Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2015, Volume 3, Issue 2
ISSN: 2321–3647(online)

Layer-by-Layer Technique: Fundamental and Application

Priti Rajendra Jadhav[1]*, Swati Gokul Talele[1], Ghanashyam Chaudhari[1], Digambar Yashawant Mali[1], Pooja Manohar Arane[1], Harshata Bhaidas Saindane[1]
1. Sandip Institute of Pharmaceutical Sciences, Mahiravani, Nashik, Maharashtra, India.

ABSTRACT

There are several requirements for the safe and effective delivery of therapeutic agents for human use. Drug permeation to the normal regions of the body is the main drawback of conventional Drug delivery system. To avoid unwanted side effects of drug the approach like targeted drug delivery is preferred. In particular, carrier drug delivery system posses some structures which are attached the drug molecule for targeted delivery. Layer-by-Layer approach also offers a delivery of drug in a targeted fashion to avoid its unintentional effects on normal tissue. LbL self-assembly systems involve simple alternative adsorption of oppositely charged polyelectrolytes on core materials. Here, in this review we have discussed the latest findings from research into LbL systems, with special emphasis on drug delivery systems.

Keywords: Layer-by-Layer, Stimuli-responsive release, Ultrasonication.

*Corresponding Author Email: 19sonukhairnar@gmail.com
Received 22 January 2015, Accepted 31 January 2015

Please cite this article as: Jadhav PR *et al*., Layer-by-Layer Technique: Fundamental and Application. American Journal of Pharmacy & Health Research 2015.

INTRODUCTION

There are few necessities of drug delivery system for human utilization. Injectable medication suffers from drawback of conveyance of drug throughout the body. Wrapping drug with suitable carrier materials is one of the potential alternatives for controlling drug release inside the body. Controlled conveyance of drug inside the body needs some transporter material.[1,2] Targeted approaches has been applicable for bringing medication (Drug) to the destination. Utilizing wrapping materials for medication delivery might likewise bring about other great qualities including improved handling during administration and enhanced stabilities of entrapped drugs. [3]. There is a growing need for advanced drug delivery systems from biopharmaceutical point of view. Hence due to its low cost, simplicity and versatility the layer by layer (LbL) technique is becoming popular method for preparing multilayer films.[4–7] Blodgett extended the Langmuir film method to create multilayer coatings known as the Langmuir–Blodgett (LB) strategy[8-14]. Layer-by-layer (LbL) self-assembly is a simple method and involves alternative adsorption of oppositely charged polyelectrolytes on core materials. It allows the design of two or more layers which are overlapped with great precision in size. This strategy includes basic option adsorption of oppositely charged polyelectrolytes on center materials. LbL assembly as polymer films, nanoparticles and micelles[15-17] are promising tool for medication conveyance and biosensing. For drug delivery and biosensing application LbL assemblies in the form of polymer films, nanoparticles and micelles can be used. The polyelectrolyte multilayer films can be build up by depositing oppositely charged polyelectrolyte's on various templates by repetitive deposition

History of Lbl Assembly

The LbL is advanced technique and having historical prospective as

1) 1920. For the creation of first monomolecular coating Langmuir converted a monomolecular oil layer to a solid substrate[18].

2) 1966. Iller tried to produce multilayer coating or alternative to LbL tech. by referring studies related to electrostatic colloid self assembly[19].

3) 1970. The potential of multilayer manipulation was realized by Kuhn et al[20]

4) 1991. Decher introduced electrostatic polyelectrolyte's self assembly in a LbL fashion[21, 22]

5) 1992 Decher et al. were first to report that by application of alternating layers of anionic and cationic polyelectrolyte's from solution onto a charged planar substrate the LbL assemblies can be manufactured[21, 22].

6) 1994, 1995. For production of LbL assemblies lvov et. al used proteins while DNA was used as polyelectrolyte by sukhorukov et. al[23, 24].

7) 1997. Hydrogel bonded LbL assemblies was first debuted by Rubner Stockton et. al[25]

8) 1998.Polyelectrolyte hollow microcapsules was constructed with application of LbL deposition of polyelectrolyte's on the surface of colloidal particles, followed by dissolution of the core material by Mohwald and co-workers.[26]

9) 2001. Qiu et. al deposited polysaccharide multilayer on ibuprofen microparticles[27].

Principle

The step-wise adsorption of various components with nanometer-scale precision is the characteristic of this technique[28]. LbL thin films can be produced by using cationic and anionic polyelectrolyte's as shown in figure 1. LbL deposition includes the various mechanisms like electrostatic force, hydrogen bonding, covalent bonding, and biological affinity. The structural and functional component for LbL films, includes synthetic polymers, biopolymers (proteins, polysaccharides, DNA, etc.), inorganic nanoparticles, carbon nanotubes.[29].

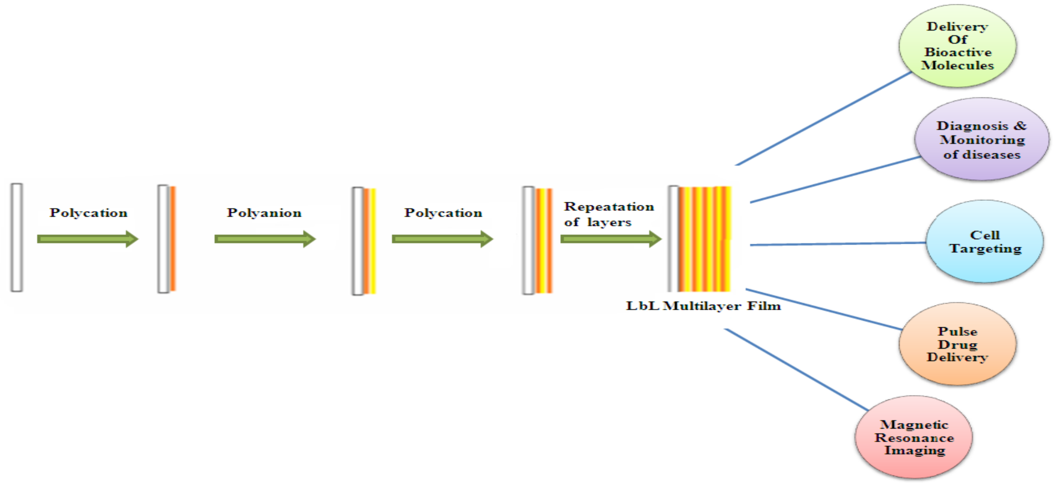

Figure.1: Principle involved In LbL Technique

Advantages of Lbl-Assembled Multilayers

LbL self-assembly offers several advantages to other methods of encapsulation, coating or fixation of substances:

(1) Thickness of capsules wall can be tailored in the nm–μm limit.

(2) Different kinds of synthetic/natural colloids are available for LbL.

