Three Roll Mills and the Mixing of Biomaterials

1. Introduction

Biomaterials are used in the field of medicine for drug and gene delivery, bio detection of pathogens, protein detections, DNA probing, tissue engineering, separation and purification of cells and molecules, MRI contrast enhancement, and phagokinetic studies.

Biomaterials consist of polymers and nanoparticles that interact with the cells of the organism, which involves integration of non-biological nanofibers with bioactive components. Living organisms are composed of cells with sub-micron sized components. Nanoparticles are comparable to that size and can be used to interact with the cellular machinery without too much interference. Utilization of bionanomaterials promotes the survival and integration of transplanted cells and control site specific delivery of therapeutic drugs.

The function and specific applications of biomaterials is achieved by mixing desired bis-prepolymer with certain bioactive molecules functionalized in the same groups [6]. The polymers are reinforced by physically dispersing a variety of nanofillers in different shapes, such as fibers, platelets, or spheres into the polymeric host inorganic fillers. This combination gives the polymers characteristics such as high modulus, high oxidation resistance, or high use temperature. Ideally, the result would be a synergic effect of the components, not just the volumetric averaging function of the individual components [7]. These qualities are attributed to the filler particle surface properties and interfacial interactions that are important when dealing with small particles.

The type of biomaterials to be used is dependent on mode of application, nature of bioactive molecules, need for surface functionalization, cell porosity, and other issues. The production of biotech materials can encounter problems such as solids settling, shear damage, air entrainment, vortexing, temperature and pH gradients, and mixing zone which can compromise its potential. Physicochemical triggers such as temperature, pH, and ionic strength can lead to self-aggregation due to separation of the colloidal solution [12]. Aggregation of the particles result in reduced efficiency of the material.

Polymeric nanocomposites dispersed in the polymer matrix determines the physical properties of the biomaterial. Decreased particle size means that there is significant increase to the surface energy. An issue with using nanoparticles is the tendency for the particles to aggregate, which then reduces the total surface energy [7]. To lessen the problem, nanoparticles are grafted or modified into organic groups that are compatible with the polymer matrix [7].

2. Using Biomaterials for Medical Purposes

In using biomaterials for medical purposes, the basic challenge is biocompatibility with the living organism. Many biomaterials are made from combinations of polymers to achieve specific characteristics. Optimizing the mixture of polymers is difficult as the cells are changing shape, resulting in an increase or decrease in contact with the films. The cell-material dynamics determine whether the biomaterial leads to abnormal cell growth or insufficient drug delivery. With biomaterials, the particle matrix has a significant role in drug delivery due to its stimuli-responses and natural polymers that control the release of drug onto specific

sites [9]. The shape of the nanoparticles is an important factor in particle design and determines the therapeutic efficacy in particle-based medicines as they affect particle distribution in the blood. Long cylindrical filaments have negligible phagocytosis compared to spherical particles with similar volume.

Biomaterials have been incorporated in many new medical technology and treatments. One of its recent applications is in wound treatment. Traditional wound dressing that involves hydrogel would promote healing, but does not allow for the wound to breath. Another type of dressing is dry films that have tiny pores to allow for air exchange, but is more vulnerable to bacterial infection. These issues are resolved using biomaterial made from the balance of positive and negative moieties from the mixed-charge polymers [4].

Another use of biomaterials is in biological regeneration. In vivo bone regeneration is carried by creating an injectable calcium phosphate biomaterial. The mechanical characteristics of the biomaterial is influenced by the mixing of liquid and powder and the various factors to modify the properties [5]. This includes temperature, humidity, and sterilization of the mixing environment. Inadequate mixing will result in a non-homogenous solution that will not have the full reaction potential.

Incorporating biomaterial into antibiotic loaded bone cement (ALBC) allows for the prevention and treatment of orthopedic infections and surgical aid. The method of mixing ALBC affects the release of the antibiotics and mechanical properties of the material. The mixture must be porous as possible to increase the spread of antibiotics, but not too much that the structure of the material is weakened [6]. Manually mixing the solution will reduce the strength of the cement by 36% compared to industrially prepared mixtures [3].

