IN SILICO DESIGN OF NANOPARTICLES FOR TRANDERMAL DRUG DELIVERY APPLICATIONS

Rakesh Gupta[1], Beena Rai[1]
1 TCS Research, Tata Consultancy Services, Pune, India, 411013
Contact Email: Gupta.rakesh2@tcs.com

Background: Human skin provides ample opportunities for various healthcare and personal care application. However, developing strategies for these applications are challenging as human skin provides a natural barrier to body and prevent permeation of foreign substances and chemical materials. The reason being skin's densely packed layered structure, which acts as a protective barrier preventing the inflow of any external species. Thus, to ensure the permeation of active components through, it is required to breach the outermost layer of epidermis known as stratum corneum.

Objective: In-silico design of nanoparticles of various shape, size, surface chemistry and surface pattern which can breach the barrier provided by the skin's top layer, stratum corneum.

Methods: The SC layer has to be breached out in a controlled manner to deliver therapeutics through it. Nanoparticles are convenient vehicles for transdermal drug delivery due to their reversible barrier breaching mechanism [1-3]. A computer simulations based (*in-silico*) approach backed by few experiments could speed up the nanoparticle formulation design process.
At first, we have developed an *in-silico* skin model based on the multiscale modeling framework linking atomistic-molecular-mesoscale to macroscale to study molecular transport across the Stratum Corneum (SC) [4-5]. At molecular level, atomistic and coarse grained molecular dynamics simulations are performed. Nanoparticles of various size [6], surface chemistry [7] and surface pattern [8] are built using Monte Carlo simulation. These nanoparticles are further *in-silico* tested on coarse grained skin SC lipid layer model via prolonged molecular dynamics simulations.

Results: Figure 1A, shows the permeability of gold nanoparticle of various sizes. The permeability decreases with increase in size. The observations are in line with several experiments carried out on real skin samples (*in-vitro*) [9]. Hence, based on the application (desired skin permeability), the size can be tuned and design *in-silico*. Further, these nanoparticles can be coated with various ligands changing their surface properties (charges) significantly. Figure 1B shows the snapshots of simulations carried on skin model in presence of gold nanoparticles coated with various ligands making them neutral, catatonic and anionic. The results show that charged nanoparticles are adsorbed on the surface of the skin while neutral molecules easily cross the skin barrier. These observations are in line with the results obtained through several *in-vitro* permeation experiments carried out on real skin samples [9, 10]. Fig 1C shows one such design case, where nanoparticle of various surface pattern are simulated along with skin lipid layer model. Out of these, only three nanoparticles, having uniform distribution of 1:0, 2:1 and 1:2 (hydrophobic: hydrophilic) beads were able to cross the skin barrier. Experimentally, it has been shown that nanoparticles, having 2:1 (hydrophobic: hydrophilic) uniform distribution of ligand over their surface, were able to breach the plasma membrane significantly [11]. Hence, these nanoparticles could be used for delivering therapeutics through skin.

References

1. Rakesh Gupta, Nishi Kashyap and Beena Rai. *Phys. Chem. Chem. Phys*, 2017, 19(11), 7537-7545.
2. Rakesh Gupta., D Sridhar, Beena Rai and Samir Mitragotri. *Nature Scientific Reports*, 2019. 9(1), 1456
3. Rakesh Gupta and Beena Rai. *Nanoscale*, 2017, 9 (12), 4114-4127
4. Kishore Gajula, Rakesh Gupta, D Sridhar and Beena Rai. *J. Chem. Inf. Model,* 2017, 57(8), 2027-2034
5. Yogesh Badhe, Rakesh Gupta and Beena Rai. J. Mol. Model. 2019.
6. Rakesh Gupta and Beena Rai. *J. Phys. Chem. B,* 2016, 120 (29), 7133-7142
7. Rakesh Gupta and Beena Rai. *Nature Scientific Reports*, 2017, 45292
8. Rakesh Gupta and Beena Rai. *Nanoscale,* 2018 10(10), 4940-4951.
9. Sonavane G et al., *Colloids and Surfaces B: Biointerfaces,* 65 (1) (2008) p 1.
10. Labouta HI and Schneider M, *Nanomedicine: Nanotechnology, Biology and Medicine*, 9(1) (2013) p 39.
11. Verma A and Stellacci F, *Small*, 6(1) (2010) p 12

Back to Programme

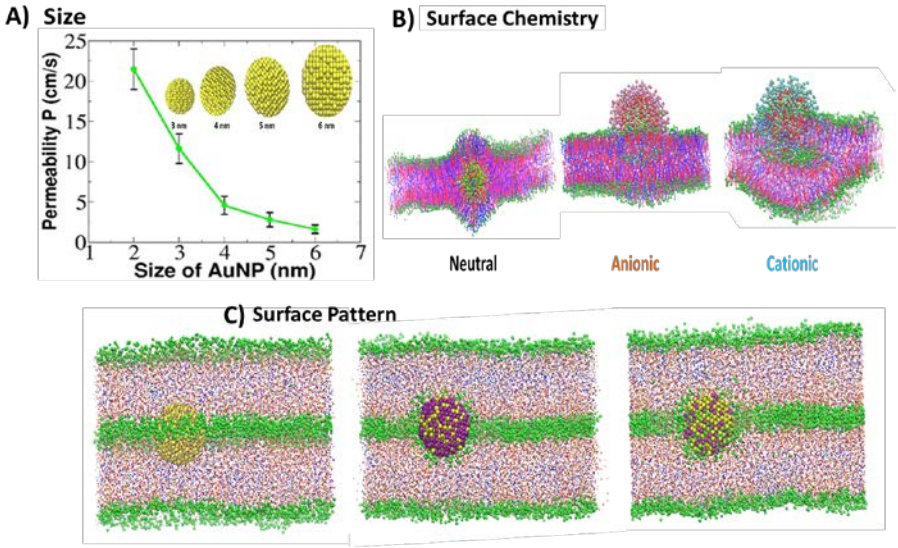

Figure 1. A) Effect of gold nanoparticle size on its skin permeability (Adapted with permission from Gupta and Rai [6] Copyright (2016) American Chemical Society). B) Effect of surface charge on skin permeation of surface coated gold nanoparticle (Images are reproduced from Gupta and Rai [7]). The skin lipids are shown in red, blue and green color. C) Effect of surface chemistry on skin permeation of nanoparticle (Images are reproduced from Gupta and Rai [8] by permission of The Royal Society of Chemistry). The green beads shows the head group of skin models. The yellow and magenta color represent hydrophobic and hydrophilic bead respectively.

Back to Programme