Low-Temperature Continuous Flow Synthesis of Metal Ammonium Phosphates

Alistair F. Holdsworth1,2, Harry Eccles1, Alice M. Halman3, Runjie Mao1 & Gary Bond1

The synthesis of the high performance inorganic materials essential to the quality of modern day life is hindered by traditionalist attitudes and reliance on outdated methods such as batch syntheses. While continuous flow methods have been extensively adopted in pharmaceutical circles, they remain largely unexplored for the preparation of inorganic compounds, despite higher efficiency, safety and versatility. In this publication, we demonstrate a step-change for the synthesis of metal ammonium phosphates through conversion of the extant batch process to a low-temperature continuous regime, exhibiting a tenfold increase in throughput combined with a significant decrease in particle size.

Although inorganic materials are essential to life in the 21st century, advancements in their preparation are underutilised as traditionalist attitudes in academia and particularly industry mean batch processes predominate. Continuous flow synthesis (CFS) is one such alternative technique: it is prevalent in pharmaceutical research1,2, yet has received lesser attention for inorganic synthesis outside of nanomaterials research3. This is largely due to the typically high capital costs associated with flow systems4; despite the technique’s inherent flexibility1,2,4, safety1-3, scalability1,3,3, and controllability1,3,7-8. Low temperature (<100 °C), ambient pressure flow syntheses presents an affordable preparative route to a plethora of inorganic materials8-15, without the high capital cost of proprietary systems4. In this communication, we demonstrate a step-change, low-cost continuous preparation of versatile metal ammonium phosphates and derivatives. We compare CFS with the commonly used batch method16 and demonstrate a tenfold increase in throughput combined with a significant reduction in particle size for continuously synthesised particles.

Metal ammonium phosphates (MAPs) and other compounds of the form AMPO4,xH2O (where A+ is Na, K, NH4 and M2+ is a divalent metal such as Mg, Fe or Zn) were first explored in detail by Bassett and Bedwell in the 1930s16. These compounds have since been investigated for a myriad of uses including catalysis17-19, pigments20, fertilisers21, energy storage22, flame retardants17 and as ion exchange materials23-28. Their preparative route, however, has changed little since the initial research16: an inefficient batch precipitation process requiring vast excesses of phosphorus reagent, and extended reaction times (>3 h) at high temperatures (>80 °C) to fully crystallise the product. Hydrothermal and solvothermal routes to MAPs and related compounds have been explored29-33, though these are often as, if not more time, resource and energy intensive than the traditional precipitation route.

Based upon a novel low temperature (<100 °C) ambient pressure continuous flow synthesis of the biomaterials brushite and hydroxyapatite8-11, we adapted the synthesis of MAPs to a continuous mode. Bassett noted that an additional source of NH4+ or performing the precipitation at an elevated pH, can serve to increase the rate of crystallisation of some MAPs16. Through a combination of these factors and the rapid mixing of a continuous flow regime, we are able to reduce the reaction time for preparation of MAPs from a typical 180 minutes down to 7 minutes. An excess of phosphate relative to the metal is required to prevent formation of the undesired M3(PO4)2 phase16,34.

We prepared six MAPs (M = Mg, Mn, Fe, Co, Ni and Zn) and one related hydrogen phosphate (M = Sn) using this technique in a variety of hydration states. Our CFS process provides two feeds: one containing the metal (M2+, 0.05 M) typically as the nitrate salt, and the other a mixture of triammonium phosphate (TAP, 0.25 M) and ammonium nitrate (AN, 0.5 M)8-11. These feeds mix continuously before heating the flow, which serves to crystallise the initially amorphous product8. For some metals (notably Fe and Co), this crystallisation results in a clear colour change. The characterisation data of our MAPs are presented in Table 1, with comparative particle sizes,

1Division of Chemistry, School of Physical Sciences and Computing, University of Central Lancashire, Preston, United Kingdom. 2Department of Engineering, University of Liverpool, Liverpool, United Kingdom. Correspondence and requests for materials should be addressed to H.E. (email: Heccles@uclan.ac.uk)
yields, and throughputs for material produced using the common batch process\(^1\). Reaction yields are expressed as a percentage of the theoretical maximum. Throughputs are expressed in grams per litre of liquor per hour, accounting for the reaction time.

