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Chitosan/PMMA Bioblend for Drug Release Applications

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ABSTRACT

This work focuses on developing some polymers of desirable properties mainly for drug release applications. These applications require some important properties for the selected material such as (biodegradable, biocompatible, and non-toxic). Chitosan is a natural biodegradable, biocompatible and non-toxic material; therefore this material was selected in this research which is mixed with Poly (methyl methacrylate) (PMMA) polymer which has high biocompatibility to obtain different degrees of degradation. Samples with different percent of chitosan with poly (methyl methacrylate) (PMMA) including 2.5, 5, 7.5 and 10% chitosan) are prepared. Many tests are done such as Fourier transforms spectroscopy (FTIR), tensile strength, flexural strength, biodegradability and morphology tests on the specimens.

FTIR results shows grafting between PMMA and amino group of chitosan through the presence of additional absorption peaks at 1732 and 2966 cm^{-1} which are created through free radical mechanism, also the shifting of some peak's wavenumbers and the increase of their intensities especially for 1643, 1450 and 3439 cm^{-1}. Mechanical tests results showed that the flexural modulus increased by (59.77%) also the maximum tensile strength increased by (46.15%) and young's modulus increased by (53.84%) with addition of 10% chitosan, this percent decreased after immersion samples in synthetic body fluid (SBF) solution. Morphology test showed the formation of vacancies and pitting in the samples after immersion in (SBF) solution. Also the swelling, weight loss, water absorbency and porosity indicate clearly to the degradation process.

Keywords: *Chitosan, PMMA, drugs release applications, Bioblend*

1. INTRODUCTION

Increased attention in previous years to polymeric materials this due to the distinct characteristics, which used in administration of pharmaceuticals and as biomedical devices. The most important biomedical applications of biodegradable polymers are in the areas of controlled drug delivery systems and in the form of implants and devices for fracture repairs, ligament reconstruction and surgical dressings. In other applications can be used non-degradable polymer such as, artificial heart valves, contact lenses, cardiac pacemakers, vascular grafts, tracheal replacements, and organ regeneration. Polysaccharides constitute an important component of life matter. Polysaccharides display a perfect biocompatibility and biodegradability, which are the basic characteristics for polymers used as biomaterials. They have several characteristics not found in other natural polymers. Recently, specific properties of antivirals, antitumorals, gene modulators, etc., have been discovered for various classes of polysaccharides [1]

Chitosan is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine. The development of new applications for Chitosan and its derivative is mainly due to the fact that these are renewable source of natural biodegradable polymers and also due to chitin and its derivative are the most abundant natural polymers. The main factors which stimulated the interest in chitosan utilization in various fields from fertilizers to pharmaceuticals are its versatility, economical and easily availability. Chitosan is no longer just a waste by-product from the seafood processing industry. This material is now being utilized by industry to solve problems and to improve existing products, as well as to create new ones. Chitosan (CS) is modified natural, biodegradable, biocompatible, nontoxic, as well as linear nitrogenous polysaccharides, a basic polysaccharide homo-polymer [2].

Poly (methyl methacrylate) (PMMA) is one of the most widely explored biomedical materials because of its biocompatibility, and recent publications have shown an increasing interest in its applications as a drug carrier. PMMA is a non-biodegradable polymer. It is classified as a hard, rigid, but brittle material, with a glass transition temperature of 105˚C.

At present, it is generally accepted that PMMA is a non-toxic polymer as it possesses a very good toxicological safety record in biomedical applications. In fact, there are no references in the literature to severe adverse effects of PMMA, such as oncogenicity, based on the observation of several years of practice in orthopedics, for which PMMA has been used as a cement implant in total hip replacement and as a vertebral stabilization agent in patients with osteoporosis. Other biomedical applications of PMMA include its use as a prosthetic material in dental and mandibular corrections and as a permanent implant for intraocular lens following cataract surgery [3].

