Nanocellulose Containing Polymethyl Methacrylate Bone Cements: Effect of Production Process and Silanization on Mechanical Characteristics

Nanoselüloz İçeren Polimetil Metakrilat Kemik Çimentoları: Üretim Prosesinin ve Silanizasyonun Mekanik Özelliklere Etkisi

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Abstract

Objective: Bone cement is one of the essential orthopedic materials in clinical applications for fixing hip implants. However, the use of bone cement is subject to some limitations like mechanical mismatch with the implantation site. Despite the use of some fillers and bone cement formulations to tackle these limitations, there is still a need for better solutions. It is possible for nanocellulose (NC) to yield successful results in creating a formulation with bone cements thanks to its natural, crystal and strong structure.

Material-Method: In this study, the mechanical performance of bone cements containing NC that is produced with varying methods, and varying ratios in bone cement was examined. Moreover, a comparative study by the silanization method; which is used for enhancing the inter-phase compatibility in composite technology; and employing the same ratios in NC formulations with silanized and non-silanized particles was conducted.

Results: The maximum forces (F_{max}) loading before shape deformation in compression tests of all samples except BC-1SNC were not significantly different ($p>0.05$). BC-1SNC improved the compression resistance increasing the F_{max} by 12.6% ($p<0.05$). Compared to BC, modulus increased about by 16% and 21.5% in BC-1FNC and BC-1SNC, respectively. The modulus value of BC-1SNC group (2666 MPa) was found to be significantly higher than that of the BC and BC-1SiSNC groups ($p<0.05$). The modulus value of BC-2SNC (2490 MPa) group was found to be significantly higher than that of BC group ($p<0.05$).

Conclusions: The silanization of NC does not create a difference in mechanical strength compared to the non-silanized formulation, however, a significant difference was detected with NC produced by different drying methods.

Keywords: Nanocellulose, Bone Cement, Silanization, Spray-Drying, Freeze-Drying.

Özet

Amaç: Kemik çimentosu, kalça implantlarını sabitlemek için klinik uygulamalarda gerekli ortopedik malzemelerden biridir. Bununla birlikte, kemik çimentosu kullanımı, implantasyon bölgesi ile mekanik uyumsuzluk gibi bazı sınırlamalara tabidir. Bu sınırlamaların üstesinden gelmek için bazı dolgu maddelerinin ve kemik çimentosu formülasyonlarının kullanılmasına rağmen, daha iyi çözümlere hala ihtiyaç vardır. Nanoselülozun (NC), doğal, kristal ve güçlü yapısı sayesinde kemik çimentoları ile formülasyon oluşturmada başarılı sonuçlar vermesi mümkündür.

Materyal-Metot: Bu çalışmada, değişik yöntemlerle üretilen NC içeren kemik çimentolarının mekanik performansı ve kemik çimentosundaki değişken oranları incelenmiştir. Ayrıca, silanizasyon yöntemiyle karşılaştırmalı bir çalışma ile kompozit teknolojide fazlar arası uyumluluğun arttırılması için kullanılan ve aynı oranların silanize edilmiş ve silanize edilmemiş NC partiküllerin kemik çimentosu formülasyonlarında kullanılması araştırılmıştır.

Bulgular: BC-1SNC dışındaki tüm numunelerin sıkıştırma testlerinde şekil deformasyonu öncesi yüklenen maksimum kuvvetler (F_{max}), anlamlı derecede farklı değildir ($p>0,05$). BC-1SNC, F_{max}'ı %12,6 artıran sıkıştırma direncini iyileştirmiştir ($p<0,05$). BC'ye kıyasla, modül, BC-1FNC ve BC-1SNC'de sırasıyla %16 ve %21,5 artmıştır. BC-1SNC grubunun (2666 MPa) modulus değeri, BC ve BC-1SiSNC grubuna göre anlamlı derecede yüksek bulunmuştur ($p<0,05$). BC-2SNC (2490 MPa) grubunun modül değeri, BC grubundan anlamlı olarak yüksek bulunmuştur ($p<0,05$).

Sonuç: NC silanizasyonunun, silanize edilmemiş formülasyona kıyasla mekanik mukavemette bir fark yaratmadığını ortaya konmuş, ancak farklı kurutma yöntemleri ile üretilen NC ile önemli fark tespit edilmiştir.

