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Antibacterial Activity of Amphiphilic Polymers and Synthesis

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Abstract: *polymer chemistry has various application in medical field in modern days lots of polymers are using in medical field such as antibacterial agent in this review we are exploring the important and collectible information about synthesis of antibecterial polymer and their biological activity .in this review we exploring some important amphiphilic polymers and their synthesis and also we making a bridge of connection that how these amphiphilic polymers are important in medical and pharmaceuticle field . we are discussing here the synthesis of some important amphiphilic polymers and their antibecterial activity*

I. Introduction

polymer chemistry have numbers of application in various field but due to modern challenges of bacterial growth ,infections and high resisting power of bacteria against traditional medicine .some researchers apply polymer application on bacteria and found tremendous results and new class of polymer started called amphiphilic polymers . Amphiphilic also known as amphipathic are chemical compound with hydrophilic and lipophilic properties .amphiphilic polymers are composed of hydrophilic (water-loving) and hydrophobic parts[1] .due to their active attention towards bacteria it has become a wide research field in these days. Amphiphilic compounds have lipophilic (typically hydrocarbon) structures and hydrophilic polar functional groups (either ionic or uncharged)[2]. Protein,peptides and some block co-polymer also example of amphiphilic compounds. by surface coating of some polymers we can also derived amphiphilicity in them

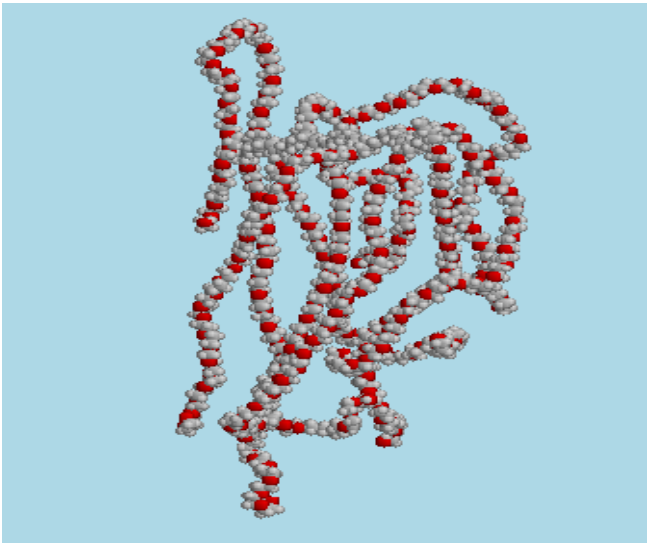


Figure 1 an example of amphiphilic polymer

Peptides are also part of amphiphilic polymers and a component of the innate immune system which are mostly positively charged molecules with short amino acid chain .the attention towards amphiphilic polymers is because of some report suggested that important bacterial infections in the U.S. and throughout the world are becoming antibiotic resistant and some would pose that the current drug pipeline is woefully[3]. Antibiotic resistance is biggest problem in public health problem. That's the reason why we exploring amphiphilic polymers in these days .some amphiphilic polymers also have anti cancer properties .amphiphilic polymer and their block polymers have special ability of self-assemble and commonly use in to stop the growth of infected tissue[3-4]. amphiphilic polynorbornene derivatives shows Lipid membrane disruption activities Against liposomes and these activity is helping to retard the bacterial infection . most amphiphilic polymers have target based activity against bacteria and infected tissue, after their job they does not exist more or does not hurt biological system because such of polymers are bio degradable[5], biocompatible[6], non-irritant and exhibits good film-forming properties and high mechanical strength and adhesion[3] . some amphiphilic polymers are neutral and some are cationic .most of cationic polymers are water-soluble . The mechanism of

antimicrobial activity depends largely on the hydrophilic–hydrophobic balance. in these day researchers is artificially balancing hydrophilic–hydrophobic balance to form polymers more target accuracy .some amphiphilic co-polymers have great defense system against bacterial activity , amphiphilic co-polymers can synthesized by Incorporating certain amounts of hydrophobic comonomers to the hydrophilic polymers. This feature of synthesis gives controlled balance that delivered great benefit to controlled drug release, gene therapy, and cancer therapy[7], etc. Water-soluble amphiphilic cationic polynorbornene derivatives, which exhibited the highest level of activities against liposome membranes have phospholipid building blocks in their membrane assemblies . These phospholipids blocks change their supramolecular Ordering by incorporating with other amphiphilic polymers within their membrane Assemblies

II. Synthesis Of Amphiphilc Polymers

Due to high demand in public health sector and serious activity of amphiphilic polymers researcher have developed various style of synthesis .there is lots of chemical technique available for synthesis but lake of physical technique put amphiphilic polymers still in developing area [7,8] .but in these days we developed some technique to controlled the amphiphilic polymers synthesis .in controlled synthesis we can manage or balance the hydrophobic and hydrophilic part according to the requirement . amphiphilic Polymer and their block co-polymer are mostly prepared by these techniques, group transfer polymerization (GTP), reversible chain transfer polymerization (RAFT) and atom transfer radical polymerization (ATRP) .sulfonation of polystyrene for the preparation of amphiphilic copolymers is also a well known process[8] .all these process are carried out by lots of different and critical path way .we are discussing here preparation of some amphiphilic polymers shown below.

2.1 hyper-branched polyglycerols (HPG) synthesized by using trishydroxy- methylpropane(TMP) as initiator.

Amphiphilic polymer HPG is widely used in pharmaceutical field not because of their direct activity against bacteria . basically HPG delivered nano-particle of moleculas that helps in drug delivery system . HPG was synthesized according to the literature procedure using TMP as initiator .A ring opening polymerization of TMP in the presence of oleic acid gives hyper-branched polyglycerols(HPG) and further esterification gives amphiphilic hyper-branched glycerols (AM-HPG) with structure of hydrophilic core and hydrophobic shell shown in fig.2 (AP-HPG)[9].we get AP-HPG in nanocapsules form .

when we treat Fe3O4 with AP-HPG ,AP-HPG gives the nanoparticles of Fe3O4. And then the Fe3O4 nanoparticles further grow in to larger Fe3O4 particles with various shapes induced by self-assembly of AP-HPG nanocapsules [10] .Fusiform, egg-shape and short rod-likeFe3O4 particles

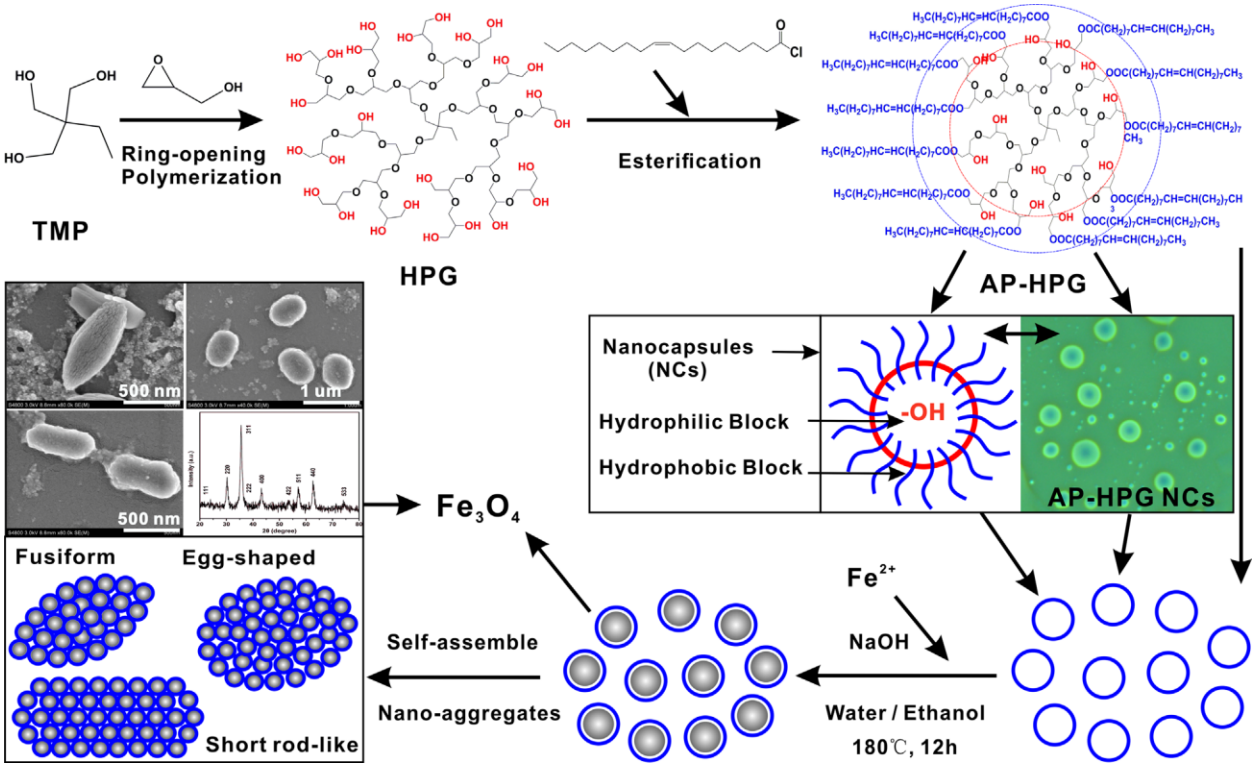


Figure 2 synthesis of AP-HPG and fabrication of Fe3O4 aggregates with various shapes via self-assembly.

Fe3O4 particles with various shapes induced by self-assembly of AP-HPG nanocapsules can controlled by treating AP-HPG in controlled condition .self-assemble is the important feature of most of amphiphilic polymers and this feature help amphiphilic polymers to adjust according to various becteria . Fe3O4 varied according to different self-assemblies of AP-HPGNCs by controlling the concentration of AP-HPG. The Fe3O4 nanoparticles with different sizes and shapes may show different interaction intensities of adsorption and desorption ,which result in forming Fe3O4 nano-aggregates with various shapes by different aggregation ways[8]. AP-HBPs exhibit the aggregation-free in solution because of the amphiphilic nature, which are the unique supramolecular self-assembly behaviors belonging to AP-HBPs[7]. The final product is mixer of fe3o4 nano-particles and AP-HPG .the AP-HPG dried by toluene and Oleoyl chloride added dropwise. we use chloroform to dry this solution and Then, The resulting products were washed with ethanol and centrifuged. and remove chloroform by rotary evaporation and also remove AP-HPG. to obtain the powder Fe3O4 (in nano-particle size) 10mL ethanol solution of AP-HPG with different concentration (0.05 mM,0.1mM,0.12mM) was added to the Fe3O4 precursor respectively . the nano-particle delivering feature of AP-HPG were confirmed by FTIR. ester bond in AP-HPG give the absorptions at 1741.9cm_1 and 1171.9cm_1 . Oleic acid used for esterification that also indicate the existence of ester bond . AP-HPG was synthesized by HPG breaking in esterification[15-17] . synthesis of Fe3O4 and HPG by solvo- hydrothermal methods generating various shapes Fe3O4 nanopar- ticle aggregates depending on different AP-HPG concentration[12] . As a magnetic nanomaterial with changeable shape ,the obtained Fe3O4 hybrid material can be widely applied in some particular fields of pharmaceutics