Biomaterials can be used to fill support, bone, and osteoarticular tissues through injection. The mixing during the aqueous phase determines the rheological properties and viscoelasticity of the composition.

Using natural polymers in the production of a biomaterial means a higher change of biocompatibility due to similar or identical macromolecular substances that the biological environment will accept. A problem with using natural polymers is their tendency to decompose or undergo pyrolytic modifications because of temperature sensitivity [11].

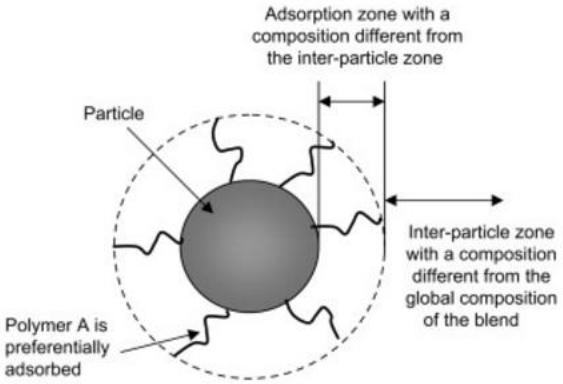

Figure 1. *Partially miscible polymer blend with a polymer interacting with the filler [13]*

3. Importance of Uniform Dispersion

Nano-particles can be made of inorganic or polymeric materials and be used as a surface for molecular assembly. To make nanoparticles biocompatible, a biological or molecular coating must bind with the bioinorganic surface. Biological coatings include antibodies, biopolymers, and monolaters of small molecules.

The potential of the particles and its benefits relies on its solubility. Nano emulsions are colloidal dispersions of two immiscible liquids. It cannot be formed spontaneously and relies on an external shear force applied to break the larger droplets into smaller ones.

Compressive strength and increase in strength of a biomaterial over time is an indicator of the setting reaction and stability of the biomaterial. Besides the composition, the uniformity of the distribution would affect the mechanical properties.

Biomaterials rely on the use of high throughput surface characterization (HTSC) which allows for correlation to physio-chemical properties and biological-material interaction. The quality of the biomaterial is affected by the level of nano-mixing. A problem with utilizing nanoparticles is that they are highly agglomerated. If used in a bulk composite, the material will lose surface area due to grain growth, decreasing the reaction potential [8]. Mixing of the reaction components is essential in creating a homogenous reaction environment for biological and chemical reactions. Devices such as biosensors depend on the mixed components which determine efficiency and resolution. In other applications, controlled mixing is important for studying reaction kinetics.

The size and distribution of size are critical due to the quantum-sized effects on the material properties. A narrow distribution of the particles would allow for the material to have very efficient fluorescent probes that emit a wide range of wavelengths. This is useful in the production of biomarkers. The core is responsible for the binding to both nanoparticle surface and various moieties such as antibodies and fluorophores.

The mechanical properties of biomaterial can be enhanced by creating a composite of high-density polyethylene (HDPE) and reinforced with hydroxyapatite (HA). Fine particles of HA are used to coat each coarse HDPE particle. Uniform dispersion of the particles determines the characteristics of the material from the microstructure of the formed composite. [1]

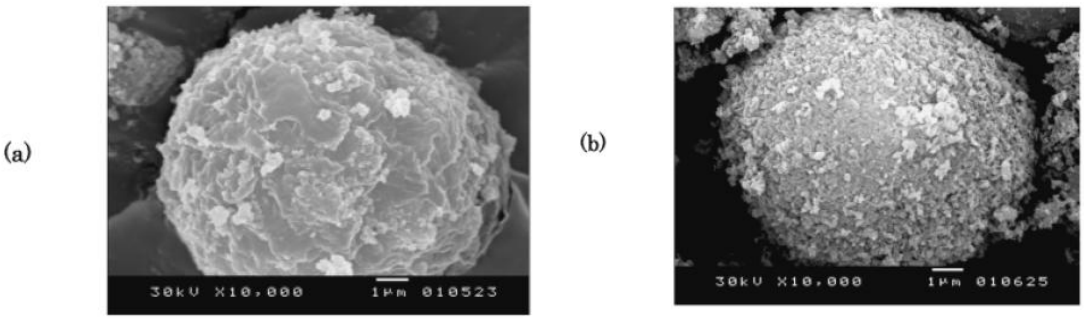

Figure 2. *SEM images of coated particles. (a) is produced by a hybridizer and (b) is produced by a mill with high compression and shearing ability [1]*

4. Different Dispersion Methods

4.1 High Shear Mixers

High shear mixers disperse the species into a main continuous phase, even if they are normally immiscible. It can homogenize, solubilize, disperse powders, and reduce particle size or accelerate reactions.