Anahtar kelimeler: Nanoselüloz, Kemik Çimentosu, Silanizasyon, Sprey-Kurutucu, Dondur-Kurutma.

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Introduction

The market for orthopedic accessories is expected to grow $2,678.8 million in 2016 in which bone cement cover $1,076.3 million of this pie (1). Poly (methyl methacrylate) (PMMA) bone cement is one of the most used biomaterials in clinical applications. It serves as a bridge between joint replacement implants and bone tissue by bonding. The cement fills the space between the implant and the bone and supports the implant mechanically. The most used area of bone cements clinically is vertebroplasty and kyphoplasty (2-5), cranio-maxillofacial complex (6), hip (7, 8) and knee replacements (9, 10). Despite the common use of acrylic bone cements clinically, there is still need for improvements to obtain the ideal bone cement. Mechanical mismatch between the cement and the bone, and poor fatigue properties are among the problems which are still waiting for solutions (11). Mechanical properties of PMMA composites have been studied by many researchers. Partial replacement of methyl methacrylate monomer with comonomers containing amine groups such as diethyl amino ethyl acrylate, dimethyl amino ethyl methacrylate or diethyl amino ethyl methacrylate reduced the bending and compressive strength while increased the fracture toughness (12). Aromatic monomers such as methacryloyloxybenzoic acid and 4-diethylamino benzyl methacrylate overcame the reduction of mechanical strength of bone cement (13). Copolymer of poly(methyl methacrylate-acrylic acid-allylmethacrylate) exhibited higher mechanical properties with optimum formulation of monomer ratio in copolymer (14). The addition of up to 40% (by weight) hydroxyapatite (HA) to PMMA cement was shown to increase the fracture toughness, (15) and the addition of HA up to 15% (by weight) led to an increase in flexural modulus while neither compressive nor tensile strength was affected (16, 17).

Chemical modifications such as silanization of bioceramics with silane coupling agents, plasma modifications of fillers are useful methods for overcoming poor interfacial bonding between cement and bioceramics. When silane coupling agents are used on the HA particle surface, tensile properties of bone cement containing silane treated HA were affected less than those of the bone cement containing untreated HA (18). However, Vazquez et al. reported that incorporation of encapsulated β-Tricalcium phosphate by polyethylene glycol into PMMA bone cement did not change mechanical properties (19). The bone cement formulations with plasma-modified ZrO2 particles were revealed to give more strength to the structure than the formulations with non-modified particles (20).

Nanocellulose (NC) has been explored in biomedical applications due to its excellent mechanical and biocompatibility characteristics (21, 22). NC is a highly crystalline nanoparticle (23, 24) and could be an effective filler candidate for PMMA bone cement formulation as a mechanical enhancer. Dong et al. and Yin et al. studied nanocellulose containing PMMA composites prepared, however these studies are not related to bone cement which is a curing formulation with polymerization (23, 24). Moreover, in this study, effects of the different production methods (spray-dry and freeze-dry) on mixing and preparation of bone cements were compared. It is important to prepare bone cement practically because it is prepared readily during surgical operation and used to fill the gap between implant and bone. So for that reason, using and removing procedure of any liquid phase for distribution of filler should be avoided. Thus, in this study, the effect of drying methods (freeze-drying and spray-drying) and the silanization of NC on the filler performance in the PMMA bone cement was attempted to understand the interfacial interaction between the filler and the complex phase of cement. The dried fillers were added directly to the bone cement formulations and a significant difference was obtained with using different drying procedures. The results revealed a mechanically improved bone cement formulation optimized with a natural filler.

Material and Methods

Materials

Sulfuric acid, PMMA, benzoyl peroxide (BPO), N,N-dimethyl-p-toluidine (DMPT) and HA, DMF were purchased from Sigma-Aldrich (St Louis, MO, USA). Barium sulfate (BaSO4) was purchased from Merck (Darmstadt, Germany). Microcrystalline cellulose (MCC), methyl methacrylate (MMA) and 3-aminopropyltriethoxysilane (APSE) were purchased from Alfa Aesar (Karlsruhe, Germany).

