Absorbable Synthetic Bone Wax for the Localized Delivery of Therapeutic Agents

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Statement of Purpose: Sternal wound infection (SWI) is a common complication following cardiothoracic surgery and poses a high risk of morbidity and mortality. Mediastinitis is reported to occur in up to 5% of patients following cardiac surgery[1], and approximately 15% of patients are readmitted for a recurrent sternal wound infection[2]. Infections are often the result of staphylococcal bacteria, and unfortunately, treatment of SWI involves an invasive procedure of surgical debridement[3]. A number of risk factors have been identified for SWI[1]; however, the only modifiable factors include the use of bone wax and the use of bilateral mammary arteries in diabetic patients. The use of bone wax in thoracic surgery can be employed as an aid in prophylactic treatment in addition to the conventional role of bone wax as a hemostatic agent to plug the bleeding sternum. By incorporating antibiotics such as rifampin, which has been shown to improve outcomes against staphylococcal SWI[4], bone wax can be engineered as a prophylactic material for use in cardiothoracic surgery. Poly-Med has developed a bioresorbable prophylactic bone wax formulation from a polyaxial copolymer of poly[(*p*-dioxanone-co-trimethylene carbonate) containing the prophylactic drugs rifampin and minocycline HCl (to broaden antibiotic coverage).

Methods: Bone wax formulations were prepared by cold-worked and hot-worked methods. Cold-worked (CW) formulations were prepared by adding 1.0 gram of polymer to a glass vial that was sealed and heated at 100°C for 30 minutes to completely melt the sample. Hot vials were quench-cooled to delay crystallization of the polymer. Vials were equilibrated at room temperature for 30 minutes, then 50 mg of rifampin and 50 mg of minocycline HCl were added to each vial and mixed thoroughly to create a homogeneous blend. Hot-worked (HW) formulations were prepared by weighing polymer and drug and adding to the same vial at room temperature. Vials were heated at 100°C for 30 minutes, then removed and mixed to create homogeneous formulations. Upon mixing, all polymer-drug formulations were stored immediately in a room temperature vacuum oven (vacuum > 28 in. H_20) for at least 24 hours. Rifampin and minocycline HCl were extracted from bone wax formulations using acetonitrile and analyzed by HPLC to determine drug stability. A standard solution of rifampin and minocycline HCl was analyzed by HPLC and used to create a photodiode array (PDA) spectra match library. Drug stability was determined by comparison of rifampin and minocycline HCL PDA spectra from the match library to the PDA spectra at appropriate retention times from exploratory extract samples. When analyzing PDA results, a match angle value below the match threshold value indicated that the exploratory PDA was statistically analogous to the match library PDA for the particular drug in question, resulting in positive molecular identification.

Results: According to HPLC PDA analysis, extracts from cold-worked formulations contained stable rifampin and minocycline HCl at T=0 and T=7 days, whereas extracts from hot-worked formulations at T=0 contained stable minocycline HCl and degraded rifampin. The major degradation product was rifampin-quinone, which readily forms as the major oxidation product of rifampin.

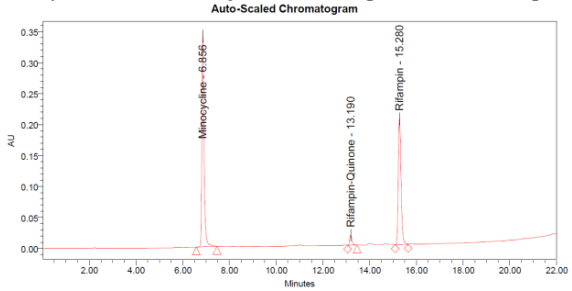

Figure 1. HPLC analysis of rifampin and minocycline HCl standards.

Table I. PDA results from HPLC analysis of rifampin control and rifampin extracts from hot-worked (HW) and cold-worked (CW) samples.

Sample	Retention Time (min)	Match Angle	Match Threshold
Rifampin Control	15.280	0.095	1.206
HW, T=0	15.201	7.175	1.202
CW, T=7	15.306	0.154	1.201

Table II. PDA results from HPLC analysis of minocycline HCl control drug sample and minocycline HCl extracts from hot-worked (HW) and cold-worked (CW) samples.

Sample	Retention Time (min)	Match Angle	Match Threshold
Minocycline HCl Control	6.856	0.027	1.138
HW, T=0	6.790	0.295	1.206
CW, T=7	6.855	0.201	1.136

Conclusions: Of the two methods investigated for the preparation of bone wax-drug formulations, only cold-working resulted in a completely stable bone wax-drug formulation over 7 days. This novel material shows great promise, not only as a bioresorbable substitute for commercially available bone wax, but also as a vehicle to release prophylactic agents for the prevention of SWI. Future studies will investigate the drug stability for cold-worked formulations over an extended time frame.

References:

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