DOI: 10.1478/AAPP.99S1A27

AAPP | Atti della Accademia Peloritana dei Pericolanti
Classe di Scienze Fisiche, Matematiche e Naturali
ISSN 1825-1242

Vol. 99, No. S1, A27 (2021)

THE RELEVANCE OF INTERDISCIPLINARY TEACHING AND RESEARCH FOR THE DEVELOPMENT OF BIOMATERIALS

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ABSTRACT. Replacement of damaged tissues by biomaterials after a disease or injury is one of the most interesting challenge in medical science. The proper approach in developing a new biomaterial for a specific application must include the evaluation of all aspects and available knowledge in the different fields of science necessary for a comprehensive understanding of the behavior of the new component (*e.g.*, a prosthetic implant) in a special environment (the human body). Starting from chemistry to know how to synthesize our material passing to physics and mechanics to understand how our material will act when stressed, going to biology to discover the reaction of the human body against this material and using mathematics to model and optimize our complex systems. In this concern, this paper reported an interdisciplinary approach used in developing a new material for biomedical application. The importance of the development of innovative teaching methods was also deeply discussed.

1. Introduction

Biomaterials have special and strict requirements which can be adjusted to meet the necessities of a specific application in human body (Barbucci 2002). In fact, a biomaterial must have a high biocompatibility, excellent corrosion resistance, suitable mechanical properties (strength, stiffness and fatigue properties) and has low wear and toxicity in order to attain clinical success. Nevertheless, depending on the application, differing requirements may arise. Occasionally, these requirements can be totally opposite. For example, in the bone tissue engineering, the polymeric biomaterial must be biodegradable to allow the bone cells generate their own extracellular matrices, the polymeric scaffold, overtime, will be totally replaced with the human tissue (Bonassar and Vacanti 1998; Keane *et al.* 2012). On the other hand, in the case of orthopedic application, biomaterial needs to be stable (not degrade with time) and wear-resistant (Li *et al.* 2014; Khaskhoussi *et al.* 2018a, 2020a).

Research in the field of biomaterials has focused, throughout history, on the optimization of materials by improving their acceptance of an artificial implant by the surrounding tissues and by the human body as a whole (Lainiala *et al.* 2019).

Through the application area of these biomaterials is highly specific, it deals with almost all aspects of science and engineering. There is an on-going research and development effort for the improvement of methodologies and devices for more efficient and effective processing of biomaterials (Cohrs *et al.* 2014).

Recently, the focus has gradually shifted from conventional materials science towards an interdisciplinary research approach. An interdisciplinary approach is an approach that generates an understanding of phenomena or issues that cut across different disciplines and the connections between them and their connection to the real life. It generally highlights method and meaning rather than content and product by merging contents, notions, procedures and perspectives from more than two disciplines. Thus, the proper approach in developing a new biomaterial for a specific application must include the evaluation of all aspects and available knowledge in the different fields of applied science necessary for a comprehensive understanding of the behavior of the new component. The interdisciplinary approach used for biomaterials development can involve materials engineers as well as biologists, mathematicians and clinicians of various disciplines. This attractive interdisciplinary approach complements traditional techniques and benefits from recent advances in different fields to overcome the several challenges in the medical applications (Roy *et al.* 2019).

In this concern, an interdisciplinary experimental approach that optimizes the different properties of nanocomposite material in alumina-zirconia-titania complex system for orthodontic application is presented in current work as a case study.

