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DRUG DELIVERY AND DEGRADATION OF BIOFILM – A REVIEW

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Abstract
A biofilm is an assembly of surface-associated microbial cells that are enclosed in an extracellular polymeric substance matrix. The biodegradability of a biofilm makes it useful in drug delivery since they are easily and rapidly broken down by various bacteria and fungi to release the component drugs. Drug delivery by degradable Layer by Layer (LbL) not only found applications in biomedicine but also has potential applications in other fields such as agriculture, waste management, and the food industries. Pulse drug delivery is important in delivering certain drugs. This means that drug release happens over a well-defined period. Controlled drug release is important and useful for example, it takes care of tolerances developed whenever drugs are always available in their target site or to take care of drugs that need dosing at a certain period of the day. New approaches were developed to allow self-control of drug release to maintain a minimum dose of drugs in the bloodstream such that toxicity of drugs in vivo is minimized. Two methods of controlled drug release are common, and they are: temporal and distributional. These were affected by the film assembly's functionality, bendability, cost, and ease of synthesis. Apart from influencing drug release, the efficiency of the drug release can also be improved by polymeric encapsulation by preserving the active form of the drug with its shielding environment. In this work, a degradation study was reviewed on LbL processing technique that encompasses rapid, all-aqueous, conformal fabrication of nanoscale coatings which are highly uniform and tunable, with the capability to spatially present active and control release kinetics for multiple species to produce major trend in the delivery of drugs and other areas of applications.

Keywords: *drug delivery, degradation, layer-by-layer, wounds and inflammation*

Introduction

Biomaterials are purposed to work directly with body systems to mend, care or replace any organ, or body function (Klopfleish and Jung, 2017; De la Oliva *et al.,* 2018). Biocompatibility should be noted as one of the essential characteristics that qualifies any material as a biomaterial. Biocompatible materials have the ability to work with a given host response in each application. A wide range of materials have been investigated as biomaterials. These include glasses, metals, ceramics, and polymers. Of all these, polymers were found to be a broad class of biomaterials, which have been widely researched for medical and related applications. This could be because of its flexibility in processing or the polymer's characteristics of various organs or tissues in the body.

Recent works in biotechnology and pharmaceutical science have widened novel frontiers in biomedical fields which require materials with biocompatibility and at most times transient existence. The transient existence of materials is highly recommended for in vivo applications such as drug delivery systems (DDS) that require implants, and conduits for directing or restructuring damaged cells. Biotechnology advances are being lately reported especially, discoveries on drug delivery systems which were identified as one of the main challenges in biomedical science (Park *et al*., 2018). Any material intended for implant must be biocompatible.

Biodegradability is another factor to be considered, such that the second surgical intervention to remove the material is avoided. Inflammation may also occur due to degradation. To prevent such inflammation, some anti-inflammatory drugs can be introduced. For this reason, any drug intended to be used must be able to supply specified minimum concentration into the bloodstream to reduce toxicity *in vivo*. In this regard, new approaches were developed to allow self-control of drug release. The use of thin films in drug delivery systems is important because of their ability to incorporate different useful materials into the film preparation; this invariably allows a controlled drug release (Park *et al*., 2018; Ahmed *et al*., 2006). To achieve self-controlled drug delivery, (LbL) self-assemblies have been widely used to surface coat biomedical materials. There have been various

reported means of production of thin film for localized and precise controlled release of active drug molecule to affected areas such that side effects or resistance development of bacteria to the drug is drastically minimized. Among the popular methods are Langmuir-Blodget, self-assemble monolayer techniques, and Layer-by-Layer (LbL) assembly (Park *et al*., 2018; Li *et al*., 2017; Goldberg, Langer and Jia, 2007; Acharya and Park, 2006).

LBL technique has helped a variety of component drugs to be incorporated within the assemblies in a precise manner according to Wu *et al.* (2015). Indomethacin (IND) was incorporated into the LbL blocks to prevent inflammation caused by acidic degeneration of Lactic acid of surrounding tissue. This shows the ability of LbL technique to accommodate a variety of drugs into its building blocks.

Pulse drug release refers to the release of a portion of the total payload in a burst followed by periods of little/no release in a defined temporal pattern (Rashid *et al*., 2022; Sri-Lekha *et al*., 2022). Pulse drug delivery could be a solution to delivering some drugs. This means that there will be a release of the drug only after a well-defined period. Controlled drug release could be valuable in that, drugs that develop biological tolerance whenever they are continuously present at the target site or for drugs that need dosing at certain periods of the day (De Geest *et al*., 2006; Lazzerini *et al*., 2003; Nielsen *et al*., 2004).

