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Methylene Blue-Loaded Lipid Polymer Hybridnanoparticlesasmedicinal and diagnostic Agents

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ABSTRACT
Methylene blue (MB) is Methylthioninium chloride used as an indicator and has been used in the textile industry. It was first extracted by the German chemist Heinrich Caro.it is used for the treatment of certain diseases such as methemoglobinemia, ifosfamide-induced encephalopathy, and thyroid conditions requiring surgery. Recently, the utilization of MB as a safe photosensitizer in photodynamic therapy (PDT) has received attention. Recent findings demonstrate that photoactivated MB exhibits not only anticancer activity and also antibacterial activity both in vitro and in vivo. As the hydrophilic nature of MB, it is difficult to create MB-embedded nano- or microparticles capable of increasing the clinical efficacy of the PDT so we are using MB-loaded lipid polymer nanoparticles. This review aims to summarize MB-loaded lipid polymer nanoparticles and to provide both in vitro and in vivo examples of MB- loaded PDT, therefore it offers a future perspective on improving clinical treatment modality. We address examples of MB-loaded PDT in both cancer and infection treatments. Both in-vitro and in-vivo studies are summarized here to document recent trends in utilizing MB as an effective photosensitizer in PDT. Lastly, we discuss how developing efficient MB- loaded lipid polymer nanoparticle platforms would be able to increase the benefits of PDT.

Keywords: Methylene blue; Photodynamictherapy; Photosensitizer; Antimicrobial photodynamic therapy

I. INTRODUCTION

The recent advancement of nanotechnology represents a powerful tool to counterattack a plethora of diseases like cancer, cardiovascular disease, etc. The ability of nanoparticles to deliver drugs more effectively and efficiently to the site of interest with less harmful side effects and more favorable therapeutic action makes them an encouraging drug delivery system. The advantages of nanoparticle-mediated drug delivery system encompass (i) increased dissolution rate of sparingly soluble or water-insoluble hydrophobic drugs (ii) surface functionalization of nanoparticles enables them for target-specific delivery and ability to bypass immune system, thus prolonging in vivo therapeutic half-life, as well as (iii) controlled and sustained drug release profile, combinedly it reduces the dosing frequency and improves therapeutic efficacy [1, 2]. Thus, it is not surprising that nano-structures (1x10-9- 1x10-7 m) have been extensively used as delivery vehicles for various therapeutic substances, ranging from small drug molecules, genes, and biopharmaceuticals (e.g.-proteins) to imaging agents [2].

Among all the nanoparticulate systems, liposomes and biodegradable polymeric nanoparticles (PNPs) are two dominant classes of nano-carriers or delivery agents. The xenobiotic is typically encapsulated inside the nano-carriers, or conjugated onto the surface of the nanoparticles, where its release from the carrier is controlled by the carrier matrix formulation, or triggered by external stimuli (e.g., pH, temperature). Liposomes are self-assembled lipid vesicles consisting of one or more bilayer surrounding an aqueous core, in which lipophilic or hydrophilic drugs can be incorporated. Mostly liposomes are biocompatible, biodegradable, nontoxic or mildly toxic, flexible, and non-immunogenic for systemic and non-systemic administration if their component lipids are taken from natural sources [3]. However, liposomes have several limitations in terms of physical and chemical stability, batch to batch reproducibility, sterilization, drug entrapment, and manufacturing procedures [4]. Polymeric nanoparticles have been widely used for their high structural integrity, stability during storage, and controlled release property. In addition, they are also easy to prepare and readily functionalized for active targeted delivery, all of these properties make them highly appealing as therapeutic delivery