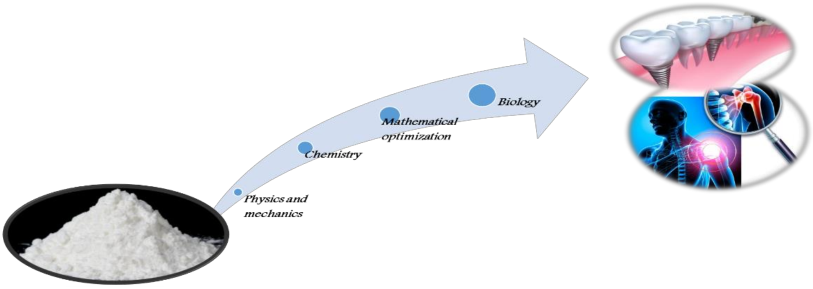

FIGURE 1. A sketch of an application

2. Experimental part

2.1. Sample preparation. Al_2O_3, $ZrO_2(CeO_2)$, TiO_2 powders (Aldrich) were used for composite ceramics elaboration. Commercial oxides were mixed at different amounts. Then, the mixtures were shaped and pressed through cold pressing. Numerous preliminary tests were realized for optimizing the sintering conditions. The samples were sintered in air at 1400 °C for 2 hours in Pyrox 2408 furnace. TiAiZi codes, where i symbolizes the amount of each compound, identified $TiO_2{-}Al_2O_3{-}ZrO_2$ samples. Content of titania in zirconia and alumina mixtures was in the range 0–10 wt%. Ceria quantity was kept on a constant proportion of 12 mol% to zirconia content. A detailed description of the preparation process can be found in (Khaskhoussi *et al.* 2017, 2020a).

2.2. Chemical analysis. The X-ray diffraction (XRD) characterization by the Bruker D8 Advance diffractometer was used to study phase transformation in the different ceramic composites. Then, the results were compared with the International Center for Diffraction

Data (ICDD standard files). In addition, the Scanning Electron Microscopy (Zeiss Cross Beam 540) coupled with Energy Dispersive Spectroscopy were used to study the morphology of the ceramic composites.

2.3. Mechanical characterization. The mechanical properties: Vickers hardness, Young's Modulus and strength were also examined.

In order to determine the tensile strength of the ceramics, the Brazilian test was used through the Lloyd EZ 50 universal testing machine. Vickers indentation was used to determine the hardness and the elastic modulus of the samples. Hardness was determined according to ASTM C1327. The determination of Young's modulus as linear slope of the unloading curves from indentation load–displacement data was done according to the Oliver-Pharr model and ISO 14577 standard (Khaskhoussi *et al.* 2018a).

2.4. Biological tests. The ceramic surface wettability was assessed by static contact angle system by means of a sessile drop measurement instrument (optical tensiometer Attension by Biolin Scientific). In addition, the mitochondrial activities of living human gingival cells were assessed by the quantitative colorimetric MTT assay to comprehend the effect of the composition of the different ceramics on the cells viability. Finally, the DNA damage was evaluated using the comet assay, also known as SCGE method (Khaskhoussi *et al.* 2020b).

3. Results and discussion

3.1. Chemical aspects. The microstructure is the most important factor that affects the physical and the mechanical properties of the material. The microstructure is determined by the chemical composition and the processing conditions. Thus, by knowing the microstructure, we can predict the behavior of a particular material. This is also important while predicting the failure of a component in certain conditions (Boccaccini 2005).

In this study, we combined three different oxides: Al_2O_3, ZrO_2 and TiO_2 to elaborate different binary and ternary composites. However, theses formulations result in complex microstructures. Figure 1 presents the phase composition of the different investigated composites. In fact, the experimental region is a triangle and each of the three vertices corresponds to a pure component. The composition of each composite was showed in the three-component system. Three families can be easily distinguished. The first family is composed of ZrO_2-based composites: T5A0Z95, T10A0Z90 and T1A0Z99. The principal phases in this region are ZrO_2-CeO_2 and ZrO_2-TiO_2 phases.

The second family is composed of Al_2O_3-based composites: T10A90Z0, T5A95Z0 and T1A99Z0, Al_2O_3 and $Al_2O_3-TiO_2$ are the principal phases in this family.

The third one is an $Al_2O_3-ZrO_2$-based composites: T7A69Z24, T7A24Z69, T1A50Z50, T10A45Z45, T5A47Z47, T2A24Z74 and T2A74Z24. This rich phase family contains seven diverse systems of oxide interactions: ZrO_2-CeO_2, Al_2O_3, $Al_2O_3-TiO_2$, ZrO_2-TiO_2, TiO_2-CeO_2, $Al_2O_3-ZrO_2$ and $Al_2O_3-CeO_2$.

In Al_2O_3-based ceramics, a clear bi-phase system was observed: Al_2O_3 and Al_2TiO_5 approving the good affinity between Al_2O_3 and TiO_2 during the sintering.