(3) The location and sequence of the layers can be controlled.

(4) Surface labeling with targeting molecules is possible.

(5) Stabilization of submicron particles is possible[30].

(6) LbL avoids the use of thermodynamically unstable mechanically-micronized particles[31]

(7) Much lower amounts of colloids (~1%) is needed to produce a functional coating compared to a minimum of ~10% with conventional techniques.

(8) The simplicity of the LbL process and equipment.

(9) Its suitability to coating most surfaces.

(10)The flexible application to objects with irregular shapes and sizes.

(11)Stabilizing coats can be formed[32].

Mechanism of LbL Assembly

Lbl innovation exploits the charge–charge collaboration in the middle of substrate and monolayers of polyelectrolytes to make various layered nano-structural engineering held together by electrostatic force. The development of LbL frameworks are credited to electrostatic collaborations, hydrogen bonding, hydrophobic interaction and Van der Waals force.

Electrostatic Interactions

The adsorption results from electrostatic associations, whereby uniform, thin film (thickness 40–600 Å) can be promptly saved on an assortment of substrates. The adsorption procedure used to manufacture the film was discovered to be determined principally by the electrostatic attractions created between the part of the way doped chains of the polycation and the contrarily charged chains of the polyanion[33]. It can be clarified by wonder of the adsorption of species with like charges; for example, remaining amino acids found on the hemoglobin (Hb) surface[34]. It was watched that a lot of glutamic corrosive and aspartic corrosive (with pka values at around 4.0) was found close to the surface of Hb. Because of the low pka values, these amino acids are adversely charged at ph 5.0, where polyamidoamine (PAMAM) and Hb are both emphatically charged. These leftover amino acids add up to a focus sufficiently noteworthy to help the electrostatic cooperation with PAMAM, framing accumulated toward self assembled layers held together weakly.

Hydrogen bonding

LbL assemblies can be done utilizing hydrogen bonding. A film is built utilizing the hydrogen bonding between poly (acrylic corrosive) (PAA, going about as a H-bond giver) and biodegradable poly (ethylene oxide)-square poly (β-caprolactone) (PEO-b-PCL) micelles, going about as a H-bond acceptor, under acidic conditions. By exploiting the feeble associations of a hydrogen-bonded film on hydrophobic surfaces, it is conceivable to create adaptable unattached film[35].hydrogen bonded LbL materials open new conceivable outcomes for LbL films, which were more hard to deliver than their electrostatically assembled counterpart. These new conceivable outcomes are: 1) simplicity of delivering LbL film receptive to environmental pH at gentle pH values, 2) probability to change over hydrogen reinforced film into single- or two part ultrathin hydrogel materials, and 3) incorporation of polymers with low glass transition temperatures (e.g., PEO) inside ultrathin films. These properties may be investigated for pH and/or temperature responsive medication conveyance frameworks, materials with tunable mechanical properties, and discharge film dissolvable under physiological conditions. Intrigued readers are recommended to allude the late improvements in the union of LbL materials focused around hydrogen holding get together, their structure–property connections, and the prospective applications of hydrogen fortified LbL nanostructures in biotechnology and biomedicine, which are carefully inspected by Kharlampieva, Kozlovskaya and Sukhishvili[36].

Hydrophobic interactions

Scientists have watched the commitments of hydrophobic associations to LbL assembly. Examination has demonstrated that both ionic and hydrophobic collaborations must be considered when considering LbL multilayer development. Utilizing new information accessible on adsorption of proteins, colors, polymers, and NPs, Using new data available on adsorption of proteins, dyes, polymers, and NPs, it has been demonstrated that the contribution of hydrophobic interactions explains a number of experimental observations that were difficult to rationalize in the framework of a pure electrostatic mechanism[37]. Albeit less data is accessible about the commitment of hydrophobic interactions in outlining LbL nano-construction modeling, this point appears enormous potential for further research. Mukhopadhyay et al. presented an interchange in the middle of hydrophilic and hydrophobic interactions for choosing the molecular-level introduction in Langmuir–blodgett film statement. They used X-ray and neutron scattering, and Fourier transform infrared (FTIR) studies to understand the effect of hydrophilicity or hydrophobicity of substrate in determining molecular orientation of three-tailed amphiphilic salt ferric stearate in Langmuir–Blodgett films [38]. As of late, Wong et al. assembled thin PEM film by substituting disposition of a hydrophobic N-alkylated polyethylenimine (PEI) and a hydrophilic polyacrylate. They inspected the protein adsorption conduct on those PEM film to explain the component in charge of a low protein adsorption on these frameworks. The film were developed utilizing the LbL deposition technique. At long last they prompt the conclusion that the presence of hydrophobic/hydrophilic nanodomains, and additionally surface charge neutrality, helps the LbL film's resistence to protein adsorption[39].

Van der Waals force

A Van der Waals force also retains the orientation of the oppositely charged layers. Film development is accomplished by consecutive adsorption of oppositely charged species and is currently broadly utilized as a part of biomedical, electrical and vitality related fields[40,41]. Sato and Sano asserted that the acid-treated Single-Walled Carbon Nanotubes (SWCNTs) scattered in water are just dynamically steady with electrostatic two fold layer aversions simply adjusting against van der Waals (VDW) attractions. Acquaintance of any outside variable with exasperate this offset causes quick coagulation of Swcnts. In their study, they submerged amine-covered level substrate in the scattering to start adsorption of SWCNTs onto the substrate surface. By rehashing an adsorption-rinse-dry cycle, they saved SWCNT packages in a LBL way and to create a 2D system comprising just of SWCNTs that are held by VDW communication. They showed that (1) adsorbed arrangement developed totals are not applicable for the network connectivity, (2) 2D permeation happens at low surface scope, (3) the electrical resistivity takes after a force law against the layering cycles, (4 the adsorbed sum as well as the included sum every layering cycle increments directly with the SWCNT focus, and (5) after the adsorption is started by amines, VDW attraction assumes control for consequent adsorption, with the result that the recently adsorbed SWCNTs are utilized to thicken each one arm of the system as opposed to cover all the more free surfaces[42]. Enthusiasm toward the LbL procedure has been developing since the early 1990s, and medication conveyance applications were created in the following decade. As of now the LbL methodology is utilized as a stage for a few medication conveyance frameworks, for example, microcapsules, NPs, films, microgels, carbon nanotubes, and resealed erythrocytes[43, 44].