When mixed with rotational impact blending, the mixture has uniform dispersion of HA and HDPE, although there must be multiple steps of coating the HDPE as there would be a high amount of powder loss during the process. [1] Turbulent flow from a mixer does not indicate how well the solution is mixed. A turbulent surface is a sign of lost mechanical energy. Instead, the surface should be as calm as possible to mix what is below the boundary layer and to interchange the surface boundary. Non-Newtonian fluids do not have fixed viscosity, but an apparent one that decreases as the product is stirred faster. Because of the thinning viscosity, an agitator is critical to mixing the fluids properly [10].

4.2 Low Shear Mixers

Low shear designed impeller mixers, or agitators, are made to use the least amount of energy possible when mixing the species. The blades of the propellers are designed to have low drag and smooth flow. The result of low-shear mixing is increased stability and enhancement of solubility in an aqueous solution, but does not work as well for mixing dissimilar species. Another aspect of agitators is that the farther the material moves away from the impeller, there is reduction in the mixing action. To avoid this, the impeller size and speed are adjusted per the viscosity and having impellers with larger diameters would provide effective mixing [10].

4.3 Elliptical-Rotor Mixers

An elliptical-rotor type of mixer achieves a uniform and tight coating of the core particles with less particle loss. However, the gentle shear and compressive stress of the machine generates aggregates due to the embedment of fine particles and HDPE of core particles escaping the thick and loose coating layer during the operation. Because of the aggregates, there is weak bonding between the coated particles which leads to lower mechanical properties in the biomaterial. [1]

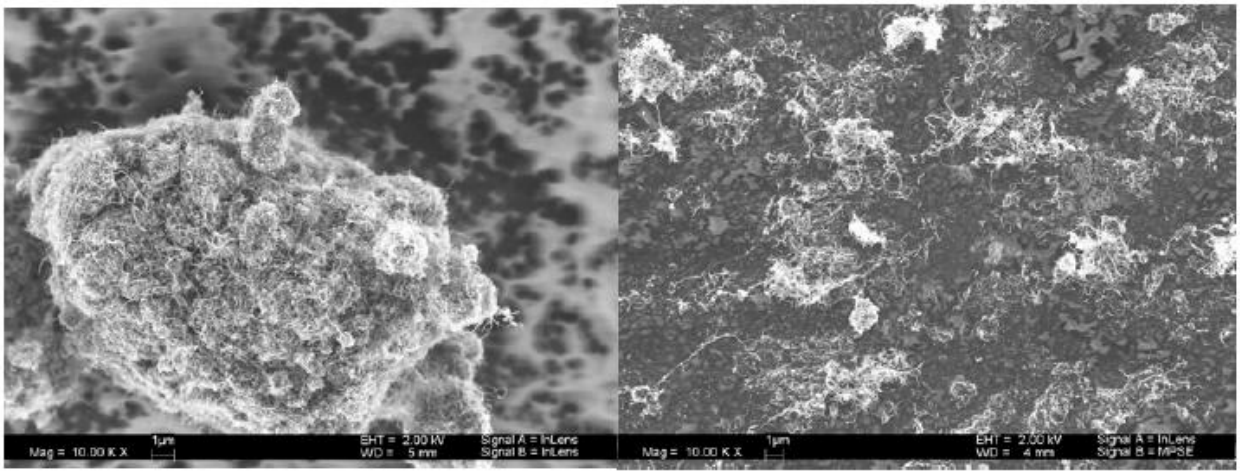

Figure 3. *Carbon nanotube agglomeration on the left and agglomeration reduction on the right [8]*

5. Dispersing with a Three Roll Mill

A Three Roll Mill has three horizontally positioned rollers. Each roller rotates in an opposite direction from the adjacent roller with a tiny gap between them, creating tremendous shear force that can finely disperse, mix, refine or homogenize viscous materials.