Production of NC

In order to produce NC, firstly, 60-65% sulfuric acid solution was added slowly into MCC. The amount of acid was adjusted so that the acid/cellulose ratio was between 8 and 10. The mixture was stirred at 50ºC for 60 min with a mechanical stirrer. At the end of the reaction, the mixture was diluted with cold water for 10 times. Then, the mixture was centrifuged at 4500 rpm for 20 min and was repeatedly washed with pure water and then diluted sodium bicarbonate solution until the pH value reached to 6-7. The acid treated solid part (AT) was put in a freeze-dryer. A 1-2% cellulose suspension was prepared and the particle size was reduced with a high pressure homogenizer (25). The suspension was either FNC or SNC to obtain final product.

Silanization of NC

500 mg spray-dried NC was suspended in 100 mL water by sonicating with a probe for 6 min and the pH was reduced to 5.4 with 1 M citric acid solution. 100 mM APSE solution was added to the suspension (25). The suspension was mixed at room temperature for 2 h and given to spray dryer to obtain the SiSNC.

Preparation of NC Containing Bone Cements

HA (168 mg), BaSO4 (604 mg), BPO (45 mg), DMPT (56 µl), PMMA (4 g) and MMA (4 mL) were used at constant amounts in all of the experiments. NC added to the MMA solution and sonicated with a probe. DMPT was added to this suspension solution. Then, this liquid part was mixed with the powder components (HA, BaSO4, and BPO). The final product was poured into molds to form the desired shape. After being kept in molds for at least 1 h, the samples were cured and removed from the mold (26). Table 1 shows the bone cement compositions prepared in this study.

Table 1. Composition of samples

Sample Code	Sample Composition
BC	Bone cement with no filler
BC-1FNC	Bone cement containing 1% freezed-dried NC
BC-1SNC	Bone cement containing 1% spray-dried NC
BC-0.5SNC	Bone cement containing 0.5% spray-dried NC
BC-2SNC	Bone cement containing 2% spray-dried NC
BC-1SiSNC	Bone cement containing 1% silanized spray-dried NC
BC-W	Bone cement with no filler in wet state
BC-1SNC-W	Bone cement containing 1% spray-dried NC in wet state
BC-1SiSNC-W	Bone cement containing 1% silanized spray-dried NC in wet state

Characterization of The Materials

For characterization of NC, the morphological characteristics were examined with a TEM, Jeol Jem 2100 HRTEM at 200 kV (LaB6 filament). The average diameters of the cellulose nanoparticles were determined by measuring at least 20 particles using ImageJ 1.30 v (National Institutes of Health, USA). FTIR spectra were taken by Perkin Elmer, FTIR spectrometer (USA). The samples were analyzed with ATR apparatus over a 650−4000 cm−1 range with a resolution of 4 cm−1. EDX analysis after silanization reaction was conducted through a TESCAN VEGA 3 SBH electron microscope (Czech Republic). Atomic compositions of the NC surfaces were analyzed with Electron Spectroscopy for Chemical Analysis (ESCA) system (PHI 5000 Versa Probe; Physical Electronics, Chigasaki, Kanagawa, Japan) equipped with monochromatic AlKα at 600 W power at the anode.

For characterization of bone cements, the morphology of the prepared samples was characterized by SEM analysis by using TESCAN VEGA 3 SBH electron microscope (Czech Republic). The samples were sputter-coated by Au-Pd thin film before SEM investigations. The tensile and compression tests were conducted with Zwick Z250 (Germany) test machine by preparing 5 parallel samples for each group. The bone cement samples prepared according to the ASTM D638 were cured in dog-bone shaped (5×0.5×0.5 cm3) and allowed to cure for 1 h at room temperature for tensile tests. Tension force was applied with a cross-head speed of 1 mm/min at room temperature. For the compression tests, the bone cement samples prepared according to ASTM F451 were cured in cylindrical molds (6 mm diameter and 12 mm height). Tests were performed with a cross-head speed of 25 mm/min at room temperature. For the mechanical tests performed in wet conditions, the samples were immersed in PBS at room temperature for 24 h prior to the tests.

Statistical Analysis

The data of the study was analyzed statistically by IBM SPSS Statistics 22 (IBM SPSS, Turkey). Intergroup comparisons of the parameters without normal distribution were made by Kruskal Wallis test; and the group causing difference was determined by Mann Whitney U test. Significance was evaluated at a level of $p<0.05$.

