Effect of Drug Structure on Release from Absorbable Electrospun Fibers

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Introduction—In the last several years, interest in electrospinning technology has increased due to needs in tissue engineering and other pharmaceutical applications where traditional materials do not have the desired properties[1,2]. Poly-Med's interest in novel, proprietary absorbable polymers having unique properties has prompted a program that includes the study of drug release of low molecular weight drugs (molecular weight less than 240Da) of specific clinical significance from typical electrospun fabric produced through basic electrospinning procedures. This study is designed to determine the effect on release profile due to differences in chemical structure as reflected in the types of functional groups which, in turn, affect solubility and charge. More specifically, this segment of the study deals with (1) incorporation of an acidic, basic and neutral drug into absorbable elastoplastic electrospun fibers, and (2) *in vitro* release of the different drugs in a buffered solution.

Materials and Methods—A crystalline, absorbable, segmented copolyester, made as described earlier by end-grafting *l*-lactide onto an amorphous polyaxial polymeric initiator, was used as a polyaxial elastoplastic copolyester (P-6)[3,4]. Acetaminophen (Sigma Aldrich) was used as a neutral drug with slight solubility in water. Naproxen (Sigma Aldrich) was used as an acidic drug with practically no solubility in water. Proxyphylline (Sigma Aldrich) was used as a basic drug with solubility in water of 1g/mL. Solutions were prepared with 16.7% w/v in 1:1 dichloromethane:chloroform with drug added to the solution at 3% w/w of polymer. The materials were electrospun with a voltage differential of 20kV and a Tip-to-Collector distance (distance between the extruder and collector unit) of between 11 and 13 inches at a rate of 0.2mL/min, using an electrostatic spinning unit constructed in house. Electrospun microfiber constructs with a thickness of 1mm were prepared and characterized for identity (FTIR), thermal properties (DSC), molecular weight (GPC and viscometry), and morphology (SEM). A summary of the effect of drug inclusion is presented in Table I. Drug release was performed in duplicate in 7.2pH 100mM phosphate buffer at 37˚C and analyzed by HPLC (Waters system with C_{18} columns); averaged values of this data can be seen in Table II and Figure I.

Results and Discussion—Addition of drug into the spinning solution did not seem to affect the electrospinning process or melting temperature (T_m) of the resultant fabric, but the solubility of drugs into spinning solution led to changes in the polymer heat of fusion. Naproxen was the most soluble in the spinning solution, with proxyphylline less soluble and acetaminophen practically insoluble in the spinning solution. The dissolution of the drugs provided nucleation sites in the P-6 continuous phase, which led to increased polymer crystallization.

The basic drug, proxyphylline, showed the fastest initial burst, while taking 2 hours to fully release. Acetaminophen displayed the next fastest release and practically reached the release endpoint at 4 hours. Initially, naproxen release was done over a longer period of time with the first time point taken at 22 hours. This period was found to be too long and another study is being done with shorter time points. The early release of naproxen, however, is expected to be slower than the other two drugs. Available results suggest that solubility is the primary determinant of the drug release from the microfibers, within the molecular weight range used.

Table I. Effect of Drug Inclusion on Thermal Properties of P-6 Electrospun Fabric

Drug	DSC[a]		
	T_m, ˚C	ΔH_f, J/g	W_{hh}, ˚C
No Drug	151	8.2	15.4
Naproxen	151	10.2	15.4
Acetaminophen	150	7.9	14.8
Proxyphylline	150	8.9	14.2

[a]At 20°C/min heating rate; W_{HH} is the width of the endotherm at half of its height.

Table II. Description of Various Drugs and Maximum Release Period from Electrospun Fabrics

Drug	M. W.	Key Groups	Solubility in Water	Maximum Release Period
Naproxen	230	Carboxyl	Practically Insoluble	22 hours
Acetaminophen	238	Amide	Slightly Soluble	4 hours
Proxyphylline	151	Amine	Very Soluble	2 hours

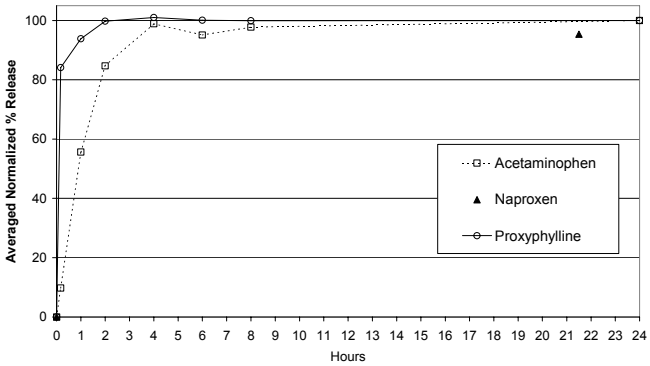

Figure I. Release Profile of Drugs from Electrospun Fabrics in 7.2pH 100mM Phosphate Buffer at 37˚C

Conclusion—Incorporation of less than 5 weight percent low molecular weight drugs with different functional groups does not change the electrospinning parameters. Solubility is the basic determining factor in the release profile of drug from electrospun fabrics.

References

1. Kenaway, E.R. et al., *J. Contr. Release*, 81, 57 (2002).
2. Boland, E.D. et al., *J. Macromol. Sci.*, 38, 1231 (2002).
3. Shalaby, S.W., U.S. Patent No. 6,462,169 (2002).
4. Carpenter, K.A. et al., *Trans Soc. Biomater*, 26, 328 (2003).