MgAP forms a mixed-phase mono- and hexa-hydrate in CFS, and a monohydrate in batch (Fig. S1)\(^{19,35–37}\). MnAP, FeAP and CoAP are all prepared in the monohydrate dittmarite phase regardless of synthesis method (Figs S2–S4)\(^{19,35–37}\), forming plate-like crystallites (Fig. 1a). NiAP forms the hexahydrate (Fig. S5) struvite-like phase in flow, and the monohydrate in batch\(^{34}\). ZnAP forms an anhydrous phase regardless of synthesis method (Fig. S6)\(^{16}\), forming flower-like crystallites (Fig. 1b). SnHP forms anhydrous rod-like particles (Figs 1c and S7).

MgAP can interchange between mono- and hexahydrated phases through hydrolysis and dehydration respectively\(^{35,38}\), though our continuous flow process forms a mix of the two phases, though a longer or hotter reaction time fully dehydrates the product. NH\(_3\) was added to the Mg\(^ {2+}\) feed to precipitate the desired product\(^8\).

| M    | XRD Phase | Yield (%)  | Particle Size (CFS, µm) | Particle Size (Bx, µm) | Throughput (CFS) | BET (CFS) |
|------|-----------|------------|-------------------------|------------------------|-----------------|-----------|
| MgAP | Mon/Hex   | 94         | 2.5, 13.6               | 44.3                   | 14.6            | 6.6       |
| MnAP | Mon       | 99         | 6.4, 22.8               | 65.1                   | 7.4             | 8.4       |
| FeAP | Mon       | 99         | 2.9, 9.5               | 23.9                   | 15.4            | 8.4       |
| CoAP | Mon       | 97         | 4.9, 23.5               | 51.3                   | 15.8            | 8.4       |
| NiAP | Hex       | 83         | 1.3, 7.7               | 26.6                   | 2.6             | 7.1       |
| ZnAP | Anhyd     | 98         | 2.0, 9.7               | 20.9                   | 6.3             | 7.9       |
| SnHP | Anhyd     | 79         | 2.7, 6.5               | 22.8                   | 2.3             | 7.5       |

Table 1. Characterisation data for MAPs: reaction yield (%), particle size for flow (CFS) and batch (Bx) produced material as 10\(^{th}\), 50\(^{th}\) and 90\(^{th}\) percentiles (D\(_{10}\), D\(_{50}\) and D\(_{90}\), µm), BET surface are (m\(^2\)/g) and observed XRD crystal hydration phase. MgAP (\*) required the addition NH\(_3\) to the Mg\(^ {2+}\) feed in flow to precipitate the desired product\(^8\).

Figure 1. SEM images of FeAP platelets, ZnAP flowers and SnHP rods.
thinner (Fig. 1a) than those of the similarly plate-like MnAP and CoAP. Throughputs for the CFS process are at least five times that of the batch process, and up to sixteen times for ZnAP due to the lengthy reaction times required in batch16.

The efficiency of the CFS process can be further improved by the feasible regeneration of the effluent liquor. Concentration, replacement of precipitated phosphate and addition of the required NH3 allows for use in further syntheses. Recovery of process heat by pre-heating precursor streams would further increase efficiency. Changing reagent stoichiometry, overall concentrations, and process parameters such as temperature, flow rate and mixing regime would allow for control of particle sizes produced within the CFR45. Use of specialist mixers such as confined impinging jet mixers may also allow for preparation of MAPs on the nanoscale due to more turbulent mixing during the precipitation step45. The flows within our demonstrated system are all laminar.

Conclusions
We have developed an efficient continuous flow synthesis of metal ammonium phosphates and compared this to traditional batch methods. We have demonstrated a step change in the preparation of these compounds as synthesised particles are smaller, more evenly sized and produced with far greater efficiency than previous syntheses. In comparison to the traditional batch methods, we observe up to a tenfold increase in throughput (in terms of mass per unit volume per unit time) with our flow process. This value can be increased further with process optimisation. For many applications, smaller particles are preferable as higher surface areas provide higher activities. Continuous flow synthesis provides this benefit with the option of greater control over particle size and morphology. Through the application of appropriate engineering and chemistry, the syntheses of other key inorganic materials could be improved in a similar manner as demonstrated here.

Experimental
Mg(NO3)2, Mn(NO3)2, (NH4)2Fe(SO4)2, Co(NO3)2, Ni(NO3)2, Zn(NO3)2, SnCl2, NH4NO3, H3PO4, NH4OH, and (NH4)2HPO4 were obtained from Fisher Scientific as reagent grade (>98%) quality and used as acquired with no further purification. (NH4)3PO4 was prepared in situ by the addition of excess ammonia to a concentrated solution of (NH4)2HPO4 and gently heating the resultant mixture to 65 °C so as to remove the excess ammonia. The solution was then cooled and diluted to the required concentration. Deionised water (>18 MΩ/cm) was used for all syntheses.

