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Melt-Processed PLA/HA Platelet Nanoparticle Composites Produced Using Tailored Dispersants

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Abstract: Hydroxyapatite (HA) nanoparticles, similar to those seen in the structure of human bone, have been produced via hydrothermal synthesis and used to produce nanocomposite materials via melt blending with poly(lactic acid) (PLA). Both of these processes are scalable and commercially relevant. Tailored dispersants were developed and used to improve the dispersion of the HA. Modest improvements in flexural properties were observed (max increases 30% of dry modulus, 13% of wet strength). Rheometry is not suggestive of achieving percolation, so there is potential to improve mechanical properties further. It was established that very dry processing conditions are essential to maintaining the molecular weight of the PLA during processing and that the use of the tailored dispersants can also help to mitigate process-induced degradation. MicroCT has proved to be a useful quality control tool to support TEM analysis.

Keywords: nanocomposite, hydroxyapatite, polylactic acid

1 Introduction

The structure of bone is one of collagen fibres reinforced with hydroxyapatite (HA) nanocrystals (nanoHA). While monolithic HA is essentially non-resorbable, the body presumably possesses the functionality to resorb nanoHA. Indeed studies have demonstrated that nanoHA has a faster rate of 'biodegradation'¹ than monolithic HA and there are resorbable HA bone fillers on the market that make use of high surface area fused HA nanoparticles (e.g. ReproBone). In the present study, nanoHA has been used as a reinforcement for polylactic acid (PLA) to produce enhanced materials for medical devices. This in itself is not new, but here a novel hydrothermal process was used to obtain nanoHA in platelet shape. This has enabled the scalable production of materials with the potential to achieve the unique properties seen in intercalated clay nanocomposites², but in a form that is fully resorbable.

The materials have been made through an industrially-relevant melt compounding process. Medical-grade PLA has been used to demonstrate that processing conditions have been identified that are appropriate to medical devices. To improve dispersion during compounding, the hydrothermal process allows for simultaneous nanoHA formation and coating using specifically designed molecular dispersants³. These dispersants are low molecular weight polymers, with functional head groups carefully designed to link to the surface of the nanoHA and PLA chain structure tails to interact with the bulk polymer⁴. The synthetic dispersants have been key to achieving not only improved dispersion of the nanoparticles in the polymer but also to enhance the interaction of the polymer with the particles during processing. Experimental data shows that the addition of plates along with a dispersant that is *not* intimately connected provides only limited improvements to material characteristics. It is necessary therefore to have intimate, bonded contact between platelet and dispersant. Extensive characterisation has been undertaken in terms of thermal, physical and rheological studies after processing and through the course of hydrolytic degradation^{5,6}, including microCT and micro-mechanical testing. The addition of nano-platelets has been shown to affect the processing conditions, to increase the yield strength (offering potential creep resistance) and to have dramatic effects on the diffusion properties (altering degradation behaviour). Specialist micro-mechanical tests and off-line rheological studies have ensured efficient use of small scale compounding trials, while enhanced imaging techniques have elucidated greater understanding of the process of degradation in PLA materials. Close contact with industrial partners has ensured that all the processes in use are commercially scalable, with and a demonstrator product under development to showcase the identified beneficial features of the new nanocomposite materials.

2 Materials and methods

2.1 Feedstock production

2.1.1 Dispersant synthesis

The dispersants used to coat the hydroxyapatite nanoparticles are based on two systems: (a) polylactide chains with mono or multifunctional hydroxyl headgroups derived from isosorbide or sorbitan and (b) headgroup functionalized polyolefins. The former use a modified ring opening polymerisation with a commercial tin catalyst and are described by Hild⁴. The latter are commercially available materials.

2.1.2 Nanoparticle synthesis and coating

Synthesis and coating of the nanoparticles was undertaken simultaneously using a laboratory scale counter-current hydrothermal reactor. The specifics of this process are described by Gimeno-Fabra³ and Lester⁷. The final product is a freeze dried powder suitable for use as feedstock for melt compounding.

