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RESEARCH ARTICLE

STABLE DRUG DELIVERY SYSTEMS: PEG-POLYDIACETYLENE LIPOSOMES.

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Abstract

In a new preliminary approach we esterified the PDA (10, 12-pentacosadiynoic acid) with oligoethyleneoxides (PEG-PDA) to prepare non-ionic tensides with polymerizable diacetylene entities. The synthetic approach coupled the activated carboxygroups of PDA to amino terminated oligoethyleneoxides. Conjugation of Polyethylene glycol to diacetylene entities enhances the stability of the liposomes. Due to their unique properties such as high water-solubility, cross-linkable micelle formation with a nano-scaled size, and stimuli-responsive chromic nature, the polymer-lipid conjugates would be useful for various biomedical applications, in particular drug delivery system and biosensors.

Introduction:-

Minimization of toxic side effects can be achieved by encapsulation of the drug in liposome's or micelles as more efficient and safest drug delivery system. Polymeric Polydiacetylene-Polyethylene glycol (PDA-PEG) conjugated vesicles can be used as platform for detection of biological entities such as bacterial cells, viruses and proteins. Polyethylene glycol (PEG) because of its better solubility, biocompatibility and less toxic in nature [13] is widely used in drug delivery systems [11, 32]. Starting with the anticancer compound Doxil [10] these vesicles play a vital role in biological systems and increasingly also in smart Microsystems. The complexity of the different process taking place in the cell membrane can be understood by mimicking the cell membrane by the stable vesicles formed from polymeric diacetylene entities.

Greater stability, less toxicity and controlled drug release are achieved by polymerization of liposome [9-10, 22-23]. The diacetylene monomers can be easily topochemically polymerized inside ordered lamella phase of appropriate diacetylene vesicles by photo polymerization[4]. During the polymerization, adjacent diacetylene units, transfer into a polyconjugated polydiacetylenic polymer backbone with remarkable optical properties. Different factors like temperature [2], pH [4], organic solvent [1] and mechanical stress [12] trigger Colour transition from blue to red due to conformational changes in the conjugated backbone in Polydiacetylene assemblies.The best examples of Polydiacetylene biosensors are carbohydrate functionalized PDA for the detection of the influenza virus, cholera toxin [5, 21, 27], and *E. coli.* The topochemically polymerization is achieved by self assembly of the diacetylene entities in ordered form depending on their molecular architecture and nature. The ordered form is maintained even in the PEG conjugated PDA along with the color transition properties. PEG conjugation imparts additional stability and improves the retention time of the drug for sustained release reducing the toxic side effects [20, 30].

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Materials And Methods:-

Polydiacetylene Vesicle Preparation:-

2.7 mmol of 10, 12- Pentacosadiynoic acid was dissolved in 10 ml of CH_2Cl_2. 3.0 mmol of N-hydroxysuccinimide, 0.596 g of 1-3-(dimethylaminopropyl) 3-ethyl carbamide is added. The solution was allowed to stir at ambient temperature for 2 h. The solution is further subjected to rotary evaporation of CH_2Cl_2. The product was extracted with ethyl acetate and water. The organic layer was dried with $MgSO_4$ and filtered. Finally the solvent was removed by rotary evaporation and a white solid of 1.21 g of PDA-NHS is obtained. 0.235 g of PDA-NHS was dissolved in 10 ml of CH_2Cl_2. 1.545 g of polyethylene glycol-bis-3-aminoproply terminated (PEG), 0.596 g of 1-3-(dimethylaminopropyl) 3-ethyl carbamide is added. The solution was allowed to stir at ambient temperature (25 ^{0}C) for 2 h. The solution is further subjected to rotary evaporation of CH_2Cl_2. The product was extracted with ethyl acetate and water. The organic layer was dried with $MgSO_4$ and filtered. Finally the solvent was removed by rotary evaporation. The PDA-PEG is further purified by extracting with dichloromethane and brine solution. Finally the organic solvent is removed by rotoevaporation and the after drying purified solid is obtained.

Polymerization:-

Polymerization of PDA was carried by ultraviolet exposure at 266 nm for about 10 to 30 min until the appearance of blue color.

Surface Modification:-

The microscopic glass slides (Menzel GMBH) is gold coated and is subjected to plasma cleaning for 15 min in order to obtain hydrophilic surface. A drop of polymerized vesicle solution is placed on this surface and dried. The sample is viewed in Scanning electron microscope (SEM) at very low voltage around 1 kV.

