydrate was a soluble by-product at concentrations greater than 27%. (Mok et al., 2020).

The soluble product may be rinsed away when the acid is removed from the tooth, but the insoluble by-product may make bonding chemicals difficult to work with. The duration of the acid etch in relation to the enamel surface has been studied in a number of studies. Mirhashemi et al., (2021) found that when the enamel surfaces were grained within 15 seconds and 60 seconds, there was no significant difference in bonding force. The clinical directive was extended for another 15 seconds due to higher enamel disintegration and thus more damage to the teeth throughout the 60 second trials. Because etching destroys hydroxyapatite crystals and provides micromechanical retention, adhesion promoters can penetrate and resin tags can develop throughout the binding process (Sakaki et al., 1994).

When phosphoric acid concentrations fall, the duration of the resin tags decreases (22 microns for 35% phosphoric acid, 12 microns for 20%, 9 microns for 10 percent and 5 percent, 5 microns for 3%) (Daub et al., 2006). When the acid etch concentration was increased by more than 35%, the length of the resin tags was also reduced, despite the fact that the total etch depth was increased. Enamel damage was almost certainly increased as well (9 microns for 65%) However, the link between resin tag length and binding strength may no longer exist, and this link could be attributable to the monomer's ability to penetrate enamel rods and crystallites (Math et al., 2021).

While it was shown that a strong bond strength is independent of an optimal etch pattern, surface etch enamel models were split into three groups, with more models being suggested (Jasso-Ruiz et al., 2020).

- Type 1: The enamel rods are dissolved and there is preferential prism core etching (thought to be most favourable for bonding).
- Type 2: The area around the enamel rods is dissolved and there is preferential prism periphery etching.
- Type 3: A combination of types 1 and 2 (considered the least favourable for bonding)

There have been some debates about whether the enamel surface etching of the anterior and posterior teeth differs. Similar studies in maxillary and mandibular teeth have revealed changes in the etch grade (Mirhashemi & Jazi, 2021). The grade of etch in the mandibular teeth is less favorable and has been continuously decreasing, according to the findings. These differences may be due to bracket adaptation, higher strength, increased humidity, and a rise of "prismless" enamel in the back teeth (Ziental et al., 2020).

4.2.2.3.2.1 Air abrasion

The use of a high-quality flux of aluminum oxide particle matter (29,50,90 μm) in an air abrasive "sandblasted" approach for the treatment of enamels has been listed. Some researchers believe that air-abrasion can be coupled with direct orthodontic brackets without the need for acid etching (Pourhajibagher et al., 2020). Other studies have found that air-abrasion preparation of the enamel surface reduces bond strength significantly and should not be used as an enamel conditioner in ordinary clinical practice (Behnaz et al., 2018).

Van Warveren Hogervorst (2000) conducted a research to examine the loss of surface enamel and shear strength caused by acid etching against sandblasting, and determined that sandblasting is not a viable alternative to acid etching.

The study found that the binding strength of sand blasting groups is significantly lower than that of etching groups, proving that sand blasting is not a substitute for acid etching (Chambers et al., 2017).

To test the shear bond strength of composite resin to the enamel surface, EspinosaCristóbal et al., (2018) used phosphoric acid, air abrasion alone and in combination with acid etching. There were no significant variations across the surface preparations (Hailan & Al-Khatieeb, 2018). On the other hand, Baranowska-Wójcik et al. (2020) demonstrated that using air abrasion before phosphoric acid increased the bond strength of orthodontic brackets.

4.2.2.3.2 Laser etching

Laser etching has been discovered to give a good bonding surface as well as a high level of resistance to caries (Musial et al., 2020). Although some studies comparing acid or self-etching with laser etching found that laser etching is preferable for orthodontic bonding (Farzanegan et al., 2021), others have questioned its efficacy due to its larger standard deviations and coefficients of variance, as well as technically induced irregular surface topography (Gul et al., 2020).

In the literature, there are conflicting research on the use of lasers for enamel etching. While some authors claim that the average laser etching strength is lower than that of acid etching (Toodehzaeim et al., 2018), others claim that laser irradiation has positive results (Yassaei et al., 2020). In other papers, the authors discovered that sandblasting and laser irradiation (0.5, 0.75, and 1 W) are unable to etch the enamel suitable for orthodontic molar tube bonding, but that 1.5 and 2.0 W laser radiation can be a viable alternative to conventional acid etching in comparison to sandblasting and laser irradiation (Al Tuma & Yassir, 2021).

4.2.2.3.3 Priming

In the resin composite system, unfilled resins were used as a bonding agent. The main distinction between these fluid bound resins and resin composites is that they lack filler particles. Fluid bonding agents differ from their composite counterparts in that they have higher ratio of co-monomers to monomers (Kambalyal et al., 2018).

The connection between the composite resin and tooth structure has been termed "adhesive promoters" by Sánchez-Tito & Tay, (2021). The adhesive enhancer functions as a weaving agent that penetrates the enamel, forming resin tags that make the adhesive promoter micromechanically interlocking (Uysal et al., 2010).

Traditional adhesives are hydrophobic, making them vulnerable to saliva contamination, which promotes rapid remineralization and weak bonding of the etched enamel surface (Aileni et al., 2021).

According to literature, an additional technique of preventing enamel demineralization by acid-etching procedures can be utilized to improve the retention of the etched enamel and reduce marginal leakages in order to increase bond strength by using adhesion promoters in the orthodontic bonding system (Assery et al., 2019).

A thin layer of primer is applied to the etched tooth surface. It is suggested using gentle bursts of air for around 2 seconds to assist thin the priming layer even more. This is a two-stage procedure. Because of their ease of use and effectiveness, self-etching primers have become increasingly popular. The enamel etching and priming are combined in one step with these self-etching primers making it incredibly convenient for the doctor because both processes may be completed at the same time (Andriani & Purwanegara, 2017). These three-part self-etching primers come in a set of three. Phosphoric acid esters, methacrylate, photosensitizers, and stabilizers are among the first. Water and fluoride are combined in the second section, and material is applied with a micro-brush in the third section. When the two compartments are combined, their contents blend together and become activated (Toodehzaeim et al., 2018). This mixture is then applied to the enamel surface with a micro-brush and rubbed in for at least 3 seconds (Salehi et al., 2018). It's worth noting that the hydrophilic nature of self-etching primers, as well as their reduced susceptibility to moisture, is another advantage (Behnaz et al., 2018). Self-etching primers have been shown in certain studies to have much lower shear-bond strength than traditional methods (Venkatesan et al., 2020), while most of them acknowledged that the survival duration varied (Satti et al., 2021). In contrast, other studies have found that SBS of SEPs are no better or only slightly better than traditional technologies.

4.2.2.3.4 Bracket adhesives

For intraoral adhesion of orthodontic attachments to the teeth, dental cements and adhesives are used (Mollabashi et al., 2020). Attachments with appropriate bond strengths and minimal failure rates are required for the performance of a fixed orthodontic appliance. The adhesive and its connections with the enamel and bracket base are subjected to a variety of stresses in the mouth, resulting in a convoluted

pressure distribution inside the adhesive and its connections with the enamel and bracket base (Pourhajibagher & Bahador, 2021).

When there is a bond failure between the bracket and the tooth, the treatment progresses much more slowly, and the materials must be changed, which can be costly. It costs not just the clinicians' time, but also the time of the patients. When it comes to bracket adhesion, there are a few principles to follow. The adhesive should ideally be strong enough to keep the brackets on the teeth for the duration of the treatment, the bond between the tooth and the appliance should not be too strong to prevent damage to the tooth surface when the appliance is removed, and it should be easy for the orthodontist to use (Chen et al., 2020).

Acrylic and diacrylate resins are the two basic forms of orthodontic adhesives. Diacrylate resins, on the other hand, became more popular than acrylic adhesives as a result of their superior strength (Farzanegan, et al., 2021). The most often utilized diacrylate resins are Bisphenol A Glycidyl Dimethacrylate (Bis-GMA) monomers (Wilson, 1988). Monomers of Bis-GMA are generally made up of C=C and double bonds at the end of each monomer chain (Song & Ge, 2019). Polymerization, which improves the stiffness of the final polymer molecule into polymers and their connection to the polymeric chains, is also included in these 'vinyl' groups. Triethylene glycol dimethacrylate (TEGDMA), a viscous liquid and a more fluid monomer, was converted into composite resin for use in dentistry (Pourhajibagher et al., 2019). The usual TEGDMA ratio is between 70 and 75 percent Bis-GMA and 25-30 percent TEGDMA; however, the higher the TEGDMA ratio, the greater the likelihood of polymerization shrinkage (Tawfik et al., 2019). As a result, a composite material can be created by mixing inorganic fillers in the resin with the Bis-GMA/TEGDMA mixture (Ahmadi et al., 2020). The fillers are constructed of glass or ground pulverized quartz that have been treated with a saline coupling agent to create a bond between the inorganic hydrophilic filler and the hydrophobic resin matrix (Babanouri et al., 2021).

Orthodontic composite adhesives differ from restorative bulk composites in that they contain a higher number of co-monomers, which reduce the viscosity or adhesive composite viscosity. Orthodontic adhesives with a lower viscosity facilitate greater diffusion into the enamel rods and increase interfacial adaptability between the enamel and bracket base (Meher Vineesha et al., 2021).

4.2.2.3.4.1 Chemically cured adhesives

The early bracket bonding systems used chemically produced composite adhesives (Florez et al., 2018). The resin's self-curing polymerization is accomplished using a two-paste method that begins right after mixing. As a result, the operator is unable to monitor time, which has an impact on bracketing precision and placement on the tooth surface (Aljubour & Aljubour, 2020). Another downside of this approach is that air bubbles are introduced into the resins during hand mixing, causing porosity and inhibiting polymerization, weakening the bond strength (De Almeida et al., 2018).

4.2.2.3.4.2 Light cured adhesives

The utilization of visible light to cure the composite resins that bond the orthodontic equipment to the enamel is a discovery that has been specified during the 1960's (Eslami et al., 2021). Because of the ease of use, extended working time, improved bracket alignment, easy cleaning, and quick curing of the composite materials, visible light-curing composites became the favored choice of adhesive (De Stefani et al., 2020).

Since the early 1980s, light-cured adhesive systems have been commercially accessible in the United States. The interaction between the adhesive catalyst and the photons generated from the light source polymerizes these adhesives (Teixeira et al., 2021). The wavelength of light emitted by the curing light must be sufficient for the catalyst to begin the process. Large, heavy, corded light curing equipment have been replaced with lightweight portable LED (light-emitting diode) systems.

4.2.2.3.4.3 Dual cured adhesives

In the 1980s, dental resins that were both light activated and chemically cured were introduced (Liao et al., 2020). The third category of orthodontic adhesives is dualcured adhesives. These adhesives have an initial polymerization caused by light exposure, followed by a chemical treatment. The key benefit of the dual cure is that it gives the operator more time to place brackets and remove excess adhesive (within the span of 4 minutes). These polymers offer a higher bonding power, which may or may not be necessary in clinical applications for light-curing adhesives (Pourhajibagher & Bahador, 2021). As a result, light-curing composites have maintained their highest level of appeal in the orthodontic community. Although micromechanical interlocking is thought to be a prerequisite for effective bonding, the potential benefit of additional chemical interactions between functions, monomers, and tooth substrate components has received a lot of study (Nanda et al., 2021).

4.3 Bond Failure

Bracket failure during treatment is an affliction of orthodontists that needs additional time in-office, increased costs for the repair of any displaced brackets, and, in some situations, a rising overall care time (Beckwith et al., 1999). (Oesterle et al., 2008). For atypical enamel surfaces, such as deciduous teeth, hypocalcified enamel, and fluoride enamel, bonding techniques are frequently ineffective (Carrouel et al., 2020). According to Kotta et al., (2020), the typical loose bracket failure rate was 11%, but the bonding of the brackets varied. Between the teeth, there were many debonds. The initial maxillary molars had the highest rate of debonding (27%) while over 90% of incisor and canine brackets remained in place throughout treatment. According to research, between 2% to 6% of indirectly bonded brackets fail for a variety of reasons (Yin et al., 2020). There was no difference in bond failure rates between direct and indirect bonds (Pinget et al., 2019).

Pushpalatha et al., (2021) found a high risk of phosphoric acid bond failure of 37 percent in patients with dental fluorosis. A variety of solutions have been developed to reduce the rate of bond failure, including the use of various adhesive materials, new bracket base constructions (Hernández-Gómora et al., 2017), enamel etching, and packaging methods (Hernández-Gómora et al., 2017) (Sharon et al., 2018). Several curing lights (Evans et al. 2002) and lasers were used to cure composite resin to increase the bracket bond's performance (Asiry et al., 2019).

4.4 White Spot Lesions In Orthodontic Treatment

White spot lesions are opacities caused by the demineralization of the tooth's enamel surface. When the pH values in dental plaque begin to fall due to acid generating bacteria in the presence of a high concentration of carbohydrates, demineralization occurs. Enamel lesions that are apparent to the naked eye are indicated by this symptom (Garcia et al., 2019). White spot lesions range from 2% to 96% after orthodontic treatment (Aguiar et al., 2020). There are preventive and/or therapeutic approaches for avoiding demineralizing and controlling/treating white spot lesions that have already developed such as use of sealants, casein phosphopeptide amorphous calcium phosphate and ICON resin infiltration.