In recent years, a number of studies have been made for the incorporation of chitosan in PMMA-based bone cement to obtain different degree of degradation of chitosan for controlled- release of drugs. Where in (2005), Yinghai Liu et al. [4] employed a novel redox system, potassium ditelluratocuprate (III) (DTC)–chitosan to initiate the graft copolymerization of methyl methacrylate (MMA) onto chitosan in alkali medium, also C. Radhakumary et al. [5] studied the Graft copolymerization of methyl methacrylate (MMA) onto Chitosan using cerium (IV) as the initiator with

varying concentrations of MMA. In (2006), Zhilong Shi et al. [6] investigated the use of chitosan nanoparticles (CS NP) and quaternary ammonium chitosan derivative nanoparticles (QCS NP) as bactericidal agents in poly PMMA bone cement with and without gentamicin. In (2007), N. Flores-Ramirez et al. [7] functionalized chitosan with glycidyl methacrylate (GMA), to ease a further reaction with MMA, and blended the resulting co-polymer with PMMA and poly(butyl acrylate) PBA which works as a damper, the polymers were cured by UV to obtain the final resin. In (2009), V. Singh et al. [8] studied the peroxydisulfate/ascorbic acid initiated synthesis of Chitosan-graft poly (methyl methacrylate) (CS-g-PMMA) and characterized it by FTIR, XRD and 13C NMR. In (2010), Chia-Hsien Yeh et al. [9] fabricated a PMMA as for drugs release controlling. Different ratios of chitosan adding to PMMA for controlling of degree of bioblend degradation. FTIR, mechanical tests, enzymatic degradation and morphology test will achieving on bioblend for characterizing it.microfluidic chip with a 45° cross-junction microchannel using a CO_2 laser machine to generate chitosan microfibers.

The aim of the present research is to develop polymers of desirable properties (mainly as a drug release) by using naturally based polymer (Chitosan) prepared from chitin which is extracted from carp shell-fish and mix it with synthetic biopolymer poly (methyl methacrylate), the resulting bioblend are widely used in pharmaceutical and biomedical application, such as for drugs release controlling. Different ratios of chitosan adding to PMMA for controlling of degree of bioblend degradation. FTIR, mechanical tests, enzymatic degradation and morphology test will achieving on bioblend for characterizing it.

2. MATERIALS AND METHODS

2.1 Materials

In this research chitosan has been prepared in a laboratory by the extraction of chitin from the commercial carp fish sell. Chitin prepared by many steps including, (1) deproteinization achieved with 3 % (w/v) NaOH solution for 1 hr at boiling point with constant stirring at a solid to solvent ratio of 1:10 (w/v). (2) demineralization achieved with 1N HCl for 60 min at room temperature with a solid to solvent ratio of 1:15 (w/v). Deacetylation process used to convert chitin to chitosan by removal of acetyl groups from chitin, achieved by treating chitin with 50% sodium hydroxide solution (NaOH) at 90ºC for 2hr, with a solid to solvent ratio of 1:10 (w/v). The product chitosan has degree of deacetylation (75.6 %), molecular weight (970.12 g/mol) and solubility (90.3 %) laboratory measuring.

Poly (methyl methacrylate) (PMMA) powder was obtained from Yonghui chemical Holdings Limited Company, china. This type was used in medical applications for its good biocompatibility. The average molecular weight ~15000 by Gel permeation chromatograph (GPC) and glass transition temp. (Tg) 105 °C. Methyl methacrylate monomer (MMA). All these materials were used as the major component in the bone cement samples, also it has been used some of the materials to assist in the preparation of the samples, such as N, N dimethyl para-toluidine (N, N-DMPT) which was obtained from Aarti industries limited Company, India, with molecular weight (135.21g/mol), also Benzoyl peroxide (BPO), Barium sulphate (BaSO4) and ethanol.

2.2. Blend Preparation

Different ratios (2.5, 5, 7.5 and 10% w/w) of chitosan were added. The blend was prepared by mixing powder (PMMA and Chitosan) and liquid monomer with ratio (2:1.6) g/ml by using a small-scale turbo blender at a speed of 1500 rpm for 30 sec. The mixture was subsequently inserted into the mold at approximately dough time; usually about 1 min.

The filled mold was pressed between two glass plates for 1 h. After the blend had hardened, it was pulled out of the mold and stored under dark, sterile conditions at room temperature. Table 1 shows the composition of the blend.