Various Stimuli Responsive Release of Active Molecules From LbL System

pH

There are numerous stimuli to trigger the drug release from LbL assembly, mainly includes temperature, light, electric fields, magnetic fields, pH and biological ions etc.[45,46]. Ionizable moieties such as carboxylic acid, amine, azo, imidazole, pyridine, sulfonamide, and thiol groups provide pH-sensitivity. The pH alters the swelling behavior of the hydrogels depending upon the nature of polymer used. Polymers respond in way like either accepting or donating protons. To become a candidates for pH-responsive systems, the pKa value for Ionizable polymers should range in between 3 and 10. [47,48]. The critical pH of LbL film dissolution is depend upon two factors like the strength of hydrogen bonding interaction within the layers and the hydrophobicity of LbL film components. The dye-containing films prepared from Hydrogen bonded poly(ethylene oxide) /poly (methacrylic acid) (PEO/PMAA) shows high retention of dye at constant pH 4.2, and release at high pH due to film disintegration this activity is useful for rapid release of bioactive molecule[49]. As reported by Addison and coworkers LbL microshells can be manufactured from a cationic/ zwitterionic pair of pH-responsive block copolymer micelles[50] Another study by Erel et al. pave the use of block co polymer containing pH responsive LbL film for release of hydrophobic drug[51].

Temperature

To control the release of active molecules from LbL coatings the polymers which shows Temperature-induced hydrophilic-to-hydrophobic phase transitions are used. Polymer like poly (N-isopropylacrylamide) (PNIPAM)) is used as heat sensitive polymer[52] Ultrasound induced local heat play a role in film destruction. For that purpose Metal nanoparticles (NPs) like silver gold and metal oxide (TiO2) are incorporated into LbL films which will convert laser-light into heat[53,54].

Light

Light is also used as stimuli to release active molecule from light-responsive LbL films. Light which is used in this approach is of near-IR type. Metal nanoparticles absorb this radiation and generate heat which will decompose LbL film and thereby releases drug from assembly[55]. PEM (poly electrolyte multilayer) films are used as light responsive LbL films[56], Such type of Optically sensitive PEM were first reported by Tao et al[57].

Electrochemical

Electrochemical stimuli is applicable for various drug delivery devices like implants and transdermal patches for continuous or pulsed release. Processes like film degradation or reversible swelling is responsible for drug release[58] Redox polyelectrolyte's approach can be useful to build up electrochemically active LbL films [59, 60]

Magnetic field

To achieve targeted drug delivery, magnetic Nanoparticles are introduced into Poly Electrolyte Multilayer capsule activated by magnetic field[61, 62]. Babincova et al. reported that magnetic liposome containing doxorubicin will release its content after meting of liposome due to local increase in temperature as a result of static magnetic field[63].

Ultrasound

Ultrasonic vibrations with a frequency of more than 20 kHz are generally employed. Ultrasonic waves arrived from the sonicator probe tip, generates microbubbles which finally collapse this is known as cavitation. Ultrasound causes a significant disruption of the capsule membrane and therefore releases its content[64].

Glucose responsive system

LbL films prepared from glucose-sensitive materials like lectin phenylboronic acid (PBA) derivatives, glucose oxidase (GOx) are used[65]. The release of insulin from the drug delivery device by sensing the glucose concentration in surrounding environment is the main aspect of Glucose responsive system[66]. To upgrade the performance of electrochemical glucose sensors, LbL films are widely used[67]. Stimuli induced drug release by various means has shown in figure.2.

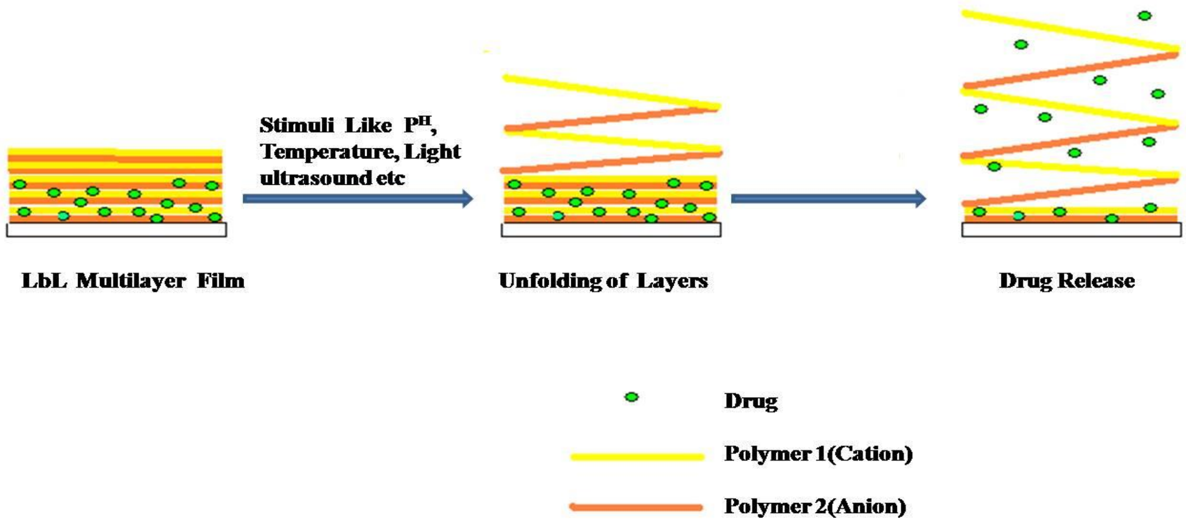

Figure 2: Stimuli Induced Drug Release

Various LbL Technologies

Different Lbl self-assembly procedures have been accounted for in the writing. A portion of the advances in these strategies are highlighted in the accompanying segments.

Core sacrificial method

Oppositely charged polyelectrolytes can be successively adsorbed onto charged colloidal centers utilizing LbL procedures. The core-shell serve as conciliatory templates[68]. Ensuing evacuation of the colloid either by calcination or by deterioration affected by introduction to suitable arrangements produces empty shells[69, 70]. Such hollow PEMs have polymer walls and inward cavities that may be stacked with different sorts of molecules including compounds[71, 72], low-molecular-weight drugs[73], polymers[74], protein antigens[75], and DNA[76].

Ultrasonic encapsulation of insoluble core

In this procedure, acqeous suspensions of ineffectively solvent medications, for example, paclitaxel, tamoxifen[77], dexamethasone[78], and ketoprofen[79], with molecule estimate in the micron extent, are subjected to ultrasonic treatment. The measure of individual medication particles is decreased in this manner to the nano level (approximately 100 and 200 nm). The NPs are settled by application of a LbL covering (substitute expansion of polycation and polyanion layers) to keep their agglomeration. The LbL covering creates a thin polyelectrolyte shell (thickness 5 to 50 nm) on the surface of the NPs (Figure 3)[80]. To avert collection of structured colloidal NPs, they are balanced out with first layering of polyelectrolyte. It can be further covered up to the sought thickness to structure a multilayered nanoshell self assembled structure.