LbL assembly is recommended as a better method of fabrication of thin films for drug delivery systems because it imposes little or no restrictions on the shape or size of the substrate. It can produce wound dressing that will deliver a complex schedule of a variety of compositions of drugs, for effective therapeutic efficacy, because of its simple build-up. This could be so since some treatments may require sequential administration of multiple active agents. Fabrication of LBL does not also require high pressure or temperature. Construction of LBL is such that many layers of films are built on the substrate by alternate adsorption of the constituting materials which include different polyelectrolytes (PEs). In this process, materials interact with each other by electrostatic, hydrogen bonds, covalent bonds, and bio-specific interactions (Park et al., 2018). The main advantage of the LbL method is that it is possible to control the thickness on a nanoscale and therefore control the properties and the permeability of the shell (De Geest *et al*., 2006; Zhang, Chan, and Leong, 2013).

In considering thin film fabrication for drug delivery systems, some factors to be considered include recognition of the ability in vivo and in vitro toxicity of the drug molecules and the thin film before the film is incorporated with the specific drugs such that, appropriate materials selection for the film preparation is ensured as well as the right concentration (Li *et al*., 2017; Goldberg, Langer and Jia, 2007). Furthermore, the ability of the intended fabricated thin film to be stable physically and chemically Park *et al*., 2018; Goldberg et al., 2007). However, several methods of building and crosslinking methods are being used for drug loading onto thin films. Another consideration of interest is the targeting of drugs to the aimed sites. Park *et al*. (2018) reported in their work that stimuli-responsive polymers can be affected by the target environment, as well as been adopted as film materials such that specific drug targeting is achieved.

The release period and the rate at which the drug is released is another factor that determines the effectiveness of a pulse drug release from the developed biofilm from LBL. Drug release should take place in the aimed area without undergoing losses when delivered. In addition, the kinetics of the release should be correctly controlled such that a sustainable pulse release rather than a burst release. The controlled release can be achieved by controlling the degradation rate of the fabricated biofilm, which is dependent on the drug added, the thin film component, and the technique of fabrication of the biofilm (Park *et al*., 2018; Acharya and Park, 2006).

Preparation of Biofilm

Immobilization of drugs into the film is achieved through adsorption or by another different method which could be electrostatic interaction, hydrogen bonds, hydrophobic interaction, and van der Waals interactions (Khan and Shakoor, 2023; Yoo *et al.*, 2009). However, sometimes, porosit s required within the LbL assembly for protein delivery. The introduction of a nonporous structure into the multilayered thin film gives room for the effective building and release of protein drugs. Park *et al*. (2018), developed LbL system using poly (allylamine hydrochloride) (PAH) and dextran Sulfate (DS) by alternate adsorption unto a substrate, followed by nanoparticle production. Figure 1 is a schematic diagram of the sequence of the preparation of biofilm. The direction can also be reversed to achieve a biofilm of interest according to De Geest *et al*. (2006).

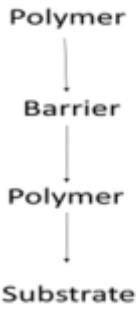

Figure 1. Schematic illustration of the sequence of biofilm preparation (De Geest *et al*., 2006)

Controlled Drug Release

A controlled release can be defined as a drug released into the body in a specified amount over a specified period (Taylor and Sakiyama-Elbert, 2006; Mehler *et al.*, 1998). Controlled release is obtained using a membrane-diffusion method. Solubilization materials are always added to the drug to improve its solubility as required. The controlled release was intended to increase efficacy and decrease toxicity influences by keeping the concentration of the drug at an optimal level. Toxicity results from higher concentrations of drugs. This informed the choice of LbL assembly method to be highly desired in controlling drug delivery and at the same time maintaining a drug concentration well above the lowest inhibitory level of concentration.

Nanocarriers are produced to locally gather around tumors by utilizing abnormal vasculatative composition of tumors, referred to as the enhanced permeability and retention (EPR) effect, described by Matsumura and Maoda as reported by Lee and Yeo, (2015). Most tumours have leaky capillary walls, by which drug-loaded nanocarriers attach to tumors. The EPR effect encourages the nanocarriers to get to the tumors selectively combined with free drugs, this means, there will be relatively low toxicity in normal cells and high drug efficacy in tumors (Lee and Yeo, 2015; Acharya and Sahoo, 2011). To utilize the EPR effect, nanocarriers remain stable in the bloodstream resisting combination and untimely drug leakage, and prevent separation by renal filtration and the organs of the reticuloendothelial system (RES) (Lee and Yeo, 2015; Ohya, 2013). In this case, particles smaller in size than 10 nm are adjudged systematic drug carriers because they are allowed to undergo clearance by kidney excretion (Lee and Yeo, 2015; Petros and Desimone, 2010).

