Self Assembled Molecular Coatings in Medical Application

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Abstract

Molecular self-assembly (SAMS) is the assembly of molecules without guidance or management from an outside source. SAMS has been used for studies and applications in many areas like surface wetting, non-fouling property, electrochemistry, surface passivation, protein binding, DNA assembly, corrosion resistance, biological arrays, cell interactions, and molecular electronics. It has found applications in medical field as well in recent years simply because of its passive method of formation, its biocompatibility, biodegradability and reversible responsiveness to various stimuli. Inclusion of self assembly strategy has given new pathways in field of medicine. This article elucidates some of the major medical applications which involve self assembled molecular coatings.

Keywords: SAMS, ESA, Self Assembled Monolayer (SAMs), Biocompatibility, Stents, Pacing Leads, LCPs, Stimuli-responsiveness.

1. INTRODUCTION

Self assembled molecular structure (SAMS) is an extremely versatile tool for the thermodynamically controlled generation of higher order constructs. Nature uses self assembly extensively in biological systems with 'LOCK & KEY' specificity to give wide range of highly ordered system, observed in living organisms. In nature, some of the examples of self assembly are given as:

1) peptide chains which fold to form proteins & enzymes
2) single stranded DNA finds its compliment and forms double helix structure.
3) Phospholipids align themselves in order to make up cell walls.

Applying self strategy artificially has been successful in generating interest in synthesis and controlled aggregation of macromolecules (polymers for that matter) in recent years.

SAMS possesses highly ordered, directional non-covalent or covalent interaction. Strength of these non-covalent or covalent interactions is stimulus dependent, allowing for reversible control over the assembly process which contributes to the design of unique material properties.

SAMS strategy has been demonstrated to be attractive method of controlled polymer aggregation. (The higher modularity makes self-assembly can be precisely synthesized to customize the selectivity), directionality & association strength of the type of interaction which fosters shape memory & self structure regaining capabilities.[1]

SAMS is also an inexpensive, versatile surface coating for applications including control over wetting and adhesion, chemical resistance, biocompatibility, sensitization and molecular recognition for sensors and nanofabrications.[2] Areas of SAMS include biology, electrochemistry and electronics, nanoelectrochemical systems, micro-electrochemical systems. In this article we are focusing on use of SAMS in medical applications.

2. Mechanism of Formation of Sams

Of the diverse approaches for the formation of Self-Assembly, two strategies have received significant research attention:-

1) Electrostatic Self-Assembly (or Layer-by-Layer assembly)
2) Self Assembled Monolayers (SAMs)

The choice of the approach is guided by nature of substrate, application conditions, mechanism of application, end use of the coated product.

2.1. Electrostatic Self Sssembly

The present invention comprises the step of contacting a substrate having a charged surface with a starting material having an opposite charge and by electrostatic self assembly constructing a multilayered film of alternating charged molecular layers on the substrate. Multilayered coating positioned on at least a portion of the said substrate wherein adjacent layers of multilayered coating are held together by ionic attraction.

Referring to Fig.1 a substrate 2 is cleaned to remove surface impuri-

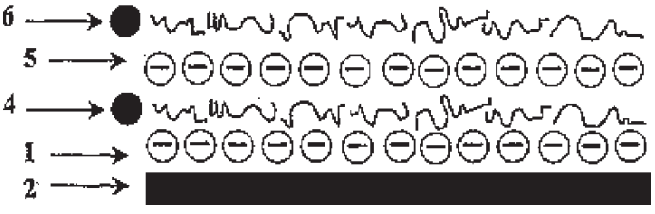


Fig.1 : Formation of ESA Assembly (Ref.3)

ties and to create net charge 1 at molecular surface of the substrate. The net charge region is shown as negative in the fig.1 by way of example, but it may be negative or positive. Although the substrate 2 is shown flat in the fig.1, it is not required that the substrate be flat or have a particular surface contour or shape.

Then cationic polymer molecules form layer 4 on the substrate. Here polymer molecules are representative, and may be instead

non-molecular clusters or other similarly sized materials with net positive outermost charge distributions. An additional negatively charged monolayer 5 is established over 4. Negatively charged clusters that are approximately spherical particles are shown, but in general different sizes, shapes and structures of negatively charged clusters may be used depending on method of their synthesis. Further, addition of second layer of cationic polymeric molecules 6 on top of the layer of clusters is done. Additionally, alternating layers of clusters and polymer molecules, where each layer has charge opposite to that of the previously deposited layers, are assembled. As long as this charge reversal is accomplished, the material in the layers may be varied throughout the composite multilayered system. The preferred aggregate thickness will vary depending on the materials used in the layers and on the application.[3] By "clusters", reference is made to substances that are not molecules, that are not chemically complete substances, and that may vary in size. Clusters preferably have sizes smaller than 30 nm.

