BonyPid™: A lipid-and-polymer-based novel local drug delivery system Physicochemical aspects and therapy

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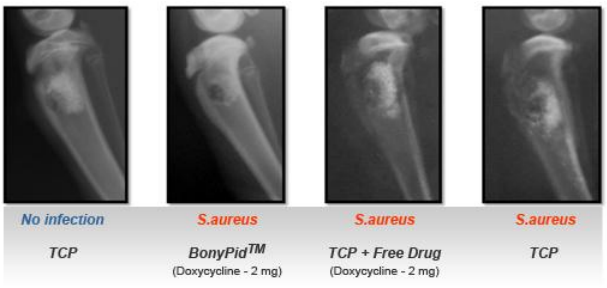
Bacterial infection of bone may result in bone destruction which is difficult to cure due to poor accessibility to bone of systemically-administrated antibiotic and poor performance of currently available local antibacterial treatments. PolyPid Ltd developed a novel local drug delivery system based on self-assembly of pharmaceutically approved lipids and polymers that encapsulate doxycycline (Doxy). The formulation is self-assembled lipid matrix via the interaction of the lipids (cholesterol and synthetic phospholipids) and biocompatible - biodegradable polymer (poly-lactic-co-glycolic). The entrapped Doxy is located within the anhydrous environment and therefore fully protected from long-term water-exposure-related degradation. The fine coating of the tricalcium phosphate (TCP) bone filler by this Doxy-containing formulation (BonyPid™) is capable of releasing intact and active drug at zero-order kinetics for a predetermined period of up to 30 days.

The coating of the TCP granules with the polymer-lipids-Doxy formula (BonyPid™) did not change the granules' macroscopic shape, but altered its color from white to pale yellow, which resemble the color of the entrapped Doxy. The average sizes of the non-coated TCP granules and the coated granules BonyPid™ were similar, as determined by measuring the widest dimension of each granule (1135±241 μm and 1072±242 μm, respectively, P=0.16). The MIC for Doxy that was released from BonyPid™ at different time points was similar to the non-encapsulated Doxy, suggesting full bioavailability of the released drug. BonyPid™ formulation structure was characterized by different physical methods including X-ray diffraction, differential scanning calorimetric (DSC), SEM. The wide angle X-ray analyses (WAXS) of BonyPid™ samples show a strong signal in the range of 1.3-1.8 $2\Theta^{o}$, suggesting that the polymer and lipid TCP coating is a highly organized substructure.

The principle lipid in BonyPid™ formulation is phosphatidylcholine, which constitutes more than 85% of the overall lipid mass. It was found that the length of the acyl chains (14, 16 and 18 carbons, respectively) can significantly alter the release rate of Doxy during the prolonged (30 days), zero-order release phase, a, but did not alter the release profile.

The anti-infection activity of BonyPid™ was tested in the rabbit tibia model contaminated with $5x10^5$ *S. aureu.* Both acute and chronic infection models were tested. Only BonyPid™ treatment demonstrated a statistically significant reduced bone absorption over the infected group ($P<0.04$ for day 7, 14 and 21) and significantly lower bacterial bone concentration ($p>0.05$) on day 21 following the bone grafting and the bacterial inoculation. In addition it was found that the antibiotic courting of the bone-filler in BonyPid did not reduce bone hilling as compared to free bone-filler.



Therefore a clinical evaluation is proposed for testing the efficacy and toxicity of B BonyPid™ for therapy of both acute and chronic bacterial bone infections.