Methods of Controlled Release

Temporal drug delivery control is intended for rapidly metabolized drugs. Temporal drug release maintains drug concentration in the bloodstream at a distinctive level. In this case, there are many drives to releasing the drug; swelling of the carrier system and the attachment of the drug-polymer to influence the rate of drug release from the carrier (Lee and Yeo, 2015). Distribution control involves drug delivery to specific areas of the body such as tumour or surgical wound. This is required to prevent some side reactions in the other areas of the body or if such drug is unable to get to the aimed region by natural distribution. Controlled drug release is attained either by an implant or the formation of a colloidal polymeric material capable of aiming ad getting to the site.

There have been several nanocarriers developed to improve the healing effect of a drug (Figure 2) as reported by Lee and Yeo, (2015). However, these nanocarriers are challenged in the control of drug release due to the large surface area per volume ratio and the limited diffusion travel distance.

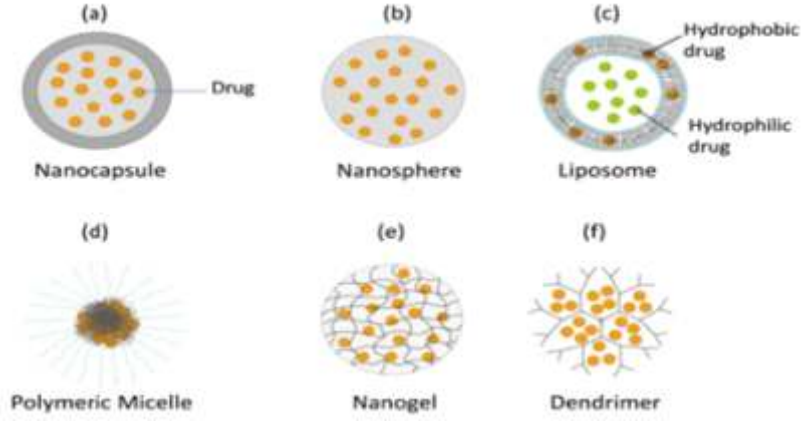

Figure 2. Typical nanocarriers for drug delivery (Lee and Yeo, 2015)

LbL can make a single delivery of active agents with a controlled profile; it is also not restricted to delivering multiple agents. The complex profile could involve many distinct profiles which is achievable through proper layering of participating drugs. An example of this is DTP (diphtheria, tetanus, and pertussis) vaccine given as a multiple-dose to infants between 2 – 15 months of age and lastly, at age 4-6 years as a final follow-up can be administered as a single dose which could automatically release the drugs with the planned desired doses. This will help eliminate parental incompliance and help reduce stress on the infant (Negut *et al.*, 2024; Chuang, 2008).

Importance of Degradable LbL

Drug delivery by degradable LbL not only found applications in biomedicine but has potential applications in many fields. In Agriculture, the controlled release of pesticides and nutrients into the soils while in oil and gas industries, the controlled release of chemicals helps reduce maintenance and repair costs.

Many works have been done on drug delivery by LbL assembly (Sukhorukov *et al.*, 1996; Schuler and Caruso, 2001; Khopade and Caruso, 2002; Sukhishvili and Granick, 2002; Cung and Rubner, 2002; Hahn and Hoffman, 2004) but none of these developed systems addressed multiple agents' delivery in controlled and sequential manner. The existing systems are not without flaws, some systems require high salt concentration to degrade while some require pH (3.6-6.9) to degrade (Dubas and Schlenof, 2001; Sukhishvili and Granick, 2002; Thierry *et al*., 2003; Chuang, 2008). Several of the systems suffer undesirable release behaviours, unsustainable release, or even initial bursts. Some require specific enzymes for the polymer to degrade. This could be perfect for a certain situation but unsuitable for general applications (Khopade and Caruso, 2002; Chuang, 2008; Srilekha *et al*., 2022).
Most biomedical composite materials are developed in a way that they are characterized with the ability to biodegrade to prevent any second surgical intervention (Herich and Polaj, 2002; Wu *et al*., 2015). In the past years, layer-by-layer self-assemblies have been widely investigated (Boudou *et al*., 2010; Hammond, 2012; Shah *et al*., 2012; Wu *et al*., 2015). pH-sensitive LbL coatings were found capable of releasing drugs as a result of pH-induced decomposition or changes in the permeability of the LbL building blocks. LbL systems built by hyperbranched polymers have stimuli-responsive behaviours which are better compared to their counterparts since they have distinct conformations (Tomita *et al.*, 2008; Kim *et al*., 2009; Wu *et al.,* 2015). Dendrimers such as poly(amidoamine) most likely enhance the dissolution of drugs that are hydrophobic by covalently interacting with drugs and therefore, good to build anti-inflammatory drugs in the dendrimers and then use them as LbL building blocks (Bock *et al*., 2014; Wu *et al*., 2015).