Results

Transmission electron microscopy (TEM) images of the re-dispersed freeze-dried (FNC) and spray-dried (SNC) particles are shown in Figure 1a and b, respectively. The images reveal that the FNC particles have a needle-like structure while SNC has a rod shape. Furthermore, both FNC and SNC particles have a quite homogeneous structure both morphologically and dimensionally, however; drying process affected the particle sizes significantly with an average particle sizes of 132.5±43.1 nm and 1468±384 nm, respectively (Figure 1a and 1b). The large difference in particle size could be resulted from the denser agglomeration of SNC particles during drying process (27).

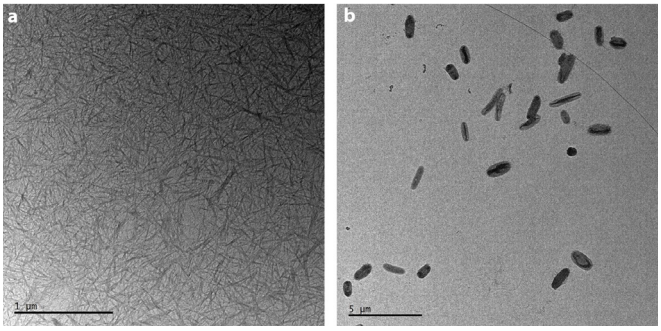

Figure 1. TEM micrographs of (a) FNC and (b) SNC

Next, NC to be used in bone cement formulations (Figure 2a) was prepared. Firstly, FNC and SNC were compared in terms of mechanical properties based on the same ratio (1% by weight in formulation) with preliminary studies. The studies indicated SNC was more effective in improvement of mechanical properties than FNC. Afterwards, different bone cement formulations with varying SNC ratio were prepared (0.5% and 2% by weight) and silanization was conducted on SNC to detect the effect of silanization in bone cement formulations. APSE is reported to be one of the efficient silylation agent for cellulose (25) and rich hydroxyl group on NC enables the reaction (Figure 2b).

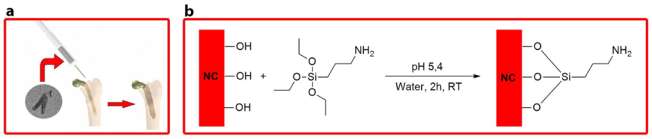

Figure 2. (a) Schematic illustration of NC containing bone cement and its application, (b) silanization reaction mechanism of NC

Figure 3a shows the Fourier transform infrared (FTIR) spectra of microcrystalline cellulose (MCC), FNC, SNC and SiSNC. In the FTIR spectrum of MCC, there are specifically observed -OH stretching at around 3500 cm-1, aliphatic C-H stretching at around 2900 cm-1, water adsorbed in fiber at around 1630 cm-1, and pyranose ring skeleton at about 1170-1082 cm-1 which are characteristic peaks for the cellulose (28). It was observed that the fiber-absorbed water was removed in the spray-dried SNC and silanized NC particle (SiSNC) samples. Also, the decrease in the -OH stretching band at

3500 cm-1 in SiSNC sample reveals that silane molecule bonds with cellulose molecule through free hydroxyl groups. The intermolecular hydrogen bonds at around 1425 cm-1 decrease depending on the drying method (29). In addition, there is an increase observed in the peak strength of the C-O stretching band in pyranose circle and in the Si-O bonds at the range between 1170-1082 cm-1 (30). The wide scan X-ray photoelectron spectroscopy (XPS) and The Energy-dispersive X-ray spectroscopy (EDX) graphs from SNC and SiSNC prove the presence of Si on the SiSNC sample after silanization (Figure 3b-e, Table 2 and 3). The appearance of nitrogen in the SiSNC sample points out the –NH2 group on the APSE (Table 3).

FTIR spectra also gives information about crystallinity of the cellulose samples. There are a number of small peaks that vary with the degree of crystallinity. Significant differences of the peaks at 706, 1056, 1110, and 1315 cm-1 work for crystallinity degree of the samples (31). The peak at 1640 cm-1 become larger with the decreasing of the crystallinity (31). According to this perspective, FNC has the lowest crystallinity while both SNC and SiSNC have higher crystalline structure compared to MCC.

