Role of *Intermediate Water* in Biopolymers and Biocompatible Synthetic Polymers

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The recent development of novel biomaterials and their applications to biomedical problems have dramatically improved the treatment of many diseases. Biocompatible materials are especially imperative as they are used in medical devices. Although various types of materials have been used widely in medical devices, most biomaterials lack the desired functional properties to interface with blood and have not been engineered for optimum performance. Therefore, there is increasing demand to develop novel materials to address such problems in the medical devices arena. Numerous parameters of polymeric biomaterials can affect biocompatibility in a controlled manner. The mechanisms responsible for the biocompatibility of polymers at the molecular level have not been clearly demonstrated, although many theoretical and experimental efforts have been made to try and understand them. Moreover, water interactions have been recognized as fundamental for the blood response to contact with polymers. We have proposed the "*Intermediate Water*" concept, and hypothesized that intermediate water, which prevents the proteins and blood cells from directly contacting the polymer surface, or non-freezing water on the polymer surface, plays an important role in the biocompatibility of polymers. Intermediate water exhibited clearly defined peaks for cold crystallization in the differential scanning calorimetry (DSC) chart, a strong peak at 3400 cm^{-1} in a time-resolved Infrared (IR) spectrum and higher mobility of water in a ^{2}H-NMR. Intermediate water was found only in hydrated biopolymers (proteins, polysaccharides, and nucleic acids, DNA and RNA) and hydrated biocompatible synthetic polymers (Table 1). Intermediate water could be one of the main screening factors for the design of appropriate biocompatible materials. This presentation provides an overview of the recent experimental progress of biocompatible polymers measured by thermal, spectroscopic, and surface force techniques. Additionally, it highlights recent developments in the use of biocompatible polymeric biomaterials for medical devices, and provides an overview of the progress made in the design of multi-functional biomedical polymers by controlling the bio-interfacial water structure through precision polymer synthesis.

Table 1 Classification of water in hydrated polymers

Water structure (mode of binding)		*Tightly bound water/ Non-freezing bound water*	*Loosely bound water/ Freezing bound water/ Intermediate water*	*Scarcely bound water/ Freezing water/ Free water*
Biopolymers (Proteins, polysaccharides, nucleic acid)		○	○	○
Synthetic polymers	**Biocompatible**	○	○	○
	Non-biocompatible	○	—	○
Freezability		Not freezable at 0 ℃, not freezable below 0 ℃	Not freezable at 0 ℃, freezable below 0 ℃	freezable at 0 ℃
NMR correlation time (t_c)(s)		10^{-8}～10^{-6}	10^{-10}～10^{-9}	10^{-12}～10^{-11}
***in-situ* ATR-IR O-H stretching region (cm^{-1})**		3600	3400	3200
Binding constant to polymer		strong	medium	week

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