

Synthesis and Characterization of Different Chain Length Sodium Polyphosphates

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Introduction:

Our group has recently focused on a novel injectable in-situ forming system, based on polyphosphates, with the potential to deliver and release drugs locally in procedures such as trans-arterial chemoembolization (TACE). In TACE, a biomaterial is administered directly into blood vessels feeding a tumor thereby blocking its nutrient supply and also releasing chemotherapeutics locally. This in-situ forming system is comprised of sodium polyphosphate (NaPP) and calcium chloride solutions which, on contact, form a coacervate or a gel-like material. NaPP chain length is an important factor determining the physical and biological properties of this in-situ forming system; therefore, preparing different chain length polyphosphates has been a major part of our research. In this abstract, our results on synthesis and characterization of NaPP with the average degree of polymerization (D_p) from 50 up to 25,000 are reported.

Materials and Methods:

To prepare NaPP with $D_p < 500$, $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ was melted at 700°C for 1 hr followed by quenching on a copper plate. NaPP was dissolved in water and fractioned by serial addition of acetone. After each acetone addition, the precipitate was collected and freeze-dried resulting in narrowly size distributed NaPP with $D_p < 500$. In contrast, to prepare NaPP with $D_p > 500$, KH_2PO_4 was kept at 775°C for either 2 or 50 hr to yield a water insoluble crystalline phase, potassium Kurrol salt consisting of very long chain polyphosphates. Water soluble NaPP was obtained from Kurrol salt by an ion exchange process in which potassium cations were replaced by sodium cations. The Kurrol salt/resin weight ratio, mixing time and concentration of the Kurrol salt in the slurry were varied in order to determine the optimum conditions in which a maximum amount of potassium is replaced by sodium without wasting too much resin. Using atomic absorption spectroscopy (AAS), titration and ICP, the efficiency of the ion exchange process was evaluated by measuring the remaining potassium to phosphorus mole ratio in the NaPPs that were obtained through the ion exchange process. The amount of residual water in all NaPP samples after lyophilization was determined by DSC/TGA analysis. The D_p of prepared NaPPs was determined by liquid ^{31}P NMR, titration and viscosity measurements. Both NMR and titration give number average D_p and the number average molecular weight (M_n) is equal to $102 \times D_p$. In NMR, respectively, the peaks around 0, -9, -21, -23 and -35 ppm represent the Q^0 (Orthophosphates), Q^1 (End of chain phosphorus atoms), Q^2 (Middle of chain phosphorus atoms in polyphosphates), Meta- Q^2 (Middle of chain phosphorus atoms in rings) and Q^3 (Branched phosphorus atoms). The ratio of the areas under Q^2 and Q^1 peaks is used to determine the D_p . In titration, the volume of NaOH used within pH range of 4.5 to 9 is a direct measure of number of phosphate groups at the end of the chains and it is used to determine the D_p . In contrast, viscosity measurements give the weight average molecular weight (M_w) based on the Mark-Howink equation.

Results:

Figure 1(a) shows the NMR spectra of NaPPs that were obtained by fractionation of a NaPP glass with D_p of 197. As the chains get longer the Q^1 peak becomes smaller while the Q^2 peak becomes larger. Figure 1(a)-inset shows the titration of the same fractioned NaPPs. The required volume of NaOH increases as the chains become shorter. The M_n results correlate perfectly in NMR and titration studies. However, as the chains get longer the accuracy and precision of these methods

decrease. In fact, these two methods were not capable of determining the D_p of long chain NaPPs that were prepared by the ion exchange process. For instance Figure 1(a) shows the NMR spectrum of an ion-exchanged NaPP indicating no Q^1 peak even after 2300 scans, and therefore making D_p determination not feasible. Viscosity measurements confirm that these NaPP are extremely long having M_w up to $\sim 2,500,000$ g/mol.

