ABSTRACT

Self-assembly of proteins resulting in the formation of amyloid fibrillar aggregates has emerged as a subject of fundamental importance in biomedical research as well as in protein chemistry due to its involvement in a number of neurodegenerative disorders. The similarity found between the amyloid fibrils formed *in vitro* and those isolated from pathological conditions has facilitated the scope of investigating the amyloid fibrillation process *in vitro* to understand the molecular mechanisms of amyloidogenesis and also the influencing factors involved therein. In this regard, human serum albumin (HSA) has received a significant attention as a model protein for the *in vitro* amyloid fibrillation studies due to its physiological importance and also its tendency to easily form amyloid fibrils under modified solution conditions.

The thesis consists of seven chapters. **Chapter 1** provides a brief overview of amyloid fibrillation and the rationale behind the present work. The work in the thesis is focussed on the modulation of HSA fibrillation by differently functionalized nanoparticles of various core compositions and physicochemical properties and also disruption of the preformed amyloid fibrils of HSA by the application of the alternating current (AC) electric field. All the details about the materials and methodologies used for the studies have been described in **Chapter 2**. **Chapter 3** illustrates the effect of bare and functionalized (aminated and carboxylated) magnetic MnFe2O4 nanoparticles on the HSA fibrillation process. The electrostatically more favored interaction between HSA molecules and the amine functionalized $MnFe_2O_4$ nanoparticles is found to cause the most effective inhibition of the development of HSA fibrillar species compared to the others. In **Chapter 4**, the effect of surface chirality of the gold nanoparticles, induced by the two enantiomeric forms (i.e. D- and L-) of glutamic acid, on the fibrillation process of HSA is explored where D-glutamic acid acid-mediated gold nanoparticles exhibit greater efficiency in inhibition of the HSA fibrillation in comparison to its counterpart. The surface chirality of the gold nanoparticles is found to affect the protein adsorption dynamics including the modes of orientation of adsorbed HSA molecules, causing the inhibition of fibrillation to different extents. In **Chapter 5**, the mechanistic details about both the interaction behavior of the silver nanoparticles, synthesized using nontoxic and biodegradable chitosan as a reducing and stabilizing agent, with HSA and also the effect of the nanoparticles on the amyloid fibrillation of the protein have been discussed. The formation of a stable bioconjugate by chitosan-based silver nanoparticles through spontaneous binding to HSA is considered to be the reason for the hindrances in protein self-assembly process leading to the appreciable reduction in amyloid fibril formation. Additionally, cytotoxicity and hemolytic assays have been performed to ensure the biocompatibility of the nanoparticles within the application limit. **Chapter 6** describes the effect of oscillation induced by a frequency-dependent AC electric field on preformed amyloid fibrils of HSA. The experimental results suggest that the frequency of the applied AC field plays a crucial role in the disruption of preformed HSA fibrils. It appears that the shape deformation induced hydrodynamic flows inside the fibril droplets and the torque induced by the intrinsic electric dipoles of protein due to their continuous periodic realignment in presence of the AC electric field augments the destruction of the fibrillar species. **Chapter 7** summarizes the key findings from the research work presented in Chapters 3 to 6 followed by the contribution of the thesis and certain scopes of future research in this field.

Key words: Amyloid fibrillation; Human serum albumin; Modulation of fibrillation, Functionalized $MnFe_2O_4$ nanoparticles, Gold nanoparticle surface chirality, Chitosan-based silver nanoparticles, AC electric field, Disruption of fibrils