MD simulations and atomic force spectroscopy (AFS) were applied to rationally design inhibitors which indicated blocking of amyloid-amyloid bonds formation that was the initial phase in the formation of toxic amyloid oligomer [103]. The pseudo-peptide amyloid-β (Aβ) inhibitors (which were bound onto the Aβ peptide) were created that efficiently prevented formation of the amyloid-amyloid bonds. The binding affinities for the Aβ and inhibitors besides the inhibitors to themselves were achieved by Umbrella Sampling computations. AFS experimentally examined some inhibitors to measure their capacities in blocking the formation of amyloid-amyloid bonds. It was found that the AFS results were consistent with the MD simulations as three pseudo-peptides bound to the amyloid fragment by diverse affinities that successfully prevented the Aβ-Aβ binding. Hence, these pseudo-peptides were proposed as promising drugs that illustrated the ability to hinder the toxic effect of the Aβ in the Alzheimer's syndrome.

MD simulations were done on the ibuprofen (IBU) load and release using $(AF)_6H_5K_{15}$ amphiphilic peptide, FA32, and its analogues $F_{16}H_5K_{15}$ and $F_{12}H_5K_{15}$ [104]. After the IBU is loaded into the FA32, core-shell sphere-like micelles were created. The IBU drug was primarily positioned inside the hydrophobic core that was enclosed with the alanine and phenylalanine residues but lysine was within the hydrophilic shell. Increasing the IBU concentration enlarged the micelles upon increasing the hydrophobic contacts. The IBU loading into the FA32 analogs afforded various morphologies especially using $F_{16}H_5K_{15}$ formed a nanofiber structure. When pH was changed, the IBU release from the $F_{16}H_5K_{15}$ nanofiber was faster compared with that of the from FA32 micelles signifying the latter was a superior controlled release system. Also, it was demonstrated that the IBU-encapsulated morphology was varied upon altering the peptide type that significantly affected the IBU release. Accordingly, such bottom-up method was beneficial to rationally design drug vehicles that could efficiently load and release drugs.

## 8. PROTEINS AS DRUG DELIVERY SYSTEMS

Proteins are also utilized as DDSs particularly human serum albumin (HSA) is frequently applied in transporting various pharmaceutics [105]. HSA is comprised of 585 amino acids that can transport numerous exogenous and endogenous substances such as nutrients, fatty acids, metal ions, steroids, drugs, and hormones [106]. The HSA structure contains three homologous areas of I, II, and III and each domain is divided to two subdomains A and B so that merely one tryptophan residue (Trp-214) exists within the subdomain IIA [107]. Different materials are usually bound to the two main HSA areas located inside the hydrophobic cavities in subdomain IIA and IIIA called Sudlow's sites I and II, respectively. Site I is situated within the hydrophobic cavity in the subdomain IIA that can bind diverse heterocyclic and neutral materials through strong hydrophobic contacts but site II existing in the subdomain IIIA is attached onto several aromatic carboxylic acids via hydrogen bonds and van der Waals forces [107].

The C-1027 aromatic chromophore (Chr) that is able to selectively cleave DNA is delivered and stabilized in vitro using apoprotein (apo) but it is released when the holoprotein, apo + Chr, is penetrated to the cultured sarcoma cells [108]. The holoprotein is used as an attractive DDS in clinical trials whereas the mechanism of Chr release is unclear. Hence, MD simulations were done to find the release paths indicating they were dependent on local movements by 3 loops including Asn97–Leu100 (L9), Thr75–Thr79 (L7), and Val39–Gln42 (L3). Major problems in the Chr release were hydrophobic interactions, direct hydrogen bonds, and steric hindrance happened through the three loops. As well, Ser98 was a significant residue throughout the release course.

The interactions of HSA and phthalic acid esters (PAEs) as endocrine disruptor were examined using MD simulations and fluorescence spectra to evaluate the HAS-PAEs distances energy transfer between them [109]. It was revealed that all four types of PAEs quenched the inherent HSA fluorescence through non-radiative transfer of energy and static quenching mechanisms. Thermodynamics tests and molecular docking proved that binding was mostly controlled by hydrophobic forces. Also, four PAEs were primarily bound onto the subdomain IIIA of HSA demonstrating good agreements between the computational and experimental data. MD simulations illustrated that HSA conformation was a slightly changed on its binding to the PAEs. Moreover, PAEs-HSA complexes had higher stabilities than the native HSA protein.

The interactions among HSA and aflatoxin G1 and B1 were studied by MD simulations molecular docking and fluorescence spectra [110]. The fluorescence spectra verified that the HSA fluorescence emission was substantially quenched by adding aflatoxin G1 and B1 by mechanism of static quenching. The calculated thermodynamic factors specified that the spontaneous nature of the interactions so that the van der Waals and hydrogen bond forces significantly affected the HSA binding to aflatoxin G1 and B1. The binding constants for the aflatoxin G1 and B1 linking onto the HSA were