In ZrO_2-based ceramics, the $Ce_{0.1}Zr_{0.9}O_2$ is the principal phase in the T1A0Z99 ceramic. The increase of TiO_2 content allows the reaction between ZrO_2 and TiO_2 and the apparition of new phases such as $ZrTiO_4$ and $Zr_{0.81}Ti_{0.19}O_2$.

In $Al_2O_3-ZrO_2$ ceramics, the addition of $\approx$50 wt.% of Al_2O_3 to $ZrO_2(CeO_2)$ leads to the formation of two phases ($Zr_{0.76}Al_{0.24}O_2$ and Al_2O_3). When a supplementary 5 wt.% of TiO_2 was added to the preceding system, a portion of CeO_2 reacted with Al_2O_3 and TiO_2 probably thanks to the elevated reactivity of nanoscale powders. As mentioned in the work realized by Dudczig et al. (Dudczig *et al.* 2012), thanks to the important specific surface area of the nanoparticles, they are highly reactive, that decreased the starting temperature of sintering. Indeed, nano-Al_2O_3 added to Al_2O_3-based composite raw materials can accelerate the densification and acts as a binder (Hahn 2003). As a result, two CeO_2-based phases were formed $CeAl_{11}O_{18}$ and $Ce_{0.6}Ti_{0.4}O$. Three ZrO_2-based phases were also present with different quantities. In fact, the disappearance of the $Zr_{0.76}Al_{0.24}O_2$ phase induces the increase of $Ce_{0.9}Zr_{0.1}O_2$ and the formation of small amounts of -ZrO_2-TiO_2 phases: $Zr_{0.81}Ti_{0.19}O_2$ and $ZrTiO_4$.

The increase of the amount of TiO_2 induces a clear rise of the TiO_2-based phase amount: $Zr_{0.81}Ti_{0.19}O_2$ (from 3% to 21.6%) and $ZrTiO_4$ (from 4% to 10%) with the presence of the traces of a new phase Al_2TiO_5.

In addition, the presence of 2.5wt.% of TiO_2 and 23.75 wt.% of Al_2O_3 in T1A0Z99 conducts to the formation of a traces of $Zr_{0.81}Ti_{0.19}O_2$ phase (1%) with the presence of the two main phases $Ce_{0.1}Zr_{0.9}O_2$ and $\alpha - Al_2O_3$. However, the rise of the amount of titania (5 wt.%) increase the amount of this phase. A decrease of 25% in $Ce_{0.1}Zr_{0.9}O_2$ amount was clearly observed. The CeO_2 reacted with alumina and the zirconia was instead consumed by the ZrO_2-TiO_2 system ($ZrTiO_4$ and $Zr_{0.81}Ti_{0.19}O_2$).

The incorporation of 2 wt.% TiO_2 and 24 wt.% ZrO_2 in alumina (T2A74Z24) induces the formation of equal amounts of $Ce_{0.6}Ti_{0.4}O_2$ and $ZrTiO_4$ (2%). 5 wt.% additionl of TiO_2 (T7A69Z24) induced the increase of the quantities of this two phases and the creation of $Zr_{0.81}Ti_{0.19}O_2$ phase. In addition, the reaction of 5% of Al_2O_3 with TiO_2 induces the formation of Al_2TiO_5.

A detailed study of the complex microstructure of multiphase $TiO_2-Al_2O_3-ZrO_2$ systems and an explication of the formation mechanisms of diverse ceramic phases are reported in (Cohrs *et al.* 2014; Roy *et al.* 2019).

Based on the promising findings presented in this section, evidencing the formation of phases and their distribution in the complex Titania-Alumina-Zirconia systems, the mechanical behavior of these composites has been evaluated to understand the influence of microstructure on the different properties of ceramic composites in Titania-Alumina-Zirconia system.