2.2 Synthesis of Methyl methacrylate and sodium styrene sulfonate amphiphilic polymers by atom transfer radical

It has been found that block polymer have higher antibacterial activity rather then source polymers Blocks polymers are incompatible giving rise to a rich variety of well-defined self-assembled structures both in bulk and in selective solvents. for this polymerization the macroinitiator We use are I-PSSNa, PMMA-II-PMMA and III-PMMA macromonomer that initiates the polymerization reaction[11-12] . The I-PSSNa macroinitiator was synthesized for this polymerization by adding to a dried round-bottom flask of SSNa , benzoate copper(I)bromide and for other polymer we use MMA as microinitiator and 2,20-bipyridine This Synthesis is based on living polymerization technique like anionic polymerization[13] .the co-polymer of methyl methacrylate and sodium styrene sulfonate self-associate in water with balancing in water by hydrophobic core and hydrophilic poly styrene sulfonate corona[13-14] . The I-PSSNa-b-PMMA (PIa) block copolymer was synthesized using the I-PSSNa macroinitiator , MMA , CuBr and 2,20-bipyridine with ratio 20/1/1/2 in a methanol/water (80/20) solution. The resulting co-polymer is dried in flask at 25 _C for 24 h, under argon charged with SSNa and purified by dialysis . The characterization of such block copolymers is not straight forward mainly due to the tendency of the different block to aggregate .these block change according to their surrounding molecules

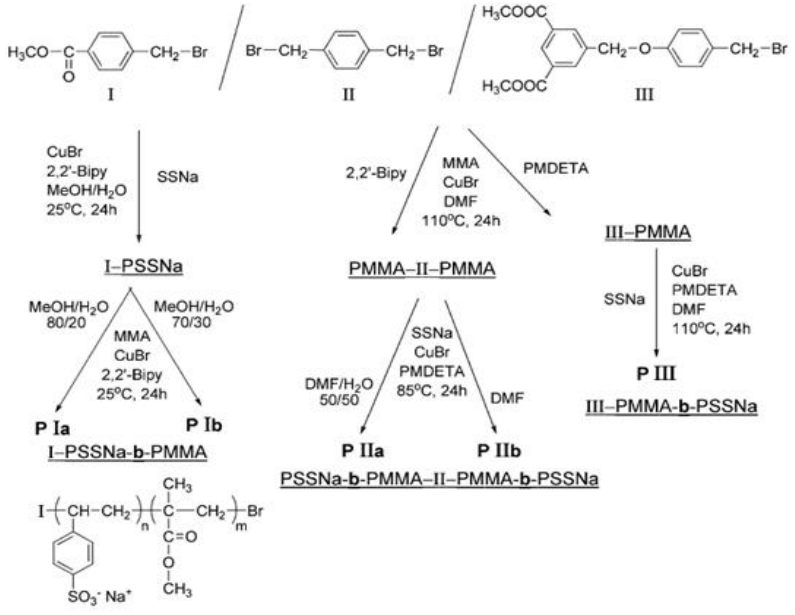


Figure 3 synthesis of macroinitiators and block co-polymers via atom transfer radical polymerization

The above picture showing the initiation by macroinitiator and further polymerization and resulting diblock polymers . With this free radical polymerization some random copolymer also synthesized[14] .after the completion of polymerization no propagation of block copolymer was observed as it was verified by 1H NMR and FTIR spectroscopy. the hydrophobic character of this copolymer is very high.and that were found to be readily soluble in water[16]. The spectral study of these macroinitiator In the 1H NMR spectrum of the I-PSSNa macroinitiator, the two peaks observed in the 6–8 ppm region are attributed to the aromatic protons, while the large peak observed at _1.5 ppm is assigned to the protons of the polymeric backbone. the peaks at _3.7 ppm and _1 ppm are attributed to the methoxy- and a-methylgroups of PMMA .first co-polymer above _250 _C and it is completed rapidly, resulting in an almost 95% weight loss at 400 _C that showing the depolymersization the second one PMMA is more stable at high temperature[15-17] . The differences in the thermal decomposition of the two polymers can be used for both the qualitative and quantitative characterization of the synthesized amphiphilic block copolymers[16]. Pyrene fluorescence probing studies were performed to investigate the possible self-assembly of these water-soluble copolymers. surfactant micelles in water show that the self-assemble property of co-polymers vary according to operator concentration[18] . This change suggests that these copolymers self-associate in water, consisted of a hydrophobic PMMA core and stabilized in water through a hydrophilic PSSNa corona[19].and this self-assemble feature make a good antibacterial agent

2.2 Synthesis of amphiphilic derivative

Chitin gives so many different kind of amphiphlic polymers which is most abundant in organic materials .chitin gives chitosan which is one of the most important amphiphilic polymers in material industry and also some study shows the utilization as antibacterial agent. chitosan is N-deacetylated derivative of chitin .this production is based on microwave assisted synthesis this is a power full utilizing method to obtain chitosan under extremely low reaction time without any degradation and/or property modifications. it exhibits good film-forming properties[20] .

The presence of amino groups on macromoleculas chain gives the opportunity of specific reactions such as N-alkylation, N-carboxylation or crosslinking[21] . this is thickening agents mostly used in such as paints,oil recovery, cosmetic or foods

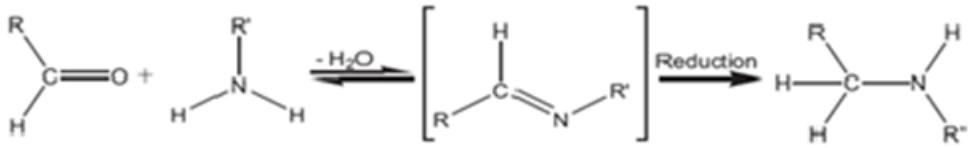


Figure 4 synthesis of amphiphilic derivative of chitosan

The above reaction is reductive amination[19] .this above process is best to performing a covalent bond between a substrate and the amine function of the chitosan[22]. On the basis of chitosan, the amine protonation in acidic condition gives cationic amphiphilic polymers . this derivatives has special core capture ability against infected tissue .

For this reaction we need constant temperature so there is Two types of process have been used to keep the tempera-true constant: the conventional heating using a jacketed reactoror microwave irradiation. and further ethenol and sodium cynobromo-hydried use to reach the adequate composition (in relation with the required degree of alkylation)[20].after about one hours of process The obtained derivative was precipitated in 10% NaOH solution.and then washed several times in ethanol/water (70/30, vol) up to the centrifugation supernatant had a conductivity value lower than a few dozens of _S cm−1,.to study microwave irradiation during the polymer reaction. Microwave-assisted synthesis we use Pulsed power mode (SPS) and dynamic mode(DYN) are commonly[22] .

One is temperature controlled mode and second is power and temperature control mode[23-24] .because of in modern days we resulting more accuracy towarding the resulting yield just because of controller environment[21] . the yields obtained under microwave irradiation are larger than those obtained with con-ventional heating. With every sample of chitosan . SPS microwave irradiation mode[31], the irradiation percentage is directly dependent on the reaction temperature. this process is also defining the compression between microwave-assisted synthesis and conventional heating synthesis[25] . Microwaves allow reaching the target temperature in a shorter time and this feature explains the great yields obtained from the first minutes .and the spectral study of final product The1H NMR spectroscopy demonstrates than no deacetylation occurs during this microwave assisted reaction and also no chain degradation . this driven amphiphilic polymers has property like as their ability to auto-associate interfacial properties of emul-sions or foams[17-20]. The final product property the surface tension experiments showed that pre-cursor chitosan has no tensioactive properties .the surface tension is show some variety .The surface tension kinet-ics is quicker and quicker when the degree

of alkylation andhydrophobicity increase. And also the surface tension values at equilibrium state seem to decrease when the degree of alkylation increases .and this is showing by both method microwave-assisted synthesis and conventional heating .finally it showing that both of synthesis property are applied but conventional heating show some breakdown in undergoing process but it doesn't seems in microwave-assisted[26] .this polymers or derivative is often use as antibacterial agent against bacteria that harm the protein structure

2.4 hydrophobic substitution synthesis

The internal substitution of some polymers is quite often in some of recent researches and their derivative have great capacity to fight against bacteria . Three amphiphilic co-polymers are synthesized by poly 2-(N,N dimethylaminoethyl)methacrylate and alkylacrylate.basically their co-polymer are synthesized by their internal hydrophobic substitution[27]. These co-polymer have shorter hydrophobic chain exhibits larger hydrodynamic diameter in dilute solution. They have good antimicrobial activity evaluated by MIC value .The mechanism of antimicrobial activity depends largely on the hydrophilic hydrophobic balance. the detailed self-assembly studies along with the evaluation of antimicrobial activity, DNA binding ability, and toxicity will open up opportunities for their use in other areas also[28]. The copolymer with shorter hydrophobic chain exhibits larger hydrodynamic diameter in dilute solution is mostly depend on concentration . The copolymer with the octyl group as pendent hydrophobic chain was found to be more effective in killing these microorganisms. The polymer-DNA binding was found to be purely electrostatic in nature.

The hydrophobes on the polymer backbone were found to have a significant influence on the binding process [25]. The hydrophobically substituted co-polymer are cationic co-polymer their ability are killing pathogenic microorganisms and acting as an antimicrobial agent.the specialty of these co-polymers is they are nonvolatile, chemically stable, and more efficient in comparison to the commonly used low-molecular-weight antimicrobial agents. for killing those pathogenic microorganisms. Moreover, the detailed self-assembly studies along with the evaluation of antimicrobial activity, DNA binding ability, and toxicity will

open up opportunities for their use in other areas also. this hydrophobic modification is based on polyelectrolyte with different hyhdrophobic side chain.the purified monomers, radical initiator and fluorescence probes are use to initiate the polymerization[26] .three monomers Dodecylacrylate (DA), octylacrylate (OA), and hexylacrylate (HA) were prepared by acylation of the respective alcohol with acryloyl chloride in a manner analogous to the synthesis of N-alkylacrylamide. The final product is a mixed polymer which was recovered by passing dry HCl gas through the reaction mixture[27]. For complete precipitation, the mixture was poured into large excess of chloroform.and further methanol with chloroform used to purify the final product .the finally observed co-polymer were chemically identified by FT-IR and 1H NMR spectroscopy .the finalized product confirmed by surface activity surface tension by surface tensiometer[29] . Viscosity measurement, Steady-state fluorescence spectra, Transmission electron microscopy.and for checking the antibacterial activity of these co-polymer an equal amount of bacterial culture was added to test tubes containing desired concentration of polymer solution in liquid LB medium. The test tubes were then inoculated at 37 ◦C for 5–7 h. Then, 50 _L from each tube was spread onto LB agar plates inside laminar flow. Finally, plates were incubated at 37 ◦C for 24 h, and the viable cells were counted .and also homolytic activity also determine by co-polymer absorption on RBC plate . to find pH activity of co-polymer the fluorescence observed in the presence of copolymers at different solution pH.and a very weak fluorescence is detected in aqueous medium with emission maximum (_max) at 460 nm