Our continuous flow reactor (CFR) was constructed based on previous literature references8–11. Simply, this consists of two peristaltic pumps (Watson Marlow SciQ 323), a simple Y-mixer and a coil of PVC tubing (16 m length, 4 mm internal diameter, wall thickness 1 mm, total volume 210 cm3) contained within a thermostatically-controlled water bath (Grant JB Aqua 18 Plus). This is illustrated in Fig. 2.

The rotational rate and thus flow rate of each pump can be varied from 5–40 ml/min, corresponding to a total flow rate of 10 to 80 ml/min and thus a residence time of between 3 and 20 minutes, though a total flow rate of 30 ml/min and thus a residence time of 7 minutes was used in this work. Both pumps were run at the same flow rate in all cases, with one providing the metal salt feed, and the other the phosphorus source and any ancillary reagents. The temperature of the water bath could be varied between ambient and 100 °C. All reactions presented here were performed at 80 °C. A narrow aperture (c.a. 1 mm) at the outlet of the CFR served to even the flow within the system, and check valves after each pump ensured a continuous unidirectional flow. Products were purified by repeated washing with deionised water, and were then dried overnight at 80°C. The batch syntheses of MAPs were adapted from the work of Bassett and Bedwell16, using the same procedure but scaled to give the same volume of product as in our flow process.

The rate of heating within the process is rapid, as a total flow rate of greater than 120 ml/min emerges from the reactor at 80 °C with the same tubing setup utilised for these syntheses, suggesting that temperature equilibrium is attained within 2 minutes and thus 5 minutes are spent at temperature to allow completion of reaction. Further modelling of this factor is beyond the scope of the research presented here.

Powder X-Ray Diffraction (PXRD) analysis was conducted using a Brucker D2 Diffractometer with a copper kα radiation source with data collected between 5 and 80 degrees 2θ. XRD patterns were converted from

![Figure 2. Schematic of CFR.](image-url)
proprietary formats using PowDLL. Scanning Electron Microscopy (SEM) and X-Ray Energy Dispersive elemental analysis was conducted under high vacuum using a FEI Quanta 200 scanning electron microscope equipped with an EDAX Sapphire Energy Dispersive X-Ray detector. Surface areas were determined using the BET (Brunauer–Emmett–Teller) model at 77 K using nitrogen adsorption (Micrometrical ASAP2010), with accuracy checked against an alumina standard. Particle size distribution analysis (PSD) was conducted using a Malvern Mastersizer 2000. Samples were sonicated in deionised water before analysis to disperse any agglomerates. Results are expressed as D50, the 50th percentile of particle size.

Data Availability Statement
The data underpinning this publication can be found on https://clok.uclan.ac.uk/.