4.5 Shear Bond Strength

4.5.1 Shear bond strength universal testing machine-tensile tester

Universal Testing machines “UTM” – tensile tester is the most common machine that is used for tensile tests. It comes with wider verities for various materials and has various capacities of load ranging from, 5 kN, 50 kN to 600 kN. This Universal Tensile Testing Machine uses the motor to drive the screw to move fixtures, fixing sample between the upper and lower fixture and pulling the sample by the upper fixture upward with specified speed. The load cell connecting with the upper fixture will sense the force and then convert it into a voltage sign to the display screen. Force value will be displayed automatically on the screen. It has been efficient and effective in tensile

testing as well as shear bond strength. The universal tensile testing machine is considered the “gold standard” in terms of accuracy and precision (Shamsuri & Darus, 2020).

It is advantageous to use Universal Testing Machine-Tensile Tester because it only takes one machine to take a variety of tests such as tensile testing, sheer testing, compression testing, peel testing, bend testing, puncture testing among other required tests. It is capable of pulling, stretching, as well as compressing materials until they reach their breaking limit. A Universal Tensile strength tester is used to determine how strong a material is. It also finds out how much the material can be stretched. Universal Tensile strength tester can also be used to determine the stiffness of the material as well as how much tension the material can absorb before it reaches its breaking limit. The testing machine is designed to determine the stress-strain curves of polymer materials such and particularly metallic films deposited onto polymeric substrates.

4.5.2 Shear bond strength in orthodontics

Shear bond strength is the factor of main concern in the evolution of bonding materials. The bond strength of the orthodontic bracket must be capable of withstanding the forces that are usually applied during the orthodontic treatment. The optimal shear bond strength (SBS) of the bracket to enamel is expected to be capable of preventing bracket debonding during treatment. It is not expected to cause enamel damage during debonding. Also, it should keep the enamel intact after treatment. Therefore, clinicians need to achieve this bond with an approach that is easy and fast while ensuring maximum patient comfort. According to Reynolds, 5.9–7.8 MPa resistances are enough to withstand masticatory forces (Reynolds, 1975). Bishara et al. made a comparison between the bond strengths of an acidic primer and composite resin with a conventional adhesive system. They found the mean bond strengths to be about 10.4 and 11.8 MPa, respectively. The shear bond strengths of self-etching primers vary from 2.8 to 16.6 MPa (Reynolds, 1975).

A standard orthodontic adhesive should have sufficient bond strength and at the same time be able to maintain perfect enamel after debonding. For this reason, researchers have been working towards achieving the best quality and gentlest procedures for bonding orthodontic brackets. Self-etching primers produce a smoother etch pattern, and scanning electron microscope (SEM) tests demonstrate that these conditioners result in shorter resin tags (Sharma et al., 2014). The ideal result from bracket bonding to any surface is an attachment that is strong enough to withstand the stresses of orthodontic therapy.

The amount of force delivered and the length of therapy are both determined by shear bond strength. The strength of a shear bond is determined by a number of elements. The adhesive characteristics of the bonding materials, as well as the attachment at various interphases such as the tooth to composite interphase and the composite to bracket interphase, are examples of such parameters. The polymerization of the composite bonding material also affects shear bond strength. The procedure of bonding involves processes such as etching, primer solution, and the application of adhesive, which is followed by the application of composite. There are various adhesives generations that have been developed for the purpose of improving the bond strength as well as reducing the duration (Shaik et al., 2018). Additionally, the search for methods that are capable of improving the bond strength is still going on.

4.6 Nanoparticles

Nanoparticles are particles of issue that are somewhere in the range of 1 and 100 nanometers (nm) in measurement. The term is now and again utilized for bigger particles, up to 500 nm, or filaments and cylinders that are under 100 nm in just two ways. Nanoparticles are not basic particles themselves. In this manner, they are made out of three layers: (a) The surface layer, which might be functionalized with an assortment of little atoms, metal particles, surfactants, and polymers. (b) The shell layer, synthetically unique material from the center in all perspectives, and (c) The center, which is basically the focal segment of the nanoparticles, typically alludes to

the nanoparticle itself. These outstanding attributes make these materials get the enormous interest of specialists in the multidisciplinary field (Khan et al., 2019).

Nanoparticles can be classified into various types, according to their size, shape, and properties of the material. There are classifications that differentiate between organic and inorganic nanoparticles. Organic nanoparticles include liposomes, dendrimers, and polymeric nanoparticles. On the other hand, inorganic nanoparticles include quantum dots, fullerenes, and gold nanoparticles. The other classifications group nanoparticles with relation to whether they are ceramic, carbon-based, polymeric, or semi-conducting. Additionally, nanoparticles can also be grouped as hard, for instance, titanium dioxide (titania), silica dioxide (silica) particles, and fullerenes or as soft for instance, liposomes, nanodroplets, and vesicles. The classification of nanoparticles is typically based on their application, like in therapy or diagnosis versus basic research, or may be related to their way of production (Khan et al., 2019).

Nanoparticles have three major physical properties, all of which are interconnected: (1) Nanoparticles are very mobile in their free state; for example, a 10nm diameter nanosphere of silica has a sedimentation rate of 0.01 mm/day in water in the absence of any other external impact; (2) Nanoparticles have large specific surface areas; for example, a teaspoon of 10-nm-diameter silica nanospheres has more surface area than a dozen doubles-sized tennis courts; 20% of all atoms in each nanosphere are usually located at the surface; and, finally, (3) Nanoparticles may exhibit quantum effects. Hence, nanoparticles come in a variety of compositions, depending on the product or application (Khan et al., 2019).

4.6.1 Nanoparticle-Based Technologies

Nanotechnology is used in many aspects of our daily lives, including medical. It is possible to study and modify atoms, chemical bonds, and molecules present between various compounds using nanotechnology. The term "nano dentistry" refers to the application of nanotechnology in the dental discipline. The chemical, physical, and biological aspects of nanostructures are all considered while selecting a nanoparticle

for usage in the field of nano dentistry. To construct the functional structure, several atoms or molecules are frequently added. Nanostructures are employed in dental advances and diagnosis. Oral disease prevention medications, prostheses, and tooth implantation all use nanoparticles.

In general, nanoparticle-based technologies offer maximized opportunities for improvement in sustainability, efficiency, and speed of the processes that exist already. This is achievable because nanoparticle-based technologies employ less material, with a considerable proportion of it already in a more "reactive" condition than materials used in standard industrial processes. Other possibilities for nanoparticle-based advancements include the use of nanoscale zero-valent iron (NZVI) particles as fielddeployable technologies for removing organochlorine chemicals from the environment, such as polychlorinated biphenyls (PCBs). NZVI particles can permeate rock layers in the ground, killing the reactivity of organochlorines in deep springs as a result. Nanoparticles have a variety of applications, including those that stem from controlling or orchestrating matter at the nanoscale to create better coatings, composites, or added substances, as well as those that explore the particles' quantum impacts (e.g., quantum spots for imaging, nanowires for atomic hardware, and advancements for spintronics and sub-atomic magnets) (Muhammad et al., 2017).

4.6.2 Nanoparticle Applications in Materials

Most of the unique properties of nanoparticles are related specifically to the sizes of the particles. Thus, normal endeavors have been made to catch some of such properties by joining nanoparticles into composite materials. An illustration of how the extraordinary properties of nanoparticles have been put to use in a nanocomposite material is the advanced elastic tire, which regularly is a composite of an elastic (an elastomer) and an inorganic filler (a building up a molecule, for example, carbon dark or silica nanoparticles).

4.6.3 Nanoparticles in Medicine

The fast development of nanotechnology for biological purposes has had a significant impact on medicine. Nanotechnology enables the nanometer-scale assembly and control of materials. This enables the development of new treatment equipment, as well as devices for analyzing, monitoring, and controlling organic structures. Nanomedicine is the word used to describe this type of nanotechnology use in the realm of medicine. According to the American Society for Testing and Materials (ASTM), the most often employed nanotechnology stages in nanomedicine are particles with two or more nanometer measurements (Mauricio et al., 2018). These nanoparticles have better physical and chemical characteristics than their bulk counterparts. A high surface-area-to-volume ratio and a unique quantum size effect that results in distinct electronic structures are two of these specific characteristics (Singh, 2016). Nanoparticles' properties are determined by their shape and size, as well as their content (Ghosh Chaudhuri & Paria, 2011). In general, controlling the form and size of nanoparticles is necessary for creating monodispersed nanoparticles and promoting their uptake by cells. This reduces aggregation (Chithrani & Chan, 2007).

Nanoparticles' characteristics have led to their use in biomedical applications as therapeutic, diagnostic, and carrier agents (Bao et al., 2013; Celardo et al., 2011). Because their surface-volume ratio is greater than that of other particles, some applications, for example, can adhere to, absorb, or transport other molecules (De Jong, 2008). They can also be modified or created using two or more components to improve their physical characteristics.

4.6.3.1 Types of Nanoparticles.

Nanoparticles are classified into three groups based on the chemical components they contain. Organic nanoparticles (liposomes and polymers), inorganic nanoparticles (metals, metal oxides, ceramics, and quantum dots), and carbon-based nanoparticles are the three types of nanoparticles. Nanoparticles, for the most part, retain the chemical characteristics of their mass elements. This comes in handy when selecting a

nanoparticle for a biomedical application. The most common nanoparticles employed in nanomedicine are listed below and summarized in Figure 1.

4.6.3.1.1 Liposome nanoparticles.

Spherical vesicles with a lipid bilayer membrane containing an aqueous material are this form of nanoparticle. The amphiphilic chemicals employed to make these vesicles are similar to biological membranes, which are used to improve the safety and efficacy of numerous medications (Panahi et al., 2017). The dynamic chemical can be hydrophilic and thus be found in the fluid area, or it can be hydrophobic and remain in the lipid layer. The blend of a liposome relies fundamentally upon the accompanying boundaries: (a) the physicochemical properties of the material to be entangled and those of the liposomal complexes; (b) the concept of the medium in which the lipid vesicles are broken down, the grouping of the captured material, and its likely poisonousness; (c) further cycles involved in the manufacture, application, or conveyance of the vesicles; (d) vesicle scatter, size, and time range of usability for the suggested application; and (e) clump to clump manufacturing and plausibility of largescale fabrication of safe and effective liposomal items.

Liposomes can be produced by sonicating a dispersion of amphipathic lipids in water, such as phospholipids. Low shear rates, in fact, can produce multilamellar liposomes. The original clusters are usually made up of several layers. As a result, they produce ever smaller liposomes until they arrive at unilamellar liposomes. Because sonication might disrupt the structure of the drug to be encapsulated, it is the "rough" precursor for the synthesis. Furthermore, a variety of methods, such as extrusion and the Mozafari method, can be employed to create human-use materials. Using lipids instead of phosphatidylcholine can make liposome preparation much easier (Mozafari, 2005).

4.6.3.1.2 Polymeric nanoparticles

Biocompatibility and biodegradability are well-known properties of several i.e. polymethyl methacrylate (PMMA), polylactides (PLA), or polyethylene glycol, are used to make polymeric nanoparticles (PEG). They have a lot of possibilities when it

comes to surface alteration. They also have a superior pharmacokinetic profile since their dimension and ability to dissolve can be adjusted throughout the manufacturing process. Polymeric nanoparticles can be prepared using a variety of processes. Emulsification-solvent diffusion, emulsification-solvent evaporation, and emulsification–reverse salting-out are a few of these processes (El-Say & El-Sawy, 2017).

There are also single-step approaches including nanoprecipitation technologies, dialysis, and supercritical fluid techniques for preparing polymeric nanoparticles. Fourier transform infrared spectroscopy (FTIR), energy dispersive spectroscopy (EDS), Raman, X-ray photoelectron spectroscopy (XPS), and zeta potential (ζ potential) are some of the techniques that can be used to analyze surface features. Such techniques bring out the chemical composition of the surface of the polymeric nanoparticle and that of functionalization. However, only microscopic techniques can be used to determine shape and morphology. It is crucial to consider the nature of polymer-drug interactions, as well as the polymer type and its physicochemical properties, in order to increase drug absorption and prolong dissolution rate (Crucho & Barros, 2017).

4.6.3.1.3 Metallic nanoparticles

Magnetic metals and precious metals are examples of metallic nanoparticles. Gold and silver are precious metals, while iron oxide, cobalt, and manganese doped ferrites are magnetic metals. Metallic nanoparticles, i.e. gold (Au), exhibit distinctive optical and electrical features. These metallic nanoparticles are non-toxic and biocompatible. Because of their negative charge, they have a surface that can be changed with other biomolecules (Oyelere, 2008). Gold surfaces are good for producing ligands with functional groups like phosphines, thiols, mercaptans, and amines that have a great affinity for the gold surface, such as proteins, oligonucleotides, and antibodies. Imaging approaches for the diagnosis of many diseases have used gold nanoconjugates combined with gold nanoparticles with considerably increased limited surface plasmon reverberation.