2.2 Composite manufacture

2.2.1 Melt compounding

Melt compounding of the dispersant-coated nanoparticles and medical grade PLA (RESOMER® LR706S – Evonik, Mw of 445.9 kDa⁶) was performed by using a HAAKE MiniLab II Microcompounder (Thermofisher Scientific), utilizing a co-rotating screw configuration. The compounder has a volume of approximately 7 ml. Processing temperature, time and speed were varied to optimise mixing conditions, to maximum values of 210 °C, 15 mins and 150 RPM respectively. All the feedstock was dried under vacuum at 50 °C overnight to minimize water content. Dry nitrogen was used to purge the system and reduce degradation from atmospheric water. Wall shear stress was measured during compounding via two pressure transducers located in a rectangular recirculation channel.

2.2.2 Compression moulding

Extrudate from the MiniLab compounder was compression moulded into sheets for subsequent mechanical and degradation studies. Before moulding, the materials were dried in a vacuum oven at 50 °C overnight to minimize water content. The compression moulding was conducted using cavity moulds at 170 °C for 15 minutes, followed by water cooling to below 55 °C before demoulding.

2.3 Visualisation

2.3.1 Micro computed tomography (MicroCT)

MicroCT imaging was performed using a Shaw Inspection Systems VENLO H 350/225 CT cabinet inspection system at 35 kV, with a current of 0.265 mA and a 25 ms exposure time. A copper sheet was placed in front of the source as a filter and the specimen was positioned on a rotating stage. Images were processed using Mimics and 3-matic software.

2.3.2 Transmission electron microscopy (TEM)

A FEI TECNAI G2 BioTWIN with tungsten filament gun (TEM-FEI) was used to obtain micrographs of the nanocomposite materials, using an accelerating voltage of 100 - 120 kV. Sample sections ~100 nm thick were cut using a glass knife at room temperature and supported on copper grids.

2.4 Chemical, thermal and mechanical analysis

2.4.1 Gel permeation chromatography (GPC)

Molar mass measurements were made using an Agilent Technologies 1200 Infinity Series GPC with refractive index detector, in tetrahydrofuran at 25 °C relative to polystyrene standards. A first order Mark-Houwink-Sakurada calibration for linear PLA was achieved from a first order calibration for polystyrene using linear, narrow dispersity standards. Specimens were dissolved in THF at a concentration of 2 mg/mL. Sample sizes range from 5 to 7 specimens.

2.4.2 Thermogravimetric analysis (TGA)

TGA measurements were made on a TA Instruments TGA Discovery using N₂ as the purge gas. Samples were heated in Pt pans at a rate of 5 °C/min, up to a maximum

temperature of 500 °C. Between 3 and 5 repeats were performed for each sample.

2.4.2 Rheometry

Dynamic rheological measurements were performed with an Anton Paar MCR302 rheometer fitted with a CTD620 temperature chamber using Ø25 mm parallel plates with a 0.5 mm gap size in air. Isothermal frequency sweeps were carried out at angular frequencies (ω) between 50 rad s⁻¹ and 1 rad s⁻¹ in the linear viscoelastic region, for temperatures from 90 °C to 210 °C. Mastercurves were produced by horizontally shifting the moduli in the frequency domain to a reference temperature of 180 °C. Details of the rheological process can be found in Choong et al.⁶ and Tomczynska et al.⁸.

2.4.4 Mechanical properties

Mechanical properties were determined using a custom-built micromechanical flexural testing setup, equipped with 10 and 100 N load cells and capable of bending beams as small as 6 x 2 x 0.5 mm³. Force is applied using a precision linear actuator. Results from the system were validated against larger specimens and against commercial test machines. The system can also be immersed in liquid, allowing for testing during degradation.

2.4.5 Water uptake and degradation

Water uptake and degradation studies were performed in phosphate buffered saline (PBS) at 37 °C and 50 °C, with a solution to specimen ratio of 30:1. For degradation studies, the PBS was replaced with fresh solution at each measurement point and studies were conducted for up to three weeks at 50 °C. Specimens were blot dried before weighing and testing.