It is appreciated that Electrostatic Self Assembled (ESA) thin coatings may be applied selectively and entire surface of the substrate need not be coated. To obtain uniform thin films, concentration and pH value of solution of starting material are carefully controlled during dipping process. High purity alumina (Al_2O_3) and zirconia (ZrO_2) are among the most widely used ceramics that are suitable for fabricating thin films by ESA process because of their positive charge character in acidic conditions. Film thickness ranges from 0.1 nm to 100μm.
Details of different Substrates and Starting materials are given in table below.

2.2. Self-Assembled Monolayers (SAMs)

ESA CONDITIONS FOR FABRICATION OF THIN FILMS

Substrate/ Materials	pH values of the solution	Dipping time (min)	pH value of rinse
PVA/PAA	4.5	30	5.0
PEI/PAA	4.5	30	5.0
Al_2O_3/PAA	4	30	4.0
ZrO_2/PAA	3.5	30	3.0
TiO_2/PAA	9	30	3.0
PDDAC	4.0/5.5	2.0/5.0	9.0

Table 1 (Ref.3)

Self Assembled Monolayer (SAM) is an organized layer of amphiphilic molecules in which one end of molecule i.e. hydrophilic head group shows affinity for the substrate. Chemisorption of hydrophilic groups over substrate is followed by slow and two dimensional organization of hydrophobic tail group, which initially causes a disordered mass of molecules. Over a period of time it begins to form crystalline or semi-crystalline structures on substrate surface.[2] Process of formation of Self Assembly typically involves immersing a substrate (e.g. Gold in fig.2) in a dilute solution of said solvent, e.g. solution of alkanethiols in ethanol. Monolayer spontaneously assembles at a surface of substrate over next one to twenty four hours. Initially

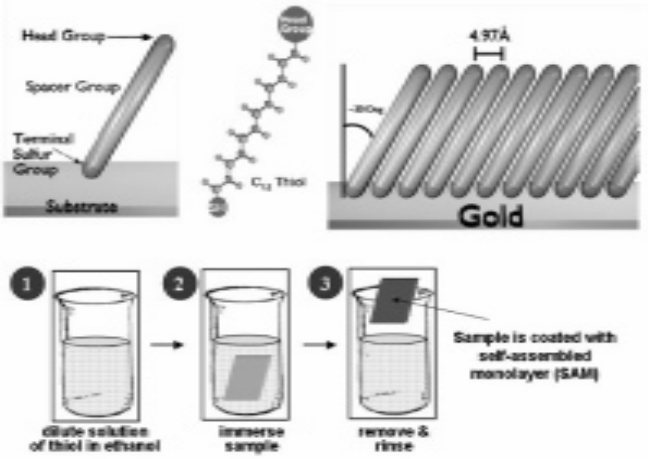


Fig.2 : Self Assembly Process for Monolayer Formation (Ref. 4)

thickness of around 80-90% of its final value is formed by disordered monolayer in few minutes. As layer continues to form, Vander Waal forces between hydrocarbon chains help pack the molecules to form into a well ordered, crystalline layer. Properties of head group define surface properties of assembled monolayer, since it is the group that is present at outer surface. It is the difference in spacing, due to the driving force to maximize the Vander Waals interactions between the alkyl chains, that causes the axis of the alkyl chains to tilt by 30° from the surface normal (Figure 2). The tilt angle is virtually independent (within a few degrees) of the functionality of the head group, with the only requirement being that the head group is not larger than the spacing of the alkane chains (~5Å).[5]
Factors that Influence Monolayer Order:

The final order and quality of the assembled monolayer are dependent on several factors, including:
1. The cleanliness and purity of the original gold surface.
2. The purity of the alkanethiol and assembly solution.
3. The length and composition of the spacer chain.
4. The type of head group (size and properties).
5. The amount of time the monolayer is allowed to assemble

3. Stimulus Responsiveness of Sams

The developments and analysis of stimuli-responsive polymeric materials which play a key driving role in advancing polymer-based biomaterials, nanotechnologies and materials science and engineering are quite recent. Stimuli-responsiveness of man-made materials is clearly demonstrated in the development of biomaterials which are typically derived from biological building blocks. These building blocks like amino acids play an enormous role in the development of medical devices such as polymer-coated stents or drug delivery systems, which are probably one of the most illustrative examples of the recent utilization of stimuli-responsive polymers.

The stimuli-responsive behaviors of polymeric materials that are significant for the current and future developments of SAMS in medical applications exhibit responses to temperature, pH, electric fields. Stimulus responsiveness of SAMS is discussed hereafter.