Inflammation of tissue and degradation can cause a reduction in the pH of the tissues closer to the implant material. The pH-sensitive release profile can be evaluated in vitro to study the self-regulated release technique from the LbL coatings. In the work by Wu *et al*. (2015) where P/S ({PAMAM-COOH/star-PDMAEMA + (IND-loaded PAMAM-COOH/star-PDMAEMA)$_6$} and AP/S ({ALN-PAMAM-COOH/star-PDMAEMA + (IND-loaded PAMAM-COOH/star-PDMAEMA)$_6$} were used as LbL coatings, both coatings released more of IND at pH 6.0 than pH 7.4 during the whole process, showing the pH sensitivity of these LbL coatings furthermore, in both cases, faster release were observed at the beginning and subsequently slowed down with time. These LbL coatings, therefore, have all it takes to release IND at normal physiological conditions (pH 7.4). This may be connected to the swelling of the buildup in the solutions. IND release profile in response to changes in pH is influenced by the permeation of H^+ into the LbL buildup developed by the star polymers and dendrimers. These could further be characterized by structure rearrangement of the star-polymer, leaving a large microsized pore. The large microsized pores were formed by the acidic treatment, showing that the LbL buildup went through phase separation and reorganization in the solution (Lutkenhaus *et al.*, 2008; Rashid *et al*., 2022).

Degradation with time variation results in very rough surfaces. This could be due to breaking off from the coating and significant substrate degradation. The degradation and collapsing of the LbL coating layers and the degradation of the polymer created a rough surface. The exposed surface would accelerate the rate of and cause more inflammation. This informed the use of IND to suppress local inflammation and by its adsorption tightly to the substrate surface; the degradation did not destroy the interface.

Dissolution of nanoparticle components would cause an additional level of release that can be controlled with poly (ethyl methacrylate (PEM) dissolution for complex drug release profiles. As a result of drug diffusion, polymer arrangement, and other factors that may reduce the stratification of PEMs, LbL however, may not show controllable organized release. It is therefore pertinent to identify and develop effective ways to improve release control. As a result of vast differing timescales and importance in infections which range from acute infections to longer-term chronic modes (Harris and Richards, 2006; Chuang, 2008; Lynch and Robertson, 2008), antimicrobial coatings with controllable drug release rates are required. A coating that has control over those parameters would be highly needed. This can be obtained by a biodegradable coating that will control the sheds from the surface to release antibiotic drugs loaded into the LBL.

LbL is a hydrolytically degradable thin film developed by layer-by-layer (LbL) build-up comprising of antibiotics used in the treatment of infections (Lucke *et al*., 2003; Wood *et al*., 2005; Esposito and Leone, 2007; Chuang, 2008). To discourage bacterial infection on medical implants surface, an effective coating with control release is desired. Some antibiotics i.e. gentamycin has been proven to go directly into LbL system without any pre-modification which makes LbL buildup a simple one (Chuang, 2008).

Many attempts have been made to improve multi-day release for full infection control. These include alternations of components, antibiotic encapsulation, insertion of nano-degradable layers, and thin film cross-linkages. Most of these did not yield satisfactory results. However, the inclusion of protein co-excipients has proven to show good promise. To achieve better result, synthetic prodrug design, and sophisticated carrier systems are suggested.

Alternatively, the natural use of polymeric antibiotics such as antimicrobials and peptides (AMPs) was adjudged a better candidate because of their broad-spectrum, charged structure, and potent activity.

Electrochemically degradable LbL films

The degradation of fabricated film is always affected by the potential difference between the film and the body or target site. (Gorantla *et al*., 2024; Chuang, 2008) confirmed that constant voltage and cycling voltage ranges between 0 and 1.5 V can influence film dissolution and subsequent release of drug which means, drug delivery systems can actively be influenced by the voltage applied externally. This method is expected to minimize unexpected or uncontrolled drug releases.

The reductively degradable system is degraded by intracellular glutathione and is thereby stable in the extracellular environment. This was said to be normal for drug delivery, which is meant to be released between a cell, which includes plasmids for gene therapy (Chuang, 2008). The drugs must be deposited on a particle that is small enough for efficient cellular uptake. This concept is demonstrated by *Wood et al*. (2005) in which [Cys(Lys)$_{10}$ Cys]n were produced by the Oupicky method and covered with polyanionic heparin in a 20-bilayer film. It was reported that degradation occurred only in the presence of glutathione (Oupicky *et al.*, 2002). More so, the system that is prone to hydrolytic degradation still holds the most potential as it has been extensively characterized and has a broader range of prospective usages. When electrochemical and reductive systems are produced successfully, it will be important since they have unique properties such as intercellular targeting and active control which means additional insights into LbL drug delivery systems that is not available from the hydrolytic system. Deposition of barrier layers in between different therapeutics LbL was meant to introduce greater control on sequential release. The control is further achieved by thickness and level of crosslinking in a way to prevent interdiffusion of the drugs in between layers.

