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To Develop a Biocompatible and Biodegradable Polymer-Metal Composite with Good; Mechanical and Drug Release Properties

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Abstract

For achieving additional benefits and improving the material characteristics two or more materials are often combined together in the form of composites. Composites are important because of their light weight, high strength and flexibility of design. Composite materials provide various advantages based on their particulate or fibrous nature and on the basis of individual qualities of the constituting elements of the composites. Besides the multiplied benefits achieved with the composite materials, they being composed of two different materials exhibit greater challenges and biocompatibility threats which need to be addressed while developing a composite material. A structural composite of bioabsorbable nature is developed using a polymeric material and metal particles. The composite material so developed would provide altered strength and flexibility, better than the individual constituting materials for use in various biomedical devices and would eventually degrade on subject to exposure to the physiological environment. The two different varieties of the composite have been developed using metal particles and metal salt and they have been tested for their tensile, degradation and drug release properties, which have been found satisfactory for use of the composite in various biomedical devices and drug release applications.

Keywords: Composites; Organo-metallic; Polymer-metallic; PVA

Introduction

Several devices being used in the biomedical industry like artificial joints, implants, templates for tissue repair, external and internal fixation devices; require the use of biocompatible and biodegradable materials, so for this purpose researchers are focusing on developing new biomaterials that could be used for aforementioned applications.

Biocompatibility of materials is of prime importance to avoid inflammatory reactions and cyto-toxic responses. With metallic implants, biocompatibility is difficult to attain because of the corrosive nature of metals. Moreover metals exhibit mechanical properties which are not comparable to the natural tissues and thus their mechanical properties need to be altered. This can be done by making composite materials [1].

When particles (as flakes or powder) of the reinforcement material are embedded or distributed in the matrix material, the particulate types of composite is formed, the other types being the fiber reinforced composites and laminar composites [2]. In this article a particulate reinforced composite has been developed by embedding metal particles in a polymeric matrix.

Polymers are used as matrix material for being light in weight, more economical, easily process able, widely available and for their environmental acceptability. The type of polymer matrix and its interaction with the reinforcement material greatly affect the physical and mechanical properties of the composite [3].

A novel composite material of biodegradable and biocompatible nature with good drug release properties can be developed by using polyvinyl alcohol and magnesium. Magnesium is a biodegradable metal with an established biocompatibility and is added to polyvinyl alcohol (PVA) to develop a novel composite with properties better than those of the constituting metal (magnesium) and polymer (polyvinyl alcohol). Aspirin serves as a model drug, to establish the drug release properties of the composite.

Poly-vinylalcohol (PVA)

Poly-vinyl alcohol (PVA) is a very promissing functional polymer. Its hydroxyl groups make it easy to be modified chemically which can ultimately result in modifications in itsphysical structure and properties. Owing to it's good chemical and physical properties, excellent film forming nature and hydrophillicity, Poly-vinyl alcohol (PVA) is widely used for making polymeric films [4]. Poly-vinyl alcohol (PVA) blends have better properties in terms of physical characteristics, biological compatability and film forming behavior [5]. Poly-vinyl alcohol (PVA) is the polymer of choise for many bio-medical devices and implants because of its hydrohilic nature which makes it a highly permiable material. PVA membranes are commonly used in medical devices which are in contact with the blood, like hemodyalysis membranes. For improving compatability with blend PVA is often blended with polyelectrolytes, heparin and poly-ethylene glycol [6].

Acetyl-salicylic acid (ASA)/Asprin

It improves the blood compatibility of the device because of its anti-coagulant, blood thinning effect which it creates through its anti-platelet nature, therefore prevents arterial and cerebral thrombosis. It is a known anti-inflammatory and analgesic drug with worldwide acceptance. It also prevents the adhesion of platelets to artificial devices and implants [6].

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Keeping in mind the wide range of benefits of polyvinyl alcohol (PVA) and magnesium (Mg) metal, a particulate composite material has been developed in two different forms; using metal particles and by metal salt. The composite so formed has been tested and compared with the mother polymer (PVA) for its tensile strength, degradation rate and drug release behavior, with aspirin as a model drug, which can be replaced and tested with any other drug according to use.