3.1 pH Responsiveness

Poly(methacrylic acid), poly(methyl methacrylate-stat-methacrylic acid) which are the starting material used for ESA coatings over

substrates, swell under alkaline conditions. The synthesis and characterization of a new class of acid-swellable, sterically stabilized microgel particles based on 2-(diethylamino) ethyl methacrylate (DEA) or 2-(diisopropylamino) ethyl methacrylate (DPA), swell at physiological pH (pH=7.4), thus have potential biomedical applications. Water-soluble stimuli-responsive polymers are of interest due to their applications in controlled drug delivery. Stimuli such as pH cause the polymers, which are soluble in aqueous solutions, to undergo phase transitions. New types of pH-responsive polymers have been synthesized from piperazine-based monomers and the increased chain length

in the N-substituted alkyl group of the polymer have increased its hydrophobicity.

Changes in environment, pH can cause these chemically cross-linked polymer gels to undergo discontinuous volume-phase transitions and different degrees of swelling in solution will respond to different environmental changes.[6]

3.2. Electric Responsiveness

Electric fields play a crucial role in the orientational ordering of molecules in the liquid crystalline (LC) state. Biological self-assembling systems are composed of a variety of discrete molecules forming heterogeneous and hierarchical structures varying in length. Hydrogen bonding and ionic interactions play a critical role in the formation of self-assembled liquid crystal (LC) structures, Self Assembled LCPs are capable of responding to external stimuli by changing their self-assembled structures and through the dissociation and association of non-covalent interactions.[7]

A particular type of Self Assembled Molecular Structure consists of electrostatically charged polymers which are electrically responsive. SAMS are polymer chains which are tethered to a surface or an interface with such high grafting density that the chains are forced to stretch away from the tethering site. These tethered chains can be formed by polymer physisorption, where a diblock copolymer is used to strongly adsorb to the surface and stretch away to form the brush layer. The chains can also be formed by the chemical bonding of chains to the interface. Through the combination of SAM, formation and free radical polymerization techniques, the thickness and architecture of the SAMS coating can be controlled. These types of SAM-forming materials are biocompatible, and can be used for medical applications and drug delivery.[8]

4. Applications in Medical Field

4.1 Self Assembled Thin Film Coatings to Enhance Biocompatibility of Materials

4.1.1 Need of Invention

Medical and pharmaceutical technologies have developed over the years to the point that many medical conditions are treated by implanting or putting into the body a foreign object that is not naturally occurring in the body. In the body, such foreign material may come in contact with fluids and tissues. Thus using artificial materials internally in body poses many challenges. Body has complex system of recognizing 'self' and 'non self' materials and attacking 'non self' materials found in the body. Also reaction occurs between body fluid and the implant. Often implanted materials do not go unnoticed and face variety of immune and other response reactions, interfering with the intended use of the implant. This causes the patient to suffer from complications, so this has to be taken care of. Attempting to influence the body to ignore the foreign implant, such as through drug treatment to suppress the immune protective response of body to 'non self' implant has serious risks and disadvantages. In suppressing immunity to reduce attack on a desirable 'non self' implant, undesirable 'non self' foreign material may not receive necessary attention, leading to different problems. Thus a more localized approach has developed of manipulating characteristics of foreign materials itself. Biocompatibility technology has come with the solution, focusing on the acceptance of artificial implant by surrounding tissue and by the body as a whole.[3]

4.1.2 Process of coating

Any substrate which is to be introduced is made biocompatible by contacting it with starting material and initiating alternating charged layer of Electrostatic Self-Assembly (ESA) to form thin film. The substrate to be made biocompatible can be quartz, metal, glass, plastic, ceramic or rubber tubing, material for bone implant, bioactive glass, polyester fiber, bandaging material, composite material, semiconductors, artificial hip, pacemaker, catheter, or other substrates.

Starting material may be poly(N-vinylpyrolidone), poly{bis (carboxylatophenoxy)phosphazene}, poly(ethylene glycol), poly(ethyleneamine), poly(methacrylic acid), poly(l-lysine), poly(D-glucoseamine), poly(diallylmethylamine), copolymers of ethylene-methyl methacrylate, poly(tetrafluoroethylene),Poly(caprolactones), poly(L-lactide), hydroxyfullerene or a long-side chain fullerene.[9]
ESA processes generally proceeds as follows:

1) Providing a substrate;
2) Optionally modifying the substrate to create a surface charge;
3) Dipping the substrate into a charged inorganic cluster solution;
4) Rinsing the substrate with solution;
5) Dipping the substrate into an oppositely charged polymer solution;
6) Rinsing the substrate with the solution;
7) Optionally repeating steps 3)-6) to yield multilayered coated substrate.[3]

4.2.3. Advantages

- ESA process allows ultra low cost manufacturing using simple dipping with alternating charged ionic molecules at room temperature.
- Fabrication of thin films is possible on nearly any solid material substrate plastic, ceramics, metal or tissues, without degrading or destroying the substrates.
- It provides uniform thin films with any size and shape.
- Films formed by ESA provide a charge surface and may improve adherence with osteoblasts, bone-forming cells and other cells.
- Biocompatible materials do not irritate the surrounding structure; do not provoke an abnormal inflammatory response and do not incite allergic or immunologic reactions.