Gold nanoparticles (AuNPs) can be employed for cancer imaging, according to Dreaden et al., 2012. This would be accomplished by delivering gold nanoparticles into the nucleus of cancer cells in a targeted manner. This emphasizes the significance of nanoparticles in biomedicine (Dreaden et al., 2012). To do so, they used 30 nm AuNPs to construct an arginine–aspartic corrosive glycine peptide and an atomic restriction signal peptide. The generated arginine–aspartic corrosive glycine peptide binds to v6 integrin receptors on the cell's surface, and the lysine–lysine–lysine–arginine–lysine (Gao et al., 2005).

4.6.3.1.4 Metal oxide nanoparticles

Metal oxide nanoparticles have synergistic and cancer-prevention capabilities, as well as synthetic safety, optical qualities, and biocompatibility, making them suitable for a variety of biomedical applications. Iron oxide (Fe_3O_4), titania (TiO_2), zirconia (ZrO_2), and, more recently, ceria (CeO_2) are the most often used (Andreescu et al., 2011). Titania NPs, for example, are incorporated into therapeutic embeds due to their surfaces being biocompatible, while CeO_2 NPs are gaining popularity due to their synergist and cell reinforcement limit, allowing them to act as cancer prevention agents and calming specialists (Celardo et al., 2011). Because of its biocompatibility, compound stability, and optical properties, TiO_2 is a well-studied material with important uses, such as a biosensor (Andreescu et al., 2011). Cerium dioxide (CeO_2) nanoparticles, also known as nanoceria, are another metal oxide nanoparticle that is gaining popularity due to its potential biological applications. Nanoceria has the one-of-a-kind characteristic of being able to flip through oxidation states (Celardo et al., 2011), making it ideal for treating oxidative stress-related diseases.

Permeable silica nanoparticles are a variety of metal oxide nanoparticles (SiO_2). Because of their one-of-a-kind qualities, such as vast explicit surface territory, porevolume, controlled molecular size, and high biocompatibility, these nanoparticles are finding new applications in biomedicine. Mesoporous silica nanoparticles have been researched for use in pharmaceutical research in biomedicine and biosensors due to these features (Wang et al., 2015). Other NPs, i.e. zinc oxide (ZnO), have been

demonstrated to be viable for drug delivery and bioimaging in studies. A unique feature of ZnO nanoparticles is that the surface should be modified to ensure their stability in organic frameworks, as they are easily dissolved in water and acidic environments. Moreover, because the transmission capacity of ZnO nanoparticles is in the UV band, which cannot penetrate tissues and can be detrimental to cells and tissue, they must first be doped before being used for fluorescence imaging (Zhang et al., 2013).

4.6.3.1.5 Ceramic nanoparticles

Ceramic nanoparticles are inorganic mixtures with permeability properties that have recently gained popularity as drug delivery vehicles. They have the ability of transporting atoms like proteins, chemicals, or pharmaceuticals without expanding or contracting their permeability due to external influences such as pH or temperature. Silica and aluminum are the most common components in clay nanoparticles. In any event, the nanoparticles' centers aren't confined to these two components; they can be comprised of a mixture of metallic and nonmetallic materials. For example, CeO₂coated mesoporous silica nanoparticles (MSN) have been improved to participate as drug delivery carriers in lung cells by transporting α -cyclodextrin into cellular breakdown (Singh et al., 2014).

Earthenware materials include dirt minerals, concrete, and glass, among others, and are used in a variety of purposes. Bioceramics, or biocompatible earthenware, is primarily used in the manufacturing of bone, teeth, and other clinical purposes. Bioceramics are highly biocompatible, hydrophilic, osteoconductive, biodegradable, and absorbable. The most commonly used ceramic nano biomaterials are calcium phosphate (CaP), calcium sulfate and carbonate, tricalcium phosphate (TCP), hydroxyapatite (HAP), TCP+HAP, bioactive glasses, bioactive glass pottery, Titaniabased ceramics, alumina ceramics, zirconia earthenware production, and artistic polymer composites. All have been employed in nanomedicine, muscular health, bone recovery, dentistry, and tissue development, in addition to numerous biomedical applications in the humans (Dziadek et al., 2017).

4.6.3.1.6 Quantum dots

Nanoparticles constructed of semiconductor materials having fluorescence characteristics are known as quantum dots. Quantum specks (QDs) are made up of a semiconductor center such as cadmium–tellurium (CdTe), cadmium–selenium (CdSe), indium–arsenate (InAs), or indium–phosphate (InP), that is overcoated with a shell i.e. zinc sulfide (ZnS) to increase optical and physical qualities and prevent hazardous heavy The most often used nanoparticles in bioimaging and biosensing techniques are these. However, this application anticipates that they will be synthesized into biomolecules such as oligonucleotides, peptides, or proteins allowing them to attach to specific places (Ghaderi et al., 2010).

The biocompatibility of quantum dots is critical for their organic and medicinal applications. Biocompatible Quantum dots are typically obtained through one of three routes: (1) biomimetic amalgamation, which involves the use of fake cell structures or biomolecules (proteins, peptides, nucleic acids, and catalysts) as templates; (2) biosynthesis, which involves the use of living organisms in bioreactors; or (3) changing the outside of Quantum Dots obtained from a compound blend. The biosynthetic methodology provides a green means to make biocompatible Quantum dots without the use of toxic materials or strong reaction conditions, while the surface adjustment method may provide a high QY for a wide range of applications (Cao, 2002).

In this manner, Lin et al. combined Gold Quantum Dots with a peptide moiety comprising an atomic fare indication and caspase-3 acknowledgment groupings to use them as protease-intervened cytoplasm-core transports for powerful apoptosis checking. When apoptosis is triggered, caspase-3 is activated, separating the useful peptide on Gold Quantum Dots and altering the subcellular transport of Gold Quantum Dots, which is measured as a function of time by the ratio of photoluminescence in the center to that in the cytoplasm. Gold Quantum Dots serve as sub-atomic assays for monitoring cell apoptosis in real time, making them excellent for cancer research (Lin et al., 2010).

4.6.3.1.7 Carbon-based nanoparticles

Fullerenes and nanotubes are included in carbon-based nanoparticles. Fullerenes are a new type of carbon allotrope with a polygonal form made up of only 60 carbon molecules. Carbon nanotubes are commonly made from synthetic graphite fume affidavit. Carbon nanotubes are divided into two types: single-walled (SWCNT) and multiwalled (MWCNT), the second mentioned of which has potent antibacterial capabilities. Because of their actual properties, such as high electrical conductivity and fantastic mechanical strength, in biomedical applications, carbon-based nanoparticles are of interest. However, they are non-biodegradable and require surface enhancements, as they have a high potential of proclivity to frame enormous compounds (Cha et al., 2013). Carbon nanotubes (CNTs) are used as naming and imaging specialists because of their exceptional optical characteristics (Cha et al., 2013). Because NIR has a lower excitation dispersion and a greater entrance depth, carbon nanotubes are beneficial in organic tissue and cells. Furthermore, autofluorescence in the near-infrared range is substantially lower than in the visible or bright ranges. For each of these reasons, carbon nanotubes are powerful imaging experts with a higher goal and uncommon tissue profundity for NIR fluorescence microscopy and optical lucidity tomography. Cherukuri et al. used NIR fluorescence to efficiently assess Carbon nanotubes in phagocytic cells and mice (managed intravenously) (Cherukuri et al., 2004). Yang et al. investigated further into behavior of Carbon nanotubes in this condition, such as agglomeration, cell take-up, and oxidant transport (Yang et al., 2012). The majority of in vivo studies involving carbon nanotubes have shown that they are harmless, with no adverse effects observed. Carbon nanotubes were identified in the liver, spleen, and lungs, among other organs. Likewise, a few in vitro cell cultures examine have shown that the connected cytotoxicity is more articulated at the cell level (Wick et al., 2007).

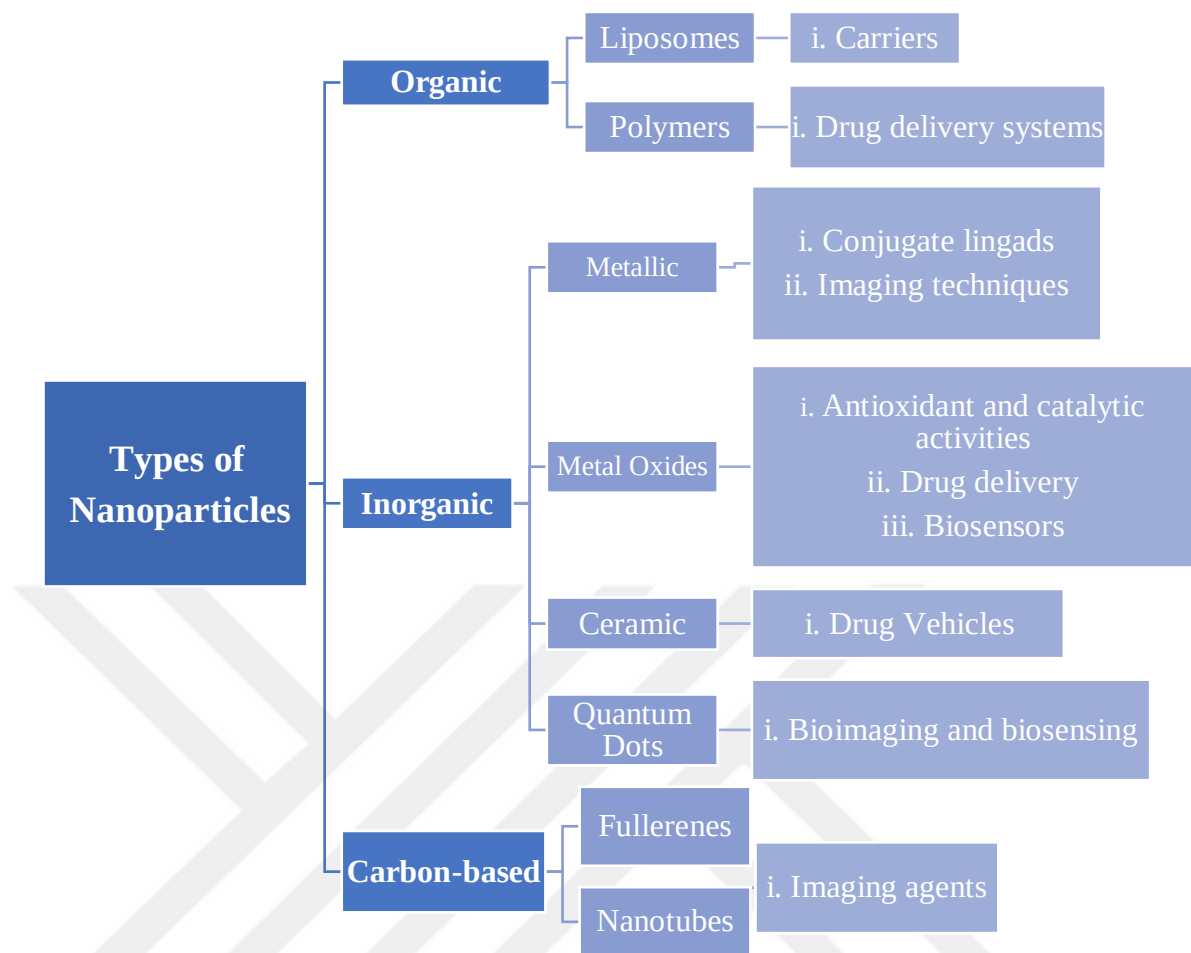


Figure 1: A diagram showing the types of nanoparticles and their main biomedical applications

4.6.4 Nanoparticles in dentistry

Nanotechnology is used in dentistry and is known as nano dentistry. Nanoparticles are used for a variety of applications in the field of dentistry. The metals or chemicals used to produce nanoparticles determine their chemical and physical properties. Bio-composite materials, such as hydroxyapatite-like calcium phosphate crystallites, have biological features including building a chemical bond interface with bone. Hydroxyapatite is a natural nanocomposite made from collagen that can be found in the human body. They're commonly utilized to coat implants with biocompatible, wear-resistant coatings and to prepare bone grafts.

When selecting a nanoparticle for usage in nano dentistry, its composition, physical properties, and nanostructures are all taken into account. To frame the practical construction, different particles or atoms are added on a regular basis. Some nanoparticles are used in the treatment of oral diseases, prosthetics, and dental implants. Nanomaterials also transport oral liquid or tranquilize, preventing and reversing some oral infections (oral disease) and ensuring that oral medical care is maintained to a high level (Priyadarsini et al., 2018).

It is possible to insert a dental implant made of biocompatible materials such as hydroxyapatite and titanium into the alveolar bone, coupled with a prosthetic crown. This implant mostly produces a periodontium, which differs from the native tissue's structure. When alveolar bone comes into direct touch with the dental implant, it might induce dental ankylosis. By electrochemically anodizing silicon, titanium, and aluminum, nanoporous anodic alumina (NAA), porous silicon (pSi), and titanium nanotubes (TNTs) are employed to generate drug-releasing implants. TNTs, NAA, and pSi nanopores are electrochemically modified to vary the length, shape, and diameter of the pore in order to create implants that can release pharmaceuticals. Drug-releasing activity can be examined by precisely fabricating a nanoporous structure depending on therapeutic requirements such as drug loading, drug doses, drug release rate, and so on.