Table 1.Composition of the blend

	Pure (w/w%)	2.5%CS (w/w %)	5%CS (w/w %)	7.5%CS (w/w %)	10% CS (w/w %)
Powders					
PMMA	44.25	42.25	39.75	37.625	35.75
	5	4.5	4.5	4.25	3.75
BaSO4	0.75	0.75	0.75	0.625	0.5
Liquids					
MMA	44.25	44.25	44.25	44.25	44.25
	1.25	1.25	1.25	1.25	1.25
N,N-DMPT	4.5	4.5	4.5	4.5	4.5

2.3. Characterization

Blend samples were characterized by using Fourier transforms spectrophotometer (FTIR) model (8400S –FTIR-Perkin-Elmer spectrophotometer).

2.4. Biodegradability Test

To measure the degradability, specimens were placed in an incubator at 37 ± 0.5°C for 7, 14, 21,28 and 35 days, with synthetic body fluid (SBF) solution (pH = 7.4). The water absorbency, weight loss and porosity, during the degradation period were determined by using the following relationships [10]:

$$Water\ absorbency\ (\%) = [(W_w - W_d)/W_d] \times 100 \quad (1)$$
$$Weight\ loss\ (\%) = [(W_i - W_d)/W_i] \times 100 \quad (2)$$
$$Porosity\ (\%) = [(\rho_{max} - \rho_{min})/\rho_{max}] \times 100 \quad (3)$$

Where W_w and W_d is the wet weight and dry weight of the specimen after degradation, W_i is the initial weight of the specimen, ρ_{max} is the density of the original specimen, and ρ_{min} is the density of the dried specimen after degradation.

2.5. Morphology Test

The morphology for the samples were performed by using digital microscope (model AM4815T Dino-Lite Edge) with Magnification Rate (20x~220x). Samples were colored to clarify the surface morphology of the samples.

2.6. Mechanical Properties Test

The tensile test and three-point bending test were performed by using the controlled electronic universal testing machine (model WDW 5 E) made in China. The tensile test (according to ASTM D638-IV) was conducted at a cross-head speed of (0.5 mm/min). For the three-point bending test (according to ISO 5833 (2002)) with dimensions (75×10×3) mm, the span length 20 mm and loading rate (0.5 mm/min).

The modulus of elasticity in bending, or the flexural modulus (E_f), is calculated in the elastic region Eq. 4, where ∂ is the deflection of the beam when a force (F) is applied, (m) is the slope of the load (F) /deflection curve, L is the distance between the two outer points, W is the width of the specimen and h is the thickness of the specimen.

$$E_f = FL^3/4\partial wh^3 = mL^3/4wh^2 \quad (4)$$

3. RESULTS AND DISCUSSION

3.1. Infrared Spectroscopy

Fig. 1 represents the FTIR spectrum of chitosan, PMMA and 10% chitosan (CS). The spectrum of 10% CS had additional sharp absorption peaks at 1732.08 and 2966.52 cm^{-1} due to ester carbonyl group (stretching) and symmetrical of the methyl group respectively. This provided a substantial evidence of grafting of PMMA on to the chitosan [8]. In the spectrum of 10% CS, the presence of additional –NH deformation at 1473.62 cm^{-1} to the carbonyl absorption at 1732.08 cm^{-1} could confirm the complexation between PMMA and chitosan [11].

Also we can explain the grafting occurred through the shifting of carbonyl group C=O from 1643.35 to 1427.72 cm^{-1}, and the shifting of –NH group in chitosan from 1450.47 to 1473.62 cm^{-1} in 10% CS, this is an indication for breaking these side groups and formation of a new bonds. Also the change in intensity of the peak in 3439.08 cm^{-1} indicates the breaking of the bonds in $–CH_3$ for PMMA and –OH for chitosan which leads to formation of a new bonding. This new bond can be represented by the increase in the intensity of the peak in 2966.52 cm^{-1}. Table 2 shows the variation in bands wavenumbers between PMMA, 10% CS and chitosan.