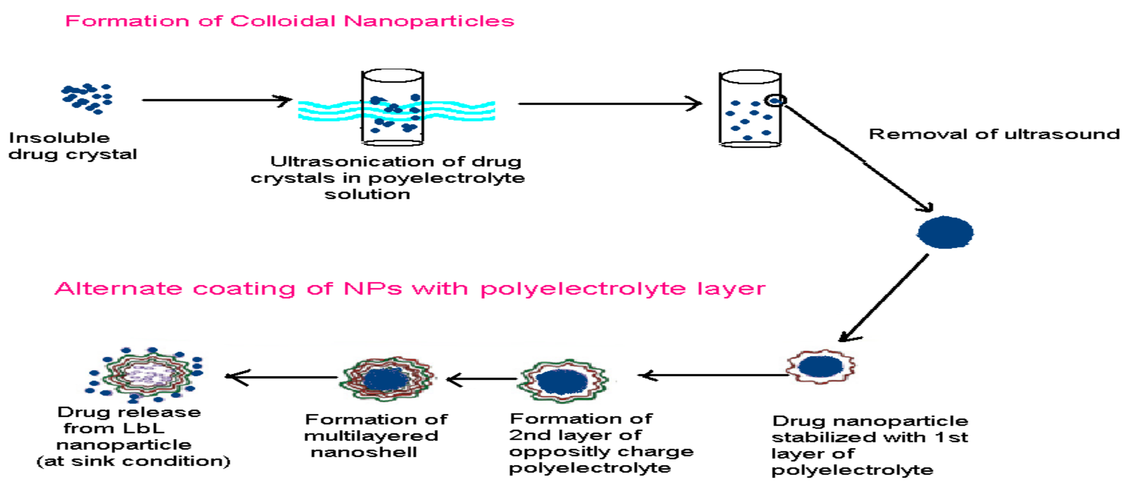

Figure 3: Formation of stable colloidal NPs of insoluble drug crystals by ultrasonication

Dissolution assisted by co-solvent followed by nucleation

Water-insoluble drug can be dissolved first in a water-miscible natural dissolvable, for example, ethanol or ch3)2co. Drug nucleation can be launched then by progressive expansion of a watery arrangement (containing oppositely charged polyelectrolytes) under influential ultrasonication(figure. 4)[81].

Characterization of LbL Assembly

UV (Ultra-violet Spectroscopy)

UV–VIS spectroscopy can be useful to observe Multilayer growth[82, 83]

Confocal Laser Microscopy (CLSM)

It is used to study the polyelectrolyte multilayer stability if fluorescently-labeled polyelectrolytes are assembled[84]. Multilayer thickness can be figure out from the fluorescence intensity[85].

IR And FTIR

Infrared analysis can be used to determine the PEM moisture content. PEM assembly in the presence of moisture and the structure of ionizing groups as well as the permeability of water-leachable substances can be reveal by this type of spectroscopic study[86, 87]. To study the interaction in between active moiety and polymer FTIR play an important role[88].

Atomic Force Microscopy (AFM)

The surface texture and roughness of PEMs can be drawn out by atomic force microscopy (AFM)[89], AFM can be a useful technique for studying the changes in contact angle wettability and surface energy[90].

The surface morphologies of multilayers were computed by AFM[91].

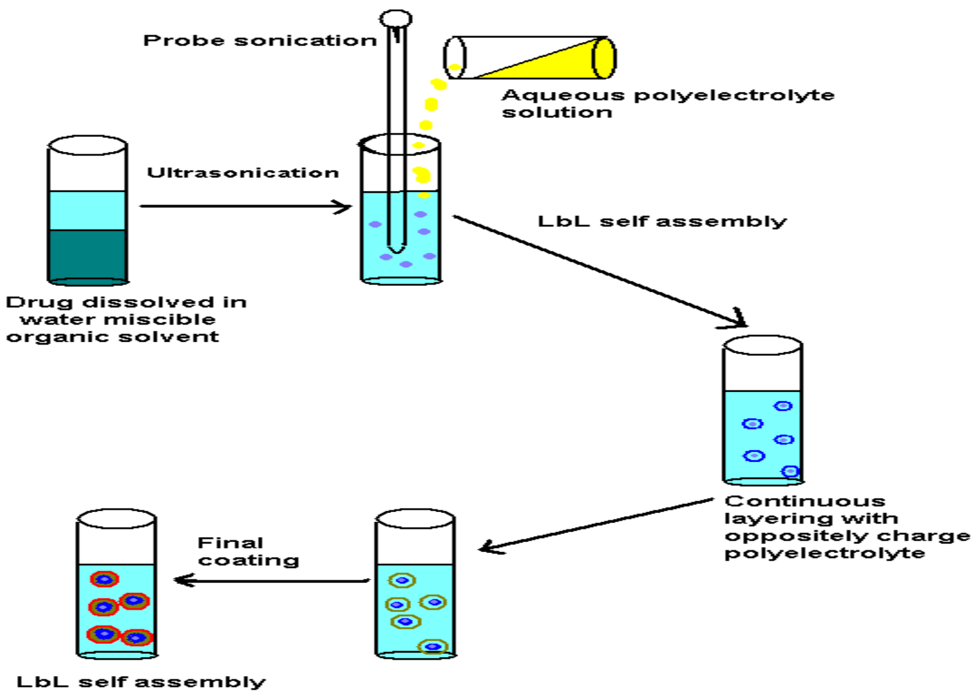

Figure 4: Sonication assisted formation LbL self assembled stable nanocolloids.

Nuclear Magnetic Resonance (NMR)

Hydration as well dehydration properties of multilayers can be well studied by Spin relaxation NMR[92].The mobility of polyionic multilayers were also studied by Spin relaxation NMR[93].

X-ray reflectivity

X-ray reflectivity can be used to study internal arrangement PEM structure[94].

Ellipsometry

The multilayered film thickness can be measured by determining the distance-dependent change in polarization of a light source as a function of reflection or transmission through a substance by using Ellipsometry[95, 96].

Field Emission Scanning Electron Microscopy Field Emission Scanning Electron Microscopy was used for particle imaging[97]. SEM also used to study morphology of PEM.[98].

Dynamic Light Scattering (DLS)

Dynamic Light Scattering (DLS) is used to determine the particle size[99,100].

Zeta-Potential Measurement

The surface charge of the microparticles was determined by zeta potential measurements with a Zetasizer[101] zeta potential can be calculated from electrophoretic mobility[102].

Applications

1. For gene silencing new class of Self-assembled siRNA–PLGA conjugate micelle are used[103].

2. LbL coatings finds its application in delivery of bioactive molecules at the interface of a biomedical device and biological tissue, such as surfaces of orthopedic implants, urinary catheters or cardiovascular stents[104, 105]

3. Poly electrolyte capsules can be used for biomedical applications, like controlled encapsulation and release of small molecule drugs[106], enzymes[107, 108], protein drugs[109] and DNA[110].