Pda-Oligoethyleneoxides Preparation:-

2.7 mmol of 10, 12- Pentacosadiynoic acid was dissolved in 10 ml of CH_2Cl_2. 3.0 mmol of N-hydroxysuccinimide, 0.596 g of 1-3-(dimethylaminopropyl) 3-ethyl carbamide is added. The solution was allowed to stir at ambient temperature for 2 h. The solution is further subjected to rotary evaporation of CH_2Cl_2. The product was extracted with ethyl acetate and water. The organic layer was dried with $MgSO_4$ and filtered. Finally the solvent was removed by rotary evaporation and a white solid of 1.21 g of PDA-NHS is obtained. 0.235 g of PDA-NHS was dissolved in 10 ml of CH_2Cl_2. 1.545 g of polyethylene glycol-bis-3-aminoproply terminated (PEG), 0.596 g of 1-3-(dimethylaminopropyl) 3-ethyl carbamide is added. The solution was allowed to stir at ambient temperature (25 ^{0}C) for 2 h. The solution is further subjected to rotary evaporation of CH_2Cl_2. The product was extracted with ethyl acetate and water. The organic layer was filtered after drying with MgSO4. Finally the solvent was removed by rotary evaporation. The PDA-PEG is further purified by extracting with dichloromethane and brine solution. Finally the organic solvent is removed by rotoevaporation and after drying purified solid is obtained.

Optical Properties:-

The optical properties were analyzed by visible absorption spectroscopy UV–visible spectrophotometer. The chromatic properties of PEGPDA vesicle solution were analysed at different absorption maxima (540-635nm) .

Microscopic Techniques:-

Results:-

We investigated different preparative methods sonication, extrusion and rotoevaporation to produce uniform narrowly distributed polydiacetylene vesicles from 10, 12 Pentacosydiynoic acid (PDA). In most cases the polymeric species from this compound resulted in formation of flat sheet like aggregates. At very low concentrations we could produce diacetylene vesicles.

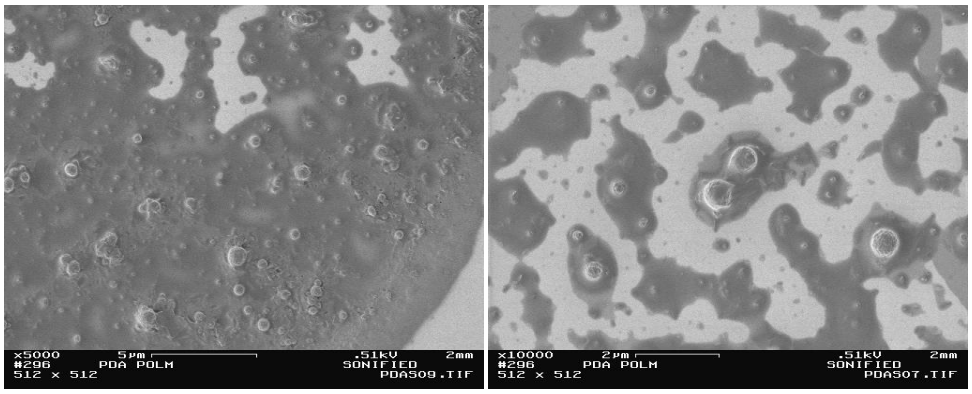


Fig. 1:- Scanning Electron Micrograph image of extruded polydiacetylene liposomes

These vesicles when subjected to heating changed in colour from blue to red, demonstrating thermo chromism. In a new preliminary approach we esterified the PDA with oligoethyleneoxides (PEG-PDA) to prepare nonionic tensides with polymerizable diacetylene entities. The NMR spectra of PDA-PEG is shown in the Fig 2. The synthetic approach coupled the activated carboxy groups of PDA to amino terminated oligoethyleneoxides.