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vehicles. Polymeric nanoparticles can be prepared from natural (e.g., chitosan), synthetic biodegradable and biocompatible polymers (e.g., poly-lactic-co-glycolic acid (PLGA)) using wide technological approaches [2]. Despite of this favorable characters polymeric nanoparticles also have some disadvantages (i) use oftoxic organic solvents in the production of PNPs, (ii) poor drug encapsulation in case of hydrophilic drugs, (iii) drug leakage before reaching target tissue, (iv) cytotoxicity of polymer and their degradation material [4].To address the multifaceted drug delivery challenges outlined above, several research groups have turned to prepare a hybrid lipid- polymer nanocomposites with the primary aim to combine the most valuable features of both polymeric and liposomal drug delivery systems excluding their individual drawbacks[5]. To use this hybrid lipid-polymer nanoparticle (LPN) system as a combination of medicinal and diagnostic/ imaging purpose, a fluorescently active photosensitizer molecule has to be incorporated into the LPN system for effectual photodynamic therapy, which is a contemporary treatment approach for cancer and localized microbial infections.

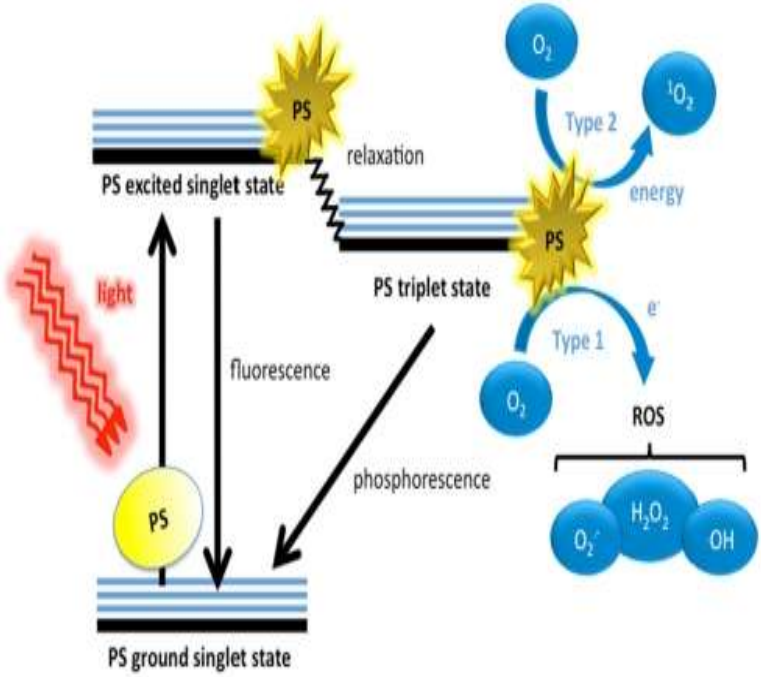

Figure 1. Schematic illustration of photodynamic therapy including the Jablonski diagram [8]

Materials

Methylene blue, acid-terminated Poly (D, L-lactide-co-glycolide) 50:50 M.W 38000-54000, Polyethylene glycol (PEG), L-α-Phosphatidylcholine type IV-S from soybean ≥30%, 9, 10-Anthracenediyl-bis(methylene)dimalonic acid (ABDA) were purchased from Sigma Aldrich. [N-(carbonyl-methoxypolyethylene.glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine] was obtained as gift sample from Lipoid (UK). Pluronic F-68, Luria Bertani (LB), and agar media were purchased from Himedia (Mumbai, India). All other chemicals used were analytical grade and purchased from the reputed vendor.

Preparation of MB-loaded lipid-polymer hybrid nanoparticles

The methylene blue loaded lipid-polymer hybrid nanoparticles were prepared by using the nanoprecipitation method [4]. The organic phase contained of methylene blue (0.99% w/w) and PLGA (10.65 mg/mL) in 1 mL of acetone as solvent, while the aqueous phase contained soy lecithin (10% w/w), DSPE-PEG (3% w/w) and pluronic F-68 (10.65 mg/mL) in 4% ethanol-water solution. The aqueous phase was heated to 65 ^oC for better dispersion of lipid molecules. Then organic phase containing PLGA and drug was added dropwise (1 mL/min) in an aqueous phase under sonication in a water bath sonicator and kept the solution in a bath sonicator for 1 h then vigorous stirring at a magnetic stirrer for 1-1.5 h at