Degradation Studies

Biodegradable polymers in drug carriers include polyesters, polyamides, poly(amino acids), and polysaccharides. All these releases the drugs by hydrolytic and/or enzymatic degradation of the ester, amide, and hydrazine bonds (Lee *et al*., 2011; Park *et al*., 2011; Lee and Yeo, 2015). Matrices formed by polymers such as poly (lactic-glycolic acid) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL) go through degradation. This results in degradation of the entire system. However, the ones that were made of poly anhydrides and poly (orthoesters) erode from the surface into the center as the polymer degradation proceeds faster compared with water diffusing into the system (surface degradation) (Middleton and Tipton, 2000; von Bukersroda *et al.*, 2002; Lee and Yeo, 2015). It is worth mentioning that when the distance covered by water diffusion is small and the domain size of crystallization can be prevented, the polymer degradation is noticeably increased. These polymers may not necessarily follow the common surface degradation behavior but rather display a sign of bulk degradation (Lee and Chu, 2008; Lee and Yeo, 2015). The degradation rate of polymers is used to determine the drug release kinetics. This will be a function of the molecular weight, group monomer composition, and crystallinity (Fredenberg *et al*., 2011). The reason why biodegradable polymeric system is used in the building block of LbL is its ability to break down into components that can be readily removed from the body with no side effects after degradation or swelling and rupture of the carrier matrix (Figure 3).

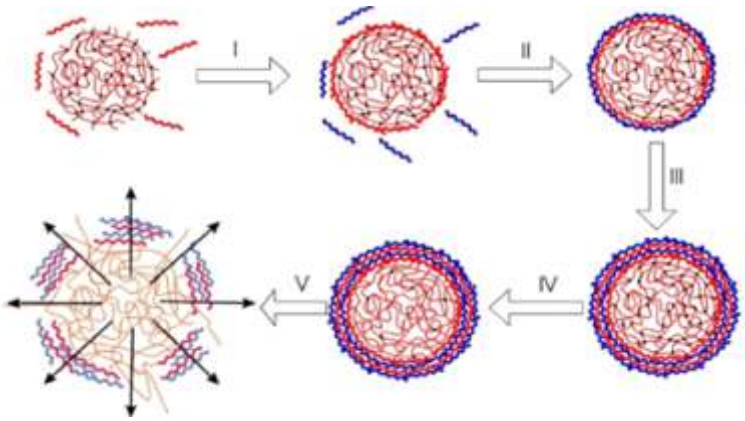

Figure. 3. Schematic Representation of a degradation procedure; (i), (ii), and (iii) represent the coating of the microgels by sequential adsorption of oppositely charged polyelectrolytes, (iv) represents degradation by hydrolysis that starts with swelling and (v) represents the rupture of the core membrane to release the drug (De Geest *et al*., 2015)

In this process, the drug will be released from the carrier by either hydrolytic or enzymatic cleavage of the linkage between the drug and the polymer. The drug release kinetics is controlled by the rate of cleavage. Enzymatically cleavable drug-polymer conjugates are used to target specific drug delivery, peradventure, the enzyme is concentrated in the target tissue (Khadke and Islam, 2022; Lee and Yeo, 2015; Almeria *et al.*, 2011).

Drug-releasing profiles are generally described in two phases: diffusion phase and polymer degradation. It was reported that the first stage, which is the diffusion phase is significantly controlled by agglomeration properties and greatly influenced by particle size in both quantity released and kinetics of release such as rate. The second phase is, however, less affected by the particle size (Almeria *et al.*, 2011; Bock *et al.*, 2014). Smaller particles were meant to degrade faster because of the increased surface area-to-volume ratio (Anderson and Shive, 2012; Bock *et al.*, 2014).

Although poly (ethylene glycol) (PEG) is known to increase burst release, PEG was equally known to reduce cumulative release because of its more acidic nature due to high protein aggregation in the solution (Lu *et al.*, 2000; Bock *et al.*, 2014). It was also noted that a low molecular weight polyethylene glycol (MWPEG) was efficient in reducing burst-release protein-polymer interactions. Importantly, particle size characteristics obtained from different processing parameters affect the release kinetics. The polymer can efficiently protect therapeutic molecules after administration. They also provide sustained delivery on system degradation (Bilah *et al.*, 2005; Bock *et al*., 2014).