3. Results and discussion

3.1 Dispersants and particles

Ring opening polymerisation has enabled the creation of very tightly controlled molecular weight oligomeric PLA dispersants to around 80% conversion. Production of shaped nanoparticles by hydrothermal synthesis has been established previously⁷ but modification of the reaction conditions of this process have allowed well-coated nanoparticles to be produced as a free-flowing powder suitable for melt compounding^{3,9}. TGA analysis is used to assess the loading of the dispersant on the nanoparticle, which can be up to 50% by weight. Adherence of the dispersant on the particle is observed to confer upon the dispersant an improved thermal stability, which is beneficial for melt-processing. An example TGA experiment illustrating these results is provided in Figure 1.

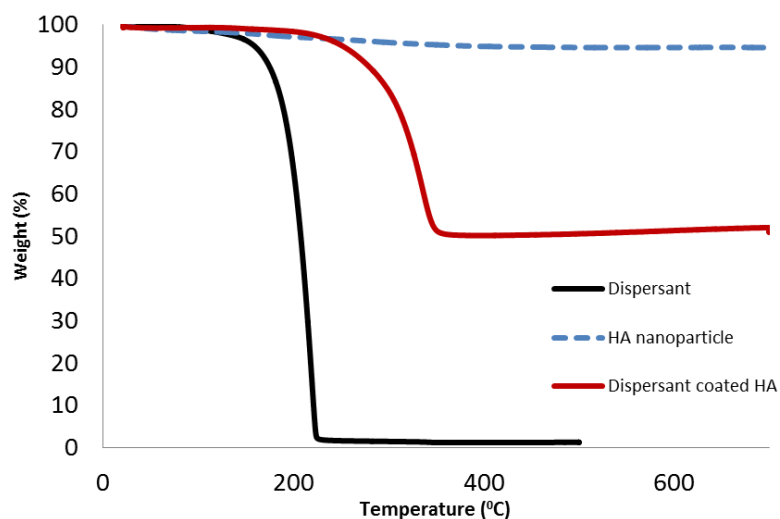


Figure 1: Typical dispersant loading on nanoparticles as determined by TGA, showing enhanced thermal stability of the dispersant and a ~50 wt% loading of an isosorbide-PLA dispersant.

Further developments in the dispersant materials are planned, through modification of the oligomer structure and by modification of the reaction scheme to minimise the use of catalyst, especially since it is anticipated that acceptable commercial levels of tin in biomedical polymers will be reduced in the foreseeable future. A greater understanding of the dispersant-particle geometry and interactions will be probed in future work by using solid state NMR and BET analysis.

3.2 Nanocomposite processing

Poly(lactic acid) is available in a wide range of molecular weights and racemic mixtures. This variation translates to a significant difference in mechanical and rheological properties, as well as crystallization behavior, all of which is exacerbated through the process of degradation. In order to obtain meaningful results, a standard medical device grade amorphous poly(L-lactide-co-D,L-lactide) (PLDLLA) with a molecular weight of around 450 kDa was used in all processing experiments.

In order to make efficient use of this expensive medical grade polymer, melt-compounding was performed using a HAAKE MiniLab II Microcompounder. This has a small processing volume (~7 ml) and a recirculating channel with continuous pressure monitoring, enabling the assessment of longer residence times with less material and with a continuous indicator of wall shear stress.

After processing, materials were assessed by using TGA to determine true particle loading and by using GPC to determine the molecular weight of the polymer. Particle loadings were typically correct to within 0.2 wt% of expectation and all experiments were repeatable. Molecular weight was found to fall significantly both for the pure polymer and even more so for the nanocomposites made without the use of dispersants. However, the presence of the dispersant coating limited the reduction in molecular weight of the polymer during processing. TEMs indicated that the dispersants were also effective in improving the dispersion of nanoparticles within the

polymer matrix, although some agglomerates remain (Figure 2).