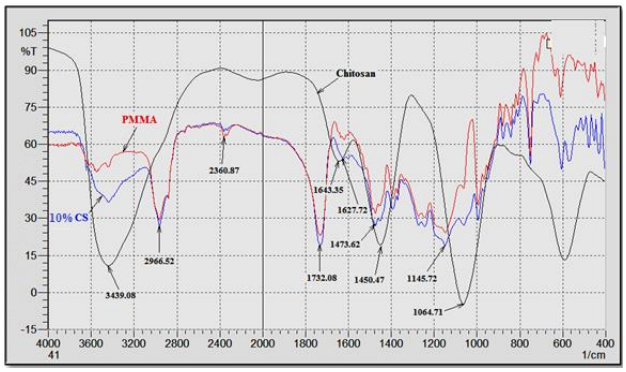

Fig.1: FTIR spectrum of chitosan, PMMA and 10% CS.

Table 2: Variation in bands wavenumbers between PMMA, 10% CS and chitosan.

Band type	Band wavenumbers (cm^{-1})		
	PMMA	10% CS	Chitosan
O-H (stretching vibration)	------	3439.08	3439.08
$-CH_3$	2966.52	2966.52	------
carbonyl (–C=O)	1620.21	1627.72	1643.35
carbonyl (–C=O)	1732.08	1732.08	------
–NH (deformation)	--------	1473.62	1450.47
–C-O-C-	--------	1046.71	1046.71

Fig. 2 represents the proposed interaction of chitosan/PMMA, as illustrated previously by the presence of additional peaks and the variation in some of the peaks wavenumbers and intensities. Where the peak at 2966 cm^{-1} increased in its intensity due to the interaction between chitosan/PMMA, as well as the appearance of the peak at 1732 cm^{-1} confirm the interaction and reaction between chitosan/PMMA as shown in FTIR spectrum (Fig. 2) and in the proposed interaction of chitosan/PMMA.

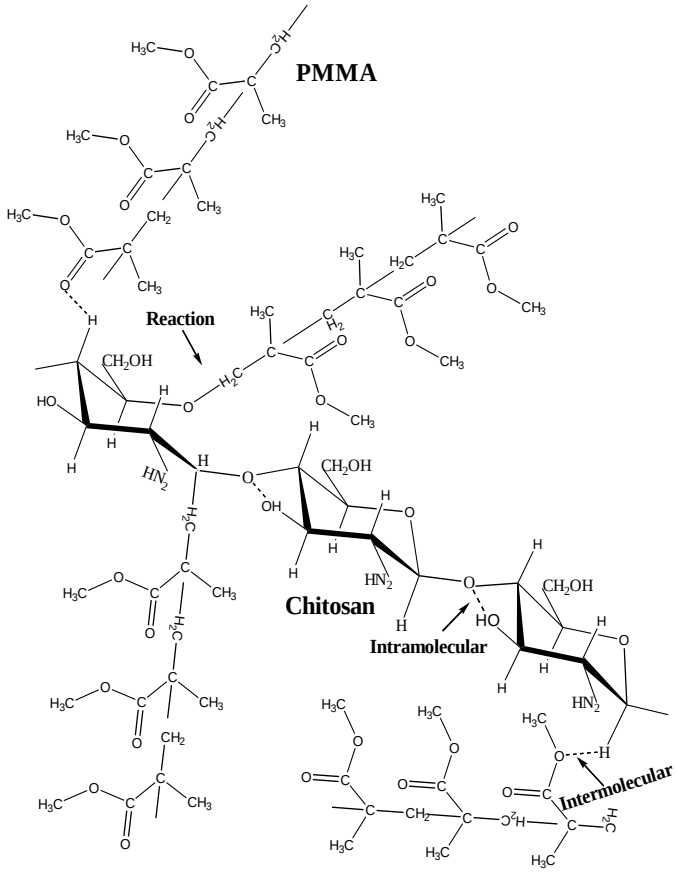

Fig.2: The proposed interaction of chitosan/PMMA.

3.2. Biodegradability

After a degradation period of 35 days, significant differences in the degradation profiles were observed between the pure and the blend. In addition, significant differences in water absorbency, weight loss, and porosity were found.