Metal nanoparticles in the 1-10 nm size range have shown the most promise. Cavity liners, pit and fissure sealants, cores and buildups, indirect restorations, crown or orthodontic device cement, provisional restorations, endodontic sealers, and root canal posts are all examples of restorative dental materials and methods that involve nanoparticles.

Nanofillers incorporated into vinyl polysiloxane have been shown to offer a new addition to siloxane impression materials, with increased flow, hydrophilic characteristics, and detail precision.

4.6.5 Nanoparticles as antimicrobial agents

The increasing growth of multidrug-resistant organisms, such as viruses, bacteria, fungus, and protozoa, has proven to complicate competitive treatment of infectious conditions. As a result, it's critical to develop novel antiviral, antibiotic, antifungal, and antiprotozoal classes that can treat resistant strains. According to studies, this large-scale antibacterial nanomaterial may eliminate a wide range of pathogens, phylum, and species in viruses, bacteria, and fungus (Pourhajibagher et al., 2019). One of the mechanisms for NP antibacterial action is cell wall lysis. In an attempt to develop a photothermal treatment transducer (PTT), Tawfik et al. (2019) noticed the breakdown of *Bacillus* cell membranes in Silver/ Copper Sulphide nanoparticles (Au/CuS NPs) when treated. In another study, the destruction of *Bacillus* species by NP antibacterial agents of Au/CuS NP was found to be effective (Ahmadi et al., 2020).

The NPs are potential wide-spectrum antibiotics because they can inhibit a wide range of multidrug-resistant bacterial strains, which have proven difficult to treat with antibiotics in the past. Adeli et al. (2013) found that silver nanoparticles (AgNPs) inhibited pan-multidrug resistant *S. aureus*, *K. pneumoniae*, *E. coli*, and *P. aeruginosa* organisms that were resistant to all antibiotics, including imipenem, in a research. AgNPs have been demonstrated to inhibit bacteria (*S. aureus*, *E. coli*, and *B. subtilis*) as well as fungi (*A. niger*, *Mucor* sp, and *Trichoderma* sp) in similar experiments by Babanouri et al., (2021). Fayaz et al. (2007) found that AgNP-coated condoms have antiviral properties (against HIV-1 and HSV-1/2), antibacterial properties (against *E. coli*, *S. aureus*, *M. luteus*, and *K. pneumonia*), and antifungal properties (against *Candida*). This demonstrates that AgNPs can be used to treat MRPs from a wide range of phyla and clinical sources. Hybrids of nanomaterials such as Cholesterol containing liposomes, phytonanosilver, and CNTs have been shown to have high antioxidant activity and antibacterial activity against *E. coli*, *Staphylococcus aureus*, and *Enterococcus faecalis* (Meher Vineesha et al., 2021). This shows that when two or more NPs are combined, the overall nano-antimicrobial activity improves. The same effect was achieved by mixing CNT with AgNP nanoparticles, which resulted in a hybrid biocomposite with stronger and superior antibacterial properties (Florez et al.,

2018). Chitosan CNT Hybrid also revealed strong antibacterial and antifungal properties (Aljubour & Aljubour, 2020). MWCNTs with ZNO-coated material (ZnO/MWCNTs), CNT/Polymer nanocomposite Triads, MWCNTs-CdS with functional MWCNTs AG2S, and QDs/single-walled nanotubes CdTe are some of the other antimicrobial CNTs (De Almeida et al., 2018). Furthermore, MWCNTs immobilized with cefalexin have been shown to increase antibacterial efficacy against a variety of pathogens, including *E. coli*, *P. aeruginosa*, *S. aureus*, and *Bacillus subtilis*. AgNPs and CNTs, particularly MWCNT-AgNPs in fiber membranes, have been shown to improve filtration and antibacterial capability for bacteria of all kinds. Furthermore, the nanocomposite coated water membrane Poly N-vinylcarbazole (PVK)-SWCNT was discovered to be effective against all species, including *Bacillus subtilis* spores. Apart from filtration and antibacterial activities, the MWCNT-AgNPs hybrid composite membrane has been shown to significantly reduce biofilm development (Eslami et al., 2021).

Antibacterial biocidal activity Nanoparticles can be used in dental materials, device coatings, and topically applied treatments. Silver nanoparticles have been found as potential antibacterial components in dental resin composites. To reduce microbial contamination of tissue conditioners, acrylic resin denture bases, and acrylic base plates of removable orthodontic equipment, low percentages of silver-zinc antimicrobial zeolites added to polymethyl methacrylate can be employed. It has also been tested to incorporate silver zeolite nanoparticles into mouth rinses and toothpaste. Because silver and zinc particles are small, they can easily pass through microbe cell membranes, altering internal processes and resulting in increased reactivity and antibacterial action.

Mixing alginate impression powders with water containing silver hydrosol can be used to make an antimicrobial impression substance, decreasing microbial crosscontamination from the diseased imprint to the poured stone model. Because the bacterial infection is one of the leading causes of titanium implant failure, a new antibiotic vehicle composite, TiO₂ NT-PSPMA, was created using atom transfer radical polymerization. By putting higher doses of antibiotic into Titanium nanotubes

(TiO₂ NTs) arranged on Ti implants, this approach enhanced local antibiotic concentration and prolonged its sustainable release. With the help of the ionic polymer 3-sulfopropyl methacrylate potassium salt, Ag nanoparticles (NPs) were loaded into TiO₂ NTs (PSPMA).

Nanoparticles have been employed for remineralization of decalcified enamel as well as antibacterial agents. Nano-hydroxyapatite has been created as a paste and has been offered as a nanotechnological development in goods for the remineralization of enamel. Calcium nano phosphate protects the enamel surface by forming a protective layer on top of it. Because of the increased surface area and moist ability of HA nanoparticles, calcium nano phosphate crystals smaller than 100nm boost the product's bioactivity.

4.6.6 Mechanism of action of nanoparticles

Nanotherapeutics can manage biofilms by utilizing nanoparticles' biocidal properties (De Stefani et al., 2020). The NPs contain spherical nanometrically formed particles that are cubic or needle-shaped (Teixeira et al., 2021). Metallic nanoparticles, such as oxides and organic NPs with polymers or covered by a variety of biomaterials, have a broad spectrum of dental applications (Ferrando-Magraner et al., 2020). Smaller diameter NPs have an increased surface-to-volume ratio, which increases not only their mechanical capabilities but also their antibacterial activity (Liao et al., 2020). When administered, NPs damage cell membranes, impairing the microorganism's ability to function. This property bestows upon NPs the ability to operate as microbiological agents and carriers, as they have few negative consequences on the host (Pourhajibagher & Bahador, 2021). Innumerable mechanisms have been proposed to explain how NPs inhibit bacterial growth in the oral cavity, including metal ion release, oxidation (Nanda et al., 2021), and nonoxidation mechanisms (Jasso-Ruiz et al., 2019), with contact-mediated biocidal activity being the most commonly proposed mechanism. This shows that positive NPs are electrostatically attracted to the negatively charged bacterial cell membrane. The permeability of the cell wall is altered as a result of this attraction, resulting in membrane rupturing and intracellular organelle

leakage. Traditional antibacterial techniques are less effective than nanoparticles because they are not influenced by antibiotic resistance mechanisms. This is because NPs make direct contact with the bacterial cell wall instead of entering it (Gomez et al., 2021).

4.6.7 Titanium dioxide and its properties

Because of its size and unique photocatalytic activity, TiO₂ nanoparticles have recently become abundantly used in industries such as medicine and food processing. These characteristics make TiO₂ nanoparticles naturally antibacterial (El-Gazzar & Ismail, 2020). The nanoparticles' small size allows them to easily pass through microorganism membranes (Mirhashemi et al., 2021).

4.6.7.1 Titanium dioxide nanoparticles as antimicrobial agent

When exposed to UV light with a wavelength less than 385 nm, TiO₂ photocatalytically produces significant oxidizing power, which is the cause of its inhibitory activity. Bacterial elimination is catalyzed by TiO₂ particles when exposed to near-UV light. The antibacterial activity is most likely caused by photoexcited TiO₂ particles, which produce active free hydroxyl radicals. It has been demonstrated that TiO₂ photocatalyst has antibacterial effects on *Escherichia coli* in water as well as photocatalytic activity against fungus and bacteria (Chawebgkijwanish and Hayata 2008).

Additionally, research has been done on the bactericidal effects of nitrogen-doped metal oxide nanocatalysts on *E. coli* biofilms as well as the photocatalytic oxidation of biofilm constituents on surfaces covered with TiO₂. In conclusion, future research into the utilization of TiO₂ photocatalysts as an alternate method of self-cleaning polluted surfaces may yield effective disinfectant treatments for preventing the growth of biofilm. In the food processing industry, TiO₂ photocatalysts can be employed as efficient biofilm disinfectants (Liu et al., 2002). *Escherichia coli* can be effectively

eliminated by TiO₂ suspensions. This prompted the creation of photocatalytic techniques that use TiO₂ in aqueous media to destroy bacteria and viruses (Duffy et al., 2002).

It has been claimed that using nanostructured TiO₂ on UV irradiation is an efficient technique to minimize disinfection time, eliminate pathogenic bacteria on surfaces that come into contact with food, and improve food safety (Chorianopoulos et al., 2011). The main disadvantage of TiO₂ is that it requires UV light to activate the photocatalyst and start the elimination of the bacteria and viruses. Ag/AgBr/TiO₂ photocatalysts that absorb visible light have recently shown to be effective at killing *S. aureus* and *E. coli* (Hu et al., 2006).

4.6.7.2 Preparation of nanostructured titanium dioxide

The modified sol-gel technique, as previously investigated, could be employed to make TiO₂ nanoparticles. This method has the advantage of producing a size and shape-uniform TiO₂ anatase powder (Chambers et al., 2017). Titanium iso-popoxide (TIP, 98 percent Aldrich) was reacted in an isopropanol-water solution at constant temperature to generate 100 nm in diameter spherical soils (Espinosa-Cristóbal et al., 2018). The soil was recovered, cleansed, and dried in order to create a free-flowing powder. By varying the amounts of isopropanol in the alcohol-water hydrothermal solution, TiO₂-Anatases of varied crystal sizes have been produced (BaranowskaWójcik et al., 2020). Microwave treatments of amorphous titanium powder in 1 M HCl at 650 W for 1 hour resulted in big rutile TiO₂ particles. Titania-silica aerogels were created using a two-step acid-base catalyzed method (Cao et al., 2006). The tetramethyl orthosilicate (TMOS, 98 percent Aldrich) was prehydrolyzed at 323 K for 90 minutes in ethanol (99.9% Merck).

The reaction is completed with the addition of ammonia, resulting in alcohol that was aged for 10 days before being supercritically dried with ethanol. The amorphous titanium-silica aerogel's TiO₂ anatase nanoparticles are supercritically drying ethanol. In a carbolite furnace at 723 K for 1 hour, the generated aerogel was calcined to completion of TiO₂ (Farzanegan et al., 2021). A spin on the nanotextures, formed

through microwave-induced deweathering on the silicon wafer, was used to create nanotextured TiO₂ films. The sol was made by reacting a 4 mL titanium isopropoxide solution in 10 mL ethanol with an acidified ethanol solution containing 1 mL 2.3 M HNO₃ in 50 mL ethanol.

The mixture could react overnight at room temperature. The 0.20 mol L⁻¹ titanium sol was spin-coated on the substratum at 6000 rpm with ethanol dilute to 0.05 mol L⁻¹ (Gul et al., 2020). A simple TiO₂ film was also made by spin-coating titania sol on the flat silicone substratum. The materials were calcined at 723 K for 2 hours to remove polymers and crystallize anatase TiO₂ (Toodehzaeim et al., 2018).



5. METHODS AND MATERIALS

5.1 Ethical Approval

This in vitro study was approved by the Marmara University Clinical Research Ethical Committee, on 02.06.2021 with protocol number 09.2021.630 (Enc.1)

5.2 Experimental Design Sample Size Calculation

Sample size estimation was done using G*Power 3.1.9.7 software, considering a Power of 90% and α level of 0,05. To estimate the effect size we considered a difference of 2 MPa is significant as a variance explained by special effect and the variance within groups was calculated by squaring the standard deviation of SBS values from the study of (Daub, J. *et al*, 2006) which was 2,91 MPa, so the variance is 8,47. The required sample size was 57 specimens (19 specimens in each group), and this number was raised to 60 specimens (20 specimens in each group) in case of a failure in any specimen.

5.3 Grouping

A total of 70 intact teeth were collected after being extracted for orthodontic treatment purposes following the ethical committee approval at Marmara University's Faculty of Dentistry (Figure 2) . They were chosen according to these criteria:

Inclusion Criteria:

- Sound teeth, caries-free
- Intact buccal surface with no visible cracks, stains, or hypoplastic areas
- No pretreatment with chemical agents
- Exclusion Criteria:
- Carious teeth
- Teeth with cracks, stains, or hypoplastic areas
- Teeth that had previous treatment with chemical agents

The teeth were randomly divided into three groups; Study group (Group A) which consisted of 20 teeth, in which a modified bonding agent containing TiO₂ was used,

Study group (Group B) which consisted of 20 teeth in which a modified composite adhesive containing TiO_2 -NPs was used, and Control group (Group C) which consisted of 20 teeth in which conventional bonding agent and composite adhesive were used). 10 teeth were used as spare and in case of failure of any tooth in the previously mentioned groups.