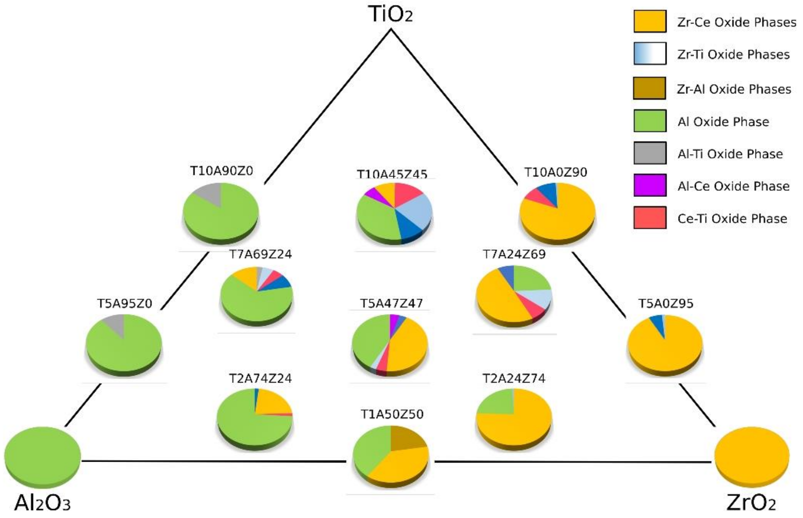

FIGURE 2. Microstructure results on ternary $TiO_2-Al_2O_3-ZrO_2$ plot (Khaskhoussi *et al.* 2017).

3.2. Mathematical analysis. Considering that usually the required properties of ceramics for dental application are complementary in order to support the complex stresses applied to the implants during their lifetime, the optimization of ceramic composition with good mechanical properties compromise is mandatory. The study based on mixture design approach can be effective, experimental design methodology has several advantages. It is cost and time economic method; In fact, this methodology reduces the number of experimental runs needed to analyze the effects of different variables. This methodology leads to overcome the shortcomings of the traditional experimental technique, which analyze the effect of only one variable at a time with a high number ofexperimental runs.

The three presented mathematical modulus of Hardness, Strength and Young's modulus correlate very well with the experimental measured responses:

***Hardness**:

$$Hv= -661.59T+15.87A+8.06Z+686.49TA+722.78TZ-15.79AZ+60.44TAZ$$

***Strength**:

$$\sigma=-10874.88T+71.78A+232.59Z+11563.38TA+10009.60TZ-229.96AZ +3725.90TAZ$$

***Youngs modulus**:

$$E=-16132.44T+352.36A+165.94Z+16940.13TA+17778.21TZ -325.58AZ+ 1320.21TAZ$$

With T is the TiO_2, A is the Al_2O_3 and Z is the ZrO_2

According to these models, the initial composition and then the phase composition (showed in the previous section) are the key factor that control the mechanical properties of the ceramics.

This mixture design mathematical method, not only highlights the effect of diverse components (TiO_2, Al_2O_3 and ZrO_2) on the mechanical performances of the ceramic composites, but it is useful as a predictive tool to fabricate ceramics with tailored mechanical performances in terms of elastic modulus, hardness and strength. Therefore, this method can be used to optimize the formulation of $Al_2O_3-ZrO_2-TiO_2$ materials that satisfies the needs of diverse bone replacements. Indeed, the commercial bone replacements are made of pure zirconium or titanium. Nevertheless, the enormous difference between the Young's modulus of bone tissues and these materials (5 to 14 time) (Misch *et al.* 2015) creates the stress shielding phenomenon that causes the bone resorption (Huiskes *et al.* 2000). To avoid this undesirable effect, materials with good strength and suitable stiffness are under development to elaborate implants.

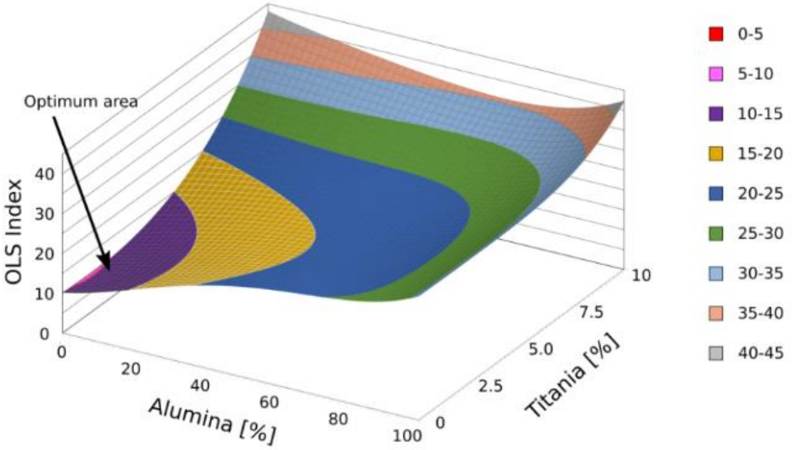

FIGURE 3. Optimization of ceramic composition for bone replacement (Khaskhoussi *et al.* 2018b).