4. A study on ovariectomized rat shows that layer-by-layer nano-matrix containing NSAID drug, kaempferol can be used in the conditions like osteoporosis[112].

5. Nanostructure LbL films find its application in the diagnosis and monitoring of diseases by utilizing different electrochemical approaches[113].

6. The LbL capsules can be used for cell targeting with controlled release[114].

7. The release of aloin (barbaloin), present in Aloe vera, can be controlled by encapsulating into liposomes and then immobilizing it into LbL films with a polyelectrolyte for transdermal delivery[115].

8. Nanogels posses drawback of burst release so it can be control by use of layer by layer assembly[116].

9. Degradable microgels coated by using Layer-by-layer technology can be used for pulsed drug delivery 8[117].

10. Layer-by-layer capsules are also used for magnetic resonance imaging[118].

11. According to Biopharmaceutical Classification System; Class 2 and Class 4 drugs (lipid-based drugs) can be delivered by LbL coated microcapsules[119].

12. The combination of sonication and layer-by-layer technology can be used to prepare Stable nanocolloids of poorly soluble drugs with high drug content[120].

13. The cancer-targeting can be done by using multilayer nanoparticles formed by layer by layer approach[121].

REFERENCES

1. Maeda H. SMANCS and polymer-conjugated macromolecular drugs: advantages in cancer chemotherapy, Adv. Drug Deliv. Rev. 2001; 46: 169–185.
2. Iyer AK, Khaled G, Fang J, Maeda H. Exploiting the enhanced permeability and retention effect for tumor targeting, Drug Discov. Today 2006; 11: 812–818.
3. Melgardt M. Villiers M , Daniel P, Otto D, Schalk J, Strydom S, Yuri M. Lvov Introduction to nanocoatings produced by layer-by-layer (LbL) self-assembly. Advanced Drug Delivery Reviews 2011; 63: 701–715.
4. Franklin B, Brownrigg W, Farish P. Of the stilling of waves by means of oil Extracted from sundry letters between Benjamin Franklin, L.L.D. F.R.S. William Brownrigg, M.D. F.R.S. and the Reverend Mr. Farish, Philos. Trans. R. Soc. Lond. 1774; 64: 445–460.
5. Rayleigh L. Measurement of the amount of oil necessary in the order to check the motions of camphor upon water. Proc. R. Soc. Lond. 1890; 364–367.
6. Pockels A. Surface tension. Nature (London) 1891; 43: 437–439.
7. Rayleigh L. Investigations in capillarity: the size of drops. The liberation of gas from supersaturated solutions. Colliding jets. The tension of contaminated water surfaces. Philos. Mag. 1899; 48: 321–337.
8. Langmuir I. The constitution and fundamental properties of solids and liquids. II. Liquid, J. Am. Chem. Soc.1917; 39: 1848–1906.
9. Langmuir I. The mechanism of the surface phenomena of flotation. Trans. Faraday Soc.1920; 15: 62–74.
10. Adam NK, The properties and molecular structure of thin films of palmitic acid on water. Part I, Proc. R. Soc. Lond. A Math. Phys. Sci.1921; 99: 336–351.
11. Blodgett KB. Films built by depositing successive monomolecular layers on a solid surface. J. Am. Chem. Soc. 1935; 57: 1007–1022.
12. Langmuir I, Schaeffer VJ. Activities of urease and pepsin monolayers. J. Am. Chem. Soc.1938; 60: 1351–1360.
13. Blodgett KB, Langmuir I. Built-up films of barium stearate and their optical properties. Phys. Rev. 1937; 51: 964–982.

14. Zasadzinski ZA, Viswanathan R, Madsen L, Garnaes J, Schwartz DK. Langmuir- Blodgett Films. Science 1994; 263: 1726–1733.
15. Kuhn H. Interaction of chromophores in monolayer assemblies. Pure Appl. Chem. 1971; 27: 421–438.
16. Poon Z, Chang D, Zhao X, Hammond PT. Layer-by-layer nanoparticles with a pH-sheddable layer for in vivo targeting of tumor hypoxia ACS Nano 5 (6) 2011; 4284–4292.
17. Tong W, Zhu Y, Wang Z, Gao C, Mohwald H. Micelles-encapsulated microcapsules for sequential loading of hydrophobic and water-soluble drugs. Macromol. Rapid Commun. 2010; 31: 1015–1019.
18. Langmuir I.The mechanism of the surface phenomena of flotation. Trans. Faraday Soc. 1920; 15: 62–74.
19. Iler RK. Multilayers of colloidal particles. J. Colloid Interface Sci. 21,569–594. Kuhn, H., 1971. Interaction of chromophores in monolayer assemblies. Pure Appl.Chem. 1966; 27: 421–438.
20. Kuhn H, Mobius D. Systems of monomolecular layers—assembling and physicochemical behavior.Angew. Chem. Int. Ed. 1971; 10 : 620–637.
21. Decher G, Hong JD, Scmitt J. Buildup of ultra thin multilayer films by self-assembly process: III. Consecutively alternating adsorption of anionic and cationic polyelectrolytes on charged surfaces. Thin Solid Films. 1992; 210/211: , 831–835.
22. Decher G. Fuzzy nanoassemblies: toward layered polymeric multicomposites. Science1997; 277: 1232–1237.
23. Lvov Y, Ariga K, Ichinose I, Kunitake T1995. Assembly of multicomponent protein films by means of electrostatic layer-by-layer adsorption. J. Am. Chem. Soc. 1995; 117: 6117–6123.
24. Lvov Y, Antipov A, Mamedov A, Mohwald H, Sukhorukov GB. Urease encapsulation in nanoorganized microshells. Nano Lett. 2001; 1: 125–128.
25. Sukhorukov GB, Mohwald H, Decher G, Lvov YM. Assembly of polyelectrolyte films by consecutively alternating adsorption of polynucleotides and polycations. Thin Solid Films. 1996; 284–285 ,220–223.
26. Wang L, Fu Y, Wang Z, Fan Y, Zhang X, 1999.Investigation into an alternating multilayer film of poly(4-vinylpyridine) and poly(acrylic acid) based on hydrogen. Langmuir 1999; 15: 1360–1363.