Figure 2: Extracted intact premolars collected

5.4 Teeth Preparation

The 60 extracted premolar teeth that were gathered from Marmara University Dental Hospital were fixed to the center of 2,5-cm diameter silicone molds using rectangular wire and then the molds were filled with self-curing acrylic resin up to the level of the cemento-enamel junction. The teeth crowns were cleaned for 5 seconds, with nonfluoride pumice slurry and low-speed hand piece. They were then labelled according to their groups.

5.5 Preparation of Bonding Agent- NPs Mix

The ideal concentration percentage of the solvent/solute mixture was found to be between 1 and 3 percent based on prior studies (Tang et al., 2019). According to researches, around 2% TiO_2 -NP loading produces the best photocatalytic capabilities under visible light conditions. Using the formula below, the mixtures were prepared;

Concentration= $\frac{\text{Quantity of Solute}}{\text{Quantity of Preparation}}$

Quantity of Preparation

- Concentration: percentage of Titanium Dioxide used (2%)
- Quantity of Solute: amount of TiO_2 added in grams

- Quantity of Preparation: amount of Bonding agent or Composite adhesive used

The amount of TiO₂ used in Group A mixed with 6 ml of bonding agent was calculated as follows;

$$2\% = \frac{X}{6 \text{ ml}} = \frac{2}{100} * \frac{X}{6}$$

X= 0,12 g of Titanium Dioxide nanoparticles mixed with 6 ml of bonding agent. A 2% concentration of TiO₂ was added to 6ml of 3M Transbond™ MIP orthodontic adhesive bonding solution (3M Unitek, CA, USA) (Figure 4) based on percentage estimates. To assure precision of quantity, 0,12 grams of TiO₂-NP were measured on a laboratory scale after conducting percentage calculations. Vortex and IKA® T25 digital ULTRA-TURRAX® machine (Merck KGaA, Darmstadt, Germany) was used to mix the NPs into the bonding agent (Figure 3). To prevent the adhesive from setting, the mixing was done in a semi-dark environment. The mixing time was around 2 minutes to ensure that the NPs were distributed evenly. This procedure was carried out at the Metallurgy and Material Engineering Department of Istanbul Technical University.



Figure 3: Vortex and IKA® T25 digital ULTRA-TURRAX® machine

5.6 Preparation of Transbond Composite Adhesive- NPs Mix

Similar to the bonding agent preparation method, the amount of TiO₂ used in Group B mixed with 4 g of composite adhesive was calculated as follows;

$$2\% = \frac{X}{4 \text{ g}} = \frac{2}{100} * \frac{X}{4}$$

X= 0,08 g of Titanium Dioxide nanoparticles mixed with 4 g of composite adhesive
A 2% concentration of TiO₂ was added to 4 grams of Transbond composite adhesive of 3M Transbond™ XT Light Cure Adhesive (3M Unitek, CA, USA) (Figure 4) based on percentage estimates. To assure precision of quantity, 0,08 grams of TiO₂-NP were measured on a laboratory scale after conducting percentage calculations. The composite paste was blended with the NPs using a high speed mixer (3500 revolutions per minute). To prevent the mixture from setting, the mixing was done in a semi-dark environment. The mixing time was around 2 minutes to ensure that the NPs were distributed evenly. Scanning electron microscope (SEM) examination was also performed on the new paste to check uniform distribution of the nanoparticles in the composite paste.



Figure 4: 3M Transbond™ XT Light Cure Adhesive and Transbond™ MIP bonding agent used

5.7 Bonding Procedures

Once the TiO₂-NP infused bonding agent and composite adhesive were prepared, the acrylic molds were labelled and designated randomly to either to group A, group B, or group C. Each tooth was dried and etched for 20 seconds with 37% phosphoric acid, then rinsed with water for 20 seconds. Once each tooth was completely dried, a thin coating of bonding agent was applied to the tooth surface. Study group A was bonded with the modified bonding agent which included TiO₂ NPs, whereas the study group B and control group C were bonded with unmodified conventional bonding agent. Afterwards, for 20 seconds, a light cure was applied perpendicularly to the tooth surface using a dental curing light (Woodpecker, Guilin Woodpecker Medical Instrument Co., Ltd., Muenster, Germany).

Next, a thin layer of conventional Transbond XT composite adhesive was applied to premolar brackets' bases and bonded to the middle third of the mounted premolars of study group A and control group C. While on teeth of study group B, the modified Transbond XT composite adhesive with TiO₂ NPs was applied to premolar brackets' bases and bonded to the middle third of the premolars. Every tooth was again light cured using a dental curing light perpendicularly for 40 seconds.



Figure 5: Group A - 20 specimens with TiO₂ nanoparticles incorporated in the bonding agent



Figure 6: Group B - 20 specimens with TiO₂ nanoparticles incorporated in the composite adhesive



Figure 7: Group C - 20 specimens with conventional bonding agent and composite adhesive (no nanoparticles).

5.8 Thermocycling Process

To simulate the oral environment, all specimens underwent thermocycling for 1000 rounds in 24 hours (Figure 8). SD Mechatronik thermocycler machine (FeldkirchenWesterham, Germany) in the R&D Lab at Marmara University Faculty of Dentistry was used for thermocycling procedure. Each cycle was comprised of 15 seconds of immersion in a 5°C water bath, 10 seconds of dwell time, and 15 seconds of immersion in a 55°C water bath.

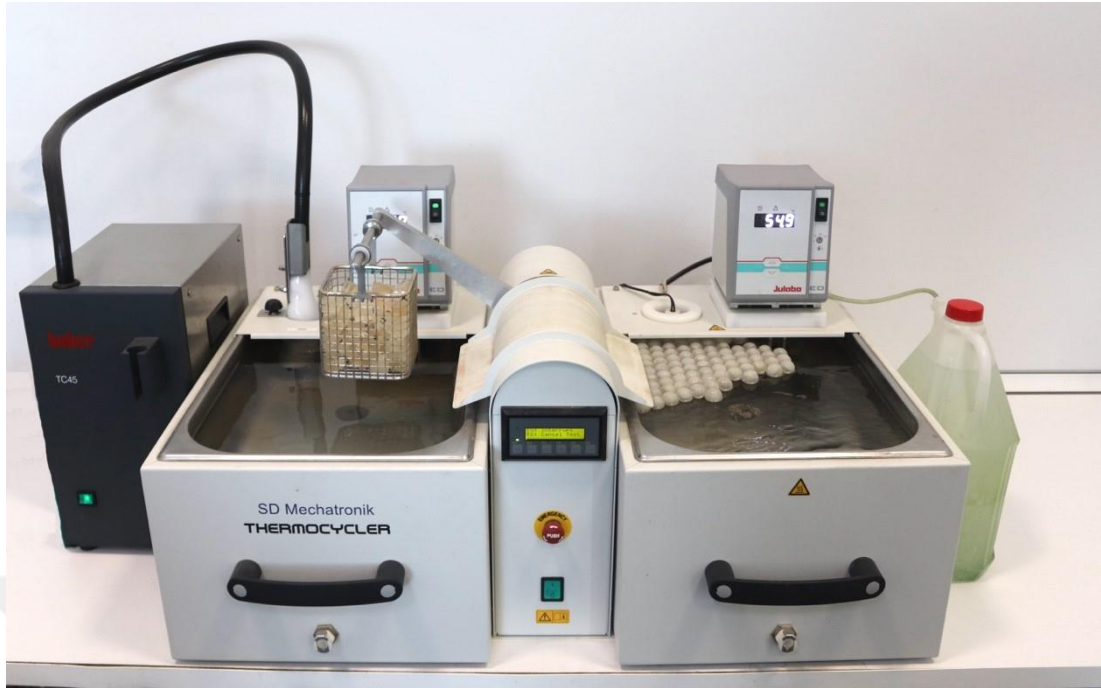


Figure 8: The specimens during the thermocycling process

5.9 Shear Bond Strength (SBS) Test

The SBS was measured using an "Instron" universal testing equipment (AGS-10k NG SHIMADZU) at the Metallurgy and Material Engineering Department of Istanbul Technical University (Figure 9).

Instron's crosshead moved at a constant pace of 0,5 mm/min. With the crown section of the teeth facing upward, the acrylic block was placed in the lower crosshead. The debonding force was delivered parallel to the bracket base direction. To apply shear force to the bracket-tooth interface, a 0,6-mm metal blade was utilized in an occlusogingival direction at a crosshead speed of 0,5 mm/min (Figure 10). The load at bracket failure was recorded electronically in MPa by a computer connected to the Universal testing machine. The maximum load necessary to debond or initiate bracket failure was recorded in mega pascals. A few samples failed during this stage and were replaced by the spare ones that were kept ready and prepared.



Figure 9: Instron Universal Testing Machine (SHIMADZU)

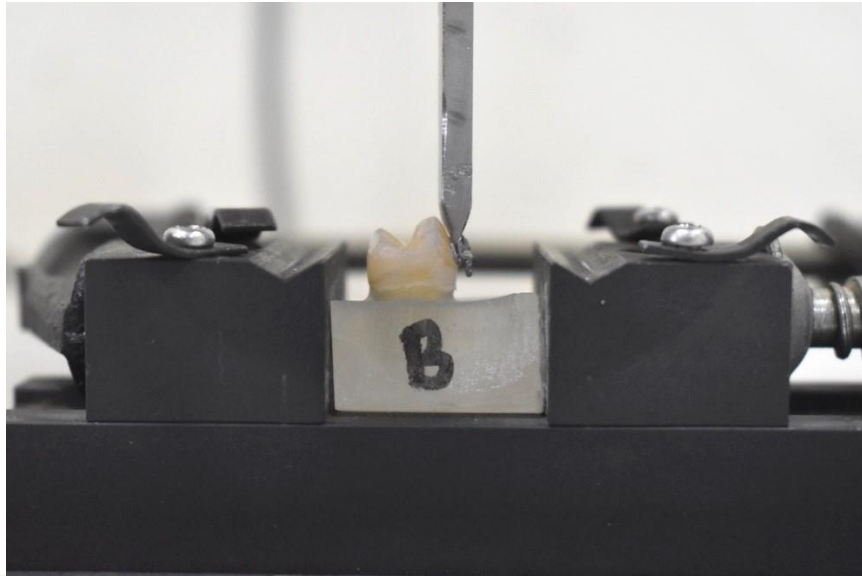


Figure 10: 0,6-mm metal blade attachment used for bracket contact

5.10 Statistical Analysis:

Statistical analysis was performed with SPSS (statistical package for the social sciences) v.26 (IBM, New York, NY). Statistical significance level was established at $p < 0,05$.

One-Way ANOVA test with Tuckey post-hoc tests were conducted to determine if SBS mean was different between study groups.

6. RESULTS

6.1 Sample's Description

The sample consisted of 60 specimens (20 in each group, i.e., Group A, B, and C)

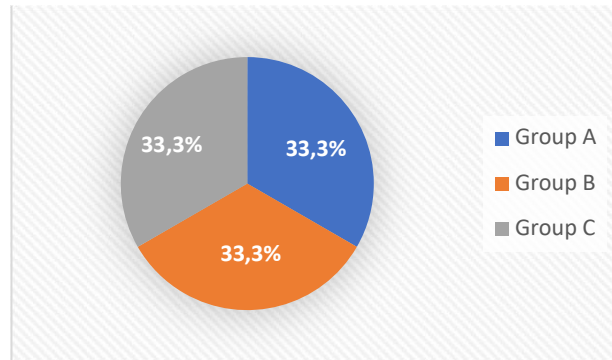


Figure 11: Specimens distribution among study groups.

Table 1: Specimens distribution among study groups

		N	%
Groups	A	20	33,3%
	B	20	33,3%
	C	20	33,3%
Total		60	100%

6.2 Shapiro-Wilk's Test

All data in study groups were normally distributed as assessed by Shapiro-Wilk's test ($P > 0,05$).

Table 2: Shapiro-Wilk's test for normal distribution

	Statistic	df	Sig.
Group A	0,965	20	0,646
Group B	0,976	20	0,876
Group C	0,986	20	0,985

6.3 Shear Bond Strength in Study Groups

Shear bond strength (SBS) in Group B ranged between 5,8 – 8,5 MPa with a mean of 7,1 MPa and a standard deviation of 2,9 MPa. In Group C SBS ranged between 3,9 – 20,7 MPa with a mean of 12,4 MPa and a standard deviation of 4 MPa. Group A SBS values ranged between 8 – 18,7 MPa with the greatest mean of all groups 13,2 MPa and a standard deviation of 3,2 MPa.

Table 3: Descriptive statistics of SBS in study groups

Group	Mean (Mpa)	Standard Deviation	Minimum	Maximum	95% CL for Mean	
					Lower	Upper
Group A	13,2	3,2	8,0	18,7	11,7	14,7
Group B	7,1	2,9	2,3	14,0	5,8	8,5
Group C	12,4	4,0	3,9	20,7	10,5	14,2

6.4 One-Way ANOVA Test

One-way ANOVA test was conducted to determine if SBS was different between study groups. There was a statistically significant difference between groups ($p < 0,001$).