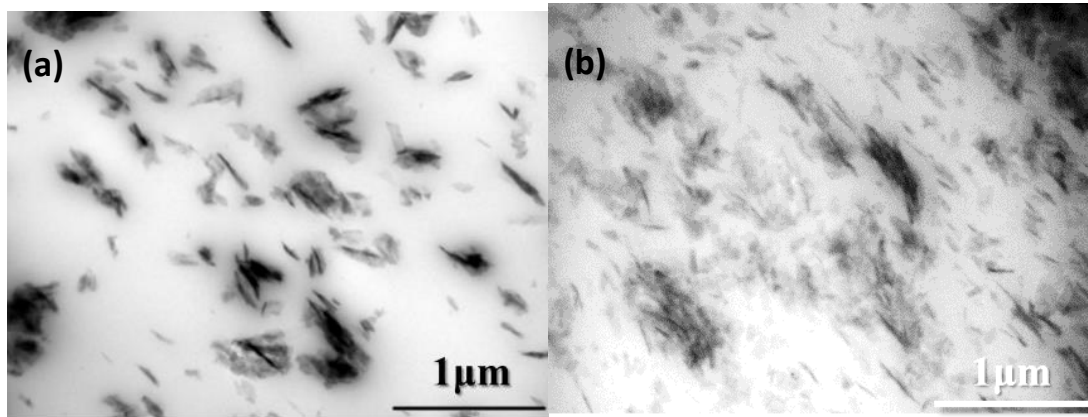


Figure 2: TEM images of nanocomposite materials processed using equivalent conditions (a) PLA loaded with 2.5 wt% of HA nanoparticles (b) PLA loaded with 2.5 wt% of particles coated with dodecyl succinic anhydride (DDSA)

3.3 Nanocomposite properties

Through the course of this work, the susceptibility of PLA to degradation during processing has become profoundly clear. Prior to the use of a dry nitrogen purge in the compounder, the molecular weight of the polymer could fall from ~450 kDa to less than 150 kDa after 15 minutes recirculation at 210 °C, even with careful drying before processing. Using a dry nitrogen purge limited this to ~300 kDa. Some degree of degradation during melt processing appears to be inevitable when using PLA. A rheological approach has been developed to account for and predict this degradation and initial work in this respect has been published⁶. A model to describe this degradation is close to completion.

Improvements in flexural strength of the nanocomposites have so far been modest. The addition of 2.5 wt% of uncoated nanoplatelets provided no significant increase in dry flexural strength although this translated to an 8% improvement in saturated properties at body temperature. This increased to a 13% improvement when using a DDSA dispersant (see Figure 3(a)). Conversely, dry flexural modulus increases substantially (~30%) but the increase is reduced to between 0 and 10% when wet at 37 °C (see Figure 3(b)).

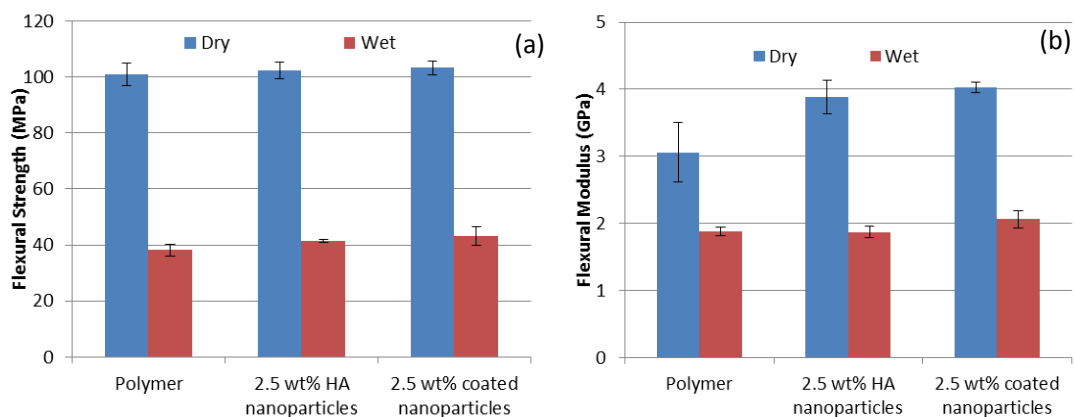


Figure 3: Example flexural properties of dry and saturated polymer and nanocomposite specimens with and without a DDSA dispersant. The wet samples were saturated by soaking in PBS at 50 °C for 24 hours.

The flexural strength does not change substantially during 14 days of accelerated degradation at 50 °C in PBS, for neat PLA or for the nanocomposites. Further addition of particles (at 5 wt% and above) had a detrimental effect on the mechanical properties.

The water uptake properties of the nanocomposites were not as expected. Conventional clay nanocomposites display enhanced barrier properties and so it was anticipated that a reduced diffusion rate might be observed with the HA/PLA nanocomposites. However, while they initially exhibit Fickian behaviour with a similar diffusion coefficient to the neat PLA, they do not reach a saturation plateau but instead continue to take in water for at least 14 days (Figure 4).