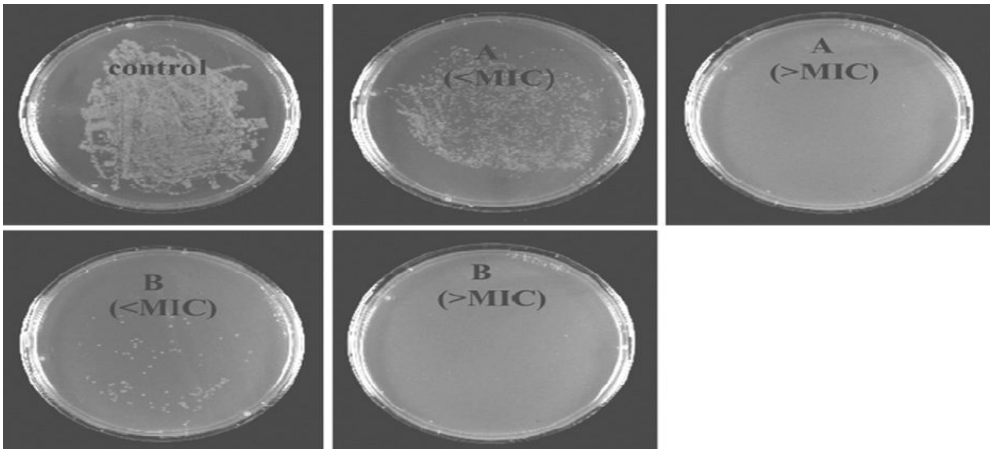


Figure 5 Antibacterial assessment images of copolymers against E.coli; (A) poly(DMAEMA-HA), (B) poly(DMAEMA-OA).

The above picture is showing the antibacterial activity against B. subtilis and E coli Bacteria. E. coli before (control) and after treatment with the HMP (above and below MIC) are shown in fig.5. first picture is showing the controlled condition and in others picture these co-polymer is clearly showing the antibacterial activity against E. coli bacteria[21-25] . deep study of above plats is showing these co-polymer have a greater killing efficiency for Gram-positive bacteria than Gram-negative bacteria. in the case of Gram-negative bacteria (E. coli), the cells are being surrounded by an additional outer membrane and hence, it is more difficult for macromolecules to diffuse through the cell wall.these three copolymer plausibly maintained the suitable balance of cationic charge with hydrophobicity for effective antimicrobial action against Gram-positive bacteria.

2.4 solid phase synthesis

In all amphiphilic polymers the peptides shows the maximum antibacterial activity so here we are discussing synthesis of some important antibacterial peptides . Gad-1 and Gad-2 are peptieds with amino acid chain and they prepared by using O-fluorenylmethyloxycarbonyl (Fmoc) chemistry[30]. For this preparation we use CS Bio peptide synthesizer with rink amide resin . Dissolution of amino acids was facilitated with 1-hydroxy-benzotriazole (HoBt) dissolved in dimethylformamide (DMF) and piperidine used for deblocking .resulting resine content peptieds were Resin washes were carried out with DMF. Upon completion of peptide synthesis, the resin containing peptide was transferred to a 10 mL syringe equipped with a filter, and washed with methanol thoroughly under vacuum . trifluoroacetic acid (TFA) use to extract peptieds from resin.the cleavage solution created by distilled water and trifluoroacetic acid (TFA) added to the resin and stirred for 2 h[31].

The resulting solution, which contained the C-terminally amidated peptide, was then extruded through the syringe into a 50 mL Falcon tube (Fisher, Toronto ON).

to remove supernatant from presipetied of peptides[32] . The precipitate was then pelleted by centrifugation at 4 °C at 2000 g for 5min. Peptide purification was performed using high-pressure liquid chromatography (HPLC) equipped with a reverse-phase DYNAMAX C-8 preparatory column .and for peptieds analysis we use high-pressure liquid chromatography matrix assisted laser desorption ionization — time of flight mass spectrometry[33] .but the finally observed peptides has various application to performed against bacteria and also it use as fundamental source in pharmaceuticals . these peptides mostly use for derived mimics or other co-polymers .

2.5synthesis by surface modification

In 1972 some scientist from Dow corning prepare antibacterial glass by using surface bonded quaternary ammonium salt [33] .by heating this glass at 70 C for 30 min with 0.1% solution of 3-(trimethoxysilyl) propyldimethyloctadecyl ammonium chloride. these surfaces were very active in killing S. faecalis bacteria even after extensive rinsing with water. Kotek and coworkers applied the same reagent on poly(ethylene terephthalate) fibers reporting that treated fibers had excellent antibacterial effect against E. coli.the antibacterial activity strongly depend on the alklyl chain length .

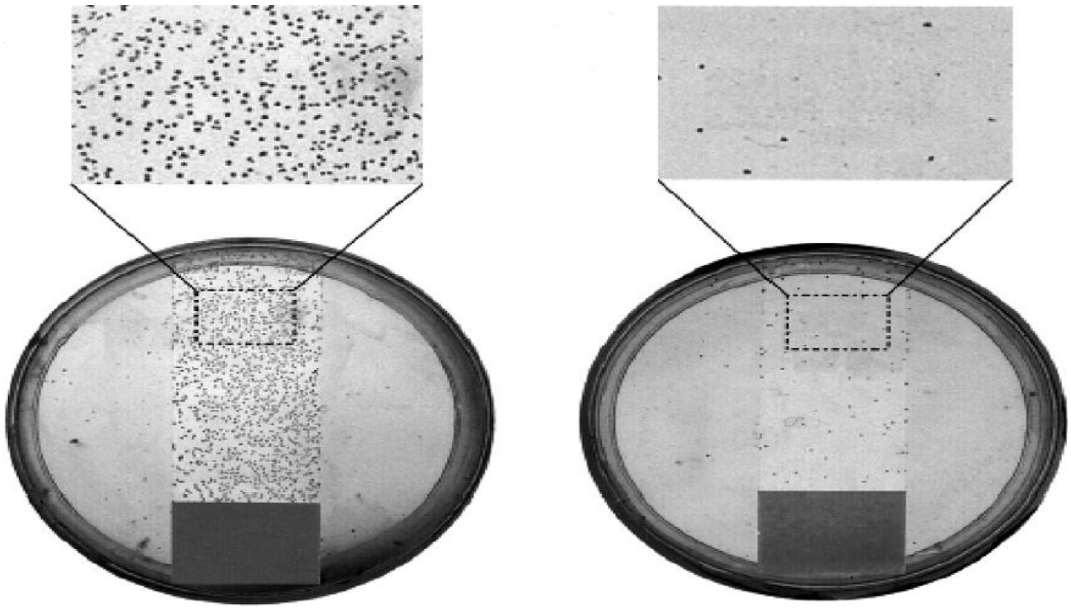


Figure 6 amino glass slide (left) and a hexyl-PVP-modified slide (right) onto which aqueous suspensions (106 cells/mL of distilled

The above fig. is showing the glass treated activity against bacteria . the untreated surface (left) has numerous colonies whereas the treated surface (right) killed almost all the bacteria (after spraying with bacteria and incubation under agar).in another study glass treated with polystyrene-b-poly(4-vinyl-N-alkylpyridinium bromides) copolymers (where alkyl is hexyl or 6-perfluorooctyl-1-hexyl) and sprayed on polystyrene-b-poly(ethylene-ran-butylene)-b-polystyrene coated glass slides. And this process show the fluorinated pyridinium surfaces are more biocidal compared to their non-fluorinated analogues. The bactericidal effect was found to be related to the molecular composition and polymer organization in the top 2–3 nm of the surface and improved with increasing hydrophilicity and pyridinium concentration at this surface.this technique is bactericidal efficiency towards S. aureus, S. epidermidis, P. aeruginosa, and E. coli.this process is also undergo not only by glass surfacing but also stainless steel surfacing too.

III. Biological Activity Of Amphiphilic Polymers

Amphiphilic surfactants and polymers display one of the most important characteristic molecular self-assemble behavior in solution .they have membranes formation ability and self assemble property to arrange themselves into bilayers.just like pepducins strongly interact with biological membranes by insertion of the hydrophobic part into the lipid membrane, while exposing the hydrophilic part to the aqueous medium, altering their physical behavior disrupting them sometimes [34].and also they create a core structure on bacteria or infected tissue to stop their growth .but when these amphiphilic polymers treated with other substant they also delivered great antibacterial power . All these activity increase their resistance against bacterial growth and that's the reason amphiphilic polymers are important part of biocidal polymer here we exploring different-different kind of amphiphilic polymers with their different activity in biological systems

3.1 Peptieds

As a antibacterial agent peptides are classified in various class .most of peptides shows their antibacterial activity in organic tissues . Peptieds and some positively charged peptieds with short amino acid chain have good target based antibacterial properties like liver-expressed antimicrobal peptieds (LEAP). LEAP-1 and LEAP-2 isolated from human blood . LEAP-2 displays constitutive expression in most fish tissues ,mainly in the livers tissue of fish[35].The isomers of LEAP also reported in servel fish species each isomers show different spectrum against gram positive and gram negative bacteria (by using method to find selectivity) . the lake of LEAP in human causes hepatitis c virus and human immunodeficiency virus infections[36] .these petieds show high expression in liver but not in kidney ,gills and heart . isomers of LEAP also found in fish species each isomers have different activity . minimum inhibitory concentration(MIC) is the method to understand the variable activity of antimicrobial peptieds .in MIC we use gram positive and gram negative bacteria and treat them on amphiphilic polymers .LEAP-2 is the human blood-derived peptide with antimicrobial activity that is predominantly expressed in the liver .basically LEAP-2 disrupts the physical integrity of bacterial membranes[37] .to find their antibacterial activity, in a experiment by He-Xiang Lia and their co-worker the LEAP-2 application on ayu (a asian fish) performed under suitable condition by injecting LEAP-2 in some fishes and put them in a overnight chamber with bacterial activity and after 24 hours brain, gills, heart, kidney,liver, and spleen were collected And after analyzing of all these organs only minimum infection was found . for study of harvested RNA and DNA of fishes tissue . we use RNA iso reagent and RNA was extracted by fishes tissue and further cDNA were synthesized from RNA iso reagent [36] .and minimum fraction was seen in RNA and cDNA. and other parameter also found into the harvested tissue by other biochemical method .the result from all fishes show good data for LEAP-2 as good antibacterial and for further study to know Antimicrobial activities of the synthetic PaLEAP-2(derived from LEAP-2) were determined against a panel of microorganisms including variety of bacteria like Vibrio vulnificus, Pseudomonas putida,Escherichia coli DH5 _, Edwardsiella tarda, Vibrio alginolyticus, Vibrioparahaemolyticus, V. anguillarum, and Pseudomonas aeruginosa . All fishes use for experiment were died in 7 days but it also important to know what amount of LEAP-2 is suitable for antibacterial activity . lower concentration LEAP-2 injected fish increased 25% servial rate . Phylogenetic tree analysis showed that LEAP-2s from ayu another fish grouped together into a fish cluster separate from the cluster containing mammalian, bird, and amphibian clusters show good antibacterial activity . maturePaLEAP-2 peptides displayed the highest antimicrobial activity ,with a MIC value of 6.25 _g/mL, toward both E. tarda and V. anguil-larum . LEAP-2 activity on V. anguillarum genomic also gives good results . DNA was studied in vitro and in vivo.and no plasmid band was detected for higher peptide concentrations but at low concentration the signal was detectable that means higher concentration in not good enough for antibacterial activity . the MIC method for PaLEAP-2 shows some several different antimicrobial activities too [37].some antimicrobial peptieds have good pathogenic organism.