Table 4: One-Way ANOVA test to study the difference in SBS between groups

	Sum	Mean	of Squares	df	Square	F	Sig.
					40176,1		20088
				1069			
Between Groups			2				
Within Groups	60931		57		18,792		,000
Total	101107,1		59				

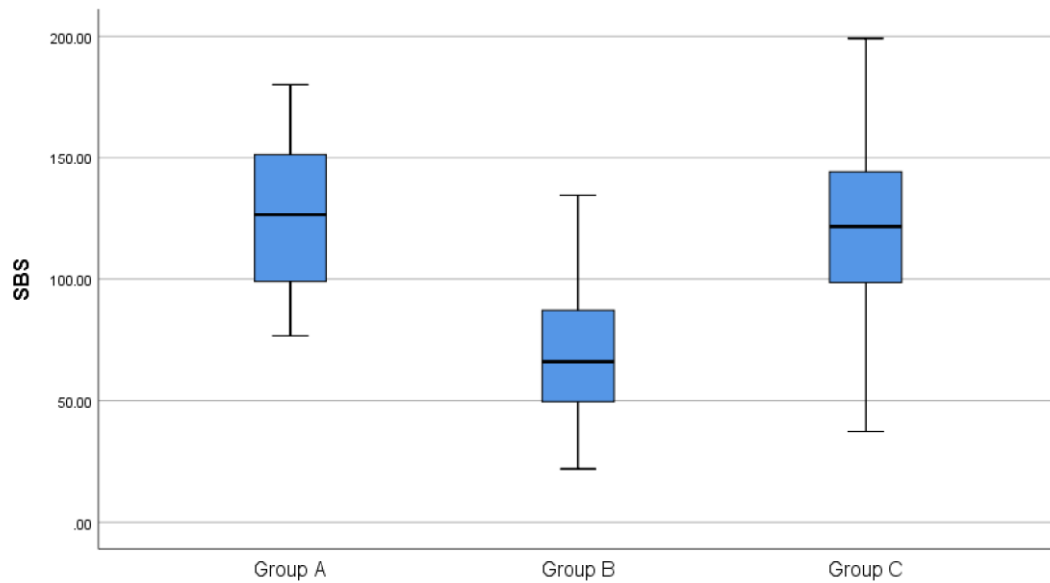


Figure 12: Box plot of SBS in study groups

6.5 Shear Bond Strength Comparisons Between Groups

Tukey post hoc analysis revealed that SBS in Group B was significantly lower than in both Group A by 6,1 MPa, and Group C by 5,3 MPa ($p < 0,001$). However, there was no statistically significant difference in SBS between Group A and Group C ($p = 0,733$).

Table 5: Pairwise comparisons of SBS between groups

Shear Bond Strength (SBS)		Mean	
	Mpa	Difference	p
Group A	Group B	6,1	,000*
	Group C	0,8	,733
Group B	Group A	-6,1	,000*
	Group C	-5,3	,000*
Group C	Group A	-0.8	,733
	Group B	5,3	,000*

* $p < 0,05$

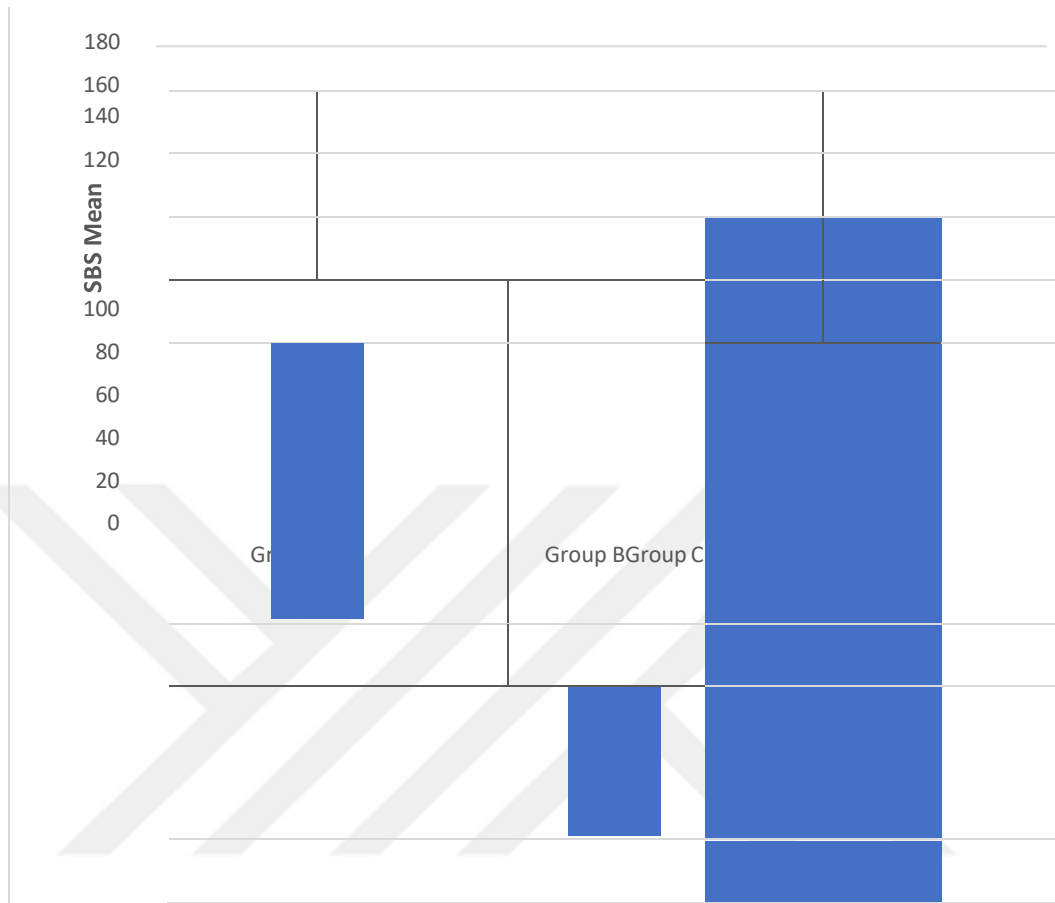


Figure 13: SBS mean and standard deviation in study groups

Statistical analysis was performed with SPSS (statistical package for the social sciences) v.26 (IBM, New York, NY). Statistical significance level was established at $p < 0,05$.

One-Way ANOVA test with Tuckey post-hoc tests were conducted to determine if SBS mean was different between study groups.

7. DISCUSSION AND CONCLUSION

Patient compliance in maintaining effective oral hygiene is frequently a challenge during orthodontic treatment; as a result, many practitioners prefer treatment approaches that do not rely on patient participation. Both orthodontic appliances and bonding materials have the potential to retain plaque. Cleaning is thwarted by archwires because they create difficulty in getting to plaque-retaining places; this is especially true when employing many loops, auxiliary archwires, and a variety of elastics. As a result, during orthodontic treatment with fixed appliances, demineralization caused by white spot lesions will occur, and new caries-prone sites will form close to the bands and brackets (Daub et al., 2006). White spot lesions can be avoided by following appropriate oral hygiene practices, such as brushing teeth with fluoride dentifrice. Enamel demineralization in individuals wearing fixed orthodontic appliances has been reduced utilizing a variety of techniques. These methods include antibacterial bonding chemicals, antimicrobial mouth rinses, and coatings on brackets/wires or remineralizing agents close to orthodontic appliances. Their effectiveness however has been reported to be limited. In dentistry, nanotechnology has been used to create materials with improved mechanical characteristics and antimicrobial capabilities. With the advancement of nanotechnology and the distinct demeanor revealed by nanoparticles, claims have been made to use this method in orthodontic bonding (Mirhashemi et al., 2021). The addition of nanoparticles in orthodontic materials has yielded promising antibacterial and mechanical qualities (Hailan & Al-Khatieeb, 2018). To avoid microbiological adherence or enamel demineralization in orthodontic therapy, nanoparticles are integrated into orthodontic bonding agents or composite adhesives and can be coated onto the surfaces of orthodontic appliances. Incorporating nanoparticles into the bonding agent rather than the adhesive body itself has proven to be a more persuasive addition and clinically beneficial. The area for precautionary efforts is the bonding agent that comes into direct contact with the enamel surface (Behnaz et al., 2018). Nanofillers can reduce enamel demineralization without affecting the physical qualities of the composite, according to studies published in the literature.

The photocatalytic action of titanium dioxide (TiO₂) nanoparticles has recently been the subject of much attention in medical and dental literature. According to studies published in the literature, resins containing TiO₂ nanoparticles have powerful antibacterial capabilities that could be used to prevent recurrent caries and enamel demineralization. The addition of TiO₂ nanoparticles to dental composites improved mechanical parameters such as modulus of elasticity, microhardness, and flexural strength, as well as providing bond strength values that were comparable to or even better than the controls (Uysal, et al., 2010).

In this study, TiO₂ nanoparticles are utilized due to the potential it holds as a beneficial nanoparticle. It can be incorporated in dental materials due to its ability to generate strong oxidizing power when it is illuminated with UV light at a wavelength of less than 385 nm. As performed in previous studies, the small size of the nanoparticles provides a more enhanced atomic diffusion into a substrate for greater bond strength and an overall increase of strength (Moradgholi et al., 2017).

Based on previous studies, a concentration percentage of between 1% and 2% was shown to be the optimal solvent/solute mixture (Tang et al. 2019). The TiO₂ nanoparticles were incorporated into 3M Transbond™ XT Light Cure Adhesive (3M Unitek, CA, USA). Transbond composite adhesive of 3M provide high quality polish, wear resistance and strength. It has been reported that the filler weight and size and contact surface relationship between the nanofillers and the surface material to be more advantageous compared to that of Esthet X (Dentsply) and Grandio (Voco) (Rosa et al., 2012) .

In this study both mixtures of the bonding agent and the TiO₂ nanoparticles were done using Vortex and IKA® T25 digital ULTRA-TURRAX® machine (Merck KGaA, Darmstadt, Germany. However, Nikpour et al. (2021) used a manual mixing method on a glass slab which was also successful in previous studies (Poosti et al., 2013, Shodgar et al., 2013 & 2016). They stated that their method was found to be more simple and clinically applicable. However, mixing it with the high speed mixers has the advantage of being more precise and homogeneous.

Thermocycling methodology was introduced as an artificial aging tool for determining the impact of thermal stressors on the bond strength of dental materials. The impact of different coefficients of thermal expansion for these restorative and repair materials can be examined using these thermal cycles in an in vitro scenario. Authors have employed this technology for adhesive systems, two-step bonding systems, luting agents, nanocomposites, and orthodontic materials in past investigations. Researchers discovered that a thermocycling program of at least 500 cycles in water between 5°C and 55°C is an effective artificial aging test (Bishara et al., 2003). Orthodontic adhesives undergo a multitude of temperature changes in the oral cavity. Resting mouth temperature can be affected by air temperature, humidity, and air velocity when breathing. Despite the fact that these fluctuations are unpredictable when testing, it is critical to establish whether they produce stresses in the adhesive that could affect its bond strength. As a result, Bishara et al. (2003) proposed that heat cycling be included in the testing process for new adhesives.

Teeth were kept in distilled water for 24 hours at 37°C. The samples were thermocycled according to ISO 11405 recommendations after 24 hours (Sodagar et al., 2017). Each specimen was subjected to 1000 full cycles in distilled water at temperatures ranging from 5 to 55 °C, with a dwell duration of 10 seconds in each bath and a transfer time of 10 seconds between baths. According to the study performed by Sodagar et al. (2017), the author's specimens were thermocycled for 1000 rounds in distilled water at the same temperatures this study underwent. It was found that performing 1000 cycles depicted a more accurate representation of the increased duration of the brackets attachment to the teeth in the oral cavity.

According to the study performed by Rosolen et al., (2015), thermocycling 1000- 3000 cycles all attributed to less than 1 year aging. This means 500 cycles would not suffice in simulating the brackets adherence to teeth during orthodontic treatment. Orthodontic resin composite adhesives are vulnerable to the moisture found in the oral cavity, have a high modulus of elasticity and susceptibility to polymerization shrinkage. Thus, thermocycling for high number of cycles and exposing the adhesive to high and low

temperatures and moisture may result in severe polymerization shrinkage stress and bond failures

TiO₂ nanoparticles, which come in a variety of sizes and crystalline forms, are ideal for incorporation into dental materials. They are cost-effective, have excellent mechanical qualities, and a pleasing hue. In addition to killing bacteria, fungus, and viruses, the anatase aspect of TiO₂ nanoparticles demonstrates significant photocatalytic activity.

Similarly to the findings of this study, (Merhashemi, A et al., 2021) stated that SBS of orthodontic adhesives with antimicrobial NPs and unmodified conventional orthodontic bonding agents showed no significant change in in vitro studies. Clinically acceptable SBS was achieved by including all types of evaluated NPs up to 5% by weight.

In (Hailan. S et al., 2018)'s study, it was shown that using 1% concentration of TiO₂ nanoparticles has no effect on the SBS. The articles also stated that in clinical orthodontic practice, obtaining an ideal bond strength value that allows for safe detachment of fixed appliance components is more important than obtaining the greatest potential value.

The thermocycling process after assessment of comparing to other studies that have been done could be the cause of this weakness. (Behnaz.M et al., 2018) agreed with our assumption and inferred SBS may be reduced by adding TiO₂ nanoparticles, yet adhesion may still be satisfactory. The highest SBS values were achieved by Transbond XT and Resilience without TiO nanoparticles, respectively.