These validated models were used to calculate the ordinary least squares (OLS) on the bases of the bone tissues requirements. Figure 3 shows the OLS index of $Al_2O_3-ZrO_2-TiO_2$ mixtures. A low value of OLS indicates a good affinity of the mixture with the required performances. As shown in the Figure 3 the optimum zone can be identified for mixtures with high quantity of ZrO_2 (consequently small quantity of Al_2O_3) and few amount of TiO_2. After the optimization of the mechanical performances of the elaborated ceramics, a biological study of them is mandatory to evaluate their applicability in bone replacement.

3.3. Biological study. Biocompatibility which is the capability of a material to be in contact with living tissues of the human body and to perform its favorite function without causing any adverse or harmful effects to this body (Palmero *et al.* 2015; Hagiwara and Nakajima 2016), is the key factor for successful applications of biomaterials.

Concerning bone, the first step in the procedure of osseointegration is the natural construction of a proteinaceous layer absorbed on the top of the implant surface in the host living tissue. The quality of this first step will affect the cells ability to proliferate and to differentiate themselves on contact with the graft (Spies *et al.* 2015). Consequently, the behavior of the surface and the wettability can be a critical feature for the implant biocompatibility and must be carefully evaluated for biomedical application, together with mechanical performances (Lutton and Ben-Nissan 1997; Sansone 2013).

Moreover, the cytotoxicity test is one of the most effective approaches for biological evaluation as it has numerous advantages, such as the simplicity and the high sensitivity, used in vitro to evaluate the cell reproduction, growth and morphological effects by medical instruments (Huet *et al.* 2011). At the same time, the genotoxicity test offers an early, easy and relatively inexpensive way to recognize materials that may cause DNA damage, that can also lead to heritable imperfections and probably cancer (Wang and Stevens 1989).

These experiments are suggested for all novel biomaterials as they offer a fast evaluation and standardized protocols and have the aptitude to discard non-compatible and toxic materials even prior to clinical testing (Pandey *et al.* 2014).

Therefore, in the current section, the wettability, cytotoxicity and genotoxicity of different $Al_2O_3-ZrO_2-TiO_2$ composites were evaluated. The surface wettability of bioceramic was evaluated by measuring the contact angle of the ceramics with the physiological liquid. Figure 4 showed the measured water contact angle on the surface of elaborated ceramics. The obtained contact angle values are ranged from 53° to 81° due to the different phases present in each composite as shown in the chemical study section. Nevertheless, the contact angles variability, the liquid was being drawn towards the ceramic surface. These contact angles, lower than 90°, designate the composite surface as hydrophilic and they display high wettability. Thus, these hydrophilic surfaces can ease the interactions between the implant and the physiological body fluids to obtain an appropriate cell adhesion and, therefore, an optimal osseointegration. The results showed that the wettability behavior strongly depends on the mixture composition of ceramics.