27. Donath E, Sukhorukov GB, Caruso F, Davis SA, Mohwald H. Novel hollow polymer shells by colloid-templated assembly of polyelectrolytes. Angew. Chem. Int. Ed. Engl. 1998; 37: 2202– 2205.
28. Qiu X, Leporatti S, Dontah E, Mohwald H. Studies on the drug release properties of polysaccharide multilayers encapsulated Ibuprofen microparticles. Langmuir.17 (17) 2001; 5375–5380.
29. Shchukin EM, Dmitry G, Shchukin DG. LbL coated microcapsules for delivering lipid-based drug .Advanced Drug Delivery Reviews. 2011; 63: 837–846.
30. Ariga K, Hill JP, Ji Q. 2007. Layer-by-layer assembly as a versatile bottom-up nanofabrication technique for exploratory research and realistic application. Phys. Chem. Chem. Phys. 2007; 9: 2319–2340.
31. Ai H, Jones SA, Villiers MM, Lvov YM. Nano-encapsulation of furosemide microcrystal for controlled release. J. Control. Release 86 (2003) 59–68.
32. Rasenack N, Müller BW. Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs, Pharm. Res. 2002; 19: 1894–1900.
33. Rasenack N, Müller BW. Properties of ibuprofen crystallized under different conditions: a comparative study, Drug Dev. Ind. Pharm. 2002; 28: 1077–1089
34. Villiers MM , Otto DP, Strydom SJ, Lvov YM. Introduction to nanocoatings produced by layer-by-layer (LbL) self-assembly,Advanced Drug Delivery Reviews 2011; 63: 701–715.
35. Villiers MM, Otto DP, Strydom SJ, Lvov YM. Introduction to nanocoatings produced by layer-by-layer (LbL) self-assembly, Adv. Drug Deliv. Rev. 63 (9) 2011; 701–715.
36. Cheung JH, Stockton WB, Rubner MF. Molecular-level processing of conjugated polymers. 3. Layer-by-layer manipulation of polyaniline via electrostatic interactions, Macromolecules 30 (9) 1997; 2712–2716.
37. Shen L, Hu N. Electrostatic adsorption of heme proteins alternated with polyamidoamine dendrimers for layer-by-layer assembly of electroactive films, Biomacromolecules 6 (3) 2005; 1475–1483.
38. Kim BS, Park SK, Hammond PT. Hydrogen-bonding layer-by-layer-assembled biodegradable polymeric micelles as drug delivery vehicles from surfaces, ACS Nano 2 (2) 2008; 386–392.
39. Kharlampieva E, Kozlovskaya V, Sukhishvili SA. Layer-by-layer hydrogen-bonded polymer films: from fundamentals to applications, Adv. Mater. 21 (30) 2009; 3053–3065.

40. Kotov NA. Layer-by-layer self-assembly: the contribution of hydrophobic interactions, Nanostruct. Mater. 12 (5–8) 1999; 789–796.
41. Mukhopadhyay MK, Sanyal MK, Datta A, Webster J, Penfold J, Interplay between hydrophilic and hydrophobic interactions for deciding the molecular orientation in Langmuir–Blodgett film deposition, Chem. Phys. Lett. 407 (4–6) 2005; 276–282.
42. Wong SY, Han L, Timachova K, Veselinovic J, Hyder MN, Ortiz C, Klibanov AM, Hammond PT. Drastically lowered protein adsorption on microbicidal hydrophobic/hydrophilic polyelectrolyte multilayers, Biomacromolecules 13 (3) (2012) 719–726.
43. Song W, He Q, Möhwald H, Yang Y, Li J. Smart polyelectrolyte microcapsules as carriers for water-soluble small molecular drug 139 (2) 2009; 160–166.
44. Sato M, Sano M. Vander Waals layer-by-layer construction of a carbon nanotube 2D network. Langmuir 21 (24) 2005; 11490–11494.
45. Roy D, Cambre JN, Sumerlin BS. Future perspectives and recent advances in stimuli-responsive materials. Prog. Polym. Sci. 2010; 35: 278–301.
46. Bawa P, Pillay V, Choonara YE, Toit LC. Stimuli-responsive polymers and their applications in drug delivery. Biomed. Mater 2009; 4: 15.
47. Bartil T, Bounekhel M, Cedric C, Jeerome R. Swelling behavior and release properties of pH-sensitive hydrogels based on methacrylic derivatives. Acta Pharma. 57(3), 2007; 301-314.
48. Kharlampieva E, Sukhishvili SA. Release of a dye from hydrogen-bonded and electrostatically assembled polymer films triggered by adsorption of a polyelectrolyte. Langmuir 2004; 20 : 9677–9685.
49. Addison T, Cayre OJ, Biggs S, Armes SP, York D. Polymeric microcapsules assembled from a cationic/zwitterionic pair of responsive block copolymer micelles. Langmuir 2010; 26: 6281–6286.
50. Erel I, Zhu Z, Zhuk A, Sukhishvili SA. Hydrogen-bonded layer-by-layer films of block copolymer micelles with pH-responsive cores. J. Colloid Interface Sci. 2011; 355: 61–69.
51. Ono Y. Shikata T. Hydration and dynamic behavior of poly(N-isopropylacrylamide)s in aqueous solution: a sharp phase transition at the lower critical solution Temperature. J. Am. Chem. Soc. 2006; 128: 10030–10031.
52. Skirtach AG, Antipov AA, Shchukin DG, Sukhorukov GB. Remote activation of capsules containing Ag nanoparticles and IR dye by laser light. Langmuir 2004; 20: 6988–6992.

53. Katagiri K, Koumoto K, Iseya S, Sakai M, Matsuda A, Caruso F.Tunable UV responsive organic-inorganic hybrid capsules. Chem. Mater. 2009; 21: 195–19.
54. Angelatos AS, Radt B, Caruso F. Light-responsive polyelectrolyte/gold nanoparticle Microcapsules. J. Phys. Chem. B. 2005; 109: 3071–3076.
55. Volodkin DV, Madaboosi N, Blacklock J, Skirtach AG, Mohwald H. Surface supported multilayers decorated with bio-active material aimed at light triggered drug delivery. Langmuir. 2009; 25: 14037–14043.
56. Tao X, Li J, Mohwald H. Self-assembly, optical behavior, and permeability of a novel capsule based on an azo dye and polyelectrolytes. Chem. Eur. J. 10 (14) 2004; 3397–3403.
57. Recksiedler CL, Deore BA, Freund MS. A novel layer-by-layer approach for the fabrication of conducting polymer/RNA multilayer films for controlled release. Langmuir.2006; 22: 2811–2815.
58. Laurent D, Schlenoff JB. Multilayer assemblies of redox polyelectrolytes. Langmuir. 1997; 13: 1552–1557.
59. Crespilho FN, Zucolotto V, Oliveira ON, Nart FC. Electrochemistry of layer by-layer films: A review. Int. J. Electrochem. Sci. 1, 2006; 194–214.
60. Wang W, Liu L, Ju XJ, Zerrouki D, Xie R, Yang L, Chu LY. A novel thermo-induced self-bursting microcapsule with magnetic-targeting property. ChemPhysChem. 10 (14) 2009; 2405–2409.
61. Hu SH, Tsai CH, Liao CF, Liu DM, Chen, S.Y., 2008.Controlled rupture of magnetic polyelectrolyte microcapsules for drug delivery. Langmuir 24 (20) 2008; 11811–11818.
62. Babincova M, Cicmanec P, Altanerova V. AC-magnetic field controlled drug release from magnetic liposomes: design of a method for site-specific chemotherapy. Bioelectrochemistry. 2002; 55 :17–19.
63. Rae J, Ashokkumar M, Eulaerts O, Sonntag C, Reisse von J, Grieser F. Estimation of ultrasound induced cavitation bubble temperatures in aqueous solutions. Ultrason. Sonochem. 12 (2), 2005; 325–329.
64. Sato K, Yoshida K, Takahashi S, Anzai J. pH- and sugar-sensitive layer-by-layer films and microcapsules for drug delivery. Advanced Drug Delivery Reviews. 2011; 63: 809–821.
65. Chu L, Liang Y, Chen W, Ju X, Wang H. Preparation of glucose-sensitive microcapsules with porous membrane and functional gates. Colloid Surface. B 2004; 37: 9–14.
66. Wang Y, Wei W, Liu X, Zeng X. Carbon nanotube/chitosan/gold nanoparticlesbased glucose biosensor prepared by a layer-by-layer technique. Mater. Sci. Eng.C 2009; 29: 50–54.