Findings reported by (Uysal. T et al., 2010) stated that the bond strength of the nanocomposite examined in their study was lower than that of traditional orthodontic adhesive. This is in line with this study's results.

Because a combination of tensile, shear, and torsional stresses are applied in the oral cavity, this study's in vitro design could not precisely reproduce oral clinical settings. Also prevalent in the oral cavity are factors such as temperature changes, humidity, acidity, and microbial plaque which are difficult to replicate in in vitro. As a result, extra caution should be taken when extrapolating results to the clinical environment. More research and studies are required to further analyze the effect of nanoparticles on the composition of different orthodontic bonding solutions and composite adhesive resins on shear bond strength. In this study, only one specific brand of both the Transbond orthodontic bonding solution and the Transbond composite adhesive (3M Transbond™ XT, Unitek, CA, USA) was utilized. More studies need to be done on other available brands of orthodontic bonding solutions and composite adhesives combined with TiO₂ nanoparticles.

TiO₂-NPs is a promising antibacterial agent that will not compromise the SBS of brackets adhering to teeth, according to the findings of the current study, when added to the orthodontic bonding agent.

Incorporating TiO₂ nanoparticles to orthodontic bonding agents and benefiting from its antimicrobial properties shows promising results and no significant effects on the SBS of brackets. The addition of TiO₂ nanoparticles to the Transbond composite adhesive might reduce SBS, but the adhesion might still be at an acceptable level. Conventional Transbond bonding agent and composite adhesive resilience without TiO₂ nanoparticles yielded the highest SBS values. However, addition of TiO₂ nanoparticles to Transbond composite adhesive decreased its SBS to an acceptable range. Thus, TiO₂ nanoparticles may be added to Transbond XT composite. The addition of TiO₂ nanoparticles to the Transbond bonding agent during orthodontic bracket attachment showed no significant difference in the SBS values when compared respectively to conventional bonding agent without the TiO₂ nanoparticles. This new era of nanoparticles in dentistry has opened more doors for Orthodontists and patients' health.

8. REFERENCES

Ahmadi H, Haddadi-Asl V, Ghafari HA, Ghorbanzadeh R, Mazlum Y, Bahador A. Shear bond strength, adhesive remnant index, and anti-biofilm effects of a photoexcited modified orthodontic adhesive containing curcumin doped poly lacticco-glycolic acid nanoparticles: An ex-vivo biofilm model of *S. mutans* on the enamel slab bonded brackets. *Photodiagnosis and Photodynamic Therapy*. 2020; 30:101674.

Aileni R, AB S, Patil SR, Tabassum S, Bandela V, Alam MK. Nanoparticles! Armour against White Spot Lesions. *Int Medical J*. 2021;28: 1-12.

Al Azzawi M, Kadhim HA, Mayali M, Elkolaly M, Hasan S. Bond strength efficiency of a high fluoride and calcium release self-adhesive resin cement: A comparative in vitro study. *Int J Oral Health Dent*. 2021;13:372.

Al Tuma R, Yassir A. Evaluation of a newly developed calcium fluoride nanoparticlescontaining orthodontic primer: An in-vitro study. *J Mech Behav Biomed Mater*. 2021; 122:104691.

Alam K, Alsuwailem R, Alfawzan A. Antibacterial activity and bond strength of silver nanoparticles modified orthodontic bracket adhesive: A systematic review and metaanalysis of in-vitro and in-vivo studies. *Int J of Adhes and Adhes*. 2022; 113:103040.

Aljubour I, Aljubour A. Antibacterial Properties of Nano-particles in Dental Restorative Materials: Literature Review. *Int J of Innov Res Sci Eng. Technol.(IJIRMS)*, 2020;10: 1-11.

Asiry A, Alshahrani I, Alqahtani D, Durgesh B. Efficacy of yttrium (iii) fluoride nanoparticles in orthodontic bonding. *J. Nanosci. Nanotechnol.*, 2019;2: 1105-1110.

Assery K, Ajwa N, Alshamrani A, Alanazi J, Durgesh H, Matinlinna P. Titanium dioxide nanoparticles reinforced experimental resin composite for orthodontic bonding. *Mater Res Express*. 2019; 12: 86-98.

Babanouri N, Ghafoori R, Ajami S, Mahdian A. Effect of high concentration nanohydroxyapatite serum on shear bond strength of metal brackets following three different enamel surface preparation methods: An in vitro study. *Int Orthod*. 2021;1: 123-129.

Balashanmugham B. Assessment of Antibacterial Property of Silver Coated Stainless Steel Orthodontic Brackets Against *Streptococcus Mutans*, *Lactobacillus Acidophilus* and *Porphyromonas Gingivalis*—An In Vitro Study. *J Orthod Soc*. 2018; 3: 59-63.

Baranowska-Wójcik E, Szwajgier D, Oleszczuk P, Winiarska-Mieczan A. Effects of titanium dioxide nanoparticles exposure on human health—A review. *Biol Trace Elem Res*. 2020;193, 118-129.

Behnaz M, Dalaie K, Mirmohammadsadeghi H, Salehi H, Rakhshan V, Aslani F. Shear bond strength and adhesive remnant index of orthodontic brackets bonded to enamel using adhesive systems mixed with TiO₂ nanoparticles. *Dent Press J Orthod*. 2018; 23: 43-51.

Behnaz M, Davani T, Abdi A, Azadi G, Goudarzi M. Efficacy of Antimicrobial Agents in Orthodontic Adhesive Systems and Brackets: A Narrative Review. *Journal of Dental School, Shahid Beheshti University of Med Sci*. 2018;37: 112-117.

Behnaz M, Fahiminejad N, Amdjadi P, Yedegari Z, Dalaie K, Dastgir R. Evaluation and comparison of antibacterial and physicochemical properties of synthesized zinc oxide-nano particle-containing adhesive with commercial adhesive: An experimental study. *Int Orthod*. 2022;20: 598-613.

Bilal R, Arjumand B. Shear bond strength and bonding properties of orthodontic and nano adhesives: a comparative in-vitro study. *Contemp Clin Dent*. 2019;10: 589-600.

Bishara. E, Ajlouni R, Oonsombat C. Evaluation of a new curing light on the shear bond strength of orthodontic brackets. *Int J of the Angle Orthod*. 2003;73: 431-435.

Budi S, Jameel F, Widjaja G, Alasady S, Mahmudiono T, Mustafa F, Kuznetsova M. Study on the role of nano antibacterial materials in orthodontics (a review). *Braz J Biol*. 2022;2: 72-84.

Cao S, Yeung L, Yue L. Preparation of freestanding and crack-free titania–silica aerogels and their performance for gas phase, photocatalytic oxidation of VOCs. *Appl Catal B: Envr*. 2006;68: 99-108.

Carrouel F, Viennot S, Ottolenghi L, Gaillard C, Bourgeois D. Nanoparticles as antimicrobial, anti-inflammatory, and remineralizing agents in oral care cosmetics: a review of the current situation. *Nanomaterials*. 2020;10: 140.

Chambers C, Stewart B, Su B, Jenkinson F, Sandy R, Ireland J. Silver doped titanium dioxide nanoparticles as antimicrobial additives to dental polymers. *Int J of Dent Mater*. 2017;33: 115-123.

Daub W, Linn J, Bradley G. Bond strength of direct and indirect bonded brackets after thermocycling. *Int J of the Angle Orthod*. 2006;76: 295-300.

De Almeida M, Da Rosa O, Meereis W, de Almeida M, Ribeiro S, da Silva F, Lund, G. Efficacy of antimicrobial agents incorporated in orthodontic bonding systems: a systematic review and meta-analysis. *J of Orthod*. 2018; 45: 79-93.

De Stefani A, Bruno G, Preo G, Gracco A. Application of Nanotechnology in Orthodontic Materials: A State-of-the-Art Review. *J Dent*. 2020;8: 114-126.

Eldebany N, Abd Elkodous M, Tohamy H, Abdelwahed R, El-Kammar M, AbouAhmed H, Elkhenany H. Gelatin Loaded Titanium Dioxide and Silver Oxide Nanoparticles: Implication for Skin Tissue Regeneration. *Int J of Biol Trace Element Res.* 2020;3: 1-12.

Eslami N, Fasihi F, Jamalinasab A, Ahrari F. Biocompatibility of several colloidal solutions containing nanoparticles on human gingival fibroblasts. *Dent Res J.* 2021;2: 1-18.

Eslamian L, Borzabadi-Farahani A, Karimi S, Saadat S, Badiiee R. Evaluation of the shear bond strength and antibacterial activity of orthodontic adhesive containing silver nanoparticle, an in-vitro study. *Int J of Dent.* 2020;10: 1453-1466.

Espinosa-Cristóbal F, López-Ruiz N, Cabada-Tarín D, Reyes-López Y, ZaragozaContreras A, Constandse-Cortéz D, Kobayashi T. Antiadherence and antimicrobial properties of silver nanoparticles against *Streptococcus mutans* on brackets and wires used for orthodontic treatments. *J of Nanomaterials.* 2018;2: 1-13.

Farzanegan F, Shafaei H, Darroudi M, Rangrazi A. Effect of the Incorporation of Chitosan and TiO₂ Nanoparticles on the Shear Bond Strength of an Orthodontic Adhesive: An In Vitro Study. *J Adv Oral Res.* 2021;3: 1-11.

Ferrando-Magraner E, Bellot-Arcís C, Paredes-Gallardo V, Almerich-Silla M, GarcíaSanz V, Fernández-Alonso M. Antibacterial properties of nanoparticles in dental restorative materials. A systematic review and meta-analysis. *Int J of Medicina.* 2020;56: 46-55.

Florez E, Hiers D, Larson P, Johnson, O'Rear E, Rondinone J, Khajotia S. Antibacterial dental adhesive resins containing nitrogen-doped titanium dioxide nanoparticles. *Int J of Mater Sci Eng.* 2018;93: 931-943.

Garcia M, Ferreira J, de Souza S, Leitune B, Samuel W, de Souza Balbinot G, Collares M. Ionic liquid as antibacterial agent for an experimental orthodontic adhesive. *Int J of Dent Mater.* 2019;35: 1155-1165.

Gea M, Bonetta S, Iannarelli L, Giovannozzi M, Maurino V, Bonetta S, Schilirò T. Shape-engineered titanium dioxide nanoparticles (TiO₂-NPs): cytotoxicity and genotoxicity in bronchial epithelial cells. *Int J of Food and Chem. Tox.* 2019;127: 89100.

Ghorbanzadeh R, Nader H, Salehi-Vaziri A. The effects of bimodal action of photodynamic and photothermal therapy on antimicrobial and shear bond strength properties of orthodontic composite containing nano-graphene oxide. *Int J of Photodiagnosis and Photodynamic Therapy.* 2021;36: 576-589.

Gilani H, Ameli N, Ghorbani R, Akhavan A, Rabiei A, Zeinabadi S, Kameli S. Effect of Adding Nano Silver-Hydroxyapatite to the Orthodontic Primer on Bracket-Enamel Shear Bond Strength. *J of Ev of Med and Dent Sci.* 2020;9: 3457-3463.

Gul H, Nayyer M, Gilani M, Aman N, Azad A, Shah T, Khan, A. S. Comparative Fluoride Release and Antimicrobial Analysis of Commercial and Experimental Bioactive Glass/Nano-Oxide-Based Dentifrices. *Eur J of Dent.* 2020;14: 038-044.

Hailan Y, Al-Khatieeb M. The Effects of Incorporating some Additives on Shear Bond Strength of Orthodontic Adhesive (An In-vitro Study). *Int J of Med Res and Health Sci.* 2018;7: 11-18.

Hasan A. Evaluation the properties of orthodontic adhesive incorporated with nanohydroxyapatite particles. *Int J of the Saudi Dent.* 2021;33: 1190-1196.

Hernández-Gómora E, Lara-Carrillo E, Robles-Navarro B, Scougall-Vilchis J, Hernández-López S, Medina-Solís E, Morales-Luckie A. Biosynthesis of silver

nanoparticles on orthodontic elastomeric modules: evaluation of mechanical and antibacterial properties. *Int J of Molecules*. 2017; 22: 1394-1407.

Imazato S, Kohno T, Tsuboi R, Thongthai P, Xu H, Kitagawa H. Cutting-edge filler technologies to release bio-active components for restorative and preventive dentistry. *Int J of Dent Mater*. 2020; 3: 2019-350.

Jasso-Ruiz I, Velazquez-Enriquez U, Scougall-Vilchis J, Morales-Luckie A, Sawada T, Yamaguchi R. Silver nanoparticles in orthodontics, a new alternative in bacterial inhibition: in vitro study. *Int J of Progress in Orthod*. 2020; 21: 1-8.

Jasso-Ruiz I, Velazquez-Enriquez U, Scougall-Vilchis J, Lara-Carrillo E, Toral-Rizo H, López-Castañares R, Morales-Luckie A. Synthesis and Characterization of Silver Nanoparticles on Orthodontic Brackets: A New Alternative in the Prevention of White Spots. *Int J of Coatings*. 2019;9: 469-480.