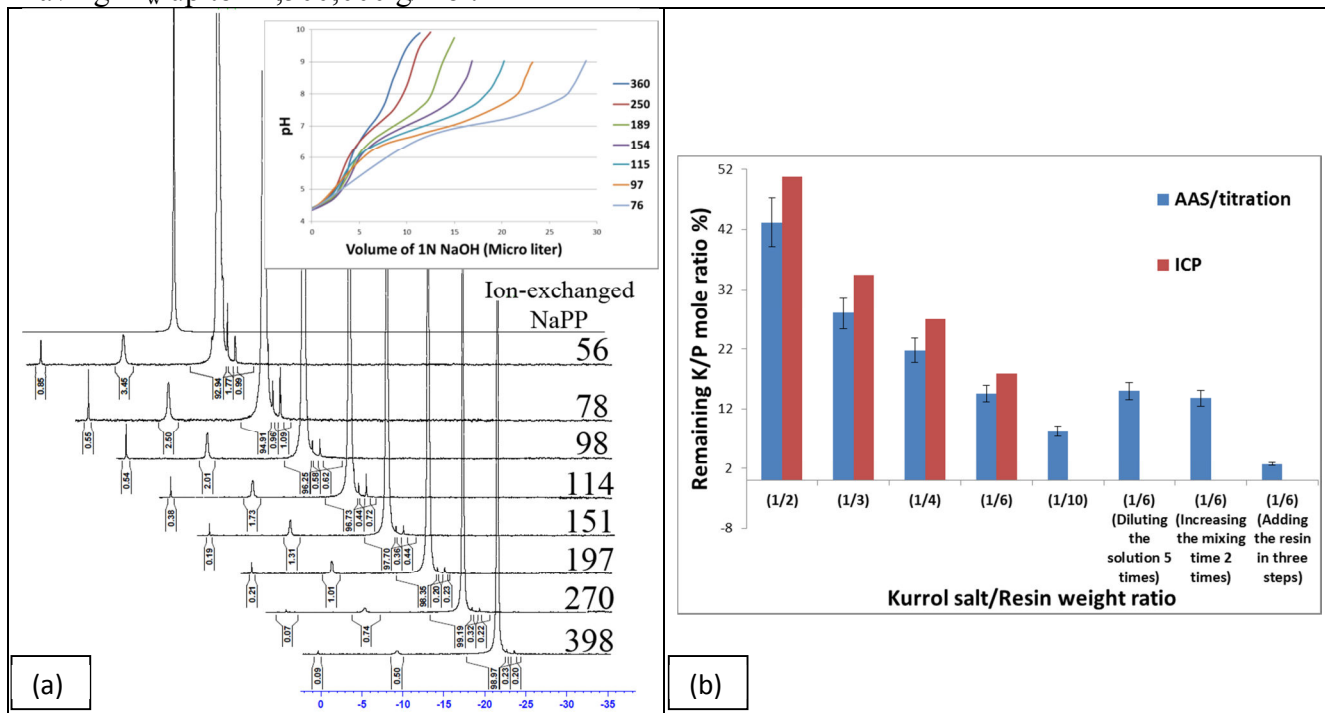


Figure 1: (a) ^{31}P NMR spectra and titration graphs (inset) of different chain length NaPPs (Numbers show D_p), (b) Dependence of the K/P ratio of NaPPs that were prepared by the ion exchange process on the experimental conditions.

Furnace time affects the chain length of NaPPs that were prepared by the ion exchange process. In fact, the intermediate chain length ($D_p=7,017\pm 1,495$ ($n=5$)) could be obtained by keeping the KH_2PO_4 for 2hr at 775°C , while longer chains ($D_p=19,454\pm 2,234$ ($n=3$)) require a 50hr furnace time. Figure 1(b) shows the effect of experimental conditions on the amount of potassium that remains in the NaPPs prepared by the ion exchange process. Increasing the resin to Kurrol salt weight ratio decreases the amount of potassium impurity in NaPPs. Increasing the mixing time or diluting the slurry during the ion exchange process has negligible effect on the ability of resin to remove potassium. In contrast, using the same amount of resin (1/6 Kurrol salt/resin weight ratio) but adding it in 3 steps (1/3+1.5+1.5) instead of one step decreases the K/P to a ratio lower than 5%. DSC/TGA analysis of fractionated NaPPs showed that they contain 10-12% (wt.%) molecular water after 24hr freeze-drying. Similarly NaPPs that were prepared by the ion exchange process also contain 6-9% (wt.%) molecular water after 72hr freeze-drying.

Discussion:

NaPPs with chain lengths shorter than 500 phosphorus per chain were produced successfully and reproducibly by fractionation of NaPP glass that was prepared from $\text{NaH}_2\text{PO}_4\cdot\text{H}_2\text{O}$. NaPPs with chain lengths longer than 500 phosphorus per chain were produced successfully by ion exchange of Kurrol salt that was prepared from KH_2PO_4 . The amount of remaining potassium in ion-exchanged NaPPs was reduced to K/P mole ratios lower than 5%. NaPP with its ability to gel in presence of multivalent cations (e.g. calcium) is a promising inorganic polymer for bio-applications drawing future investigations. We have already seen in our studies on in-situ forming calcium polyphosphate system that NaPP chain length affects the viscoelastic properties of the resulting gel significantly.