- It also offers some of the mechanical properties (for e.g. strength, stiffness, fatigue), sterilizability, manufacturability, long term storage and engineering design.[3]

4.2 Coating on Stents for Localized Controlled Drug Release

4.2.1. What is a Stent?

A stent is a small mesh tube that is used to treat narrowed or weakened arteries in body. This is to improve blood flow and to help prevent the bursting of artery, to reduce the partial or total occlusion of arteries by collapse of arterial lining and to reduce the chance of development of thrombosis and restenosis. Stents are inserted inside blocked sections of coronary artery and expanded into place using balloon catheter in a procedure called an Angioplasty.[10] A stent is implanted in lumen to maintain the vascular patency. As a mechanical intervention, stent acts as a scaffoldings, functioning to physically hold open and if desired to expand the wall of passage way.

Medicated stents provide for local administration of therapeutic substances at the diseased site.

4.2.2. Need for Localized Controlled Drug Release

Conventionally as dose is applied, the plasma level will be raised, but it will rapidly decrease as drug is metabolized and will soon be

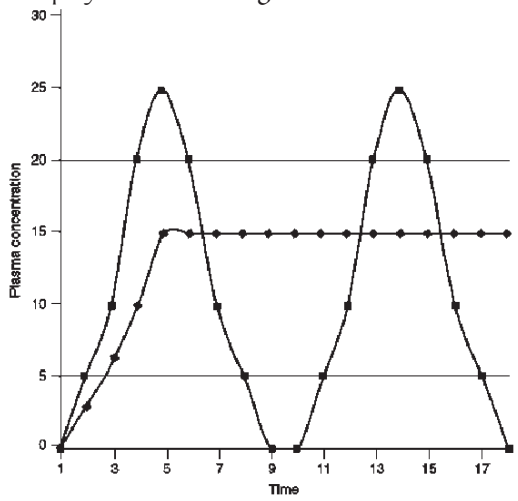


Fig. 1. Comparison of typical pharmacokinetic profiles seen for conventional vs. controled release formulations. —◆— CDR; —■— conventional; ——— toxic level; and ——— minimum therapeutic level.

Graph 1 : Controlled Drug Release (Ref.11)

below therapeutic levels. Pattern will be established, with most of the drugs, plasma levels possibly be outside the optimal range. Also drug usually permeates throughout the body and it is not targeted to the location where it is specifically required. For pharmacological therapy it is important to maintain concentration of drug at effective level for an acceptable period of time, hence controlling the release of drug is important. Local delivery produces fewer side effects and achieves more favorable results. Also it is required to rapidly increase the rate of release of drug during the process of defibrillation and then return quickly to slow delivery of drug.[12]

4.2.3. Mechanism of Formation of SAMs Coating over Stents

One method for medicating stent involves the use of polymeric carrier coated onto the surface of a stent. This coating comprises a polymeric reservoir layer disposed on the stent, and a SAM of molecules of an organic or element-organic substance disposed on the reservoir layer.

- A solution which includes the solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent. The solvent is allowed to evaporate leaving on a stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer. Alternatively, drug can be introduced into the reservoir layer by placing the polymer coated stent into a reaction flask containing the drug, allowing the drug to diffuse across the concentration gradient into the reservoir layer. The optional primer layer can be applied between the stent and the reservoir layer to improve the adhesion of the reservoir layer to the stent.
- Now the top coat is applied which is made up of Self Assembled Monolayer. SAM-forming substance is dissolved in an appropriate solvent such as Hexane. Note that the solvent used to dissolve SAM-forming substance should be incompatible with the drug and the polymer in the reservoir layer, so as to avoid extraction of the drug from the reservoir to the surface and to avoid dissolving the polymer of the reservoir layer. The concentration of SAM-forming substance in a solution can be typically between 0.01% to 100% by wt. The stent initially coated with polymer and the therapeutic substance is immersed into the solution, usually for a period of time typically between 1 hr to 72 hrs, to allow the SAM-forming substance enough time to bond to the reservoir layer.[13]

