Multilayer Films and Platelets for Biomedical Applications

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Abstract
Novel multilayer films and particles for targeted drug delivery, localized therapeutic treatment, and detection and diagnosis require unique physical properties such as superparamagnetism, quantum confinement, and/or tailored surface functionalities while being non-cytotoxic and having colloidal and pH stability. Thin film structures composed of alternating layers of metal and dielectric layers exhibit many of the desired electrical, chemical, and mechanical properties and can be improved or modified by varying the materials, layer thickness, topography of the interfaces, and the crystalline structure to incorporate multi-functionality into a single device. The subsequent comminuting of these films into high aspect ratio flakes/platelets provides a platform for administering in-vivo or in-vitro with the particle size controlled to target specific regions. The development of a multilayer film or platelet that is capped with a layer of biocompatible material provides the opportunity to take advantage of enhanced ‘nano’ properties while providing micron sized structures that can be easily handled using conventional treatment and application methodologies. The design considerations, fabrication process, and film/platelet properties for biomedical applications will be discussed.

Introduction
Advances in nanotechnology that enable drugs to be delivered in ways that preserve their efficacy and deliver to precise therapeutic targets are creating a host of opportunities for drug developers. In many cases, drugs in nanocrystalline form can be administered in smaller doses because they can be delivered directly to the tissue and in controlled doses related to the patient’s personal requirements. A variety of nanostructures are being investigated as functional drug carriers for a wide range of therapies and are already playing a significant role in the success of medical devices and drug delivery systems [1] as illustrated by the recent advances of drug coated stents [2] and controlled release systems for local delivery of anticancer drugs [3].

Magnetic Particles/Films
The use of magnetic nanoparticles in targeted drug delivery systems is under investigation by several research groups. Therapeutic drug molecules have been immobilized on the surface of magnetic nanoparticles or nanocrystals and directed to a specific target tissue using a magnetic field gradient. The drug is released by applying a radio frequency (RF) pulse. Ferromagnetic nanoparticles have been employed in this “tag and drag” approach. In hypothermal treatment, magnetic nanoparticles are directed to diseased tissue containing heat sensitive tumors. An AC magnetic field is applied such that the nanoparticles become heated, causing destruction of the cancerous cells. The nanoparticles allow the application of higher dosages of radiation at the tumor while sparing normal tissue [4-6].

Zirconia Platelets
Esthetics and the desired replacement of the mercury-based alloys presently in restorative use drives the market for tough, translucent, radio-opaque composites which match the rigidity of the surrounding dentin and tooth enamel. The elements of a dental restorative system include: (1) the photopolymerizable monomer matrix in which is dispersed (2) a high volume percent of
micron or even nano-sized inorganic fillers which impart radio-opacity and mechanical strength to a composite which is adhered to the tooth surface by a (3) dental bonding agent. High polymerization shrinkage stresses and low toughness in commercial dimethacrylate resin-inorganic particulate composites lead to premature debonding of the restorative from the surface of the dentin or to cracking of the tooth or the composite.

At SwRI a vacuum roll coating technique operated in the continuous roll-to-roll mode has been utilized to produce: (1) a tetragonal zirconia thin film of 10-100nm thickness, sandwiched between two functional oligomer layers that (2) can be fractured into nanoplatelets in the presence of a platelet edge functionalizer to prevent the typical edge to surface platelet aggregation. The functionalized nanoplatelets are (3) highly dispersible in nematic methacrylate monomers at volume fractions sufficient to generate a microdomain nematic or columnar structure that photopolymerize at zero-shrinkage to tough, high modulus dental nanocomposites of high strength.

**Experimental**
The films under development are deposited at rates ranging from 0.2 to 10.0 nm/s onto a substrate moving past the source at 1.5 to 25 ft/min. The deposited films are 10 to 100 nm thick with a thickness variation below ±5% per selected thickness. The electron beam sources operate at 8KV and 0.3 amps and deposition thickness are monitored continuously with a quartz crystal monitor. Vacuum deposition parameters, such as rate, partial pressure, substrate temperature, coating thickness and ion bombardment have been correlated to film structure (morphology and texture) and density of the film as well as to the release characteristics of the film. The coatings were carried out in a vacuum chamber that can accommodate the winding, deposition and monitoring set-up as modular components. An image of the deposition zone is shown below.