Figs. 3, 4 and 5 show the differences in water absorbency, weight loss and porosity during the different periods of degradation. The results show that, water absorbency, weight loss and porosity of the samples increased with increase chitosan percent and time immersed in body fluid, which indicates to increase in degradation. Porosity increased reached to (21.113%), and same behaviors in weight loss (3.920%) and water absorbency (6.542%) for long period of degradation (35) days, this duo to the degradation occurs in chitosan molecule that decompose and leaves voids in the samples, from this results can conclude that, the degradation percent and degradation rate can be controlled by chitosan percent addition.

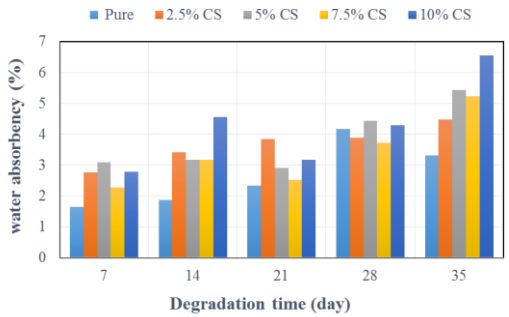

Fig. 3: Differences in water absorbency during the different periods of degradation.

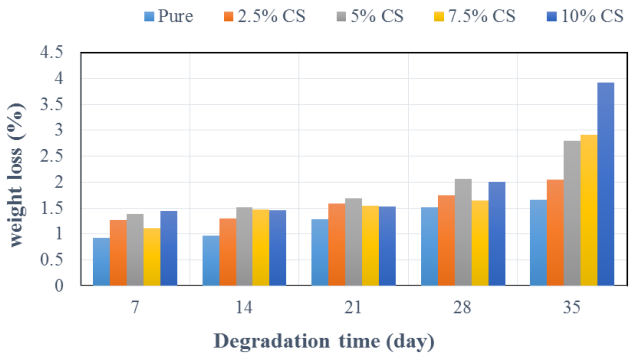

Fig. 4: Differences in weight loss during the different periods of degradation.

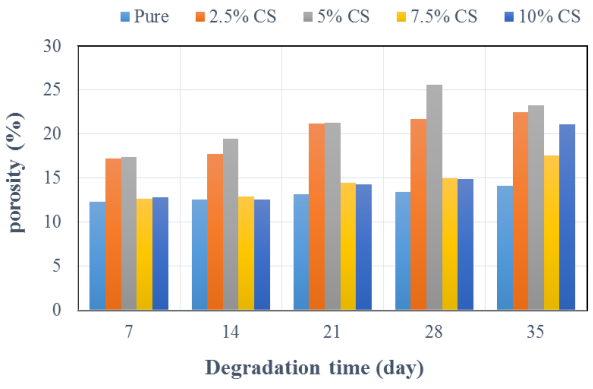

Fig. 5: Differences in porosity during the different periods of degradation.

3.3. Morphology

Fig. 6 and 7 show the surface morphology and the swelling of the blend with different percentages of chitosan before and after 35 days immersing in degradable solution. Microscopic images show good homogenized between chitosan and PMMA, after the degradation for a period of 35 days pure samples did not show any affected by solution, while blend samples clearly affected by degradation solution, shows from the voids formation in the structure resulting from the chitosan degradation. In Fig. 7 we observed the occurrence of the swelling in the samples with 15% and 20% chitosan after 35 days of degradation, and this proves the diffusion of the (SBF) solution in the blend structure. The degradation of chitosan molecules leads to the formation of voids in the structure which causes increase the spaces between chains this lead to swelling, the voids percent and swelling increase with increasing chitosan percent, all that accelerate the degradation process of blend[10].