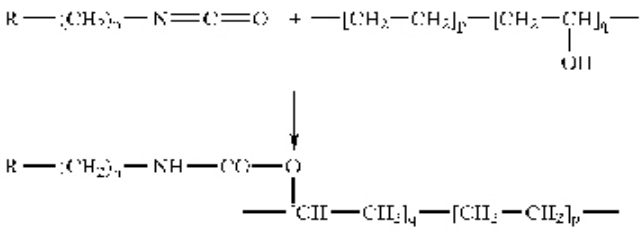
4.2.4. Chemistry

Polymers having functional group that can be used for bonding to a SAM are: poly(ethylene-co-vinylalcohol) (trade name EVAL), poly(methylmethacrylate-co-2-hydroxyethylmethacrylate), poly(ethylmethacrylate-co-2-hydroxymethylmethacrylate), poly(butylmethacrylate-co-2-hydroxymethylmethacrylate), poly(hydroxyvalerate), poly(L-lacticacid), poly(caprolactone), poly(lactide-co-glycolide) and several other biocompatible hydroxyl terminated polymers.[13]

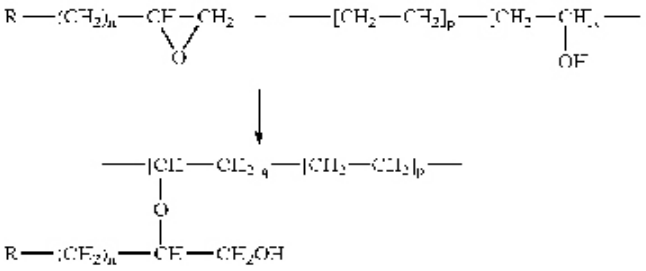
SAMs forming substance has general formula R-A-R´ where A represents a methylene chain or a silicon based chain. R is a methyl (a non-reactive group) and R´ is usually a reactive group e.g. hydroxyl, isocyanate, epoxy group etc. Given below are the some of important illustrations from variety of possible reactions between polymer of reservoir layer and SAMs forming substance.

The isocyanate terminated SAM forming substance reacts wih EVAL is illustrated as:[13]

Epoxy groups in epoxy terminated SAMs forming substance are reactive and can easily react with EVAL, via the nucleophilic substitution reaction S_N2.[13]



This reaction can take place more effectively in the presence of electron acceptors which facilitate electrophilic polarization of C-O bond of the epoxy ring, thus making a subsequent attack by the proton of hydroxyl group of EVAL easier. Tertiary amines or aprotonic acids such as amine-boron triflouride adducts.

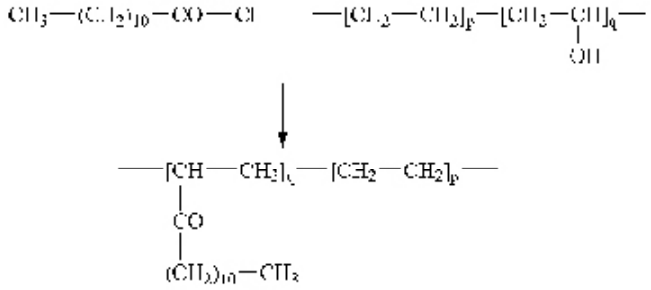


Lauryl chloride reacts with hydroxyl group of reservoir layer:

It's a typical estrification reaction that can be accelerated by an acidic or basic catalyst, if desired.[13]

Amino terminated SAM forming substance such as lauryl amine $C_{12}H_{24}NH_2$ reacts with hydroxyl terminated polymer in another embodiment.

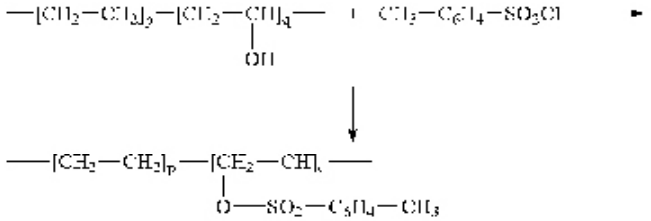
EVAL can be tosylated when treated with p-toluenesulphonylchloride:



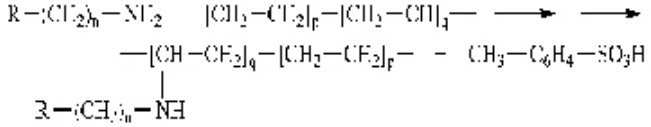
Now, amino terminated SAM-forming substance is reacted with this derivatized EVAL

Since toluene sulphonic acid is known to be a very strong acid, its anion, CH_3-C_6H_4-SO_3^- is an excellent leaving group, much better than hydroxyl group of underivatized EVAL.[13]