67. Sukhorukov GB, Donath E, Lichtenfeld H, Knippel E, Knippel M, Budde A, Möhwald H. Layer-by-layer self assembly of polyelectrolytes on colloidal particles. Colloids Surf., A Physicochem. Eng. Asp. 137 (1-3) 1998; 253–266.
68. Caruso F, Caruso RA, Mohwald H. Nanoengineering of inorganic and hybrid hollow spheres by colloidal templating. Science 1998; 282: 1111–1114.
69. Zhao Q, Han B, Wang Z, Gao C, Peng C, Shen J. Hollow chitosan-alginate multilayer microcapsules as drug delivery vehicle: doxorubicin loading and in vitro and in vivo studies. Nanomed. Nanotechnol. Biol. Med. 3 (1) 2007; 63–74.
70. Gao C, Liu X, Shen J, Mohwald H. Spontaneous deposition of horseradish peroxidase into polyelectrolyte multilayer capsules to improve its activity and stability. Chem. Commun. 2002; 17: 1928–1929.
71. Lvov Y, Antipov AA, Mamedov A, Mohwald H, Sukhorukov GB. Urease encapsulation n nanoorganized microshells. Nano Lett. 1 (3) 2001; 125–128.
72. Caruso F, Trau D, Mohwald H, Renneberg R. Enzyme encapsulation in layer-by-layer engineered polymer multilayer capsules. Langmuir 16 (4) 2000; 1485–1488.
73. Kumar KNA , Ray SB, Nagaraja V, Raichur AM, Encapsulation and release of rifampicin using poly(vinyl pyrrolidone)-poly(methacrylic acid) polyelectrolyte capsules. Mater. Sci. Eng. C 29 (8) 2009; 2508–2513.
74. Radtchenko IL, Sukhorukov GB, Mohwald H. Incorporation of macromolecules into polyelectrolytemicro and nanocapsules via surface controlled precipitation on colloidal particles. Colloids Surf., A Physicochem. Eng. Asp. 202 (2–3) 2010; 127–133.
75. Koker SD, De Geest BGD, Singh SK, De Rycke R, Naessens T, Kooyk YV, Demeester J, De Smedt SC, Grooten J, Polyelectrolyte microcapsules as antigen delivery vehicles towards dendritic cells: uptake, processing and cross-presentation of encapsulated antigens. Angew. Chem. Int. Ed. 48 (45) 2009; 8485–8489.
76. Shchukin DG, Patel AA, Sukhorukov GB, Lvov YM. Nanoassembly of biodegradable microcapsules for DNA encasing. J. Am. Chem. Soc. 126 (11) 2004; 3374–3375
77. Lvov Y, Agarwal A, Sawant R, Torchilin V, Sonication assisted polyelectrolyte nanoencapsulation of paclitaxel and tamoxifen. PharmaFocus Asia 7 ,2008; 36–40.
78. Pargaonkar N, Lvov TM, Li N, Steenekamp JH, Villiers MM. Controlled release of dexamethasone from microcapsules produced by polyelectrolyte layer-by-layer nanoassembly. Pharm. Res. 22 (5) 2005; 826–835.

79. Arida AI, Al-Tabakha MM, Encapsulation of ketoprofen for controlled drug release. Eur. J. Pharm. Biopharm. 66 (1) 2007; 48–54.
80. Ariga K, Lvov YM, Kawakami K, Ji Q, Hill JP. Layer-by-layer self-assembled shells for drug delivery. Adv. Drug Deliv. Rev. 63 (9) 2011; 762–771.
81. Zheng Z, Zhang X, Carbo D, Clark C, Nathan C.A., Lvov Y, Sonication-assisted synthesis of polyelectrolyte-coated curcumin nanoparticles. Langmuir 26 (11) 2010; 7679–7681.
82. Decher G, Hong JD, Scmitt J. Buildup of ultra thin multilayer films by self-assembly process: III. Consecutively alternating adsorption of anionic and cationic polyelectrolytes on charged surfaces. Thin Solid Films. 210/211 1992; 831–835.
83. Jeremy PK, Tan Q, Wang, Kam C. Tam.,2008 Control of burst release from nanogels via layer by layer assembly. Journal of Controlled Release 2008; 128: 248–254.
84. Sukhorukov GB, Antipov AA, Voigt A, Donath E, Möhwald H. pH-controlled macromolecule encapsulation in and release from polyelectrolyte multilayer nanocapsules. Macromol. Rapid Commun.2001; 22 : 44–46.
85. Muller K, Quinn JF, Jonhston APR, Becker A, Greiner F, Caruso. Polyelectrolyte funtionalization of electrospun fibers. Chem. Mater. 2006; 18 : 2397–2403.
86. Farhat T, YassinG, Dubas ST, Schlenoff JB. Water and ion pairing in polyelectrolyte multilayers. Langmuir1999; 15 : 6621–6623.
87. Bergwald,S., Meier-Haack, J., Jenichen,D.,1998. An insitu ATR-FTIR study on polyelectrolyte multilayer assemblies on solid surfaces and their susceptibility to fouling. Macromol. Rapid Commun.1998; 19 : 333–336.
88. Yan S, Zhu J, Wang Z, Yin J, Zheng Y, Chen X. Layer-by-layer assembly of poly(L-glutamic acid)/chitosan microcapsules for high loading and sustained release of 5-fluorouracil. European Journal of Pharmaceutics and Biopharmaceutics 2011; 78 : 336–345.
89. Dubas ST, Schlenoff JB.1999.Factors controlling the growth of polyelectrolyte multilayers. Macromolecules 1999; 32 : 8153–8160.
90. Yoo D, Shiratori SS, Rubner MF. Controlling bilayer composition and surface wettability of sequentially adsorbed multilayers of weak polyelectrolytes. Macromolecules1998; 31 : 4309–4318.
91. De Geest BG, Dejugnat C, Verhoeven E, Sukhorukov GB, Jonas AM, Plain J, Demeester J, De Smedt SC. Layer-by-layer coating of degradable microgels for pulsed drug delivery. Journal of Controlled Release 2006; 116: 159–169.