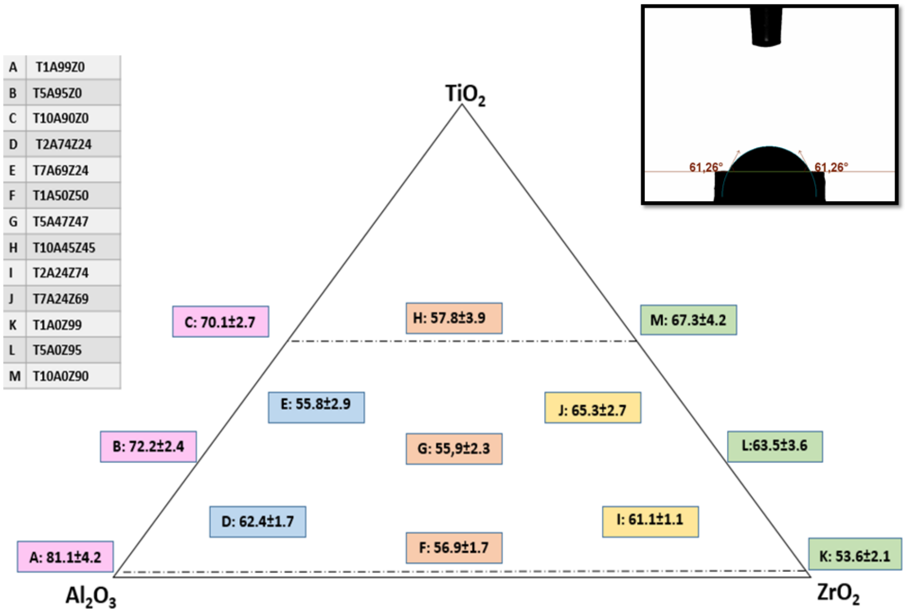

FIGURE 4. Contact angles of different $Al_2O_3-TiO_2-ZrO_2$ ceramic composites.

The cytotoxicity of ceramics with human gingival fibroblast cells, evaluated by MTT test and the results are shown in Figure 5. The ceramic composites showed a cell mortality lower than 20%. Consequently, according to the international standard guide ISO 10993-5, which categorizes a cytotoxicity as a decrease of the cell viability by around 30%, the results confirm the lack of cytotoxic effects of our ceramics (Standardization (ISO) 10993-5 2009).

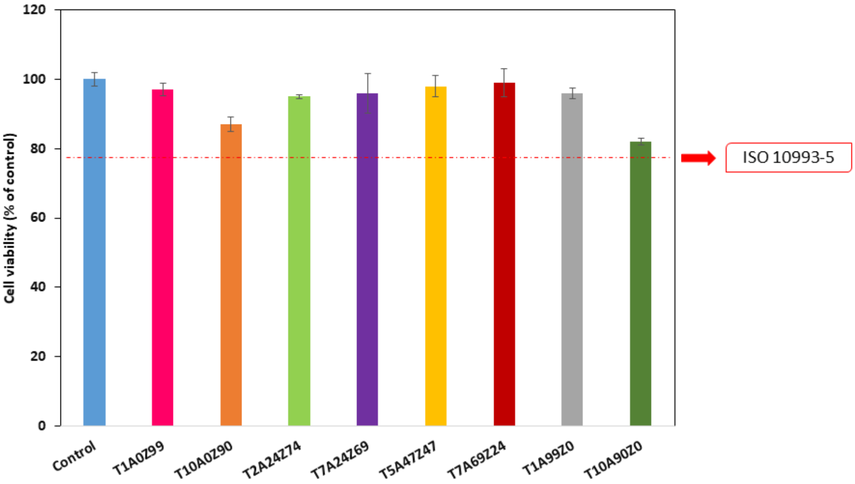

FIGURE 5. Cell viability of human gingival fibroblast (Khaskhoussi *et al.* 2020b)

The Comet test was used as complementary biocompatibility test to identify any variations in fibroblast cells DNA. The results indicated that the damages of DNA are intimately associated to the titania amount (Figure 6). Genotoxicity was principally attributed to composites having 10 wt% titania: T10A0Z90 and T10A0Z90. However, the ceramic composites that had a lower percentage of TiO_2 did not induce any significant DNA damage. Our work demonstrated that the novel developed $Al_2O_3-ZrO_2-TiO_2$ ceramic composites containing less than 10 wt% titania displays favorable properties which make them appropriate for biomedical applications.