![Figure 1. Electron beam roll coating deposition zone](image)

*Magnetic particles /Films*
The coating design is 50 pairs of a permalloy/alumina multilayer with each layer 50nm thick. The permalloy was deposited at 2.5Å/s and the alumina coated at 2.0Å/s. These coating were deposited on polyester and kapton 2 mil substrates with the multi-layer film built by passing the substrate sequentially back and forth over the two source configuration. In this configuration, each individual layer was completed in one pass in front of the source at a web speed of 1.5 ft/min.
**Zirconia Platelets**

A pre-coating of sodium chloride was applied to a 2 mil polyester substrates at 10A/s at a web speed of 15ft/min. The zirconia films were e-beam evaporated onto the web at 20A/s at a web speed of 15ft/min. The platelets are formed by passing the zirconia coated substrate with a release coat through a solvent mixture that dissolves the release layer. As the zirconia coating is stripped from the web, platelets in sizes ranging from 2-200 microns go into a solution to form a slurry. The slurry is passed through a filter to separate the platelets from the solvent and a washing step occurs to remove any residual release coat or process contaminates. The platelets are dried at temperatures above 150°C and further annealing can be performed once the platelets are dry. The platelets can be further reduced in size and the distribution of sizes narrowed by utilizing techniques such as air grinding and classification, sieving and/or sonification. The resulting platelets have an aspect ratio of at least 2:1 and a particle size distribution of ±20% from the median.

**Discussion**

**Magnetic Particles**

Magnetic nanoparticles used in many biomedical applications, require that the nanoparticles are susceptibility at room temperature, have a high magnetic moment and be monodispersed for uniform distribution and high contrast effects. Ferrite particles coated with compounds such as dextran or starch are biocompatible and easily synthesized, but the specific magnetic moment of ferromagnetic iron oxide particles is very low. Iron has a greater specific magnetization than either of these iron oxides. The problem is that pure metallic iron nanoparticles are highly sensitive to oxidation and dissolution through electrochemical reactions [7].

In metallic magnetic nanostructures, spin-dependent scattering phenomena occur when conduction electrons travel between two magnetic regions through a non-magnetic spacer material [8]. An example of an alumina/permalloy multilayer structure fabricated at SwRI is shown below.

![Figure 2. Fifty layer pairs of alumina/permalloy at 50nm per layer thickness.](image)

While the majority of magnetic nanoparticles produced at present for biomedical applications are bead-like or spherical, some research groups are fabricating nanoscale wires. At The Johns Hopkins University, a team is developing ferromagnetic nanowires for use in biomedical research or therapy. The group’s fabrication procedure enables them to make wires with diameters of 20-400 nm. Wires can range in length from 100 nm up to several tens of microns. The wires’ high aspect ratio gives them a greater dipole moment than spherical particles of the same volume, which means they can be manipulated at lower field strengths. The size, shape, and composition of magnetic nanoparticles being trialed as biochemical probes depend on their intended application, as well as the practicality of fabrication. But balancing the advantages and
disadvantages offered by super-paramagnetic versus ferromagnetic particles, or homogeneous beads versus multilayered wires, is not always clear-cut. Consequently, many researchers are experimenting with differing particulate compositions, which may later be patented, to find the optimum probe for their particular application [9].

The development of a multilayer iron/alumina platelet that is capped with a layer of gold provides and opportunity to take advantage of the enhanced magnetic properties of these multilayer structures in a biocompatible structure. The inclusion of a gold layer not only improves the platelet stability but also introduces a platform to attach medication to the surface of the platelet.

**Zirconia Platelets**

Zirconia and yttria stabilized zirconia thin films have been widely investigated for applications such as optical coating [10, 11], thermal barrier coating [12], buffer layers [13, 14], and hard and wear resistant coatings [15]. The known crystal phases (monoclinic, orthorhombic, cubic and tetragonal) are dependent upon the film thickness, stress, grain size and impurities with a variety of film preparation methods (chemical vapor deposition, atomic layer deposition and physical vapor deposition) resulting in quite different physical and electronic properties [16]. For physical vapor deposition, the ZrO₂ crystal structure is influenced by the deposition rate [17], oxygen partial pressure [18], and yttria content [19] during deposition and can be further manipulated by introducing ion bombardment [20,21], post coating annealing and/or temperature quenching immediately following deposition.

In general, electron beam deposited zirconia films exhibit a higher tetragonal phase content when deposited at rates greater than 6nm/s [17], at a film thickness greater than 5nm [16], and with increasing yttria content [19]. X-ray diffraction revealed that the majority phase in the deposited ZrO₂ platelets is the desired, tetragonal ZrO₂ and the minor phase is monoclinic ZrO₂.

![X-ray diffraction pattern](image)

**Figure 3.** ZrO₂ platelets produced by vacuum roll coating consist mostly of the tetragonal phase.

**Conclusions**

Thin film structures composed of alternating layers exhibit many of the desired electrical, chemical, and mechanical properties and can be improved or modified by varying the materials, layer thickness, topography of the interfaces, and the crystalline structure to incorporate multifunctionality into a single device. The subsequent comminuting of these films into high aspect ratio flakes/platelets provides a platform for administrating in-vivo or in-vitro with the particle size controlled to target specific regions. The development of a multilayer film or platelet that is capped with a layer of biocompatible material provides the opportunity to take advantage of
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References