References
1. Hartman, R. L., McMillen, J. P. & Jensen, K. F. Deciding whether to go with the flow: evaluating the merits of flow reactors for synthesis. Angew. Chem. Int. Ed. Engl. 50, 7502–7519 (2011).
2. Anwar, A., Rehman, I. U. & Darr, J. A. Low-Temperature Synthesis and Surface Modification of High Surface Area Calcium Hydroxyapatite Nanors Incorporating Organofunctionalised Surfaces. J. Phys. Chem. C 120, 26069–26076 (2016).
3. Dutt, M. Continuous microwave flow synthesis of mesoporous hydroxyapatite. Mater. Sci. Eng. C 56, 356–362 (2015).
4. Akram, M. et al. Instant nano-hydroxyapatite: a continuous and rapid hydrothermal synthesis. Chem. Commun. 21, 2286–2288 (2006).
5. Ayyappan, S. et al. Aerosol assisted chemical vapour deposition of hydroxyapatite-embedded titanium dioxide composite thin films. J. Photochem. Photobiol. A: Chem. 332, 45–53 (2017).
6. Akram, M., Saleh, A. T., Ibrahim, W. A. W., Awan, A. S. & Hussain, R. Continuous microwave flow synthesis (CMFS) of nano-sized tin oxide: Effect of precursor concentration. Ceram. Int. 42, 8613–8619 (2016).
7. Chaudhry, A. et al. Instant nano-hydroxyapatite: a continuous and rapid hydrothermal synthesis. Chem. Commun. 21, 2286–2288 (2006).
8. Johnson, I. D. et al. High power Nb-doped LiFePO4 Li-ion battery cathodes; pilot scale synthesis and electrochemical properties. J. Pow. Sourc. 302, 410–418 (2016).
9. Marre, S., Adamo, A., Basak, S., Aymonier, C. & Jensen, K. F. Design and Packaging of Microreactors for High Pressure and High Temperature Applications. Ind. Eng. Chem. Res. 49, 11310–11320 (2010).
10. Akram, M. et al. Instant nano-hydroxyapatite: a continuous and rapid hydrothermal synthesis. Chem. Commun. 21, 2286–2288 (2006).
11. Anwar, A., Rehman, I. U. & Darr, J. A. Low-Temperature Synthesis and Surface Modification of High Surface Area Calcium Hydroxyapatite Nanors Incorporating Organofunctionalised Surfaces. J. Phys. Chem. C 120, 26069–26076 (2016).
12. Akram, M., Saleh, A. T., Ibrahim, W. A. W., Awan, A. S. & Hussain, R. Continuous microwave flow synthesis (CMFS) of nano-sized tin oxide: Effect of precursor concentration. Ceram. Int. 42, 8613–8619 (2016).
13. Akram, M. et al. Continuous microwave flow synthesis of mesoporous hydroxyapatite. Mater. Sci. Eng. C 56, 356–362 (2015).
14. Akram, M. et al. Continuous microwave flow synthesis (CMFS) of nanosized titania: Structural, optical and photocatalytic properties. Mater. Lett. 158, 95–98 (2015).
15. Akram, M. et al. Continuous microwave flow synthesis and characterisation of nanosized tin oxide. Mater. Lett. 160, 146–149 (2015).
16. Anwar, A., Akbar, S., Sadiga, S. & Kazmi, M. Novel continuous flow synthesis, characterisation and antibacterial studies of nanoscale zinc substituted hydroxyapatite bioceramics. Inorg. Chim. Acta 453, 16–22 (2016).
17. Ayyappan, S. et al. Synthesis characterisation and acid-base catalytic properties of ammonium-containing tin(II) phosphates: [NH4][Sn3P6O17] and [NH4][SnPO3]2. J. Inorg. Mater. 2, 21–27 (2000).
18. Bogdanova, V. V. & Kobets, O. I. Synthesis and physicochemical properties of D- and trivalent metal-ammonium phosphates. Russian J. Appl. Chem. 87(10), 1387–1401 (2014).
19. Ayyappan, S. et al. Synthesis and structure of NH4CoPO4.6H2O. Ann. Chim. Sci. Mat. 26(3), 49–51 (2001).
20. Galkova, T. N., Pacewksa, B., Samuskevich, V. V., Pisyak, J. & Shulga, N. V. Thermal transformations of CuNH4PO4.H2O. J. Therm. Anal. Calorim. 60, 1019–1032 (2000).
21. Koleva, V., Stoyanova, R., Zhecheva, E. & Nhtianova, D. Dittmarite precursors for structure and morphology directed synthesis of lithium manganese phosphonate-olivine nanostructures. CrystEngComm 16, 7515–7524 (2014).
22. Castro, F. et al. Continuous Flow-Precipitation of Hydroxyapatite at 37 °C in a Meso Oscillatory Flow Reactor. Ind. Eng. Chem. Res. 52, 9816–9821 (2013).
23. Castro, F. et al. Continuous-flow precipitation as a route to prepare highly controlled nano-hydroxyapatite: in vitro mineralisation and biological evaluation. Mater. Res. Expr. 3, 075404 (2016).
24. Diky, N. P. et al. Sorption properties of magnesium-potassium phosphate matrix. Probs. Atom. Sci. Tech. 3(97), 79–82 (2015).