Biologically active peptide linkage having a general formula H[NH-



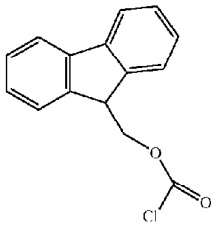
CHX-CO]$_p$-OH, where p can be 7 known as R7 and X is 1-guanidinopropyl radical. Grafting R7 to the amino group-terminated SAM forming substance is accomplished as follows. First, the



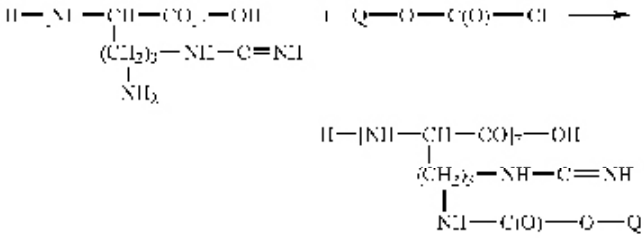
non-protonated, non-terminal primary amino groups of R7 are protected by the reaction with 9-fluorenylmethylchloroformate in aqueous dioxane. The structure is given as:

And is designated as Q-O-C(O)-Cl

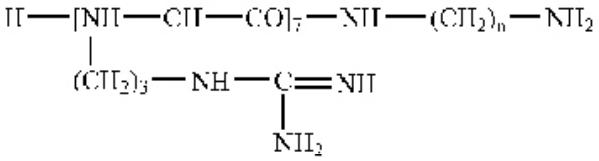
This reaction product is cleaved with 50% morpholine or other appropriate amine. As a result the 9-fluorenymethyl group is removed and R7 is tethered to the SAM-forming substance by amide bond as shown: [13]



4.2.5. Summary



This top coat SAM layer formed by any of the above explained mechanism serves as a rate limiting membrane which further controls the rate of release of the drug. By forcing the agent to diffuse through an additional coating layer prior to its release from the stent, the release of the active agent may be slowed.



Once the entire drug is being eluded, reservoir polymer layer is the remnant which is biodegradable or bioabsorbable. It is capable of being degraded, eroded, broken down, reabsorbed, eliminated by enzymolysis, hydrolysis, oxidation and metabolic process. This requires removal of stent from the body after the shelf life of the stent coating and duration of controlled drug delivery. Hence there is scope in future to come up with the technology which insures persistent incorporation of the stent in the body by recoating.

4.3 COATING OF PACING LEAD

4.3.1 What are Pacing Leads?

This Fig.3 is self explanatory about the structure and positioning of Pacemaker and Pacing Lead. Thispacemaker is placed in the vicinity of the heart and pacing lead goes into the right ventricle to stimulate the septum and another inserted through the coronary sinus to pace the lateral wall of the left ventricle. This causes proper correspondence between the heartbeat and the pacemaker.

Pacing leads are widely used for treatment of a variety of heart ailments e.g. irregularities of heart beat. It is desirable to be able to use pacing leads not only for defibrillation, but also as a vehicle for

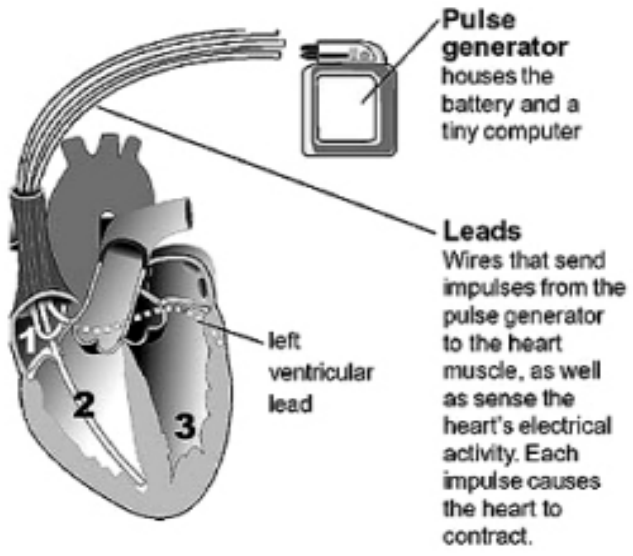


Fig. 3 : Pacing Lead Assembly (Ref.14)

providing biological therapy.

4.3.2. Need of invention

Cardiac arrest or heart attack generally proves fatal because of lack of availability of proper medication in a short span of time, after irregularity in heart beats occur. During the heart attack the person tends to become unconscious. In addition to this if he is alone, he wont be able access the medical facilities at the same time, leading to death. The technique being used, now is one which involves use of permanent pacemaker in a cardiac patient. In recent invention, this pacing lead is provided with the drug and coated with SAMs. So when irregularity in heartbeats occurs, an electrical impulse is sent by the pacemaker to the pacing lead, leading to change in crystallanity of SAMs and elution of drug. This allows the heart to return to its normal state and provides time to have further treatment.