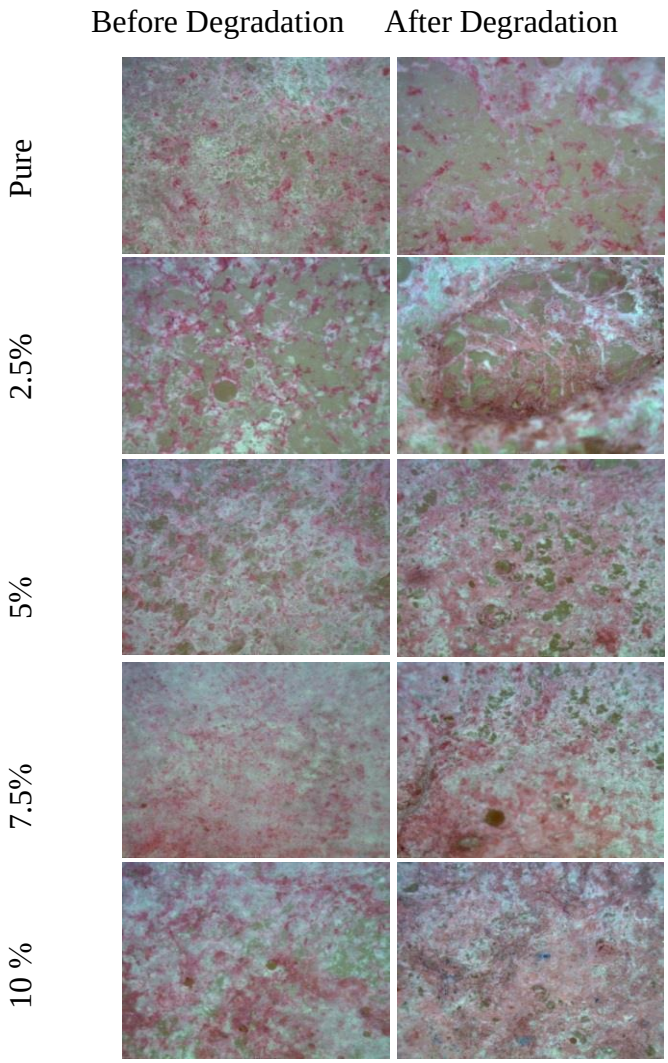

Fig. 6: Surface morphology of the blend with different percentages of chitosan before and after 35 days of degradation

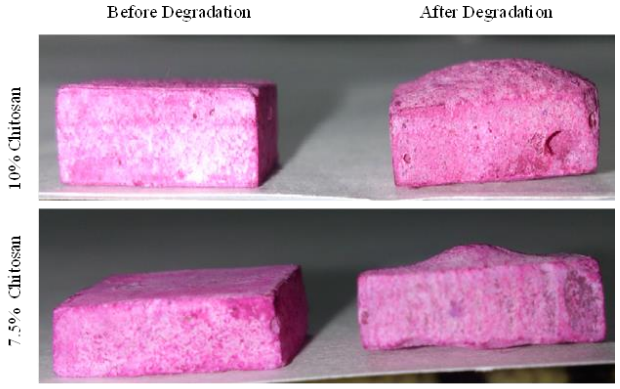

Fig. 7: Swelling of the blend with 7.5% and 10% chitosan after 35 days of degradation.

3.4. Mechanical properties of the bone cement

Mechanical properties of the blend are important in some applications such as bio implant, scaffold and orthopedic surgery which play an influential role in determining the successful long-term stability of prosthesis. Therefore in this work, the inspection of tensile properties and bending properties is very important so it will be discussed.

3.4.1. Tensile test

Fig. 8 and Fig. 9 show the maximum tensile strength ($б_{max}$) and young's modulus (E) for the blend with different percentages of chitosan respectively. Prior to degradation, there was an increase in tensile strength and young's modulus properties of the blend with chitosan percent increase. It has been stated in previous studies that no significant differences between the pure sample and the blend containing chitosan [6]. The increase in tensile strength and young's modulus properties can be explained as a result of the increase in physical interactions and chemical bonding between the large molecules and multiple effective side groups such as ($–NH_2$, -OH, -COO, C=O), with the increase in chitosan percentages, and that has been proved previously in the FTIR characterization of the blend.
After degradation, tensile strength and young's modulus properties of the blend decreased slightly, this is because the pits and voids due to chitosan degradation, which are the areas of high stress concentration and that leads to the reduction in mechanical properties.