92. Schwarz B, Schönhoff M. Surface potential driven swelling of polyelectrolyte multilayers. Langmuir 2002; 18: 2964–2966.
93. Smith RN, Reven l, Barrett CJ. 13C solid-state NMR study of polyelectrolyte multilayers. Macromolecules 2003; 36: 1876–1881.
94. Erokhina S, Berzina T, Christofolini L, Erokhin V, Folli C, Konovalov O, Marino IG, Fontana MP. X-ray reflectivity measurements of layer-by-layer films at the solid/liquid interface. Langmuir 2008; 24: 12093–12096.
95. Kurt P, Banerjee D, Cohen RE, Rubner MF. Structural color via layer-by-layer deposition: layered nanoparticle arrays with near-UV and visible reflectivity bands. Journal Mater. Chem. 2009; 19 : 8920–8927.
96. Kim YT, Collins RW, Wedam K, Allara DL. Real- time spectroscopic ellipsometry in situ characterization of pyrrole electropolymerization. Journal Electrochem Soc 1991; 138: 266–3275.
97. Agarwal A, Lvov Y, Sawant R, Torchilin V. Stable nanocolloids of poorly soluble drugs with high drug content prepared using the combination of sonication and layer-by-layer technology. Journal of Controlled Release 2008; 128 : 255–260.
98. Kaiyong C, Annett R, Jianyuan H, Jo R, Klaus, D J. Polysaccharide-protein surface modification of titanium via a layer-by-layer technique: Characterization and cell behaviour aspects. Biomaterials 2005; 26: 5960–5971.
99. Jeremy PK, Tan Q, Wang, Kam C. Tam. Control of burst release from nanogels via layer by layer assembly. Journal of Controlled Release2008; 128: 248–254.
100. Oh KS, Lee H, Kim JY, Koo EJ, Lee EH, Park JH. The multilayer nanoparticles formed by layer by layer approach for cancer-targeting therapy. Journal of Controlled Release 2013; 165: 9–15.
101. Yan S, Zhu J, Wang Z, Yin J, Zheng Y, Chen X, Layer-by-layer assembly of poly(L-glutamic acid)/chitosan microcapsules for high loading and sustained release of 5-fluorouracil. European Journal of Pharmaceutics and Biopharmaceutics 2011; 78: 336–345**.**
102. Shenoy DB, Sukhorukov G. Engineered microcrystals for direct surface modification with layer-by-layer technique for optimized dissolution. European Journal of Pharmaceutics and Biopharmaceutics 2004; 58 : 521–527.
103. Lee SH, Mok H, Lee Y, Park TG. Self-assembled siRNA–PLGA conjugate micelles for gene silencing. Journal of Controlled Release 2011; 152: 152–158.

104. Lichter JA, VanVliet KJ, Rubner MF. Design of antibacterial surfaces and interfaces: Polyelectrolyte multilayers as a multifunctional platform. Macromolecules 2009; 42: 8573–8586.

105. Karlsson AJ, Flessner RM, Gellman SH, Lynn DM, Palecek SP. Polyelectrolyte multilayers fabricated from antifungal β-peptides: Design of surfaces that exhibit antifungal activity against Candida albicans. Biomacromolecules 2010; 11: 2321–2328.

106. Ai H, Jones SA, DeVilliers MM, Lvov YM. Nano-encapsulation of furosemide microcrystals for controlled drug release. Journal of Control Release 2003; 86: 59–68.

107. Zhu H, McShane MJ. Macromolecule encapsulation in diazoresin-based hollow polyelectrolyte microcapsules. Langmuir 2005; 21: 424–430.

108. Macdonald M, Rodriguez NM., Smith R, Hammond PT. Release of a model protein from biodegradable self assembled films for surface delivery applications. J. Control. Release 2008; 131 :228–234.

109. Ye S, Wang C, Liu XZ, Tong B, Ren F, Zeng. New loading process and release properties of insulin from polysaccharide microcapsules fabricated through layer-by-layer assembly. J. Control. Release 2006; 112: 79–87.

110. Hua Ai .,2011.Layer-by-layer capsules for magnetic resonance imaging and drug delivery .Advanced Drug Delivery Reviews 2011; 63 : 772–788.

111. Kumar A, Girish K, Gupta, Khedgikar V, Gautam J, Kushwaha P, Changkija B, Nagar GK, Gupta V, Verma A, Dwivedi AK, Chattopadhyay N, Mishra PR , Trivedi R. European Journal of Pharmaceutics and Biopharmaceutics 2012; 82: 508–517.

112. Iost RM, Crespilho FN. Layer-by-layer self-assembly and electrochemistry: Applications in biosensing and bioelectronics. Biosensors and Bioelectronics 2012; 31: 1– 10.

113. Angus PR, Johnston, Christina C, Alexandra S, Angelatos, Frank C. Layer-by-layer engineered capsules and their applications. Current Opinion in Colloid & Interface Science 2006;11: 203–209.

114. Xavier AC, Moraes ML, Ferreira M. Immobilization of aloin encapsulated into liposomes in Layer-by-layer films for transdermal drug delivery. Materials Science and Engineering C 2013; 33: 1193–1196.

115. Jeremy PK,TanQ, Wang, Kam C. Tam. Control of burst release from nanogels via layer by layer assembly. Journal of Controlled Release 2008; 128: 248–254.

116. De Geest BG, Dejugnat C, Verhoeven E, Sukhorukov GB, Jonas AM, Plain J, Demeester J, De Smedt SC. Layer-by-layer coating of degradable microgels for pulsed drug delivery. Journal of Controlled Release 2006 ; 116: 159–169.

117. Hua Ai. Layer-by-layer capsules for magnetic resonance imaging and drug delivery .Advanced Drug Delivery Reviews 2011; 63: 772–788.

118. Shchukina EM, Shchukin DG. LbL coated microcapsules for delivering lipid-based drugs .Advanced Drug Delivery Reviews 2011; 63: 837–846.

119. Agarwal A, Lvov Y, Sawant R, Torchilin V. Stable nanocolloids of poorly soluble drugs with high drug content prepared using the combination of sonication and layer-by-layer technology. Journal of Controlled Release 2008; 128: 255–260.

120. Oh KS, Lee H,Kim J.Y., Koo E.J., Lee EH., Park JH. The multilayer nanoparticles formed by layer by layer approach for cancer-targeting therapy. Journal of Controlled Release 2013 ;165: 9–15.