The incorporation of filler into bone cement formulation might alter the mechanical properties of the biomaterial. Most of the fillers with tailored ratio in matrix act as plasticizers and improve tensile properties. In literature, there are some reports on PMMA and NC composites. Liu et al. studied freeze-dried NC and PMMA composites produced by solvent casting method (32). The authors suspended FNC in dimethylformamide (DMF) for prior to preparation of composites. Besides, Littunen et al. studied NC and PMMA composite by injection and compression molding with using NC as suspension (33). As seen from these studies, NC was used as suspension in water or solvent which is suitable for preparation of homogeneous composite. Thus, NC was suspended in methyl methacrylate (MMA) which is viscous component of the bone cement to increase the homogeneity of the composite structure.

Table 2. Elemental composition of SNC and SiSNC, determined by EDX

Element	Weight%		Atomic%	
	SNC	SiSNC	SNC	SiSNC
O	39.2	39.9	50.9	36.1
Na	38.0	0.2	34.3	0.1
Si	-	8.9	-	4.6
C		48.1		57.9

Table 3. Elemental composition of SNC and SiSNC, determined by XPS

	Atomic% Ratio	
	SiSNC	SNC
O	41	41.6
Na	-	0.6
S	0.5	0.6
Si	**2.7**	**0.4**
C	53.6	56.8
N	2.2	-

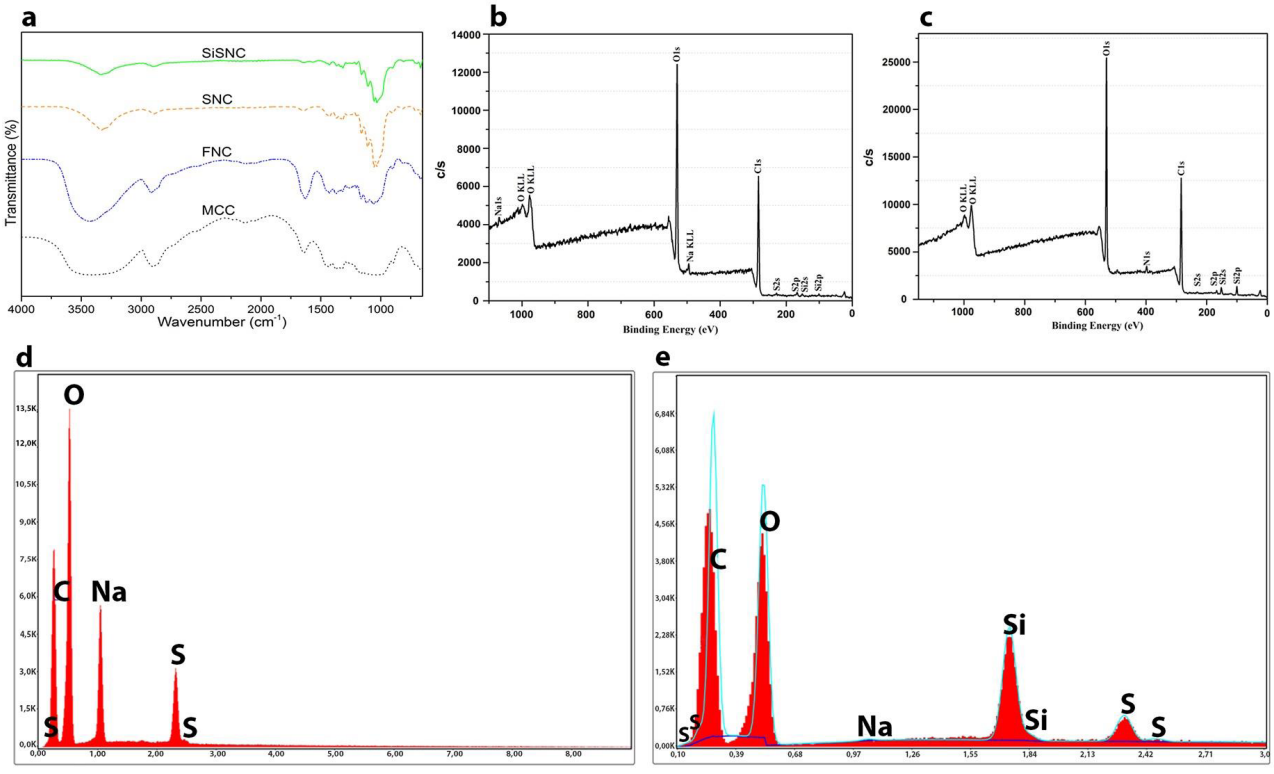

Figure 3. (a) FTIR spectra of MCC, FNC, SNC and SiSNC; XPS graphs of (b) SNC and (c) SiSNC; EDX results of (d) SNC and (e) SiSNC