25. Borai, E. H., Attallah, M. F., Shehata, F. A., Hilal, M. A. & Abo-Aly, M. M. IAEA report: EG0800311. (2014).
26. Campayo, L. PhD Thesis (University of Limoges, 2003).
27. Borovikova, E. Y. et al. Relationship between IR spectra and crystal structures of b-tridymit-like CaM2+PO4 compounds. Eur. J. Miner. 24, 777–782 (2012).
28. Korchmjen, I. V. et al. Thermodynamic properties of caesium-manganese phosphate CaMnPO4. J. Chem. Thermodyn. 78, 114–119 (2014).
29. Boudin, S. & Li, K.-H. Ammonium Iron(II,III) Phosphate: Hydrothermal Synthesis and Characterisation of NH4Fe2(PO4)3. Inorg. Chem. 37(4), 799–803 (1998).
30. Satyavani, T. V. S. L., Kumar, A. S. & Rao, P. S. V. S. Methods of synthesis and performance improvement of lithium iron phosphate for high rate Li-ion batteries: A review. Adv. Eng. Sci. Tech. Int. J. 19(1), 178–186 (2014).
31. Kirkkiukhina, G. V., Yakubovich, O. V. & Dimitrova, O. V. Crystal structure of a new polymorphic modification of niahite, NH4MnPO4.H2O. Crystallog. Rep. 60(2), 198–203 (2015).
32. Chen, C. et al. Polypyrrole-Modified NH4NiPO4.H2O Nanoplate Arrays on Ni Foam for Efficient Electrode in Electrochemical Capacitors. ACS Sus. Chem. Eng. 4(10), 5579–5584 (2016).
33. Wang, S. et al. NH4CO3.H2O micromodules consisting of one-dimensional layered microrods for high performance supercapacitors. RSC Adv. 4, 340–347 (2014).
34. Gomi, A. et al. Synthesis, crystal structure and spectroscopic properties of the NH4NiPO4.nH2O (n = 1, 6) compounds; magnetic behaviour of the monohydrated phase. J. Mater. Chem. 6(3), 421–427 (1996).
35. Frost, R. L., Weier, M. L. & Erickson, K. L. Thermal decomposition of struvite. J. Therm. Anal. Calorim. 76(3), 1025–1033 (2004).
36. Greedan, J. E., Reubnabauer, J., Birchall, T. & Ehlert, M. A magnetic and Mossbauer study of the layered compound (NH4)Fe(PO4). J. Solid State Chem. 77, 376–388 (1988).
37. Carling, S. G., Day, P. & Visser, D. Crystal and Magnetic Structures of Layer Transition Metal Phosphate Hydrates. Inorg. Chem. 34, 3917–3927 (1995).
38. Sarkar, A. K. Hydration/dehydration characteristics of struvite and dittmarite pertaining to magnesium ammonium phosphate cement systems. J. Mater. Sci. 26, 2514–2518 (1991).
39. Monma, H. & Kamiya, T. Preparation of hydroxyapatite by the hydrolysis of brushite. J. Mater. Sci. 22, 4247–4250 (1987).
40. US. Pat. 3201195 (Aug 1965).
41. Van Bommel, A. & Dahm, J. R. Analysis of the Growth Mechanism of Coprecipitated Spherical and Dense Nickel, Manganese and Cobalt-Containing Hydroxides in the Presence of Aqueous Ammonia. Chem. Mater. 21, 1500–1503 (2009).
42. Clungston, M. & Flemming, R. Advanced Chemistry. (Oxford University Press, Oxford, UK, 2000).
43. Salhi, R., Boudjouada, M., Messikh, S. & Gherraf, N. Recovery of nickel and copper from metal finishing hydroxide sludge by kinetic acid leaching. J. New Tech. Mater. 6(2), 62–81 (2016).
44. LaMer, V. K. & Dinegar, R. H. Theory, Production and Mechanism of Formation of Monodispersed Hydrosols. J. Am. Chem. Soc. 72(11), 4847–4854 (1950).
45. Pieper, M., Aman, S., Hintz, W. & Tomas, J. Optimization of a Continuous Precipitation Process to Produce Nanoscale BaSO₄. Chem. Eng. Tech. 34(9), 1567–1574 (2011).
46. Kourkoulis, N. ICDD Annual Spring Meetings, Ed. O’Neill, L. Powder Diffraction, 28, 137–148 (2013).

Acknowledgements
We wish to thank Mrs T. Garcia-Sorribes, Mr J. C. Donnelly and Mr P. Bentley for technical assistance and Prof K. K. Singh and her group for provision of analytical equipment. This work was funded as part of the EPSRC project “Advanced Waste Treatment using Nanostructured Hybrid Composites” EP/M026485/1.

Author Contributions
Principal Investigator of this research was G. Bond, the manuscript was co-written by H. Eccles and A. Holdsworth. Experiments were carried out by A. Holdsworth, with BET experiments carried out by A. Halman. Results were analysed and interpreted by A. Holdsworth and R. Mao.

Additional Information
Supplementary information accompanies this paper at https://doi.org/10.1038/s41598-018-31694-x.

Competing Interests: The authors declare no competing interests.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2018