Materials and Methodology

The poly-vinyl alcohol used for composite formation had a molecular weight of approximately 72000 g/mol. Polyvinyl alcohol 72000 BioChemica was used. Simple polymer membranes were developed using 5% and 10% PVA solutions. The solutions were made by dissolution of polyvinyl alcohol (PVA) in water. Clear solutions were made and allowed to cure on stainless steel plate over an area of 3*3 inches square to obtain 5% and 10% PVA membranes for comparison purposes with the composite membranes.

Magnesium particles of 100-200 µm. were used for composite formation. The poly-metal composite film was prepared by solvent casting method. Magnesium (Mg) particles are homogeneously suspended in the 10% poly-vinylalcohol (PVA) solution through magnetic stirring. The poly-vinylalcohol-magnesium (PVA-Mg) suspension was then cured to obtain the metalopolymer composite film. The composite formed this way was compared for its properties with a poly-metal blend of Magnesium sulphate salt ($MgS0_4$) and poly-vinyl alcohol (PVA) which is prepared by homogeneously dissolving the magnesium salt particles in 10% poly-vinylalcohol (PVA) solution and casting the resulting solution at room temperature.

For casting purposes 10 ml of each solution (both the composite and the simple poly-metal blend) was spread over an area of 9 inches square on a stainless steel plate. The surface of the casting plate was uniform and polished to achieve smooth composite membranes. Also by controlling the quantity of solution and the area of its spread, uniform thickness of the membranes was ensured. With the aforementioned quantities and dimensions, 0.1 mm thick membranes were achieved. The thickness of the membranes can be increased by increasing the quantity or decreasing the area of spread and vice versa. With the given quantities of solution, the casting time is 16-18 hours, which might increase with the increased quantity of solution.

Same procedure was adopted for developing composite-drug membranes. Aspirin was used as a model drug here. 75 mg aspirin was added into the polymer-metal composite solution and polymer-metal salt solution and mixed properly before casting. Similar curing parameters were adopted as for simple composite membranes.

The membranes developed included 5% PVA membrane, 10% PVA membrane, 1% mg fin 10% PVA composfifte membrane, 2.5% mg in 10% PVA composite membrane, 1% $MgSO_4$ in 10% PVA membrane, 2.5% $MgSO_4$ in 10% PVA membrane, 1% mg and 75 mg aspirin in 10% PVA composite membrane and 1% $MgSO_4$ and 75 mg aspirinin 10% PVA membrane.

Characterization

To establish the physico-mechanical properties of the composite, tensile testing and degradation testing were done. These tests were performed to determine the stress-strain behavior and degradation time and pattern of the composite and to have a comparative review of the properties of the composite with respect to the parent polymer. Later the drug release tests were conducted to have an idea about the pattern of drug release from the composite material.

Tensile testing was performed on a universal testing machine (UTM), SHIMADZU AGX Plus at a strain rate of 5 mm/min. which was selected by hit and trial method. The gauge length for the samples was kept 25 mm.Tensile testing was done for all the composite membranes and for the membranes of the parent polymer i.e., polyvinyl alcohol (PVA).

For degradation rate analysis 1*1 inches square samples of the membranes were weighed and placed over a plastic mesh for support and immersed in 1ml. normal saline solution at 37°C. Membrane samples of the composite dipped in the saline medium were weighed after every 15 minutes (subtracting the weight of the plastic mesh from the total weight) by taking them out of the medium and then immersing into the saline again. This was repeated till the membrane got fully degraded and only the plastic mesh was left behind. The weight of the membranes was plotted graphically with time to determine the degradation rate and pattern of the composite membranes.

To establish the kinetics of drug release from the composite, the drug containing samples of composite membrane were degraded by a similar procedure but instead of weighing the membranes as in degradation testing, the degradation medium was collected for UV spectrophotometry, by UV-2800 UV/VIS Spectrophotometer to determine the quantity of drug released into the medium. The quantity of medium taken out was replaced with the same quantity of fresh medium everytime.

Results

The results of tensile testing are a direct indicator of mechanical properties of the material. Firstly two different membranes of polyvinyl alcohol (PVA) containing 5% and 10% polyvinyl alcohol (PVA) were tested for their tensile strengths. 10% PVA membrane (maximum force of 13.059 N and maximum stress of 5.22 N/mm^2) was found to have more strength as compared to 5% PVA membrane (maximum force of 10.369 N and maximum stressof 4.147 N/mm^2) as indicated by their stress-strain curves. Thus 10% concentration of polyvinyl alcohol was selected to develop a composite with magnesium (Mg) metal powder. The results of tensile testing for 5% and 10% polyvinyl alcohol membranes in the form of stress-strain graphs are shown in Figures 1a and 1b respectively.