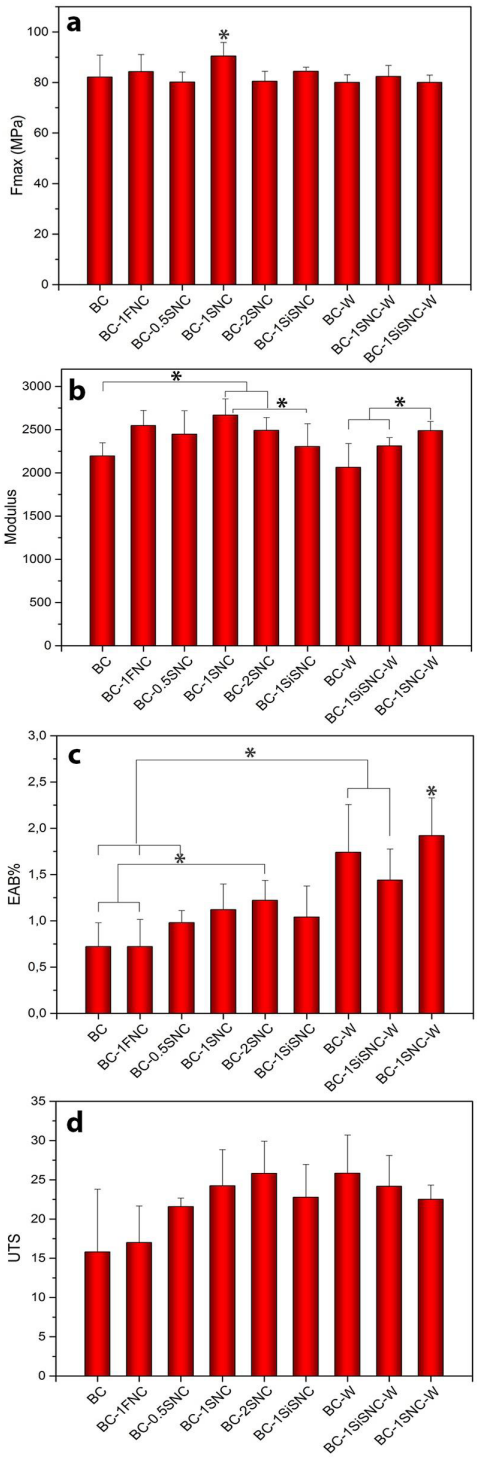

Figure 4. (a) compression test results of bone cement samples containing NC, tensile mechanical test results of bone cement samples: (b) modulus, (c) EAB% and (d) UTS. * denotes a significant difference ($p<0.05$)

Figure 4a indicates the maximum force resisting compression deformation while Figure 4b-d shows the tensile mechanical results of bone cement samples. The maximum forces (Fmax) loading before shape deformation in compression tests of all samples except BC-1SNC were not significantly different ($p>0.05$). BC-1SNC improved the compression resistance increasing the Fmax by 12.6% ($p<0.05$). All bone cement formulations provided the minimum compressive strength (70 MPa) established by ASTM F451 standard. Different PMMA bone cement formulations formulated with modified monomers, methacrylates, β-TCP and polyethylene glycol modified β-TCP gave similar compression test results (74-131 MPa) (12, 13, 19).

