Preface

Polyelectrolyte multilayer capsules fabricated by layer-by-layer (LbL) self-assembly technique consistsing of core-shell structure have emerged as potential drug delivery systems along with their applications in micro-reactors, cosmetics, vaccines and antimicrobial coatings. Various ligands and stimuli responsive entities can be incorporated into the core and shell of the capsules for targeted delivery and/or controlled release applications. Though multilayer capsules have been studied extensively as delivery systems, their utility for encapsulation of hydrophobic drugs and multiple drugs have not been explored in detail so far. Application of traditional polyelectrolyte capsules has several limitations, which renders them inapplicable for encapsulation of multiple drugs, hydrophobic drugs and also for releasing drugs on demand without addition of the external photothermal agents such as metal nanoparticles into the shells of the capsules.

Thus, in this thesis, an attempt has been made to develop novel multifunctional multilayered capsules to overcome the above mentioned limitations. We have formulated two novel methods to functionalize the core with cyclodextrin molecules and the shell of the capsules with two-dimensional material, graphene oxide (GO). The properties such as high surface area along with π bonds, broad NIR-absorption, superior photothermal conversion and antimicrobial activity of graphene oxide has been explored and it has been demonstrated that 2-D graphene oxide is unique compared to the regular polyelectrolytes. By functionalizing the shell of capsules with GO as one of the layer material, a simple and efficient way for encapsulating multiple drugs into core and shell of the capsules is achieved by utilizing the large surface area and amphiphilic nature of GO. Based on the unique optical absorption and photothermal conversion properties of GO, we have demonstrated a facile route for near-infrared (NIR)-laser triggered release with low laser power. In the second part, functionalization of the hollow core of the capsules has been functionalized using cylodextrin (CD)-incorporated $CaCO_3$ porous sacrificial templates, where both CD-$CaCO_3$ and CD-modified capsules are used as high efficient carriers for hydrophobic drugs. In the third part, synergistic antimicrobial therapy was achieved using composite graphene oxide/polymer LbL films by combining the intrinsic antimicrobial activity and photothermal conversion ability of graphene oxide and the results depicted superior antimicrobial activity towards *E. coli*. These composite films also can be used as efficient antimicrobial coatings on biomedical devices or implants.

The thesis has been divided into five chapters based on the individual works. In **Chapter 1,** a brief review on the history of LbL self-assembly, mechanism of self-assembly along with factors affecting the process have been discussed. Followed by a brief discussion about the fabrication of multilayered hollow capsules (core-shell structure), their applications in drug delivery and fabrication of multifunctional multilayered capsules through core and shell have been discussed. Finally, recent developments in LbL self-assembly and multilayered hollow capsules using carbon based materials (fullerenes, carbon nanotubes and graphene oxide) and their biomedical applications have been presented.

Chapter 2 deals with the study on fabricating multifunctional multilayered capsules for facile encapsulation of multiple drugs into the capsules, which is achieved by functionalizing the capsules with graphene oxide (GO) as one of the layer materials. The GO composite capsules exhibited unique permeability properties compared to traditional multilayered capsules made of two polyelectrolytes. Multiple drugs could be simultaneously encapsulated in the capsules in a simple and effective manner. These capsules were found to exhibit a "core-shell" loading property for encapsulation of dual drugs into the core and shell of the capsules respectively. In addition, the graphene oxide composite capsules showed excellent biocompatibility towards MCF-7 cells. This study is the first one that demonstrates the potential of hybrid polyelectrolyte capsules without the use of micelles or polymer-drug conjugates for multi-drug encapsulation.

Chapter 3 deals with the development of a facile route for near-infrared (NIR)-light triggered release of encapsulated drugs from the multilayered capsules via incorporation of graphene oxide (GO) into layer-by-layer (LbL) assembled capsules without addition of any external additives such as metal nanoparticles (NPs) or carbon nanotubes (CNTs) into the shells of the capsules. Till now, there is no report on light-responsive drug delivery system by utilizing the NIR-optical absorption properties of GO. Here, graphene oxide (GO) plays a dual role, serving as a structural component of LbL capsules as well as strong NIR-light absorbing agent, which efficiently converts absorbed light into heat. Upon NIR-laser irradiation, the microcapsules were opened in "point-wise fashion" due to local heating caused by laser irradiation. The rupturing mechanism of the capsules has been clearly demonstrated using confocal fluorescence microscopy and high resolution transmission electron microscopy. The light-triggering ability of these capsules has been applied successfully to release the encapsulated anticancer drug, doxorubicin.

Chapter 4 deals with simple and versatile simple routes for encapsulation of model hydrophobic drug. Encapsulation of hydrophobic drugs in pharmaceutical industries is always a big challenge due to limited number of available drug carrier systems and poor aqueous solubility of hydrophobic drugs. Here, by combining the special properties of cyclodextrins (CDs) with biodegradable inorganic calcium carbonate microparticles, the hybrid CD-$CaCO_3$ mesoporous microparticles have been prepared for the first time. These CD-$CaCO_3$ microparticles were utilized as sacrificial templates to prepare CDs-modified LbL capsules. We have demonstrated that both the hybrid CD-$CaCO_3$ microparticles and CDs-modified capsules are potential carriers for encapsulation of model hydrophobic drugs (self-fluorescent coumarine and nile red dyes) with high loading efficiency using supramolecular host-guest interaction between entrapped CDs and hydrophobic dye molecules. Compared with other inorganic drug carrier systems (mesoporous silica), $CaCO_3$ porous particles have better biocompatibility, biodegradability and cost-effective and without use of any organic solvents. Both these hybrid CD-$CaCO_3$ microparticles and CDs-modified capsules can be good candidates for encapsulation of hydrophobic drugs without involving extreme chemical conditions for fabrication.

Chapter 5 deals with development of facile synergistic method for killing pathogenic bacteria by combining the intrinsic antimicrobial activity of graphene oxide (GO) and unique photothermal conversion property of GO into a single material. We fabricated composite LbL films of graphene oxide (GO) and poly(allylamine hydrochloride) (PAH) films. Antimicrobial activity of these GO composite films has been studied using *Escherichia coli (E. coli)* cells by varying number of deposited layers on glass slides (20 to 80 layers) and results suggest that by increasing the number of deposited layers, antimicrobial activity is also increased gradually. Based on the unique optical properties of GO, photothermal therapy have been carried out for killing of *E. coli* using GO composite films by varying number of deposited layers (20 to 80 layers) by irradiation of NIR-pulse laser at 1064 nm wavelength (Nd:YAG, 10 ns pulse, 10 Hz). The photothermal results revealed the enhanced antimicrobial activity compared to GO composite films alone without NIR-laser irradiation. The synergistic photothermal killing ability along with intrinsic antimicrobial activity of GO films results in much faster killing compared to films alone.