But LEAP are not for target based activity For target based choice of microbs amphiphiles are most specified , their therapeutic ratios are still insufficiently high. Just like histidine rich peptides have pH

dependent charge and their interaction with charged membrane surface depend on pH .histidine are alfa-amino acid with imidazole functional group[38].

Glutamic acid decarboxylase is one of important pH dependant peptides so here we are discussing the derivative of this peptides . Gad-1 and Gad-2 are pH dependent peptieds and their ability to cover the infected tissues made them good antibacterial polymers and target based choice of microbs. solid infected tumors are covered by acidic environment so histidine rich peptieds like Gad-1 and Gad-2 have potential to treat these tumors[39] .they are pH dependent polymers Gad-1was more active than Gad-2 at both pHs for killing of multiplemyeloma cells at acidic and neutral . MIC study shows totally mismatch between Gad-1 and Gad-2 at pH 5 and pH 7 Gad-1 does not appear to be very pH dependent Gad-2 however, exhibited greater activity at pH 5 than at pH 7 .

Gad-1 and Gad-2 were carried out on Escherichia coli bacteria with different concentration [40] and we found that at lowest concentration of peptide that resulted in no bacterial culture growth as judged by visual inspection of the opacity.for showing the antibacterial activity Gad-1 and Gad-2 are applied on lung carcinoma cells, human prostate PC3 cancer cells and HEY cancer cells at different –different concentration and a routine checking to confirm the activity and the result determine by different technique and spectral study show the growth retardation by these polymer of all infected cells[41] . Gad-1 and Gad-2 application on human RBCs show almost similar effect by both of polymers around 50% lysis of RBCs, was 43 μM for Gad-1 and 56 μM for Gad-2 that means on human RBC these polymers almost behave same . The application of Gad-1 and Gad-2 on lung carcinoma cells, human prostate PC3 cancer cells and HEY cancer cells showing the anticancer activity of both of polymers shown in below fig.7 diagram .Gad are higher molecular weight polymers but in other hand Low molecular weight antimicrobial peptides (AMPs) are present in most living organisms as an integral part of the innate immune system[40]. In mammals and other higher organisms, they also function as immunomodulary agents by interacting with host cells and eliciting a response from the immune system the amphiphilic nature of AMPs promote interactions with many salts, as well as with polar and nonpolar molecules, which reduces their effectiveness in saline fluids, such as blood, or when in contact with polyanionic and hydrophobic materials, such as heparin and tissue-culture-treated plastics . and for lower molecular weight peptieds and for inorganic antibacterial amphiphilic peptieds we use Enzyme encapsulation techniques [43,37] .

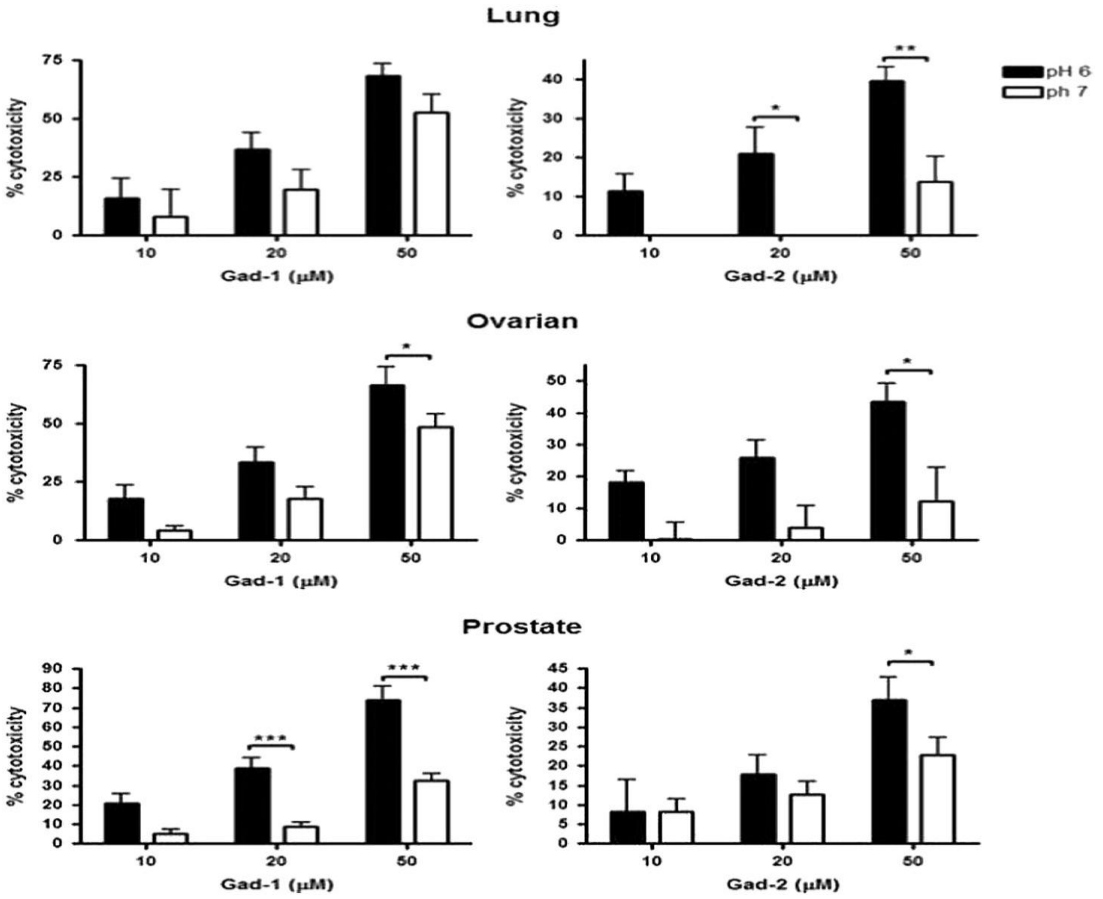


Figure 7 effect of Gad-1 and Gad-2 on carcinoma cells. Lung (LLC), ovarian (HEY), and prostate (PC3) carcinoma on pH 6 or pH 7 with different concentration

The above diagram is showing the activity of Gad-1 and Gad-2 at pH -6 and pH-7 with vary of concentration and we can see the activity against cytotoxicity . Both Gad-1 and Gad-2 demonstrated and their concentration dependent cytotoxicity against LLC cells, HEY ovarian cancer cells, and PC3 prostate cancer cells under acidic and neutral condition [44-45].as shown above Gad-1 showed a greater cytotoxic effect compared to Gad-2. In contrast to the pH dependence of the results with these cells while Gad-2 showed a significant pH-dependent alteration in activity with all three carcinoma cell The pH-dependent effect was more pronounced with Gad-2 than Gad-1 in LLC and ovarian cancer cells in which peptide-mediated killing at 50 μM was increased by approximately four-fold under acidic conditions[46]. The structural determination by spectral study show that they have hydrophobic side chains to one side of the peptide and hydrophilic side chains to the opposite face which locates to the interface between the polar and non-polar faces of the peptide.Gad-1 and Gad-2 peptieds also show display a variety of secondary structures[47] . The Gad-1 and Gad-2 NMR data were examined for indications that the peptides might be forming dimers. Gad-1 and Gad-2 depend very much on the composition of their lipid environment and show the strongest tendency to structure as an amphipathic helix, Gad-2 show highest activity with histidine charge Gad-1 has five histidine residues to Gad-2's four, and that's the reason Gad-2 is more sensitive [48].

3.2 Hyper branched polymer and cationic polymers

Hyper branched peptieds are also know for multiple bacterial activity at same time .some of research suggest that some of unique derivative in class of hyper branched has tendency of antibacterial activity against multiple bacteria at same time .they can capture multiple bacteria by core shell covering . Synthesis of AP-HPG already mentioned in this capture . AP-HPG with amphiphilic core–shell structure, can be utilized in fabrication of nanomaterials ,was synthesized based on modified HPG and firstly employed for the synthesis of Fe3O4 by solvo- hydrothermal methods ,generating various shapes Fe3O4 nanoparticle aggregates depending on different AP-HPG concentration[27,49]

Host defense peptides are positively charged polymers and they are non-toxic to mammalian cells like cationic poly-amino acids and cationic polyelectrolytes .HDP create a neutral core shell on infected tissue to retard the harmful growth[50] .

HDP are natural antimicrobial peptieds and their non-polar and charged groups extend from opposite sides of the final folded conformation. Their no-toxicity and self-assemble properties enlarge the bacteria killing activity by membrane disruption.In some active amphiphilic polymers with balance in hydrophilic and hydrophobic moieties are good membrane interacting agent.

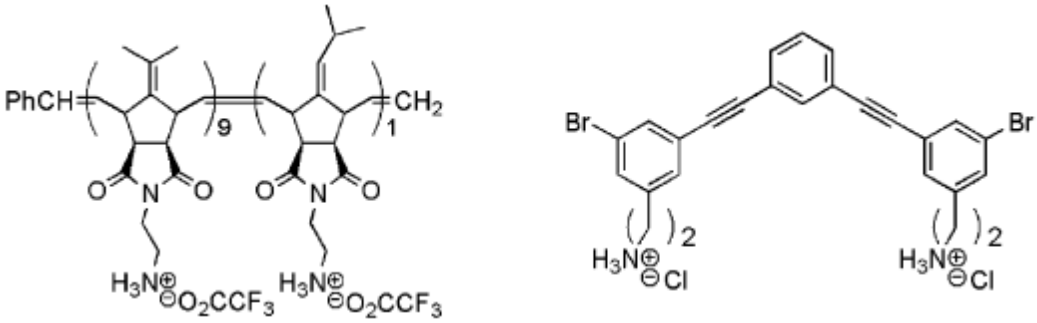


Figure 8 host defense peptieds

The above fig.8 is example of some host defense peptieds .mostly cationic polymers are use in pharmaceuticals and Anionic polymers with special ability to form micelles and often use in industrial use and nano-technology[50] .

The mechanism of antimicrobial activity depends largely on the hydrophilic–hydrophobic balance. cationic copolymers have ability of killing pathogenic microorganisms and acting as an antimicrobial agent which can be used in areas such as healthcare products, food storage, water purification systems, household sanitation, medical devices, etc. the detailed self-assembly studies along with the evaluation of antimicrobial activity, DNA binding ability, and toxicity will open up opportunities for their use in other areas also[51]. They have good antimicrobial activity evaluated by MIC value .some other polymers featuring similar properties of host defense peptieds like Semifluorinated polymer surfactants their aqueous self-assemblies were investigated as a potential to form inorganic nanoparticles.and these kind of surfactants demonstrate similar characteristics to those of polymers with linear perfluorocarbon tails, despite large differences in the tail structure. the F-MRI contrast study clearly show basic design of these polymers which can be further modified to serve as dual drug-delivery and imaging vehicles[45-48]. And some of other study also indicating in these days that most of host defense peptieds can be utilize as accurate selectivity for microbes .