The degradation rate of 5% polyvinyl alcohol membrane was found to be 0.593 mg/min. It was calculated by measuring the slope of the graph plotted between time on X-axis and the changing weight on

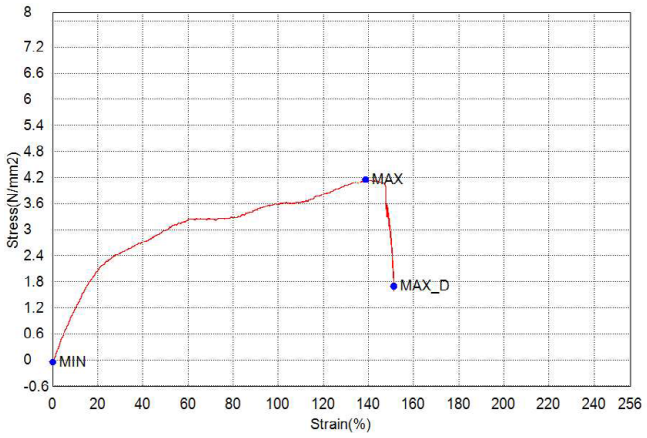

Figure 1a: Stress-strain graph for 5% PVA membrane.

Y-axis. 10% polyvinyl alcohol membrane on the other hand degraded faster at a rate of 0.350 mg/min. which can be attributed to greater concentration of solute (polyvinyl alcohol) present in it.

Composites of polyvinyl alcohol containing 1% and 2.5% magnesium powder when tested for their mechanical strength showed a considerable reduction in strength, the strength was further reduced by increasing the concentration of magnesium powder from 1% to 2.5%. Maximum force for 1% magnesium containing composite was found to be 10.4618 N and for 2.5% magnesium containing composite it was 8.4177 N. Similarly the maximum stress at entire area was calculated to be 4.184 N/mm^2 and 3.3671 N/mm^2 for 1% and 2.5% magnesium containing composites respectively. The results of tensile testing for 1% and 2.5% magnesium particles containing 10% polyvinyl alcohol composite membranes in the form of stress-strain graphs are shown in Figures 2a and 2b respectively.

When these composites were studied for their degradation rates 1% magnesium containing composite degraded quickly than the composite containing 2.5% magnesium with the degradation rates of 0.5 mg/min and 0.3 mg/min respectively.

Performing the tensile tests and degradation experiments, with 1% $MgSO_4$ (maximum force of 38.3314 N and maximum stress of 15.332 N/mm^2)and 2.5% $MgSO_4$ (maximum force of 24.792 N and maximum stress of 9.9169 N/mm^2) containing 10% polyvinyl alcohol (PVA) membranes, indicated more strength than the composite films of similar concentrations and the membranes of parent polymer, and a uniform degradation rate of 0.5 mg/min. for both concentrations of $MgSO_4$ containing membranes. The results of tensile testing for 1% and 2.5% magnesium sulphate containing 10% polyvinyl alcohol composite membranes in the form of stress-strain graphs are shown in Figures 3a and 3b respectively.

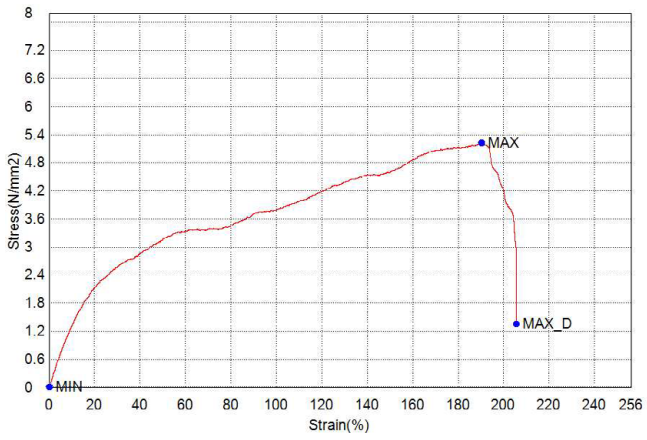

Figure 1b: Stress-strain graph for 10% PVA membrane.