On the other hand, the results differed more in tensile mechanical tests, compared to the compression mechanical tests. All bone cement groups containing NC revealed increased modulus, ultimate tensile strength (UTS) and elongation at break (EAB%) values compared to the BC sample which was used as the control group not containing NC (Figure 4b-d). Compared to BC, modulus increased about by 16% and 21.5% in BC-1FNC and BC-1SNC, respectively (Figure 4b). The modulus value of BC-1SNC group (2666 MPa) was found to be significantly higher than that of the BC and BC-1SiSNC groups ($p<0.05$). The modulus value of BC-2SNC (2490 MPa) group was found to be significantly higher than that of BC group ($p<0.05$). In wet samples, the modulus value of BC-1SNC-W (2311 MPa) group was found to be significantly higher than that of BC-W and BC-1SiSNC-W groups ($p<0.05$). There was no statistically significant difference between the UTS values of the groups ($p>0.05$). The EAB% value of the BC-1SNC-W group was found to be significantly higher than all dry and wet bone cement groups ($p<0.05$). The EAB% value of the BC-2SNC group was significantly higher than those of the BC and BC-1FNC groups ($p<0.05$). Similar tensile strength results were obtained with modified bone cement formulations (13, 14, 19). However, modulus values of bone cements developed in this study were found to be higher than those formulations with a value between 2194-2666 MPa (13, 14, 19). The wetted samples added higher expansion coefficients to the structure because of the plasticizer effect of the water taking place between the phases as well as the water-absorption of the hydrophilic filler materials like hydroxyapatite and NC in the composition (34). As a result, the wet groups generally revealed higher EAB% values than the dry bone cement samples.

Discussion

These findings point out the importance of the drying process mainly in NC production. It is evident that SNC yields better results than FNC. It is required to ensure a quite homogeneous distribution in the bone cement through mechanical force. Although particle size of SNC is bigger than FNC when re-dispersed in water after drying, the powder form of SNC provides better distribution in viscous MMA rather than FNC flakes. Thus, FNC flakes would remain agglomerated more than SNC in MMA. Furthermore, due to the water removal not by high temperature but by sublimation, the freeze-drying method does not allow a drying productivity up to 100% unlike spray-drying (Figure 3a). In addition, considering the fact that bone cement curing is an exothermic reaction, the heat in the environment resulting from the reaction may affect the NC structure. Therefore, the spray-dried SNC which has a more stable thermal structure may yield more efficient results (35).

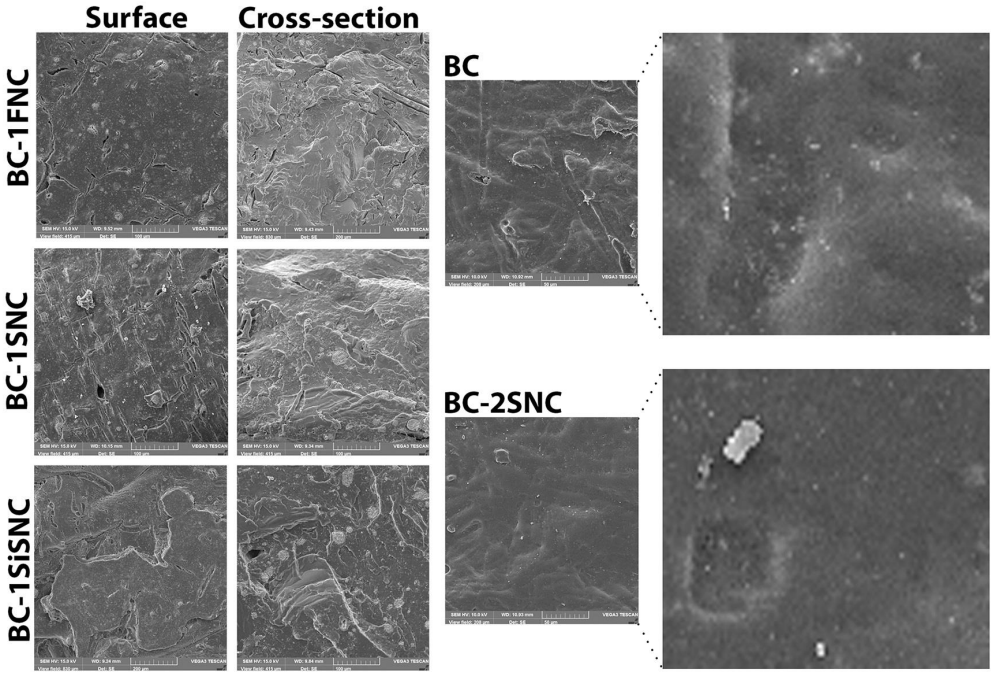

Figure 5. SEM images of BC-1FNC, BC-1SNC and BC-1SiNC samples from surface (500x) and cross-section (250x) after tensile test and surface SEM micrographs of BC and BC-2SNC samples with low (1000x) and high magnification (5000x)