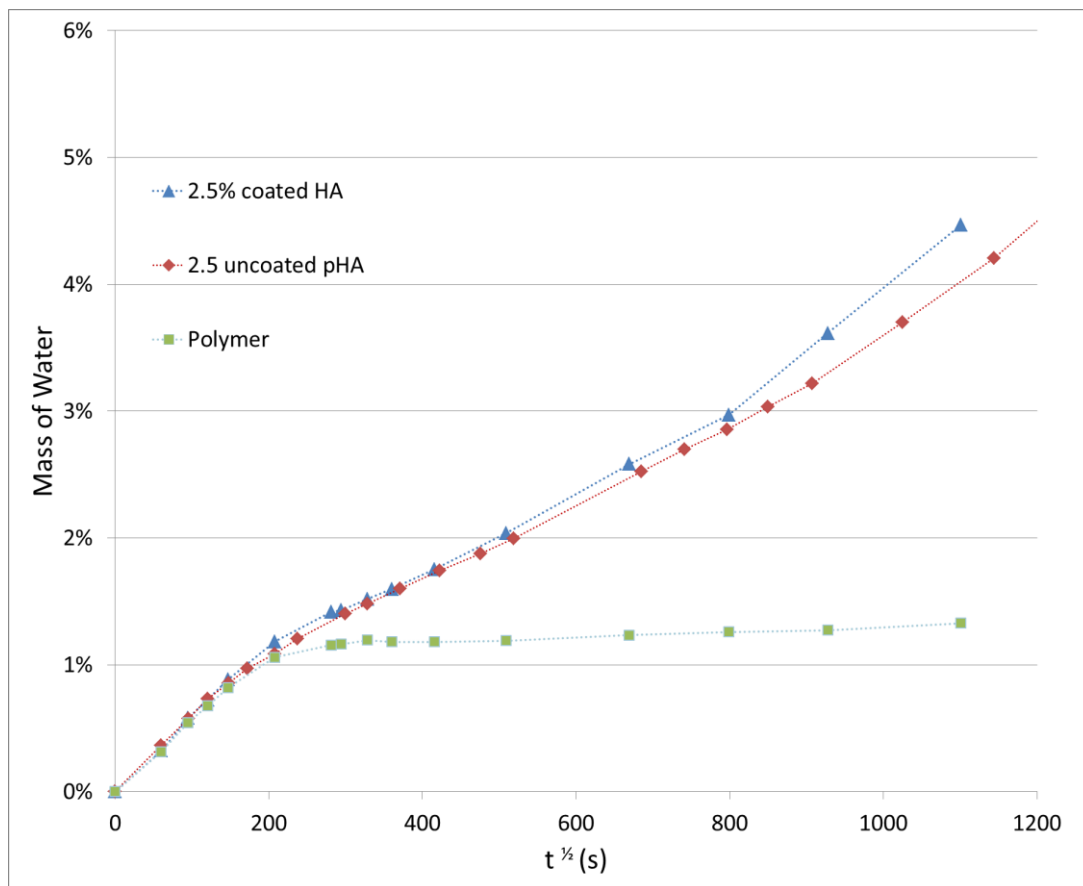


Figure 4: Example water uptake of neat PLA and nanocomposite materials with and without an isosorbide-PLA dispersant. Performed in PBS at 50 °C

The cause of the limited mechanical improvements and unusual water uptake behaviour was investigated further. While TEM is used frequently as a means of demonstrating good dispersion, it is insufficient by itself to represent large volumes. In order to consider a larger area of interest in the nanocomposite specimens, microCT was performed. An example of a reconstructed microCT image is shown in Figure 4.