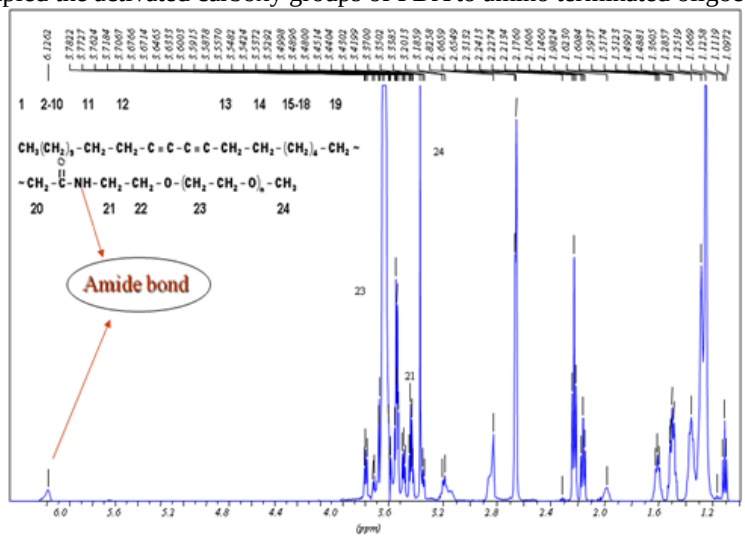
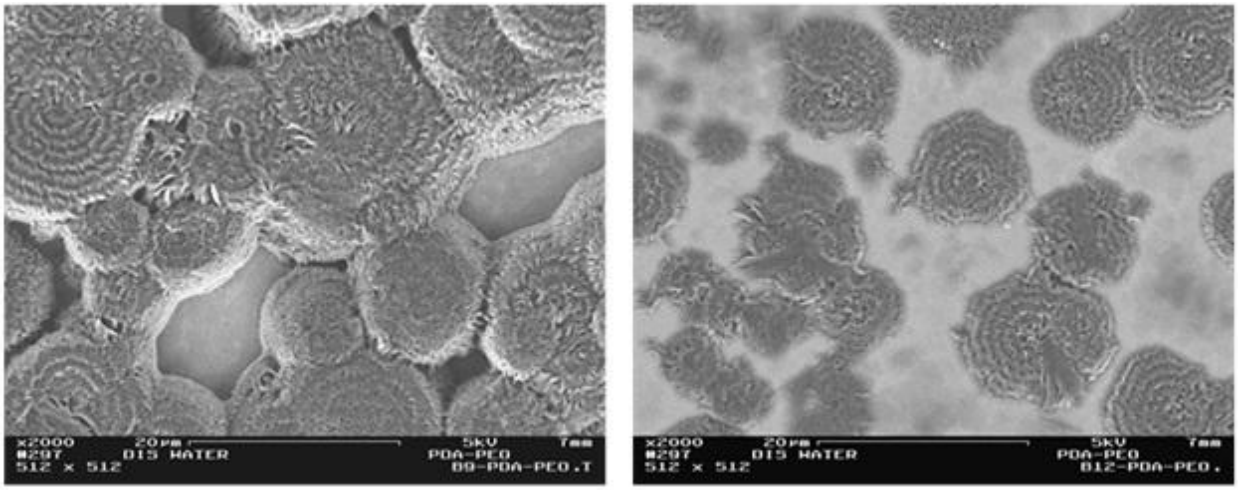


Fig 2:- NMR spectra of PDA-PEG

Polyethylene glycol (PEG)-conjugated PDA is commonly employed for stericstabilization of liposome. When added in high concentrations PEG-PDA induce formation of mixed micelles Fig.3, and depending on the lipid composition of the sample, these may adapt either a discoidal or a long threadlike shape. Polyethylene glycol (PEG)-conjugated PDA resembles a non-ionic surfactant.



SEM Images

Fig 3:- vesicles of PDA-PEG

The Polyethylene glycol (PEG)-conjugated PDA in water when subjected to sonication forms bilayers where in hydrophobic parts face each other and hydrophilic parts (PEG) face each other. Water is embedded in hydrophilic parts. This bilayer resembles non-ionic emulgators (hydrogels) which can be cross linked .The photo reactive diacetylenic groups are used as indicator for local order at the lamella surface. They undergo the photo polymerization into an auto fluorescent polydiacetylene structure only if the topochemical reaction conditions are fulfilled which requires a high molecular order [22-23].

Conclusion:-

Polydiacetylene vesicles form more stable vesicles and PEG imparts steric stability and mostly long flat sheets were observed. This stability of these vesicles can be useful for efficient drug delivery system compared to conventional systems. Polyethylene glycol (PEG)-conjugated PDA is commonly employed for steric stabilization of liposome. Due to their unique properties such as high water-solubility, cross-linkable micelle formation with a nano-scaled size, and stimuli-responsive chromic nature, the polymer-lipid conjugates would be useful for various biomedical applications, in particular as a nano-carrier for drug delivery and biosensor.

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