3.3 Effect of poly (ethylene glycol) (PEG) on protein release

The kinetics of drug release of some polymeric formulations that include poly (ethylene glycol) (PEG) as a solubilizing agent capable of tailoring the release profiles when 1 and 5 wt% serum Albumen (SA) – loaded electrospray microparticles were studied by Bock *et al*. (2014). Two molecular weights (PEG 6K and PEG 35K) and two contents (5 and 10 wt %), in the matrix were studied. The profiles for the release for SA loading of 1 and 5 wt% were compared. It was found that the higher loading generated a release of 71%, with a 66 % burst in 24 hours. This profile pattern was attributed to the protein molecules considered to be localized, and close to the surface of the particles which were subjected to quick solubilization. The diffusion coefficient of solute in an electrospray droplet decreases with increasing concentration of solute i.e. (5 wt%). At this point, solutes could no more diffuse properly toward the center of the electrospray droplet during solvent evaporation, and thereby concentrated at the surface, leading to a fast release by diffusion in the first few hours of penetration of water. However, the 1% loading did not generate a similar burst release and provided sustained release over the period of 3 months, due to a better protein distribution within the particles.

The overall cumulative release was lower after 3 months, suggesting that there was an incomplete release. This was adjudged to be either a result of protein-polymer interactions in solution or due to the protein still being released after. This might be a function of the polymer used; hydrophobic polymer can take longer time; to degrade if used in the form of microparticles Woodruff and Hutmacher, 2010).

As reported by Chuang, (2008), films were immersed in a buffer solution in an air-tight sealed glass. The films were then removed at different times and thoroughly dried in a stream of dry nitrogen; the thickness of the film was measured with an ellipsometer at about 10 different locations on the surface of the film. The measurements were taken in triplicates and average readings were recorded. The films were re-immersed in buffer solution after the measurements.

Chuang studied drug release by constructing a radio-labeled drug. Drug release experiments were performed by submersing each film in 50 ml of 1 × PBS buffer in 200 ml air-tight glass. A 1-ml sample was extracted at different time points and analyzed by the addition of 5 ml of ScintiSafe Plus 50% (Fisher Scientific) before measurement. As a means of precaution, the buffer solution was prevented from evaporation.

Data obtained in Disintegration per minute (DPM) were converted to micrograms of drug release by a conversion factor of 2.2×10^6 DPM = 1 μCi.

Investigation of drug-building systems and release are important tools in the designing and validation of a potential drug carrier system. The major challenge with the drug system was the burst release of drugs. The lack of a prolonged release would adversely limit the applicability of the system for drug delivery. Muhlen *et al*. (1998) investigated solid lipid nanoparticle (SLN) systems for drug administration to see if a prolonged release was feasible (Stankovic *et al*., 2014). In their study, lipid microparticles were prepared by dissolving the drug to be incorporated in the melted lipid, pouring the molten lipid-drug solution into liquid nitrogen, and subsequently grinding the solidified mold. Drug release from SLN was investigated at 37°C in phosphate-citrate buffer and pH 7.4 for tetracaine and etomidate-loaded SLN was done in distilled water with pH between 5.5 - 6. Samples were drawn and filtered. The filters were validated concerning drug adsorption and analysis was performed with a spectrometer. The influence of surface area was assessed by preparing lipid particles of differing sizes by grinding process, fractionated by sieving, and the drug release studied.

It was reported that a prolonged release of tetracaine for at least 6 hours was only possible with particle size >125 µm. Particle sizes below 40 µm exhibited a 100% release in only 1 hour. This means that the controlled adjustment of release can also be achieved by changing the chemical nature of the matrix: surfactant and concentration of the surfactant. The temperature of production also affects the release profile. When the particles were ground with the use of a surfactant, drug release can further be accelerated.

Factors Affecting Rate of Drug Release

The rate of drug release in LbL buildup is often affected by, the type of barrier layers, the molecular structure of the polymer, and the solubility of the polymersomes.

The Barrier Layers.

The rate of drug release is affected by the barrier layers. The delay and rate of release are a function of the multiple cross-linked barrier layers that formed part of the LbL. This is valuable and could have a direct influence on drug delivery; it implies that both the rate of drug release and timing can be extensively manipulated by the buildup of the crosslinked bilayer. The barrier layers alone might not be enough to affect the delayed release, but the top layer could also serve as additional diffusion control for the release. It was also established that the nature of the base film on which the crosslinked barrier layer was adsorbed influences the final properties of the barrier layer.

Type of Polymer System

Another factor that plays prominent roles in the drug release rate are the type of polymer systems. This refers to the molecular weights of the contributing polymers, and deposition condition or type. Molecular weight directly affects the release rate of drugs from the polymer. Stankovic *et al*. (2014) reported that the release of Ins from 30[PCL-PEG_{1500}] – 70[PCL] was slower and continuous within 80 days. Consequently, the release of Lys from the polymer was slowest, within 160 days.

Polymer 50[[PCL-PEG_{1500}] – 50[PCL] (with PEG content, 37.5 wt%) also showed an increase released as shown in Figure 4.