As you see in Figure 4, the material is loaded between the feeder roll and the center roll. Due to the narrowing space between the rolls, most of the mixture is rejected to the feed region. The part does make it through experiences very high shear force and disperses the pigment particles in the binder. As it comes out the other side, the material that remains on the center roll moves through to nip between the center roll and apron roll, experiencing even high shear force due to the higher speeds. A blade automatically scrapes the processed mixture off the apron roll transfers it to the apron. The three roll milling cycle is repeated many times until the material is perfectly dispersed and the particle size is in the good range.

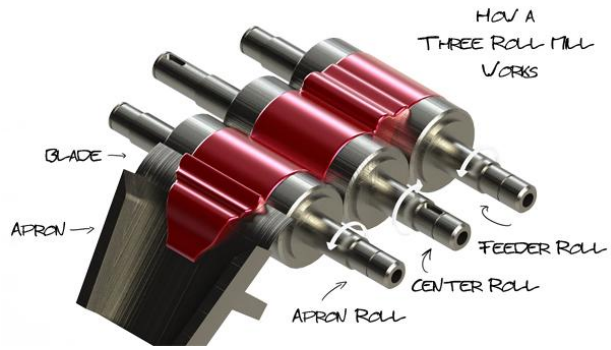

Figure 4. *How a three roll mill works.*

Mechanical mixing decreases the amount of air-filled spaces between the particles, leading to an increase in the wetted surface and improve the uniformity of the material. [2]

With the three-roll mill, species are combined by the rolls. This results in the fluids stretching and folding, inducing a chaotic advection effect that promotes species mixing. The laminar flow of the machine allows for the two species to merge into one stream. This has been shown to create a mixing distance of 300 µm instead of the average 3000 µm of turbulent mixing that must fully mix the two streams in a conventional straight channel [3].

Laminar flow occurs due to molecular diffusion. By enhancing the diffusive effects, there is increased mixing between the two species. The species travel between the rolls and their molecules will be separated by the multi-directional rotation, thereby creating separate gaps that allow for the diffusive effect. This effect can also be achieved by increasing the contact area between the two species. With the design of the three-roll mill, there is more contact area due to structure and number of rolls. The design of the three-roll mill allows for the width between the rollers to be mechanically or hydraulically adjusted to provide control over the narrow distribution of the particles. By decreasing the size of the gap, the optimal particle dispersion can be achieved with less agglomerates.

Figure 5. *Torrey Hills T65 Three Roll Mill*

By mixing the species laminarly, the species will combine due to the surface tension effects of the roll that causes the molecules to be pushed together and form a single layer. The repeated rolling cycles result in constantly changing flow lines within the liquid mix. This is a self-folding effect and it improves the mixing performance. Having a slanted well provides the lateral transport that ensures the mixing of two confluent streams. The vertical fluid motions improve the homogenization process.

A way to decrease the mixing time is to vary the flowrates of the three-roll mill. A higher difference between the flowrates will focus the stream and its mixing pass. Use of rollers provides the high shear force to integrate the nanoparticles into the material, but does not apply it in a way to cause shear stress on the sensitive biomaterials due to the rolling motion used for mixing.

Conclusion

The quality and characteristics of biomaterials depend on the components used and the dispersion of the particles within the solution. Inconsistent dispersion will lead to reduced surface area, causing less efficiency in the biomolecular reactions carried out by the material. Different types of mixing methods will affect the particle dispersion and the microstructure. Using turbulent fan motions, the shear force will disrupt the nanoparticles, while agitators do not provide consistent mixing. With the three-roll mill, the nanoparticles will evenly disperse throughout the polymers due to its high shear force, but will also avoid the formation of aggregates due to the rolling method. Because of these features, the production of biomaterials will be more efficient and yield a higher quality.

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