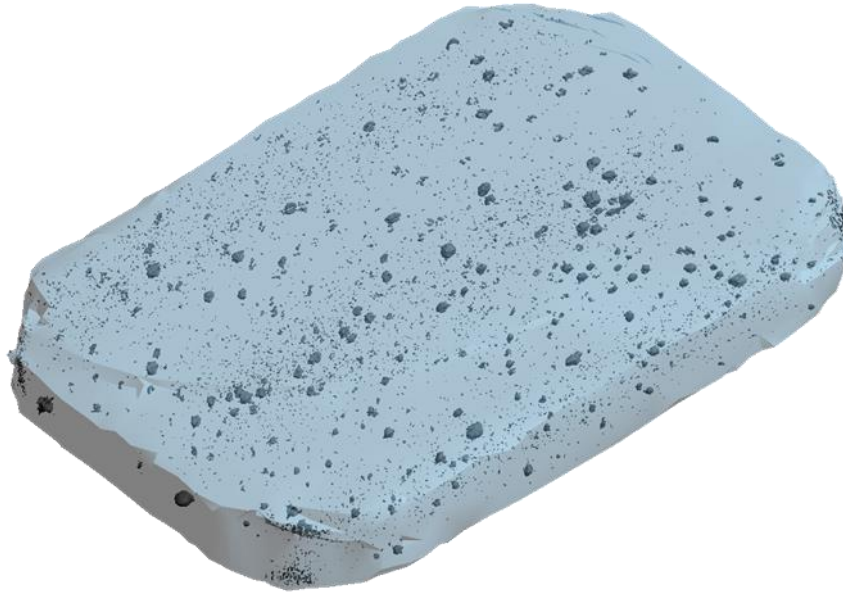


Figure 4: Reconstructed microCT image of nanocomposite material. Sample size 7.2 x 8.8 x 0.9 mm. Voxel size $12.7 \mu\text{m}^3$.

The voxel size was $12.7 \mu\text{m}^3$ and so any visible features are at least of this size. The image suggests the presence of a large number of agglomerated particles, despite the TEMs suggesting good dispersion. These micron-size particles would be expected to be detrimental to flexural strength, by providing stress concentrations and points of weakness through internal slippage of dry nanoplates. These aggregated dry particles could also expose a very large surface area hydrophilic region acting as a water sink, which may explain the continual water uptake.

Post-processing rheology of the materials was also performed. It is known that in an exfoliated nanocomposite the development of an inter-particle structure (at or beyond the percolation threshold) can be observed normally as a second plateau in the storage modulus at low shear rates¹⁰, There is no evidence of this inter-particulate structure in any of our nanocomposites (see Figure 5).

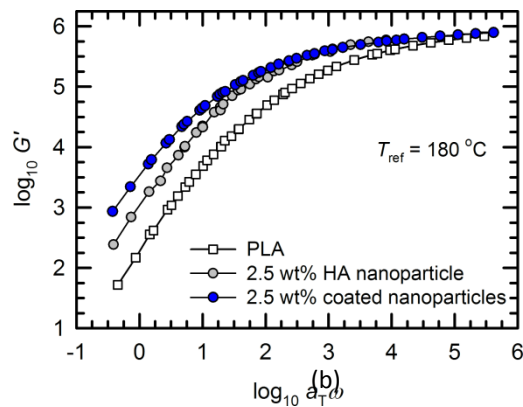


Figure 5: linear viscoelastic spectrum for PLA and PLA/HA nanocomposites with and without a DDSA dispersant, showing no second plateau in G'

Although the dispersants that have been produced to date are showing positive effects in terms of molecular weight retention, they display only modest mechanical property improvements. There is also an abrupt drop in mechanical properties when adding 5 wt% nanoplatelets to the nanocomposite. This is quite similar to the effects seen by Diao et al.¹¹, who produced nanocomposites by melt blending PLA and dispersant-coated spherical nanoparticles. They saw up to 10% improvement in tensile strength with an addition of up to 3 wt% of nanoparticles, with higher loadings causing a dramatic loss of properties. However, Wan et al.¹² utilised a nanoplate-like HA produced by a solvent-based laboratory method at loadings of up to 30 wt% and saw around a 30% increase in tensile strength, with an optimal loading at 20 wt%.

These results would suggest that nanoplatelet HA can provide significant improvements in mechanical properties, provided that the correct level of dispersion is achieved, but that achieving this through melt dispersion is challenging. Melt-processing is undoubtedly the most scalable and commercially relevant method of producing plastic parts, and certainly requires further study.