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300 rpm. The organic solvent was evaporated from the preparation under reduced pressure. The final preparation was then characterized and lyophilized to obtain free-flowing nanopowder using mannitol (5% w/v) as a cryo-protectant

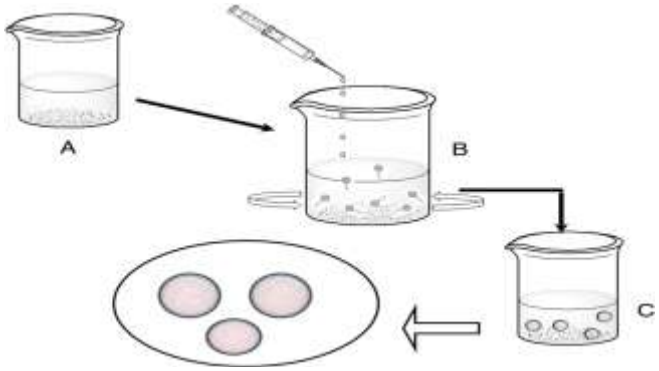

Figure 2. Schematic representation of the single-step method involving nanoprecipitation and self-assembly processes (A) Drug, a polymer dissolved in an organic solvent forming an organic phase, (B) The organic phase is added drop wise into the aqueous phase containing phospholipids, (C) The resulting dispersion is sonicated or homogenized to obtain LPNs [4]

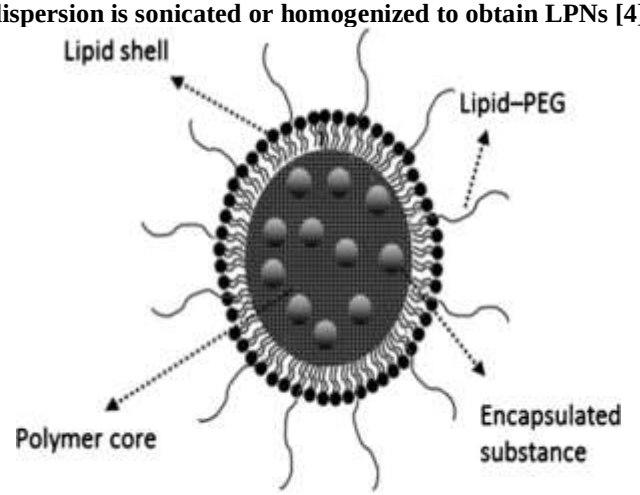

Figure 3. Structure of lipid-polymer hybrid nanoparticles [3]

II. CONCLUSION

MB has been utilized as a photosensitizer for PDT in the treatment of cancers and infectious diseases. Despite the early use of this hydrophilic molecule in PDT, few studies have been reported to improve MB has been utilized as a photosensitizer for PDT in the treatment of cancers and infectious diseases. Despite the early use of this hydrophilic molecule in PDT, few studies have been reported to improve the loading capacity of MB. It has been speculated that the hydrophilic nature of MB might limit the clinical efficacy of MB-mediated PDT. As reviewed here, however, recent technological development in creating nano and microparticles for targeted drug delivery is likely to increase the chance of the presence of MB in the target area. A polymeric micro composite complexed with MB shows the formation of singlet oxygens for cancer cell treatment. Similarly, coating onto the surface of a gold nanoparticle, covalent attachment onto the surface of a functionalized graphene, and co-formation of a silica hollow nanoparticle are good examples of MB encapsulation techniques to create a successful MB delivery system for the enhanced MB-mediated PDT. These functional materials show the potential benefit of delivering MB to a disease area of interest and provide insight into how MB-carrying materials help increase the clinical efficacy of PDT. Moreover, recently studied techniques such as liposome and aqueous core nanocapsules offer the promising potential of MB-mediated PDT, where MB can localize in the specific target area and be a safe photosensitizer for

treating a wide range of cancers and infectious diseases in the near future.

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