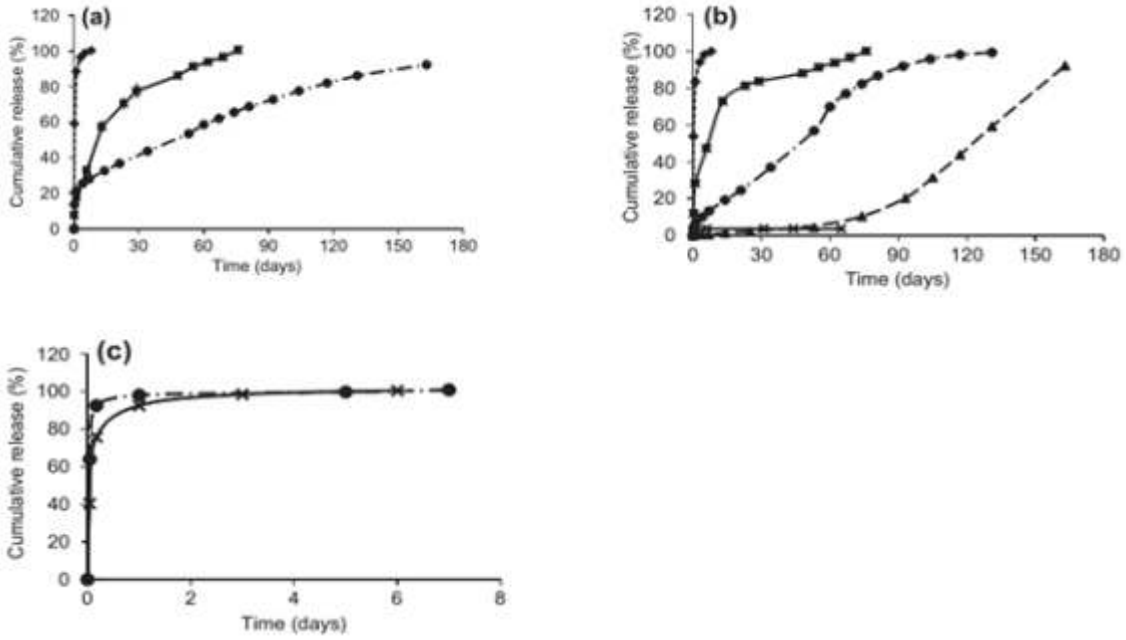

Figure 4. Proteins Release profile from some PEGs: (a) 30[PCL-PEG1500]-70[PCL], (b) 50[PCL-PEG1500]-50[PCL] and (c) 70[PCL-PEG1500]-30[PCL], Gos (♦), Ins (■), Lys (●), CA (▲), BSA (X). (Stankovic *et al*., 2014)

The fastest release was seen within 8 days, but a complete release was observed in 160 days. However, the polymer with the highest PEG content (52.5) wt%), 70[PCL-PEG_{1500}] – 30 [PCL], released over 60% of lys in the first few hours. The other protein was released within the subsequent 7 days that followed.

Solubility of the Polymersomes

Solubility is another factor that affects drug release/degradation. According to Ahmed *et al*., 2006, drug carriers that solubilize a wide range of drugs is promising in chemotherapy applications. In their work, water-soluble DOX and insoluble TAX were loaded

into biodegradable polymersomes for the purpose of multi-drug delivery. Doxorubicin (DOX) and paclitaxel (TAX) are drugs with distinct solubility features, however, they are among the popular anticancer drugs in clinical use recently, most importantly in the treatment of different aggressive breast cancer. Studies have also shown that regimens that combine DOX with TAX reduce tumours compared to the separate drugs (Gustafson *et al.*, 2005; Ahmed *et al*., 2006; Negut *et al.*, 2024). However, to obtain a better result, it must be ensured that both drugs target the same cell and maximize cytotoxicity while minimizing the chances of cell resistance to any one drug. According to the study by Ahmed *et al*. (2006), tumour shrinkage was compared when treated with the free drug and polymersomes (Tax + DOX) – polymersomes. In the work, tumors were discovered in nude mice by a single subcutaneous injection of 2×10^6 MDA – MB231 cells by a single tail–vein injection with four mice per group. The tumours were then allowed to grow to an average size of approximately 0.5 cm^2. The control group on the other hand got doses of empty polymersomes intravenously. Tumour size was measured from day one to five for each treatment group and the relative tumour volume 'V' was also estimated. From the estimate, the tumour size doubles in only over 24 hours. However, tumour size was normalized to ensure an even average size for the tumours in all the test groups.

On the first day of injection, tumours in both the treatment group and control group were the same size. A single injection of the maximum tolerated dose of polymersomes was followed by daily monitoring of tumour sizes compared with the controls. The result in Figure 5 shows that a single dose of injection of drug-loaded polymersomes has potent antitumor activity without any other obvious side effects. Treated tumours reduce in size compared to the initial area and maintain a small size below 40% of tumour size in the control group.