For drug release studies the better compositions (as shown by the results of tensile and degradation tests) of the composite and the polymer-salt blend were selected for drug incorporation into them. Thus 1% magnesium particle containing composite and 1% $MgSO_4$ containing polyvinyl alcohol-magnesium sulphate blends were added with the drug and studied for the pattern of drug release from them. The composite showed a sustained pattern of drug release while the magnesium salt containing polymer membrane showed a conventional inclined pattern of drug release.

Discussion

The fact that 10% PVA membrane is mechanically stronger than 5% PVA membrane shows that increasing the concentration of polyvinyl alcohol has a positive effect on the mechanical strength of both the polymer membrane and the metalo-polymer membrane. 10% PVA membrane degrades quickly because the larger amount of PVA in the membrane provides greater area for water interaction and eventual hydrolysis and degradation.

For polyvinyl alcohol-magnesium composite films, addition of magnesium powder decreases the overall strength thus beneficially reducing the flexibility of the polyvinyl alcohol by the hinging effect created between the polymer (PVA) and the magnesium metal particles. This reduction in the flexibility of polyvinyl alcohol is required for certain biomedical applications like stent grafts where a limited/quantified amount of expansion is required.

The reduction in tensile strength with the addition of magnesium particles in the composite and it's direct relation with the quantity of magnesium particles is because of the fact that magnesium particles

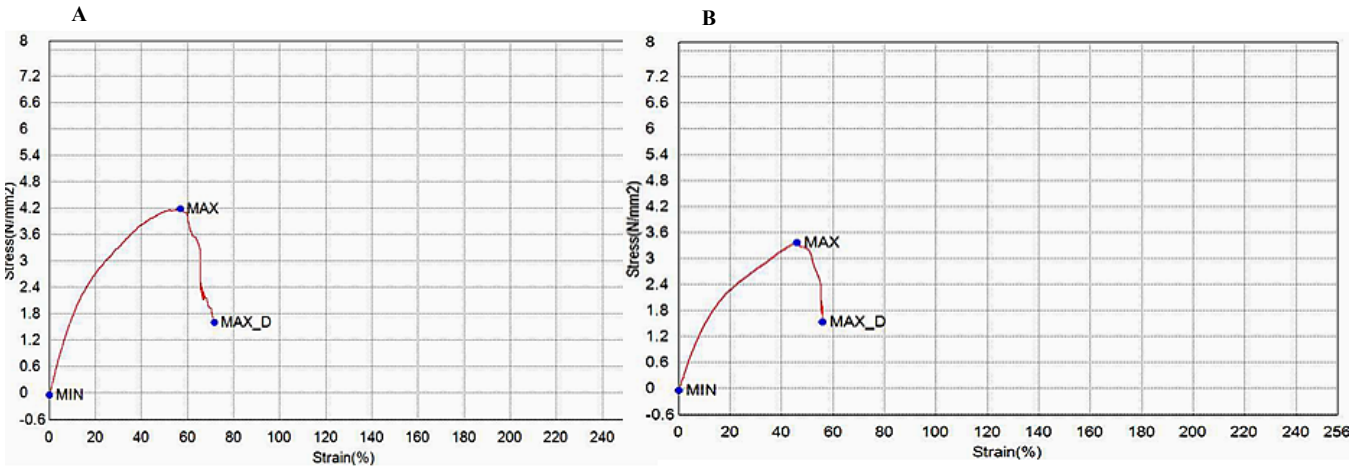

Figure 2: (a) Stress-strain graph for 1% Mg containing 10% PVA composite membrane), (b) Stress-strain graph for 2.5% Mg containing 10% PVA composite membrane.