4.3.3. Mechanism

As discussed in case of medicated stents, here also pacing lead is dipped in a solution containing solvent, polymer dissolved in the solvent and therapeutic substance dispersed in the blend. Solvent is allowed to evaporate, leaving a coat of polymer and therapeutic substance impregnated in the polymer. Top coat, which is applied over the reservoir layer consist of crystalline polymer (Liquid Crystalline Polymer) which becomes less crystalline on electrical stimulus and when stimulus is terminated it essentially regains same degree of crystallinity or more then the previous. [12]

At ambient temperature SAMs serve as a barrier, preventing the drug from substantially diffusing out of coating prior to implantation that is during the storage. After pacing lead coated with SAMs is implanted in the body it functions in following modes :

1) In a first mode of delivery, release regime is either zero or steady release depending upon the chemical compositions of SAMs-forming substances. At body temperature SAMs undergo a partial transformation which forms some amorphous portion, allowing the drug to start steadily eluting at slow and substantially constant rate from pacing lead.

2) In the second mode the drug LS in burst regime. It is used when it is required to provide short period of more substantial rate of release. Release is twice as high as background release rate. e.g. in arrhythmia- heart rhythm of patient becomes irregular and needs to receive increased dosage of medication while rhythm is being corrected. This is achieved in a burst mode. After termination of the signal, i.e. after correction of irregularity, SAMs self heals quickly restoring barrier properties and hence returning device to first mode. [12]

Now the question that arises is how current from pacing leads reaches to electrical stimulus responsive SAMs via a reservoir polymer layer. The justification can be given by the doping of the polymer. Reversible doping can be achieved both chemically and electrochemically. Chemical doping involves charge transfer redox chemistry. Oxidative doping (p type electron accepting) with dopents such as I_2, AsF_5, O_2, $FeCl_3$. [15] Or we can even include conducting polymer which is compatible with the drug.

Liquid crystal polymers (LCP) are in conformity with the properties such as change in crystallinity and regaining original orientation, which is prerequisite for SAMs coatings. Ability of the electric fields to induce the controlled alignment of lyotropic LCP thin film on microfabric substrates such as pacing leads is well demonstrated.[16]

These LCPs include poly(hexylisocyanate)(PHIC), poly(benzyl-L-glutamate) etc. The poly(isocyanates) exhibit both lyotropic and thermotropic crystallinity for side chain alkyl group lengths from n= 4 to 11. These polymers are oriented by electric field while in solution and solidified into soluble, oriented structures by solvent evaporation. With the application of electrical stimulus LCPs change from highly ordered smectic orientation to neumatic transition.[17]

The susceptibility of rigid helical poly(alkylisocyanates) to electric field orientation can be shown by measurement of Kerr constant $K= (\Delta n/cE^2)$, where Δn is difference in the refractive index parallel and perpendicular to the applied field E, with c is the concentration.[16]

Schematic illustration of changes in orientations of LCPs: (I) Change driven by the action of an electric field on the bulk of the LCP; (II and III) Surface-driven changes in orientation leading to either formation of a helical twist in the LCP (II) or an orientation of the liquid crystal that is perpendicular to the surfaces (III)

These changes in orientations either of I, II, III affects the crystallinity which causes the drug to elute. Since these are LCPs, removal of

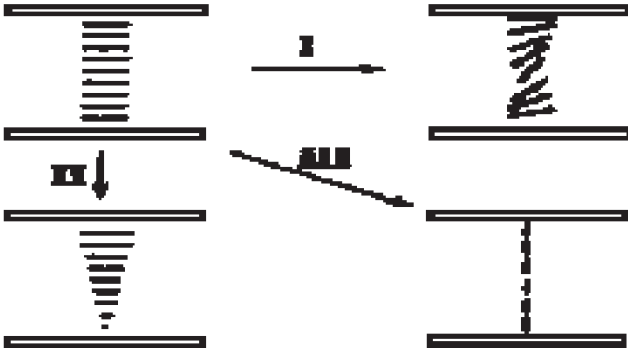


Fig. 4 : Effect of Electric field on LCPs (Ref.7)

electrical impulse will cause it to regain the smectic alignment and hence crystalline form, returning to 1st mode of drug delivery.