3.3 Biodegradeble polymers .

As the researches increases in antibacterial field one important problem also arise and this problem is the by product and the remaining product after antibacterial activity of polymers and for the solution of this problem a new field biodegradable polymers arise .here we are discussing some of highly biodegradable polymers and their antibacterial activity like The co-polymer of acryl sucrose synthesized by styrene and apply on Aspergillus niger funges with Culture Incubation method to detect the biodegradable process of their co-polymers . and it been observed that this co-polymer were used as the sole carbon source for the fungus.

During incubation with fungal culture. And after a long time we detect fungal colonization/fungal growth (visual growth) on the surface of polymer film after 90 days of culture incubation but the initiation of fungal growth could be seen by microscope within 15-20 days .and it also seen that funges using this co-polymer as a sole source of carbon, as there was complete absence of carbon in nutrient agar. increasing time of incubation, the fungal colonization was found to increase[52]. The higher colonization could be attributed to easy consumption of short chains as energy source by fungus with increasing incubation time in culture which concludes that the copolymer was bio-assimilated during microbial attack. The below image is showing eroded surface with some residue . The microbes' adhesion onto the surface was quite evident after 30 days of incubation.

Once microbes have been adsorbed, their penetration into the polymer was rapid as they consumed it[53].

Polar optical microscopy use for analyzing the sample and the result is samples have been eaten by microorganisms with respect to their biodegradability the dark region is degradable part of mixture

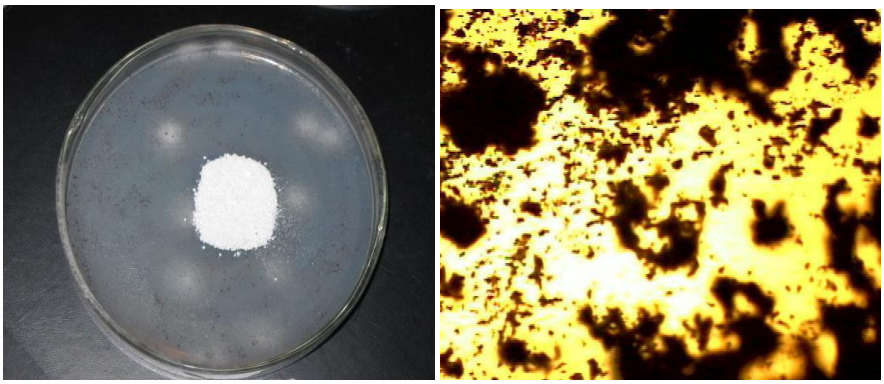


Figure 9 Photograph after 90 days of incubation of sample in fungal culture. The fungal growth (25%) indicates the biodegradability of the sample poly(acetyl methacryloyl sucrose-co-styrene).

After fungal degradation of the sugar fraction the remaining lower molecular weight polystyrene fragments were tested for toxicity[54]. No toxic effects were observed on earthworms living in soil treated with the oligo-styrene fragments. Similarly, after putting the remaining product after degradation in a fish tank and fish were not affected by the presence of the fragments in the tank for an extended period . Polyguanidinium oxanorbornene This polymer was observed to be strongly antibacterial against Gram-negative and Gram-positive bacteria as well as nonhemolytic against human red blood cells.and also studies as biodegradable polymers . Time-kill studies indicated that this polymer is lethal and not just bacteriostatic **PGON** did not disrupt membranes in vesicle-dye leakage assays and microscopy experiments. The unique biological properties of **PGON**, in same ways similar to cell-penetrating peptides, strongly encourage the examination of other novel guanidino containing macromolecules as powerful and selective antimicrobial agents[54].

3.4 carbohydrate-derived amphiphilic macromolecules

Carbohydrate-derived Amphiphilic macromolecule is become so useful in lipids membrane activity .their high activity towards membrane binding activity makes them very useful in drug delivery system .basically these macromolecules derived by attaching them with other polymers bridging by an acid lika a amphiphilic polymer stealth lipids built on aldaric and uronic acids frameworks attached to poly ethylene glycol (PEG) polymer tails developed to form self-assembling micelles and it is also a good membrane-intercalating biomaterials for drug delivery or vascular membrane targeting. with the help of lot's of modeling and experimental techniques like All-Atom MD Simulations , Molecular Descriptor Generation, QSAR Modeling,[55], we elucidated the minute variations in the behaviors of the various carbohydrate-derived amphiphilic macromolecules (AM) at the interface of lipid membranes and membrane-mimetics.and their stereochemistry, charge and amphiphilicity are also determine by these technique and all are favorable to role that polymer as antibacterial agent .and it has been founded that they have context of membrane binding in

bio-relevant environment they have attractive feature of AMs as drug delivery and surface modifying agents is their ability to interact with lipid membranes[56] .with all these observation The AMs were found to associate with the lipid bilayer. Membrane binding was strongly influenced by the unique structural features (*viz.*, charge, stereochemistry) of the AMs. Specifically, the orientation of the aliphatic arms attached to the carbohydrate backbone affect membrane binding .some membrane lipids has dipole moment so it observed specific interactions can occur at the membrane interface with electrostatic energies dependent on ion polarizability and ionic interactions. so the charge on amphiphilic polymers is the important things for membrane binding[57] . the observation also detect that with different funtional group and different concentration doesn't effect highly on membrane binding ability .as the features of AMs vary their antibacterial activity also influence . and they also treat as core-shell formation to retard the bacterial growth.

3.5 pH sensitive polymers

The use of pH sensitive polymers in pharmaceuticals is because of their target base selectivity against bacteria .by varying the pH of polymers we can adjust their bacterial selectivity . here we are discussing a important pH dependent polymers pluronic p123-DTX . pH sensitive Pluronic P123-DTX synthesize by conjugates by the combination between the Pluronic P123 and the drug docetaxel via acid-cleavage hydrazone bonds. With a low critical micelle concentration (CMC), these pH sensitive P123-DTX conjugates could self-assemble into nano-size polymeric micelles in aqueous solution. these pH sensitive polymeric conjugate micelles exhibited their stability against the rat plasma, and showed a pH dependent drug release behavior . the observation found that they have potential to balance the stability and drug release. And they might offer a great benefit for drug delivery and controlling the drug release[58]. these copolymers could self-assemble to form two distinct domains in aqueous solution: a hydrophobic core and a hydrophilic shell. the specially ability of these polymers with their hydrophobic and hydrophilic property they can entrapp the anticancer drug and These covered drug will achieved an improved water solubility capacity and be protected from enzymatic degradation and uptake by mononuclear phagocytes, macrophages and reticuloendothelial systems in the liver, spleen and bone marrow. Hence, their blood circulation time prolonged.they have enhanced permeation and retention (EPR) effect to make them stable in tumor tissue[55] . The covalent bonds in the polymer-drug conjugates can hold the drug firmly in the circulation, and there will be less anticancer drug released into healthy tissue. pH-responsive micelles have attracted great attention due to the existence of mildly acidic pH in the tumor tissues than the normal tissues, which may provide a tissues-specific stimulus that can be exploited for selective drug release. [59-60]

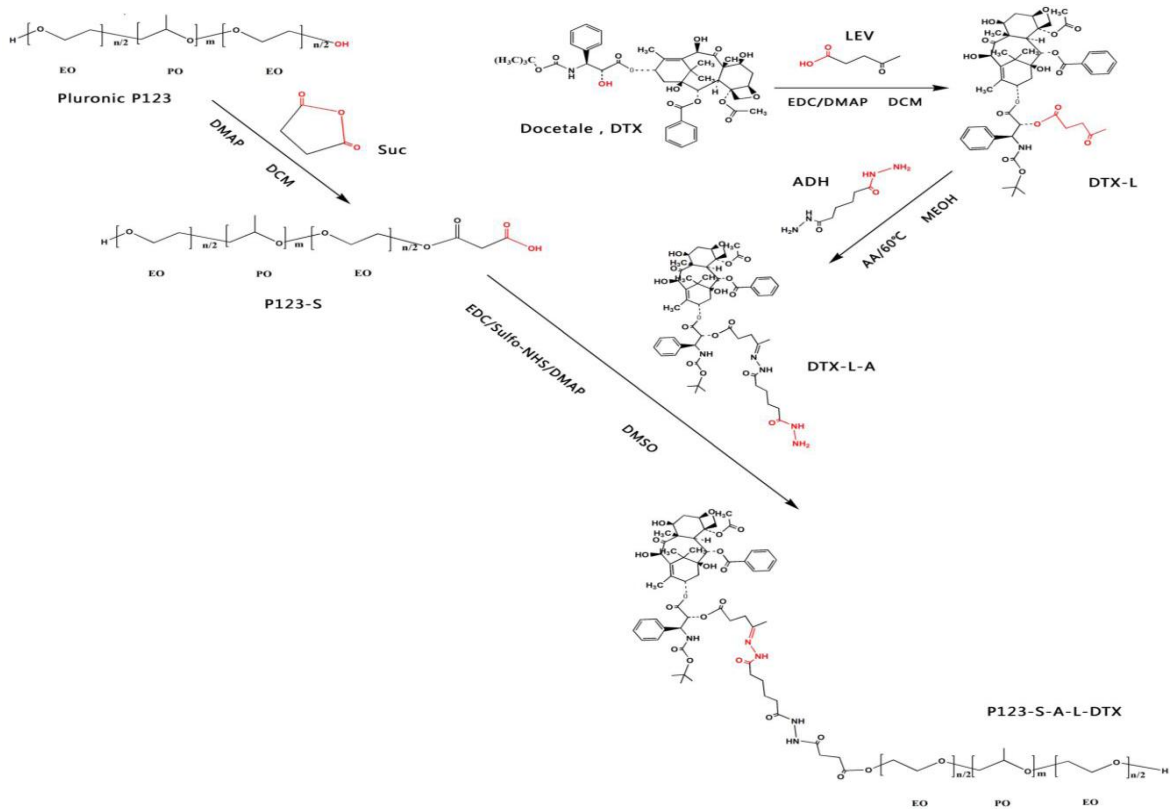


Figure 10 Synthetic routes used for the preparation of Pluronic P123-DTX

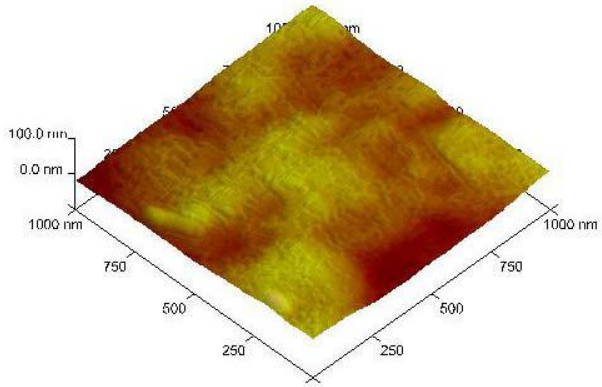
The above picture showing pH sensitive Pluronic P123-DTX conjugates by the combination between the Pluronic P123 and the drug docetaxel via acid-cleavage hydrazone bonds.in other hand a novel acid-cleavable prodrug of doxorubicin prepared by hydrezone in recent research has the potential to be a promising clinical candidate for treating a broad range of solid tumors[56].