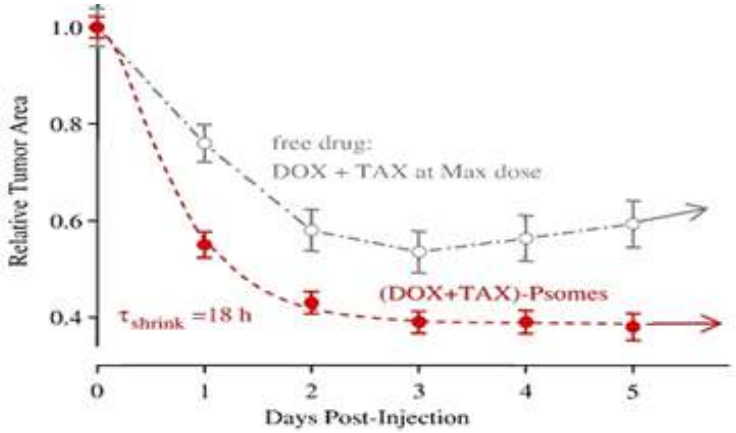

Figure 5: Effect of free drug polymersomes on tumor size (Ahmed *et al*., 2006)

Co-administration of free drugs that make polymersomes (DOX and TAX) does not reduce the size of the tumour as much, as fast, or in a sustained way. After day 5, the tumour was reported to have regrown about 50% bigger with free drugs compared with polymersome delivery.

Also, in the work, it was reported that the degradation of carriers resulted in DOX fluorescence diffusion to the tumor sections. After 2 days, which was enough time for complete hydrolysis and drug release from the copolymer carriers, DOX fluorescence looked indistinguishable from free drug which was a result of diffusion. However, a complete understanding of polymersomes mechanisms in vivo was not certain. Tumour shrinkage with dual-drug loaded polymersomes was more viable and consistent, probably due to induced degradation phase transition in a mechanism for controlled release of drugs. In any case, it was concluded that the principal goal of demonstrating that dual drug polymersomes as effective drug delivery systems in vivo was successfully achieved.

Drug release starts with hydrolysis and pore formation. The continued growth and propagation of pores in the membranes make unstable the vesicle architecture and vesicles thereafter turn into worm-like micelles (Ahmed *et al*., 2006). These micelles were said to be several microns long with an average diameter of d~14 nm which was an indication of a distinctive molecular packaging in the micelle cores. This phase transition in the degradation of copolymer systems has been reported to be simultaneous with the release of a hydrophobic drug such as TAX.

As phase transitions that played significant roles in drug release kinetics occur, it is accompanied by slow kinetic water-soluble DOX and insoluble TAX from degradable and non-degradable polymersomes at 37 °C

and neutral pH. Ahmed *et al.* (2006) further confirmed that a slight reduction of release kinetics of hydrophobic TAX versus hydrophilic DOX can be attributed to the formation of micelles which provide another deports for sustained delivery of the hydrophobic drug. However, times of drug release from the degradable matrix are expected to be slightly shorter in the tumor microenvironment due to low pH.

Future Outlook

The human suffering and high cost associated with the biomaterials and biomedical device-induced infections caused by microbial contamination and macromolecules adhesions informed the development of antibacterial, and antibiofilm coating (Srinivasan et al., 2021; Shan and Shakoor, 2023; Negut *et al.*, 2024). To tackle these problems, LbL coatings must not only be effective in presenting bacteria colonization and subsequent biofilm formation but also could prohibit the adhesion of other biomacromolecules. Polymeric molecules are considered the base units for the generation of such dual-functional coatings due to their adjustable physiochemical characteristics. A well-designed dual-functional coating on biomaterial will continue to be developed and applicable in biomedicine. Meanwhile, for effective and practical applications, researchers need to consider integrating a surface functionalized approach that will broaden the windows in LbL development.

Conclusion

Controlled or delayed release of drugs can be achieved by designing a physical interlayer separating multiple components within the LbL film such that inter-layer diffusion is blocked. It has also been established that a wide range of material properties can be developed from a single, relatively simple set of materials by careful control strategies such that interlayer diffusion is controlled. If the attributes of LbL processing technique are utilized, the method will be a great tool in biomedicine. This method encompasses rapid, all-aqueous, conformal fabrication of nanoscale coatings with the capability to spatially order active and controlled release kinetics for multiple species and the development of significant opportunities in drug delivery. Overall, the reviewed summarizes insights from survey of literature and shed light on the interplay between innovation and the practical implementation of LbL in drug delivery.

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Conflict of Interest

The author declares no conflict of interest.

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