4.4. Antimicrobial Coatings

The present invention relates to an Electro-statically Self-assembled coating having biologically active agent incorporated therein. More particularly the invention resides in a wound dressing having an anti-microbial coating within the dressing construction wherein an anti-microbial agent is released from the dressing over a period of time. As discussed earlier, this invention also provides ESA coating having flexible substrate comprising of alternative layers of cationic and anionic material, and at least one biologically active agent complexed within cationic or anionic material.

Cationic and anionic layers are deposited onto the substrate from dilute aqueous solutions of polyelectrolytes. Polyelectrolytes are polymers that are capable of anionic dissociation and may be constituent or substituent of polymer chain. Anionic layer is deposited over a substrate over a dilute solution of polyanions which are formed from dissociation of polyacids e.g. polyphosphoric acid, polyvinylsulphuric acid, polyamino acid, polyglutamic acid. Biologically active catonic layer is deposited over this from agents like chlorhexidine, bacitracine, gentamycine, clotrimazole, miconazole etc.

There are some inactive bilayers as well that contain platelet clays that are easily exfoliated in aqueous or polar solvent. E.g. crystalline aluminosilicates are polygonal 2-dimensional structures of thickness 1 nm and avg. diameter ranging from 30-2000nm. Isomorphic substitutions leads to net negative charge necessiting the presence of cationic counter-ions (Na^+,Mg^{2+},Ca^{2+},Li^+) in inter-sheet region. Substrates must conform to contours of skin e.g. PEMA, cellulosic, polyacrylonitrile, EVA. Surface of substrate is roughened to improve the adhesion and to increase the surface area so as to increase activity of antimicrobial agent.[18]

4.5 Glucose-sensitive self-Assembled Films

Layer-by-layer (LBL) assembly is a method to fabricate multilayer films by sequential adsorption of polymer pairs with complementary functional groups onto various substrates. It allows for fine control of the thickness, structure and composition of the resultant films. Common driving force for the film buildup is electrostatic interaction i.e. ESA. However other driving forces are hydrogen bonding, covalent bonding and charge transfer interaction. For the delivery of insulin, a self-regulated system is the most suitable because it is capable of adjusting the release rate of insulin automatically according to the blood glucose level, just like what pancreas does. Glucose-sensitive LBL films were synthesized by cross-linking and modifying the poly(vinyl pyrrolidone)/poly(acrylic acid) LBL films with PBA groups. The LBL films are fabricated on quartz slides and silicon wafers. The driving force for fabrication is the hydrogen bonding bonding between PVP, as hydrogen acceptor, and PAA, as hydrogen donor. This system was chosen because it is easy to fabricate a thick PBA modified PVP/ PAA films, which allows for loading large amount of drug. The binding of glucose with PBA groups in the films increases their degree of ionization, which in turn causes extensive swelling of the films. The swelling of the resultant films present a pH, thermo and saccharide sensitive behavior. ARS, in place of drug, is loaded in the films, which binds covalently with PBA groups in the films.

The release of ARS is faster in presence of glucose, which competes with ARS for binding sites.

In future, we expect that drugs containing diol structure, especially the glycosylated insulin, may bind to and release from the film in similar way as ARS. This novel multi-stimuli-sensitive films may find applications in self-regulated insulin delivery.[19]

5. Conclusion

SAMS has stimulated and facilitated numerous surface chemical studies and opportunities. The ability to specifically and precisely control surface chemistry enables studies of the effects of surface chemistry on countless systems. SAMS are ideal models that can be used to study phenomena such as wetting, friction, adhesion, and biological interaction. SAMS facilitate studying surface phenomena and chemistry with unprecedented control. The field of Self assembled molecular coatings is progressing rapidly.

This document has provided an overview of SAMS and its uses in medical application. The applications requirements can be complex in this area. Hence, polymers have to be introduced that can be multifunctional. It would be difficult to summarize all the uses of SAMS, but hopefully this article has provided enough information and references so that the interested reader can understand and digest the information av ailable in the literature.

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POEM

THE GOLDEN TREE....

Once upon a time a seed was sown,

It was the seed of a pleading curiosity, one's own.

The seed, lying quiet in the brain fertile
Is watered by knowledge nectar like.

It grows, slowly and surely the plant rising
Upto the height and depth of strength.

The sunlight of wisdom, makes the leaves gold,
Enchanting, is the robust tree bold.

The tree is of an enlightenment eternal,
With branches wide and roots reaching deep.

Dense is its shade of understanding,
Giving respite, from a world scorching.

Watching it remain firm, bend just as humbly,
The storms of treachery, trying it to humble.

It withstands all, not a bark is ruptured,
Its soul heads away to a liberation divine.

As its glory is being quietly contemplated,
It's torn to infinite bits, by a light infinitely strong,

Enigmatic, is the smile of that Infinite One,
Creating and consuming both, seed and the light.

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