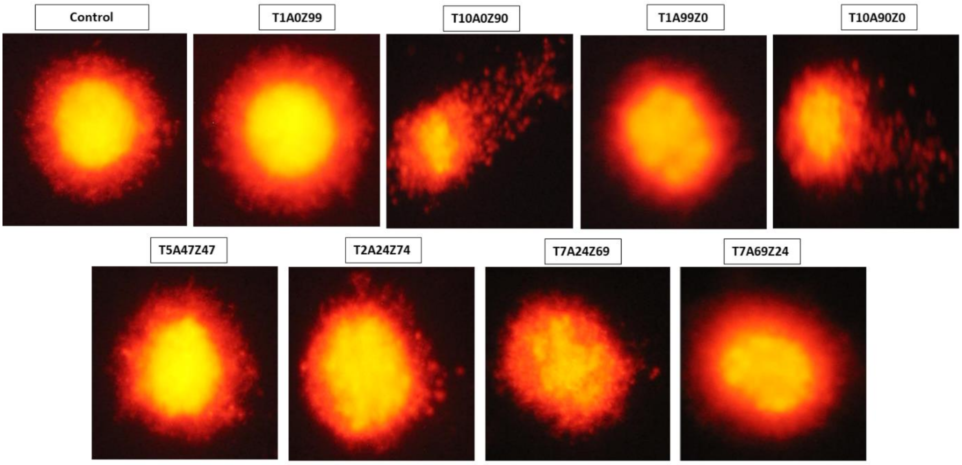

FIGURE 6. DNA damage analysis of differentiated HGF-1 cells (modified from Khaskhoussi *et al.* (2020b)).

As discussed in the previous section, the biomaterials field is a complex field. Thus, researchers with an adequate interdisciplinary background that followed a specific education should carry out this type of work. In this regards, the teaching methods should be developed.

4. Innovative teaching method

There are various important but complex problems, phenomena and concepts that resist understanding or resolution when approached from single disciplines. They require investigators who can engage in interdisciplinary translation and synthesis, as part of multidisciplinary teams or individually, in order to develop more complete pictures than would be possible from any one disciplinary perspective. The implication is that we must educate for both disciplinary and interdisciplinary expertise.

Interdisciplinary subjects are pivotal for this interdisciplinary education, teaching how to understand, navigate and employ multiple and often contrary ways of knowing. In these subjects, students develop a meta-knowledge about different disciplines, methods and epistemologies, and learn how to purposefully and reflectively integrate and synthesize different perspectives in order to advance understanding and solve problems. Yet because of the complexity of working across multiple ways of knowing, interdisciplinary subjects are challenging to teach. In this regards, there are different way to create innovative learning space:

- ✓ **Flipped Classroom**: When teachers use a flipped classroom model, the traditional order of teaching and classroom events are reversed. Typically, students can view lecture materials, read text, or do research as their homework prior to coming into class. The time spent in class is reserved for activities that can include peer-to-peer learning, group discussions, independent learning, as well as engaging discussions or collaborative work.

- ✓ **Using the Design-Thinking Process**: The design thinking process is a set of structured strategies that identify challenges, gather information, generate potential solutions, refine ideas, and test solutions. There are five phases to the process: discovery, interpretation, ideation, experimentation, and evolution.
- ✓ **Using Problem-Finding**: Instead of problem-solving, teachers can help students look at the world by finding gaps to fill using problem-finding. Problem-finding is equivalent to problem discovery. Teachers can use problem-finding as part of a more significant problem process as a whole that can include problem-shaping and problem-solving all together. Problem-finding requires an intellectual and imaginative vision to seek out what might be missing or should be added to something important. Using this strategy, teachers can provide students with the opportunity to think deeply, ask critical questions and apply creative ways to solve problems.

These strategies are ways to form innovation and inspire creativity in the classroom. Teachers can start with one new project to see how things go with their students while revising, learning and building repeatedly.

5. Conclusions

Interdisciplinary education must supplement disciplinary teaching and learning so students can learn how to respond to challenges that transcend disciplines, work in the confluence of multiple disciplines, and develop research trajectories that do not conform to standard disciplinary paths. In this regards, this paper show the need for interdisciplinary approach to elaborate materials for medical applications. In the first part, the importance of the chemical science was highlighted to demonstrate some of the complexities of biomaterial morphology including its structural complexity, its variable phase composition, its stability and its dependence to the initial formulation. Then, the mechanical properties was discussed and employed to model the complex mechanical behavior of these composites with a focus upon the role of the chemical composition in changing the material properties. The obtained mathematical models were used to point out the importance of mathematical science on the optimization of the mechanical performances of the biomaterials. Afterwards, a biological study was introduced to evaluate the biocompatibility of these materials. Thus, this work has highlighted the need for an interdisciplinary approach to study the biomaterials, which requires a team with skills in chemical, mechanical, mathematical, experimental and biological approaches. Future progress will be gradually depend on the collaborations between the different fields.

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Paper contributed to the international workshop entitled “New Horizons in Teaching Science”, which was held in Messina, Italy (18–19 november 2018), under the patronage of the *Accademia Peloritana dei Pericolanti*

Manuscript received 15 Month 2020; published online 30 September 2021