Jowkar Z, Fattah Z, Ghanbarian S, Shafiei F. The Effects of Silver, Zinc Oxide, and Titanium Dioxide Nanoparticles Used as Dentin Pretreatments on the Microshear Bond Strength of a Conventional Glass Ionomer Cement to Dentin. *Int J of Nanomedicine*. 2020;15: 4742-4755.

Kambalyal B, Shanmugasundaram K, Rajesh V, Donthula S, Patil R. Comparative Evaluation of Antimicrobial Efficacy of Silver, Titanium Dioxide and Zinc Oxide Nanoparticles against *Streptococcus mutans*. *Pesquisa brasileira em odontopediatria e clinica integrada*. 2018;18; 4144-4150.

Kang W, Son S, Park B, Kim S. Effect of thermocycling on shear bond strength and mode of failure of ceramic orthodontic brackets bonded to different porcelain restorations. *Korean J of Orthod*. 2009;39: 225-233.

Khezerlou A, Alizadeh-Sani M, Azizi-Lalabadi M, Ehsani A. Nanoparticles and their antimicrobial properties against pathogens including bacteria, fungi, parasites and viruses. *Int J of Microbial pathogenesis*. 2018;123: 505-526.

Kielan-Grabowska Z, Bącela J, Zięty A, Seremak W, Gawlik-Maj M, Kawala B, Sarul M. Improvement of Properties of Stainless Steel Orthodontic Archwire Using TiO₂: Ag Coating. *Int J of Dent*. 2021;13: 1727-1734.

Kotta M, Gorantla S, Muddada V, Lenka R, Karri T, Kumar S, Tivanani M. Antibacterial activity and debonding force of different lingual retainers bonded with conventional composite and nanoparticle containing composite: An in vitro study. *J of the World Federation of Orthod*. 2020;9: 80-85.

Liao C, Li Y, Tjong C. Visible-light active titanium dioxide nanomaterials with bactericidal properties. *Int J of Nanomaterials*. 2020;10: 116-124.

Math M, Shah G, Gangurde P, Karandikar G, Gheware A, Jadhav S. In-vitro Comparative Assessment of Antibacterial and Anti-adherent Effect of Two Types of Surface Modificants on Stainless Steel Orthodontic Brackets Against *Streptococcus mutans*. *J of Indian Orthod Soc*. 2021;2: 1-13.

Meher Vineesha C, Varma K, Bhupathi A, Priya P, Anoosha M, Harsha D. Comparative Evaluation of Antibacterial Effects of Nanoparticle-Incorporated Orthodontic Primer: An In Vitro Study. *J of Indian Orthod Soc*. 2021;55: 390-398.

Mirhashemi A, Akhondi S, Sodagar A, Jalali F, Jazi L. Effect of nano-zinc oxide and nano-chitosan particles on the shear bond strength of dental composites used as orthodontic adhesive. *J of the World Federation of Orthod*. 2021;10: 172-176.

Mirhashemi A, Jazi L. Evaluation of the effect of antimicrobial nanoparticles on bond strength of orthodontic adhesives: A review article. *Int J of Dent Res*. 2021;18: 110.

Mirhashemi A, Bahador A, Sodagar A, Pourhajibagher M, Amiri A, Gholamrezayi E. Evaluation of antimicrobial properties of nano-silver particles used in orthodontics fixed retainer composites: an experimental in-vitro study. *J of Dent Res Dent Clin*.

2021;15: 87-93.

Mobeen N, Kishore S, Gandhi R, Duraisamy S, Ravi K. Biosafety of Nanoparticles Used in Orthodontics--A Literature Review. *J of Evol of Med and Dent Sci.* 2021; 10:2658-2665.

Mok H, Proctor G, Thanou M. Emerging nanomaterials for dental treatments. *Int J of Emerging Topics in Life Sci.* 2020;4: 613-625.

Mollabashi V, Farmany A, Alikhani Y, Sattari M, Soltanian R, Kahvand P, Banisafar Z. Effects of tio₂-coated stainless steel orthodontic wires on streptococcus mutans bacteria: A clinical study. *Int J of Nanomedicine.* 2020;15: 8742-8759.

Moradpoor H, Safaei M, Mozaffari R, Sharifi R, Imani M, Golshah A, Bashardoust N. An overview of recent progress in dental applications of zinc oxide nanoparticles. *Int J of Dent.* 2021;11: 21189-21206.

Musial J, Krakowiak R, Mlynarczyk T, Goslinski T, Stanis J. Titanium dioxide nanoparticles in food and personal care products—What do we know about their safety?. *Int J of Nanomaterials.* 2020;10: 1097-1110.

Nanda M, Bagga K, Agrawal P, Tiwari S, Singh A, Shahi. K. An overview of nanotechnological advances in orthodontics. *Indian J of Dent Sci.* 2021;13: 198-209.

Nikpour S, Shahroudi S, Saffarpour A, Akhavan A, Sodagar A. Shear Bond Strength of Self-Adhesive Composite Containing TiO₂ and SiO₂ Nanoparticles with an Additional Etching Step for Orthodontic Brackets Bonding to Enamel. *Int J of Folia Med.* 2021;63: 854-865.

Papp A, Horváth T, Igaz N, Gopisetty K, Kiricsi M, Berkesi S, Vezér T. Presence of Titanium and Toxic Effects Observed in Rat Lungs, Kidneys, and Central Nervous System in vivo and in Cultured Astrocytes in vitro on Exposure by Titanium Dioxide Nanorods. *Int J of Nanomedicine.* 2020;15: 9927-9939.

Pinget G, Tan J, Janac B, Kaakoush O, Angelatos S, O'Sullivan J, Macia L. Impact of the food additive titanium dioxide (E171) on gut microbiota-host interaction. *Int J of Frontiers in Nutrition*. 2019;6: 48-57.

Poosti M, Ramazanzadeh B, Zebarjad M, Javadzadeh P, Naderinasab M, Shakeri T. Shear bond strength and antibacterial effects of orthodontic composite containing TiO₂ nanoparticles. *Eur J of Orthod*. 2013;35: 676-679.

Pourhajibagher M, Bahador A. Antimicrobial properties, anti-virulence activities, and physico-mechanical characteristics of orthodontic adhesive containing Cphycocyanin: a promising application of natural products. *Int J of Folia Medica*. 2021;63: 113-121.

Pourhajibagher M, Bahador A. Orthodontic adhesive doped with nano-graphene oxide: physico-mechanical and antimicrobial properties. *Int J of Folia Medica*. 2021;63: 413-421.

Pourhajibagher M, Sodagar A, Bahador A. An in vitro evaluation of the effects of nanoparticles on shear bond strength and antimicrobial properties of orthodontic adhesives: A systematic review and meta-analysis study. *Int J of Orthod*. 2020;18: 203-213.

Pourhajibagher M, Vaziri S, Takzaree N, Ghorbanzadeh R. Physico-mechanical and antimicrobial properties of an orthodontic adhesive containing cationic curcumin doped zinc oxide nanoparticles subjected to photodynamic therapy. *Int J of Photodiagnosis and Photodynamic Therapy*. 2019;25: 239-246.

Rosolen A, Bridi C, Basting T. Bond strength of different bracket bonding materials to the enamel subjected to thermal cycling. *RGO-Revista Gaúcha de Odontologia*. 2015;63: 25-32.

Salehi P, Babanouri N, Roein-Peikar M, Zare F. Long-term antimicrobial assessment of orthodontic brackets coated with nitrogen-doped titanium dioxide against *Streptococcus mutans*. *Int J of Progress in Orthod*. 2018;19: 1-6.

Sánchez-Tito M, Tay Y. Antibacterial and white spot lesions preventive effect of an orthodontic resin modified with silver-nanoparticles. *J of Clin and Exp Dent*. 2021;13: 674-685.

Satti H, Raja I, Javed B, Akram A, Mashwani R, Ahmad S, Ikram M. Titanium dioxide nanoparticles elicited agro-morphological and physicochemical modifications in wheat plants to control *Bipolaris sorokiniana*. *Int J of Plos one*. 2021;16:869-880.

Sharon E, Sharabi R, Eden A, Zabrovsky A, Ben-Gal G, Sharon E, Beyth N. Antibacterial activity of orthodontic cement containing quaternary ammonium polyethylenimine nanoparticles adjacent to orthodontic brackets. *Int J of Envr Res and Public Health*. 2018;15: 591-606.

Siddiqui A, Khan R, Abd_Allah F, Parveen A. Titanium dioxide and zinc oxide nanoparticles affect some bacterial diseases, and growth and physiological changes of beetroot. *Int J of Vegetable Sci*. 2019;25: 409-430.

Sodagar A, Akhoundi A, Bahador A, Jalali F, Behzadi Z, Elhaminejad F, Mirhashemi, H. Effect of TiO₂ nanoparticles incorporation on antibacterial properties and shear bond strength of dental composite used in Orthodontics. *Dent. press J of Orthod* 2017;22: 67-74.

Song W, Ge S. Application of antimicrobial nanoparticles in dentistry. *Int J of Molecules*. 2019;24: 1021-1033.

Souza, B. M. D., Santos, D. M. S. D., and Magalhães, A. C. Antimicrobial and anticaries effect of new glass ionomer cement on enamel under microcosm biofilm model. *Brazilian Dent J*. 2018;29: 599-605.

Subramani, K., Seo, H. N., Dougherty, J., Chaudhry, K., Bollu, P., Rosenthal, K. S., and Zhang, J. F. In vitro evaluation of antimicrobial activity of chlorhexidine hexametaphosphate nanoparticle coatings on orthodontic elastomeric chains. *Int J of Mater Res Exp.* 2020;7: 75392-75401.

Surmelioglu D, Yavuz A, Ozcetin K, Özdemir M, Aydın U. Effects of a Newly Developed Experimental Bleaching Agent on Tooth Color and Shear Bond Strength of Composite Resins. *J of Adhesive Dent.* 2020;22: 1-15.

Syed S, Kulkarni D, Todkar R, Bagul S, Parekh K, Bhujbal N. A novel method of coating orthodontic archwires with nanoparticles. *J of Int Oral Health: JIOH.* 2015;7: 21-30.

Tahmasbi S, Mohamadian F, Hosseini S, Eftekhari L. A review on the applications of nanotechnology in orthodontics. *Nanomedicine J.* 2019;6: 11-18.

Tavakolinejad Z, Sadeghi M. Effect of Pretreatment with Fluoride, Chlorhexidine, and Mixed Fluoride-Chlorhexidine Gels on Shear Bond Strength of Orthodontic Brackets: An Ex-Vivo Study. *J of Res in Dent. and Maxillofacial Sci.* 2021;6: 24-29.

Tawfik A, Mehesen R, Maaly T. Evaluation of Modified Glass Ionomer Cements with Protein repellent and Nanostructured Antibacterial Properties in Prevention of Enamel Demineralization. An in vivo study. *Egyptian Dent J.* 2019;65: 959-964.

Teixeira P, Gontijo C, Júnior F, Pereira F, Schuenck P, Malacarne-Zanon J. Evaluation of antimicrobial potential and surface morphology in thin films of titanium nitride and calcium phosphate on orthodontic brackets. *American J of Orthod and Dentofacial Orthopedics.* 2021;3: 1-12.

Toodehzaeim H, Zandi H, Meshkani H, Firouzabadi H. The effect of CuO nanoparticles on antimicrobial effects and shear bond strength of orthodontic adhesives. *J of Dent.* 2018;19: 1-12.

Uysal T, Yagci A, Uysal B, Akdogan G. Are nano-composites and nano-ionomers suitable for orthodontic bracket bonding?. *The Eur J of Orthod.* 2010;32: 78-82.

Venkatesan K, Kailasam V, Padmanabhan S. Evaluation of titanium dioxide coating on surface roughness of nickel-titanium archwires and its influence on *Streptococcus mutans* adhesion and enamel mineralization: A prospective clinical study. *American J of Orthod and Dentofacial Orthopedics.* 2020;158: 199-208.

Wu T, Tang M. The inflammatory response to silver and titanium dioxide nanoparticles in the central nervous system. *Int J of Nanomedicine.* 2018;13: 233-249.

Yassaei S, Nasr A, Zandi H, Motallaei N. Comparison of antibacterial effects of orthodontic composites containing different nanoparticles on *Streptococcus mutans* at different times. *Dent. Press J of Orthod.* 2020;25: 52-60.

Yin X, Zhang J, Zhao S, Mei M, Li Q, Chu H. The antibacterial mechanism of silver nanoparticles and its application in dentistry. *Int J of Nanomedicine.* 2020; 15:2543-2555.

Yu J, Huang X, Zhou X, Han Q, Zhou W, Liang J, Cheng L. Anti-caries effect of resin infiltrant modified by quaternary ammonium monomers. *J of Dent.* 2020;97: 342-355.

Zhu Z, Cai H, Sun W. Titanium dioxide (TiO₂) photocatalysis technology for nonthermal inactivation of microorganisms in foods. *J of Trends in Food Sci and Tech.* 2018;75: 23-35.

Ziental D, Czarczynska-Goslinska B, Mlynarczyk T, Glowacka-Sobotta A, Stanis B, Goslinski T, Sobotta L. Titanium dioxide nanoparticles: prospects and applications in medicine. *Int J of Nanomaterials.* 2020;10: 376-387.