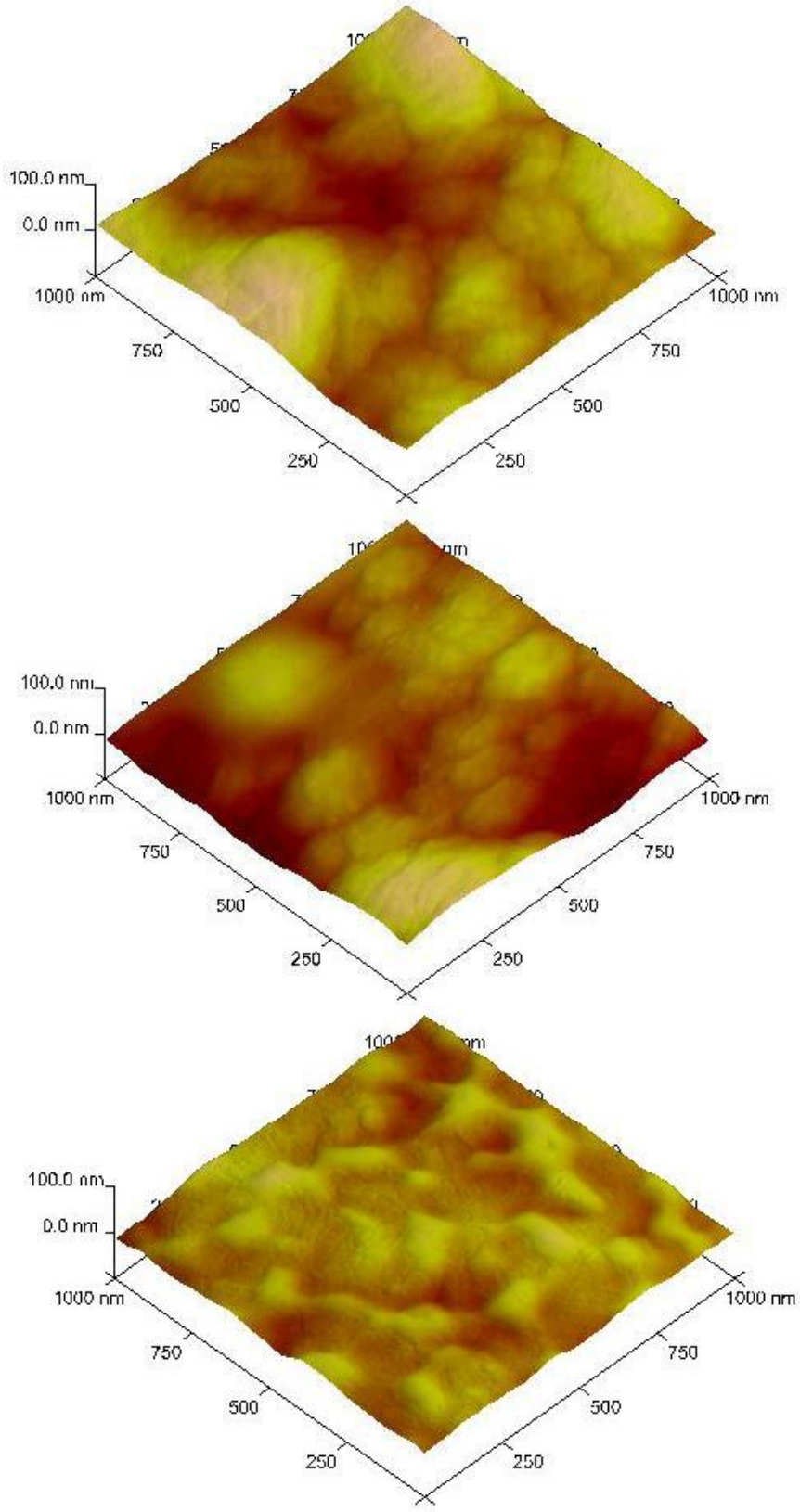
Similar with doxorubicin, docetaxel (DTX) is another one of the most potent chemotherapeutic agents, which exhibits a more effective antitumor activity than paclitaxel. Docetaxel has shown a broad spectrum of activity against a variety of tumors, especially for the treatment of breast, gastric, ovarian, prostate and non-benign lung cancer.

3.6 Polyethylene (PE)

PE is widely used in many biomedical applications including the production of catheters for percutaneous, transluminal, coronary angioplasty in medical and pharmaceutical industries . but infections resulting from application of this medical polymer represent the main clinical complication. The important things about PE is that their Biocompatibility depends on many surface characteristics such as wettability [5], roughness, chemistry, surface charge, density of functional groups. But if we manage the surface free energy and its low wettability . it can be a good antibacterial agent .therefor The solution of the problem consists in PE surface modification[57] . Low-temperature plasma can be suggested as the appropriate procedure for the hydrophilization of the surface. Due to the plasma treatment of surface the free energy is increased as a result of introduction of polar functional groups on the treated surface, thus making the surface of PE more hydrophilic[58]. In this process a polymer is exposed to a plasma reactive species such as ions, electrons, excited atoms and molecules, which cleave existing chemical bonds and form new reactive functional groups, which may initiate or participate in grafting, polymerization, or cross-linking reactions on the surface. For increasing the resistance can be achieved by treating PE surfaces with substances containing antibacterial groups such as triclosan (5-Chloro-2-(2,4-dichlorophenoxy)phenol) and chlorhexidine (1,1'-Hexamethylenebis[5-(4-chlorophenyl)biguanide]) [59] .these antibacterial substances immobilized on low-density polyethylene (LDPE) via polyacrylic acid (PAA) grafted on LDPE by low-temperature barrier discharge plasma[60]. This LDPE surface treatment led to inhibition of *Escherichia coli* and *Staphylococcus aureus* adhesion.so PE treated with plasma can be a great combo as antibacterial agent . Diffuse Coplanar Surface Barrier Discharge (DCSBD) plasma generator appears to be an effective tool for creating macroscopically homogeneous plasmas, which has many advantages compared with conventional devices. by this generator plasma doesn't directly contact to electrodes[61-62] . in these days Adhesion and surface growth of bacteria, also called biofilm formation, is a widespread problem [23]. To prevent its formation, anti-infection modification of polymers for medical applications may be applied[63]. Anti-infective properties of polymers can be achieved by following: (a) anti-infection agents mixed in the polymer; (b) copolymerization anti-infection agents with monomer; (c) appropriate surface treatment of medical polymers.the physical –chemical interaction between bacteria and polymer it does not influence the bulk properties of the polymer, antibacterial agents are not released from the polymer volume, and the technique is relative simple and effective[64]. Triclosan and chlorhexidine with PE. This treatment in combination with plasma can affect significantly biochemical and physical properties of LDPE . the interaction mainly depend on surface interaction..

Surface free energy changes are closely related to adhesion between two materials in contact. Therefore, the increased wettability resulted in an increase of adhesion strength of adhesive joint to more polar poly(acrylate). However, adhesion depends not only chemical composition and the chemical nature of the surface, but also on surface morphology (roughness)[65-67]. The rougher is the surface the higher is the adhesion and *vice versa*. Thus, adhesion is a complex parameter consisting of several related chemical and physicochemical properties. The plasma effect led to the slightly increase of LDPE surface roughness as a result of surface changes by re-organization of the surface microstructure by chemical (functionalization) and mechanical (ablation) processes.

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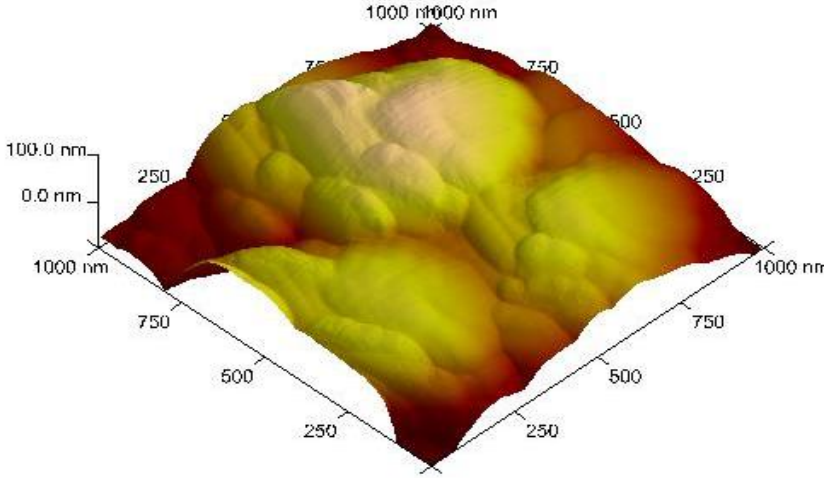


Figure 11 surface morphology change Sample 1–5: 1 - untreated LDPE; 2 - plasma-treated;

3 - AA grafted; 4 - triclosan coated; 5 - chlorhexidine coated.

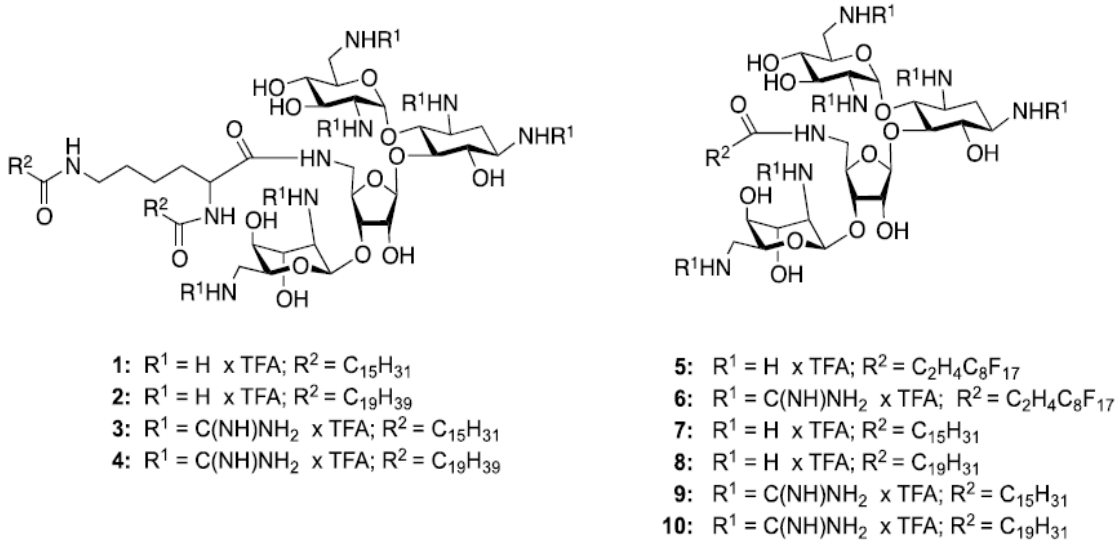
The above picture showing the diametrical changes on surface by different treatment such with plasma,acrylic acid , triclosan and chlorhexidine .first sample is showing untreated surface . the interaction change the surface morphology completely and change the antibacterial activity[65] .