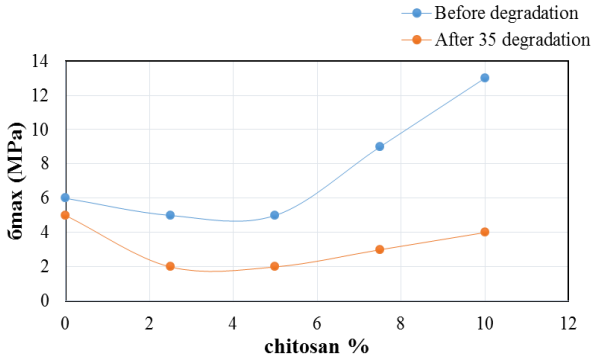

Fig. 8: Maximum tensile strength with different percentages of chitosan.

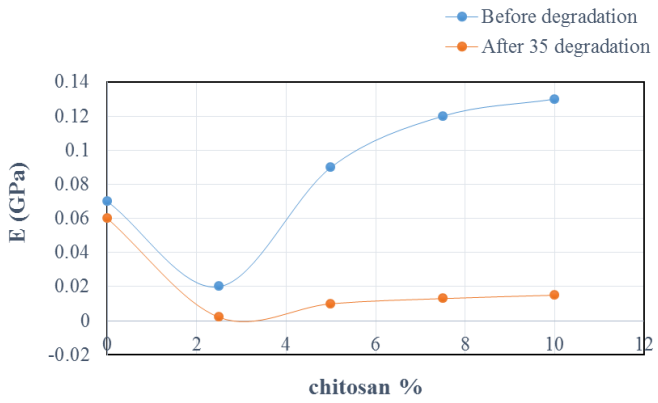

Fig. 9: Young's Modulus with different percentages of chitosan.

3.4.2 Bending test

Fig. 10 shows the flexural modulus (E_f) for the blend with different percentages of chitosan. Before degradation the flexural modulus is higher than that of the pure sample and increased with increasing chitosan percentage. From the previous studies it has been noticed that a significant increase in flexural modulus of the blend containing 3–5% w/w chitosan [10]. As in tensile properties we can explain that due to the increase in intermolecular interaction and chemical bonding between the effective side groups. After degradation the flexural modulus of the blend with chitosan significantly decreased compared to the pure sample, this is due to the formation of pits and pores in the samples and that leads to the reduction in flexural modulus.

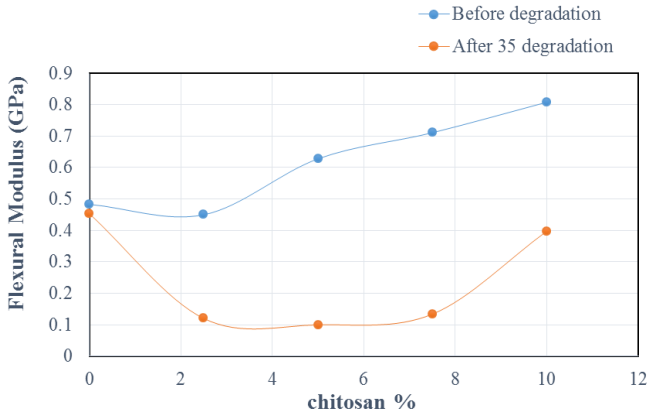

Fig. 10: Flexural Modulus with different percentages of chitosan.

4. CONCLUSION

From this work we can conclude that, the grafting process between PMMA/chitosan is deduced from the presence of additional absorption peaks at 1732 and 2966 cm−1 which are created through free radical mechanism, also the shifting of some peak's wavenumbers and the increase of their intensities especially for 1643, 1450 and 3439 cm^{-1}. The biodegradability test showed that the degradation increased as both chitosan percentage and time of immersion increased. The increase in chitosan percentages leads to the increase in the mechanical properties of the blend in general, but it is decreased after the samples immersion in SBF solution and degradation process, where the flexural modulus increased by (59.77%) also the maximum tensile strength increased by (46.15%) and young's modulus increased by (53.84%) with addition of 10% chitosan. Morphology test showed the formation of voids and pitting in the samples after the immersion in SBF solution and increased with increasing immersion period of degradation which indicates clearly the prevalence of degradation process. Also swelling was observed in 7.5% and 10% chitosan after 35 days of degradation which indicates on the diffusion of SBF solution in the microstructure of the samples and leads to farther degradation.

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