Controlling multiphasic, multi-drug release kinetics from single delivery matrix

Kyle Kleinbeck[1], Ashley Stajkowski[1], and Weiyuan John Kao, Ph.D.[1,2]
[1]School of Pharmacy, University of Wisconsin-Madison, Wisconsin.
[2]Department of Biomedical Engineering, College of Engineering, University of Wisconsin-Madison, Wisconsin

Statement of Purpose: Photopolymerized interpenetrating networks (IPNs) made of modified gelatin and poly(ethylene glycol) (PEG) have shown improved efficacy in the treatment of full-thickness wounds. IPN properties have been modified in a variety of ways in attempts to idealize drug delivery and cellular response toward the goal of faster, quality wound healing. The purpose of this study is to observe the release kinetics of representative drugs (low molecular weight dye molecules) loaded in the IPN via 2 different loading modalities, and apply their kinetic trends to control the release of clinically relevant wound care drugs. Drug release goals consist of fitting at least two different drugs to their therapeutic dosing regimen within the same biomaterial platform.

Methods: Two model compounds, Azure A (AZA) and 7-amino-4-methylcoumarin (AMC) were PEGylated and tethered onto a gelatin backbone according to protocols established by Stevens et al. Unmodified or modified gelatins were dissolved in water then mixed with PEG diacrylate and 2,2-dimethoxy-2-phenylacetophenone. Molecules were also loaded as soluble compounds in the IPN. Bupivacaine hydrochloride (BupHCl) and silver sulfadiazine (AgSD) were solubilized into the IPN and release was measured via UV/Vis spectroscopy.

Results/Discussion: Figures 1 and 2 show the release of solubilized and/or conjugated dye molecules. Releases were observed with a focus on loading modality and the presence of an accompanying molecule. AMC generally exhibited greater release than AZA with respect to total release and release rate. Also, independently loaded, conjugated molecules showed greater release than solubilized molecules. Release of these molecules proved to be influenced more by physical and chemical properties of the molecule than by loading modality.

The above knowledge of release is currently being applied to the release of clinically relevant drugs, BupHCl and AgSD. BupHCl should be delivered to the wound, in soluble form, at 950 µg/hr for as long as possible up to one week, while AgSD should be delivered to the wound 735 µg/hr, with Ag ionized or complexed with SD, for up to 4 days. Preliminary release of solubilized 1% BupHCl and AgSD was scant. Less than 1% of the total loaded drug was released from the IPNs. Table 1 shows that 10% BupHCl IPNs with no AgSD did not significantly increase release with 10% gelatin.

Understanding the reasons for limited release will involve further investigation into the relationship between structure and function of the IPN-drug interface. Current and future work focuses on drug interactions with gelatin, gelatin conformation, pH of the IPN solution, PEGdA molecular weight, and loading modality. If the component limiting drug release can be controlled, then the therapeutic indexes will be targeted with changes in dose loading.

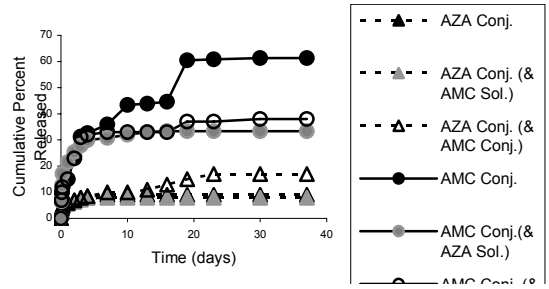

Figure 1. Release kinetics of conjugated AMC and AZA.

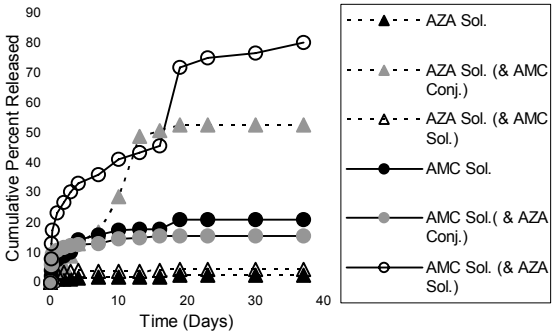

Figure 2. Release kinetics of solubilized AMC and AZA.

	2 hours		4 hours		6 hours	
	10%	15%	10%	15%	10%	15%
BupHCl	^20.87	^20.44	^1.78	^*2.31	^0.45	^*0.79
BupHCl (& AgSD)	^17.72	^16.52	^0.40	^*2.53	^0.27	^*1.05

	24 hours		48 hours		72 hours	
	10%	15%	10%	15%	10%	15%
BupHCl	0.16	^*0.84	0.05	^*0.22	0.02	0.11
BupHCl (& AgSD)	0.21	0.68	0.03	*0.16	^0.03	*0.12

* indicates that 1G1P IPN supernatant exhibited significantly different absorbance from 10% gelatin ($p < 0.05$, $n = 3$)
^ indicates that absorbance is significantly different from unmodified (no solutes) IPN supernatant absorbance ($p < .05$, $n = 3$)

Table 1. BupHCl release from IPNs polymerized along gelatin concentration gradient. (absorbance)

Conclusions: Release kinetics of AMC, AZA, BupHCl, and AgSD are mediated by loading modality as well as the characteristics of other loaded compounds. These items in addition to other material properties will continue to be tested and altered to achieve clinically relevant release of BupHCl and AgSD in full-thickness wounds.

References:

Babu R. Biomaterials. 2006;27:4304-4314.
Chang WH. J. Biomater. Sci. 2003;14:481-495.
Stevens KR. J. Biomater. Sci. 2002;13:1353-1366.

Acknowledgements: NIH RO1HL77825 & RO1EB6613, UW-Madison I&EDR