The results show that untreated (Sample 1), plasma treated (Sample 2) as well as acrylic-acid grafted sample (Sample 3) do not display any antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus* strains[66]. The sample coated with triclosan (Sample 4) does meet the expected antibacterial requirements. The average inhibition zone for the Gram-negative *Escherichia coli* strain is of 115.1 mm2 and for the Gram-positive *Staphylococcus aureus* 493.1 mm2. These values prove the antibacterial activity of the prepared layers as well as confirm XPS measurements. There is a considerable interest in the development of innovative techniques to remove or to kill micro-organisms present in aqueous solutions, not only for drinking water but also for sanitizing biomedical, pharmaceutical, and cosmetic formulations[63] . these amphiphilic polymer have great surface-initiated activity like Silica and paramagnetic silica microparticles are surface-modified by an antibacterial macromolecular coating . the known water-soluble antimicrobial agents such as chlorine, ozone, antibiotics, or poly(quaternary ammonium) salts but their use is controversial. Indeed, it has been revealed in the last two decades that chemical disinfectants, such as chlorine used for water treatment, induce the formation of harmful by-products [64-68] . here is a macroparticle Silica and paramagnetic silica which is surface coated by an antibacterial agent Such particles offer the advantage to treat efficiently various sensitive aqueous solutions while avoiding any dissemination of bactericidal substances in the environment. As a consequence, they are of a great interest for various applications in medical, cosmetic, or biomedical fields To overcome these shortcomings related to water-soluble antimicrobial substances, processes based on water-insoluble materials have been recently developed [69]. These materials consist essentially of insoluble particles such as polymeric latexes, clay platelets, glass fibers, ceramic particles, or polyelectrolyte capsules coated by a conventional bactericidal agent immobilized by adsorption or chemical grafting and these coated macromolecular are capable of killing a broad range of Gram-positive and Gram-negative bacteria[70] . and also use in water purification

3.7 neomycin B-based bilipids

Bilipids are thin polar membrane made of two layer of lipids molecules .bilipds has great antibacterial activity against various of bacteria .they have special self-association ability not only in solution but also in membrane of becteria and form continues barrier around cells . derivatives of neomycin B are good example of bilipids and also have good antibacterial activity . A study of mechanism shows that six polycationic amphiphiles created by neomycin B are conjugate with bacteria by backbone. Fig 12 is showing the all six derivatives of neomycin B and it has been found that the hydrophobic region of all six amphiphiles have different tails some have provides cationic charge and either palmitic and arachidic bilipids or fluorinated undecanoic monolipid on hydrophobic region [72] . all synthesis are by Reducing the size of the lipid tail to twelve carbons eliminated activity, confirming that the gain was due to an increase in aminoglycoside hydrophobicity. And some study shows that all six polycationic amphiphiels increased their self-association in both the bacterial membrane and solution, through the incorporation of either a fluorocarbon tails or two hydrophobic tails . Self association in the membrane was postulated to decrease the concentration required for membrane disruption, by forming pockets of high PA concentration, while self-association in solution could

lead to micelle formation and general exclusion of the hydrophobic portion of the amphiphiles from circulation[73].



1: R^1 = H x TFA; $R^2 = C_{15}H_{31}$
2: R^1 = H x TFA; $R^2 = C_{19}H_{39}$
3: $R^1 = C(NH)NH_2$ x TFA; $R^2 = C_{15}H_{31}$
4: $R^1 = C(NH)NH_2$ x TFA; $R^2 = C_{19}H_{39}$

5: R^1 = H x TFA; $R^2 = C_2H_4C_8F_{17}$
6: $R^1 = C(NH)NH_2$ x TFA; $R^2 = C_2H_4C_8F_{17}$
7: R^1 = H x TFA; $R^2 = C_{15}H_{31}$
8: R^1 = H x TFA; $R^2 = C_{19}H_{31}$
9: $R^1 = C(NH)NH_2$ x TFA; $R^2 = C_{15}H_{31}$
10: $R^1 = C(NH)NH_2$ x TFA; $R^2 = C_{19}H_{31}$

Figure 12 Structures of neomycin B-based bilipids 1–4, the fluorinated monolipids 5 and 6, hydrocarban monolipids 7-10

Above picture is showing the all amphiphiels synthesized by neomycin B with different chain of hydeocarbon and different functional group all amphiphiels also demonstrated on gram-positive and gram-negative bacteria and the resulting behavior depend on the tails of amphiphles[74] . and all six compounds were tested against a panel of clinically relevant and ATCC Gram positive and Gram negative bacteria. Guanidinylation of neomycin B was found to increase activity 2–8. fold, with di-palmitoyl guandilyated neomycin B (**3**) displaying good activity against a number of Gram positive bacteria bilipids has good antibacterial activity rather then monolipids , compounds **1**–**6** displayed reduced activity[75]. However, the PAs with fluorinated tails, **5** and **6**, had significantly less toxicity towards red blood cells, suggesting that fluorination may increase the therapeutic window of membrane-active amphiphiles. Starting from first six amphiphiles Four of the new compounds incorporated either palmitic or arachidic di-lipid lysine tails, while two had single fluorinated undecanoic acid tails. The basicity of half of the compounds was increased through the incorporation of six guanidine moieties, in order to assess the effect of base strength on antimicrobial activity[76]. And later 7-10 hydrocarbon monolipids the PAs all compounds were found to have reduced activity, though the hemolytic activity of the compounds with fluorinated tails was sharply reduced, with only a moderate reduction in antimicrobial activity[75 77].and this study suggesting and open –up the new opportunity for lots of monolipids to convert them into bilipids to increase their antibacterial activity .

Reference

[1]. J. Wiesner, A. Vilcinskas, Antimicrobial peptides: the ancient arm of the human immune system, Virulence 1 (2010) 440–464.
[2]. P. Bulet, R. Stocklin, L. Menin, Anti-microbial peptides: from invertebrates to vertebrates, Immunol. Rev. 198 (2004) 169–184.
[3]. K. De Smet, R. Contreras, Human antimicrobial peptides: defensins, cathelicidins and histatins, Biotechnol. Lett. 27 (2005) 1337–1347.
[4]. W.C. Wimley, K. Hristova, Antimicrobial peptides: successes, challenges and unanswered questions, J. Membr. Biol. 239 (2011) 27–34.
[5]. H.W. Boucher, G.H. Talbot, J.S. Bradley, J.E. Edwards, D. Gilbert, L.B. Rice, M. Scheld, B. Spellberg, J. Bartlett, Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America, Clin. Infect. Dis. 48 (2009) 1–12.
[6]. P.C. Oyston, M.A. Fox, S.J. Richards, G.C. Clark, Novel peptide therapeutics for treatment of infections, J. Med. Microbiol. 58 (2009) 977–987.
[7]. K. Matsuzaki, Control of cell selectivity of antimicrobial peptides, Biochim. Biophys. Acta 1788 (2009) 1687–1692.
[8]. Maria Teresa Barros 1,*, Krasimira T. Petrova 1,* and Raj P. Singh 2 Int. J. Mol. Sci. 2010, 11, 1792-1807; doi:10.3390/ijms11041792
[9]. Adriana A. T. Martin 1,2,†, Michael Tomasini 3,†, Vladyslav Kholodovych 1,6, Li Gu 5, Sven Daniel Sommerfeld 4, Kathryn E. Uhrich 5, N. Sanjeeva Murthy 4, William J. Welsh 1 and Prabhas V. Moghe 2,3,* J. Funct. Biomater. 2015, 6, 171-191; doi:10.3390/jfb6020171
[10]. Yanchao Liang, Zhihui Su, Yao and Na Zhang * Materials 2015, 8, 379-391; doi:10.3390/ma8020379
[11]. Anton Popelka 1, Igor Novák 1,*, Marián Lehocký 2, Ivan Chodák 1, Ján Sedliačik 3, Milada Gajtanska 3, Mariana Sedliačiková 3, Alenka Vesel 4, Ita Junkar 4, Angela Kleinová 1,
[12]. Milena Špírková 5 and František Bílek 6 Molecules 2012, 17, 762-785; doi:10.3390/molecules17010762