Rheological assessments in the studies to date did not provide evidence of nanoparticle percolation, so there remains a need to improve the overall dispersion/exfoliation of the nanoplatelets in order to maximise mechanical properties. Future studies will concentrate on improving dispersion through two routes. One is to use a pre-mixing or 'master batch' approach utilising a solvent-based approach, the other is the use of increased shear during compounding.

4. Conclusion

Tailored dispersants have been produced successfully and attached to hydroxyapatite composite nano-platelets to create a free flowing powder feedstock. This feedstock has been combined with polylactic acid by melt-compounding to form nanocomposite materials. Process-induced molecular weight loss has been mitigated by the use of rigorous processes and through the action of the dispersants. The nanocomposite materials show some improvements to mechanical properties but require improved dispersion/exfoliation to achieve a greater effect. MicroCT has proved to be a useful quality control tool to support TEM analysis.

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References

- 1) Fathi, M.H., Mortazavi, V. & Esfahani, S.I.R. Bioactivity Evaluation of Synthetic Nanocrystalline Hydroxyapatite. *Dent. Res. J.* 5(2), 81-87 (2008).
- 2) Mittal, V. Polymer Nanocomposites Technology: An Overview in *Advances in*

Polymer Nanocomposites Technology (ed Mittal, V.) 1-26 (Nova Science, 2010).

- 3) Gimeno-Fabra, M., Hild, F., Dunne, P. W., Walton, K., Grant, D.M., Irvine, D.J. & Lester, E.H. Continuous synthesis of dispersant-coated hydroxyapatite plates. *Cryst. Eng. Comm.* 17, 6175-6182 (2015).
- 4) Hild, F. & Irvine, D.J. Selective synthesis of 1,4-sorbitan, isosorbide and isosorbide esters from D-sorbitol dehydration under acidic catalytic conditions using conventional heating (CH) and microwave heating (MWH). Sustainability Research Symposium, April 23rd, (2014), University of Nottingham, Nottingham, UK
- 5) Ward, M., Brisse, A.-L., Choong, G.Y.H., Parsons, A.J., Grant, D.M. & De Focatiis, D.S.A. Mechanical response and structure evolution of degrading medical polylactides for resorbable medical implants. 16th International Conference on Deformation, Yield and Fracture of Polymers, March 29th - April 2nd, (2015), Rolduc Abbey, Kerkrade, Netherlands
- 6) Choong, G.Y.H., Parsons, A.J., Grant, D.M. & De Focatiis, D.S.A. Rheological Techniques for Determining Degradation of Polylactic Acid in Bioresorbable Medical Polymer Systems. 30th Annual Conference of the Polymer processing society, June 8-12th, (2014), Cleveland, Ohio, US
- 7) Lester, E. Hydroxyapatite material and methods of production. Patent No. WO2010122354 (2010).
- 8) Tomczynska, M.M., Choong, G.Y.H., De Focatiis, D.S.A., Grant D.M. & Parsons, A.J. Compounding and rheometry of PLA nanocomposites with coated and uncoated hydroxyapatite nanoplatelets. AIP, Proceedings of PPS2015 (in press)
- 9) Hild, F., Walton, K., Gimeno-Fabra, M., Lester, E.H. & Irvine, D.J. Continuous, Single Stage Synthesis of Dispersant Included Nanoparticles. NanoBioTech -Montreux, November 17-19th, (2014), Montreux, Switzerland.
- 10) Vermant, J., Ceccia, S., Dolgovskij, M.K., Maffettone, P.L. & MacOsco, C.W. Quantifying dispersion of layered nanocomposites via melt rheology. *J. Rheol.* 51, 429-450 (2007).
- 11) Diao, H., Si, Y., Zhu, A., Ji, L. & Shi, H. Surface modified nano-hydroxyapatite/poly(lactide acid) composite and its osteocyte compatibility. *Mat. Sci. Eng. C.* 32, 1796-1801 (2012).
- 12) Wan, Y., Wu, C., Xiong, G., Zuo, G., Jin, J., Ren, K., Zhu, Y., Wang, Z. & Luo, H. Mechanical properties and cytotoxicity of nanoplate-like hydroxyapatite/poly(lactide) nanocomposites prepared by intercalation technique. *J. Mech. Behav. Biomed. Mater.* 47, 29-37 (2015).