Considering the effect of SNC ratios in bone cement formulation, 1% comes to the forefront as the one yielding the best result. BC-2SNC sample with 2% SNC displayed lower tensile properties than BC-1SNC. The reason may be the increased deteriorations in BC-2SNC samples due to overloading which could lead to a decrease in mechanical strength. Figure 5 shows the scanning electron microscope (SEM) images from the surfaces and cross sectional areas- after tensile test- of the sample containing maximum NC and the sample without NC. Actually, there is no significant morphological difference in the cross-sectional images of the bone cement samples. However, on the surface images of BC and BC-2SNC with higher magnification, there are easily recognizable micro-cracks on the surfaces (Figure 5). The incidence of these deformations increases along with the presence of NC filler. These deformations were not significant in BC while micro-cracks were clearly observable on the surface of BC-2SNC. On the other hand, these deteriorations were not significantly different in BC-1SNC sample compared to BC-2SNC sample (the image is not shown here). Moreover, there could be some scratches or deteriorations in nanoscale that could not be detected by SEM and may lead to a decrease in tensile values. To attain an improvement in mechanical properties, SNC should be incorporated in bone cement matrix by less than 2%.

Silanization method is of great importance because it constitutes a chemical bridge among the filler materials to be distributed especially in the organic matrix and allows a good level of homogeneity in the composite structure. Silanization has allowed mechanical improvements in many composite structures. There are reported findings that silanization of NC contributes to properties (36). In our study, the efficiency of NC was examined by silanizing it with APSE with proven silanization efficiency in the literature (25). However, the BC-1SiSNC sample that contained silanized NC revealed weaker mechanical properties than the BC-1SNC sample that contained non-silanized NC. This could be resulted from the structure deterioration in NC due to high silanization level as well as the deformation of the original morphology (23). It is reported in studies that, in order to avoid any damages on morphology during modifications, the surface substitution level should not exceed 1 (23). However, in this study, the surface substitution level detected by XPS after the silanization of NC was 2.7; and it is possible for such a high level of silanization to deteriorate the NC morphology. Thus, although silanization technique yields quite good results by creating a bridge between filler materials and matrix, it alters structural characteristics of NC, and in this study, it revealed weaker mechanical performance than silanized bone cement samples.

Considering the intense use of clinical hip implantations, bone cement is one of the essential biomaterials in orthopedics. As the principal features, the ideal bone cement is expected to match with the mechanical characteristics of the hip, which is the most important load-bearing area of the body, and to have bioactive properties (37). Calcium phosphate derivatives have long been considered as the perfect match for filler materials in PMMA thanks to their strong mechanical support as well as their bioactive properties. However, despite their bioactive properties, calcium phosphate particles can dissolve and degrade in the course of time. On the other hand, the absorption of the body fluids due to their hydrophilic structures may lead to the loss of brittleness in bone cement (38). NC, on the other hand, has an industrial application potential thanks to its rapid, cost-effective and efficient production. Even a little amount in the matrix yields quite good mechanical results

(39). Despite the abundance of hydroxyl groups on its surface, its high crystallinity reduces the water absorption capacity of the matrix structure (40). These findings make NC an ideal material for biomaterials requiring mechanical strength and bioactivity especially in orthopedic applications.

Conclusion

In this study, it as shown that NC is an efficient filler candidate for improving the mechanical characteristics of PMMA bone cements and the improvements can be maximized by optimizing production conditions and amount in formulation. The efficiency of NC in bone cements firstly by drying procedure then by ratio-based parameters was investigated, and finally, the effect of NC silanization in PMMA matrix through mechanical characteristics was examined. It is concluded NC produced by spray-drying method yield better results for including bone cement formulations and the optimum ratio was 1%. Besides, the silanized NC had no mechanical improvement against the non-silanized one with a high silanization efficiency. Consequently, NC is an ideal filler material that offers mechanical strength to PMMA bone cement as long as it does not exceed 1% ratio.

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