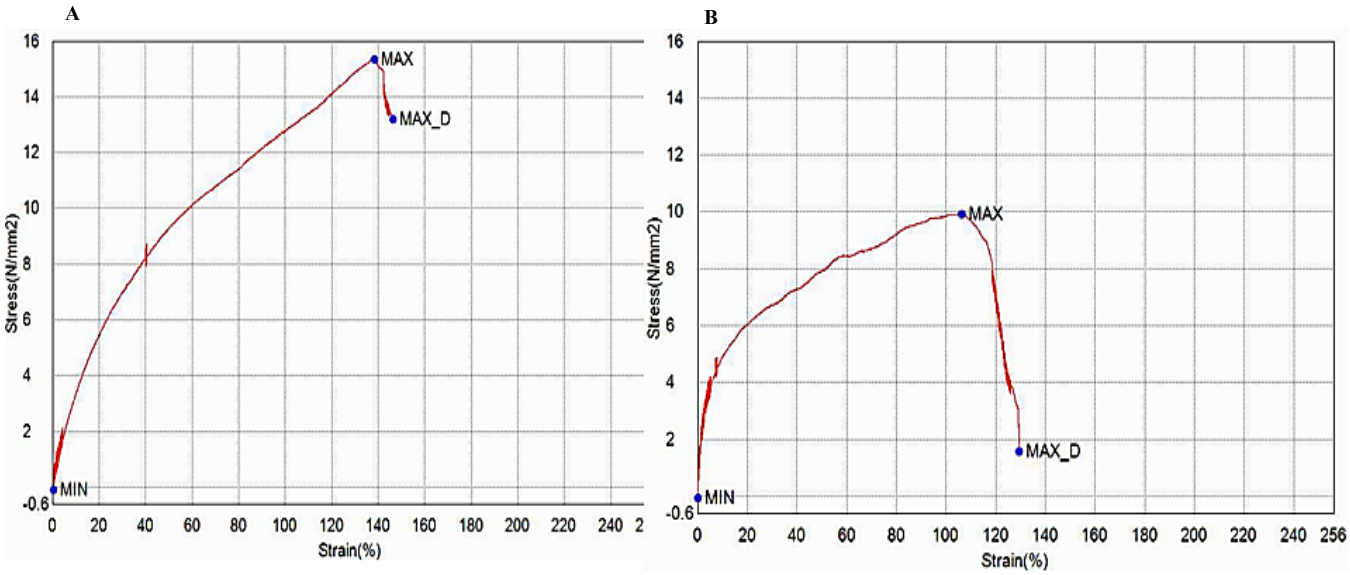

Figure 3: (a) Stress-strain graph for 1% $MgSO_4$ and 10% PVA composite membrane, (b) Stress-strain graph for 2.5% $MgSO_4$ and 10% PVA composite membrane.

provide crack propagation sites in the composite membrane, higher the number of magnesium particles in the composite, greater are the chances of crack initiation and propagation and lesser is the flexibility and strength of the composite membrane in comparison to the parent polymeric membrane.

1% magnesium containing composite degrades quickly than the composite with 2.5 magnesium powder in it. This could be because of the reason that the magnesium particles hold around portions of polyvinyl alcohol (PVA) with them, thus creating islands of PVA around magnesium particles, these islands degrade slowly with time, with the rest of the membrane being degraded quickly. Since the composite with 2.5% magnesium particles has more number of such islands so it degrades slowly as compared to the composite containing 1% magnesium particles.

The magnesium sulphate containing PVA membranes have better tensile strength because they do not undergo crack initiation and propagation in an accelerated manner as in the composites containing magnesium metal particles. Moreover the presence of foreign solute material ($MgSO_4$) in the polymer membrane increases its flexibility in comparison to the mother polymer sheet because of the possible hydrogen boding between the sulphate ions and hydroxyl groups of solvent (water). Lesser amount of foreign solute (1% $MgSO_4$) containing polymer membrane therefore has relatively more strength because of more active hydrogen bonds than in the other with higher concentration (2.5% $MgSO_4$).

As far as the same degradation rate for both the concentrations of $MgSO_4$ (1% and 2.5%) is concerned, the homogeneously dissolved $MgSO_4$ forms a uniform blend with the polymer, without creating islands of salt particles with the polymer around them, thus enabling degradation at similar rates regardless of the quantity of magnesium salt present.

The sustained release of drug from the composite membrane is because of the polymer surrounded magnesium islands which keep on releasing the drug at regular intervals, on the other hand the polymer blend of magnesium sulphate releases the drug based on the concentration of drug in the reservoir (the membrane) which decreases with time following first order kinetics of drug release.

Conclusion

Adding magnesium in small quantities to polyvinyl alcohol alters the tensile, degradation and drug release properties of the mother polymer. Increasing the quantity of reinforcement material to larger levels however doesn't lead to ideal improvement in properties. Different results are obtained by changing the form of the reinforcement material (pure metal powder or metal salt) with decrease in mechanical strength by the addition of metal particles and an increase in mechanical strength by the addition of metal salt; so any of these altered composite materials of biodegradable nature can be used based on the area of application for which they are intended to be used.

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