[13]. Smritilekha Bera 1,2, Ramesh Dhondikubeer 1, Brandon Findlay 1, George G. Zhanel 3 and Frank Schweizer 1,3,* Molecules 2012, 17, 9129-9141; doi:10.3390/molecules17089129
[14]. Ricchard Hallan Felix Viegas de Souza, Mirelli Takaki, Rafael de Oliveira Pedro, Juliana dos Santos Gabriel, Marcio José Tiera and Vera Ap. de Oliveira Tiera * Molecules 2013, 18, 4437-4450; doi:10.3390/molecules18044437
[15]. Fatemeh Bahadori 1,2,3, Aydan Dag 1,4, Hakan Durmaz 1, Nese Cakir 1, Hayat Onyuksel 2, Umit Tunca 1, Gulacti Topcu 1,3,* and Gurkan Hizal 1,* Polymers 2014, 6, 214-242; doi:10.3390/polym6010214
[16]. M.J. Browne, C.Y. Feng, V. Booth, M.L. Rise, Characterization and expression studies of Gaduscidin-1 and Gaduscidin-2; paralogous antimicrobial peptide-like transcripts fromAtlantic cod (Gadus morhua), Dev. Comp. Immunol. 35 (2011) 399–408.
[17]. K. Chikakane, H. Takahashi, Measurement of skin pH and its significance in cutaneous diseases, Clin. Dermatol. 13 (1995) 299–306.
[18]. S. Al-Benna, Y. Shai, F. Jacobsen, L. Steinstraesser, Oncolytic activities of host defense peptides, Int. J. Mol. Sci. 12 (2011) 8027–8051.
[19]. 19]Amanda C. Engler,† Anita Shukla,† Sravanthi Puranam, Hilda G. Buss, Nina Jreige, and Paula T. Hammond* macromoleculas
[20]. Yong Xiao Baia*, Yao Bin Liub, Yan Feng Lib and Qi ZhangcMacromolecule wiely
[21]. Nicolas Pasquier, Helmut Keul, Elisabeth Heine, Martin Moeller,*
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[22]. Thomas Blin,† Viswas Purohit,† J_er^ome Leprince,‡ Thierry Jouenne,† and Karine Glinel*,§ macromoleculas
[23]. D. Matthew Eby,*,† Karen E. Farrington,‡ and Glenn R. Johnson*, Biomacromolecules 2008, 9, 2487–2494
[24]. Gregory J. Gabriel,† Ahmad E. Madkour,† Jeffrey M. Dabkowski,‡ Christopher F. Nelson,‡ Klaus Nu¨ sslein,‡ and Gregory N. Tew*, Biomacromolecules 2008, 9, 2980–2983
[25]. D.W. Hoskin, A. Ramamoorthy, Studies on anticancer activities of antimicrobial peptides, Biochim. Biophys. Acta 1778 (2008) 357–375.
[26]. T. Xu, S.M. Levitz, R.D. Diamond, F.G. Oppenheim, Anticandidal activity of major human salivary histatins, Infect. Immun. 59 (1991) 2549–2554.
[27]. R.J. Baumann, G.D. Mayer, L.D. Fite, L.M. Gill, B.L. Harrison, In vitro and in vivo candicidal activities of 2-(p-n-hexylphenylamino)-1,3-thiazoline, Chemotherapy 37 (1991) 157–165.
[28]. C.J. Park, C.B. Park, S.S. Hong, H.S. Lee, S.Y. Lee, S.C. Kim, Characterization and cDNA cloning of two glycine- and histidine-rich antimicrobial peptides from the roots of shepherd's purse, Capsella bursa-pastoris, Plant Mol. Biol. 44 (2000) 187–197.
[29]. I.K. Poon, K.K. Patel, D.S. Davis, C.R. Parish, M.D. Hulett, Histidine-rich glycoprotein: the Swiss Army knife of mammalian plasma, Blood 117 (2011) 2093–2101.
[30]. F.D. Silva, C.A. Rezende, D.C. Rossi, E. Esteves, F.H. Dyszy, S. Schreier, F. Gueiros-Filho, C.B. Campos, J.R. Pires, S. Daffre, Structure and mode of action of microplusin, a copper II-chelating antimicrobial peptide from the cattle tick Rhipicephalus (Boophilus) microplus, J. Biol. Chem. 284 (2009) 34735–34746.
[31]. R. Lai, H. Takeuchi, L.O. Lomas, J. Jonczy, D.J. Rigden, H.H. Rees, P.C. Turner, A new type of antimicrobial protein with multiple histidines from the hard tick, Amblyomma hebraeum, FASEB J. 18 (2004) 1447–1449.
[32]. I.H. Lee, Y. Cho, R.I. Lehrer, Effects of pH and salinity on the antimicrobial properties of clavanins, Infect. Immun. 65 (1997) 2898–2903.
[33]. He-Xiang Lia,b, Xin-Jiang Lua, Chang-Hong Lia, Jiong Chena,b,∗ Molecular Immunology 65 (2015) 406–415
[34]. Mark McDonald a, Michael Mannion a, Damien Pike a, Krystina Lewis a, Andrew Flynn a, AlexM. Brannana, Mitchell J. Browne a, Donna Jackman a, Laurence Madera c, Melanie R. Power Coombs b, David W. Hoskin b,c,d, Matthew L. Rise e, Valerie Booth f, Biochimica et Biophysica Acta
[35]. Evdokia K. Oikonomou a,b, Aikaterini Bethani a, Georgios Bokias a, Joannis K. Kallitsis a,b,⇑ European Polymer Journal
[36]. C. Petit, S. Reynaud, J. Desbrieres∗Carbohydrate Polymers
[37]. Pranabesh Duttaa, Joykrishna Deya,∗, Anshupriya Shomeb,1, Prasanta Kumar Dasb International Journal of Pharmaceutics
[38]. Jiaqing Xiong a, JinTao a, SijunXu b, A'nan Xiu a, HongLin a, YuyueChen Materials Letters
[39]. Eudokia K. Oikonomou a,b, Elefterios K. Pefkianakis a, Georgios Bokias a, Joannis K. Kallitsis a,b,* European Polymer Journal
[40]. E.J. van Kan, R.A. Demel, E. Breukink, A. van der Bent, B. de Kruijff, Clavanin permeabilizes target membranes via two distinctly different pH-dependent mechanisms, Biochemistry 41 (2002) 7529–7539.
[41]. Z. Tu, A. Young, C. Murphy, J.F. Liang, The pH sensitivity of histidine containing lytic peptides, J. Pept. Sci. 15 (2009) 790–795.
[42]. Sunder A,HeinemannJ,FreyH.ChemEurJ2000;6:2499–506.
[43]. Gao C,YanD.ProgPolymSci2004;29:183–275.
[44]. KumarKR,BrooksDE.MacromolRapidCommun2005;26:155–9.
[45]. StiribaS-E,KautzH,FreyH.JAmChemSoc2002;124:9698–9.
[46]. Zhou Y,YanD.ChemCommun(Camb)2009:1172–88.
[47]. Liu J,HuangW,PangY,ZhuX,ZhouY,YanD.Langmuir2010;26:10585–92.
[48]. HanQ,ChenX,NiuY,ZhaoB,WangB,MaoC,etal.Langmuir2013;29:8402–9.
[49]. Chen S,ZhangX-Z,ChengS-X,ZhuoR-X,GuZ-W.Biomacromolecules 2008;9:2578–85
[50]. SunderA,HanselmannR,FreyH,MülhauptR.Macromolecules1999;32:4240–6. WanD,FuQ,HuangJ.JApplPolymSci2006;101:509–14.
[51]. E. Katchalski, L. Bichowski-Slomnitzki, B.E. Volcani, Biochem. J. 55 (1953) 671–680.
[52]. E. Katchalski, L. Bichovski-Slomnitzki, B.E. Volcani, Nature 169 (1952) 1095–1096.
[53]. E.F. Panarin, M.V. Solovskii, N.A. Zaikina, G.E. Afinogenov, Makromol. Chem. (Suppl. 9) (1985) 25–33.
[54]. T. Ikeda, H. Hirayama, H. Yamaguchi, S. Tazuke, M. Watanabe, Antimicrob. Agents Chemother. 30 (1986) 132–136.
[55]. T. Ikeda, S. Tazuke, Y. Suzuki, Makromol. Chem. 185 (1984) 869–876.
[56]. Asokan, A., Cho, M.J., 2002. Exploitation of intracellular pH gradients in the cellular delivery of macromolecules. J. Pharm. Sci. 91, 903–913.
[57]. Bhattacharya, S., Bajaj, A., 2009. Advances in gene delivery through molecular design of cationic lipids. Chem. Commun., 4632–4656.
[58]. Domagk, G., 1935. A new class of disinfectants. Dtsch. Med. Wochenschr. 61,829–832.
[59]. Kuzuya, M.; Sawa, T.; Mouri, M.; Kondo, S.I.; Takai, O. Plasma technique for the fabrication of a durable functional surface on organic polymers. Surf. Coatings Technol. 2003, 169-170, 587–591.
[60]. Zhang, W.; Chu, P.K.; Ji, J.; Zhang, Y.; Fu, R.K.Y.; Yan, Q. Antibacterial properties of plasma-modified and triclosan or bronopol coated polyethylene. Polymer 2006, 47, 931–936.
[61]. Costa, F.; Carvalho, I.F.; Montelaro, R.C.; Gomes, P.; Martins, M.C. Covalent immobilization of antimicrobial peptides (AMPs) onto biomaterial surfaces. Acta Biomater. 2011, 7, 1431–1440.

[62]. Goddard, J.M.; Hotchkiss, J.H. Tailored functionalization of low-density polyethylene surfaces. J. Appl. Polym. Sci. 2008, 108, 2940–2949.
[63]. Faucheux, N.; Schweiss, R.; Lutzow, K.; Wemer, C.; Groth, T. Self-assembled monolayers with different terminating groups as model substrates for cell adhesion studies. Biomaterials 2004, 25, 2721–2730.
[64]. Michael, K.E.; Vernekar, V.N.; Keselowsky, B.G.; Meredith, J.C.; Latour, R.A.; Garcia, A.J. Adsorption-induced conformational changes in fibronectin due to interactions with well-defined surface chemistries. Langmuir 2003, 19, 8033–8040.
[65]. Keselowsky, B.G.; Collard, D.M.; Garcia, A.J.J. Surface chemistry modulates fibronectin conformation and directs integrin binding and specificity to control cell adhesion. J. Biomed. Mater. Res. A 2003, 66, 247–259.
[66]. Luk, Y.Y.; Kato, M.; Mrksich, M. Self-assembled monolayers of alkanethiolates presenting mannitol groups are inert to protein adsorption and cell attachment. Langmuir 2000, 16, 9604–9608.
[67]. Vesel, A.; Junkar, I.; Cvelbar, U.; Kovac, J.; Mozetic, M. Surface modification of polyester by oxygen and nitrogen-plasma treatment. Surf. Interface Anal. 2008, 40, 1444–1453.
[68]. Drnovská, H.; Lapčík, L., Jr; Buršíková, V.; Zemek, J.; Barros-Timmons, A.M. Surface properties of polyethylene after low-temperature plasma treatment. Colloid Polym. Sci. 2003, 281, 1025–1033.
[69]. Novák, I.; Števiar, M.; Chodák, I.; Krupa, I.; Nedelčev, T.; Špírková, M.; Chehimi, M.M.; Mosnáček, J.; Kleinová, A. Study of adhesion and surface properties of low density polyethylene pre-treated by cold discharge plasma. Polym. Adv. Technol. 2007, 18, 97–105.
[70]. Olifirenko, A.S.; Novak, I.; Rozova, E.Y.; Saprykina, N.N.; Mitilineos, A.G.; Elyashevich, G.K. Hydrophilization of porous polyethylene films by cold plasma of different types. Polym. Sci. 2009, 51, 247–255.
[71]. Lloyd, G.; Friedman, G.; Jafri, S.; Schultz, G.; Fridman, A.; Harding, K. Gas plasma: Medical uses and developments in wound care. Plasma Process. Polym. 2010, 7, 194–211.
[72]. Sanchis, R.; Fenollar, O.; García, D.; Sánchez, L.; Balart, R. Improved adhesion of LDPE films to polyolefin foams for automotive industry using low-pressure plasma. Int. J. Adh. Adhesives 2008, 28, 445–451.
[73]. Pappas, D. Status and potential of atmospheric plasma processing of materials. J. Vac. Sci. Technol. A 2011, 29, 020801:1–020801:17.
[74]. Yang, L.; Chen, J.; Guo, Y.; Zhan, Z. Surface modification of a biomedical polyethylene terephthalate (PET) by air plasma. Appl. Surf. Sci. 2009, 255, 4446–4451.
[75]. Zhang, X.; Dong, Y.; Zeng, X.; Liang, X.; Li, X.; Tao, W.; Chen, H.; Jiang, Y.; Mei, L.; Feng, S.-S. The effect of autophagy inhibitors on drug delivery using biodegradable polymer nanoparticles in cancer treatment. Biomaterials 2014, 35, 1932–1943.
[76]. Chen, W.; Zhang, J.Z.; Hu, J.; Guo, Q.; Yang, D. Preparation of amphiphilic copolymers for covalent loading of paclitaxel for drug delivery system. J. Polym. Sci. A Polym. Chem. 2014, 52, 366–374.
[77]. Ke, X.; Ng, V.W.L.; Ono, R.J.; Chan, J.M.; Krishnamurthy, S.; Wang, Y.; Hedrick, J.L.; Yang, Y.Y. Role of non-covalent and covalent interactions in cargo loading capacity and stability of polymeric micelles. *J. Controll. Release* 2014, *193*, 9–26.