

Smart nanocarriers for theranostic formulations biology essay

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Drug delivery is a critical issue in any disease treatment. Now-a-days much more effort is being focused on integrating imaging agent and therapeutic drugs in a single formulation to achieve a simultaneous disease diagnosis and targeted drug delivery. This new terminology 'nanotheranostics' have been used to describe these nanoparticle formulations. In past few years, number of nanocarriers (liposomes, nanoparticles, dendrimers, micelles, antibodies etc.) has been studied for targeted delivery of chemical or biological molecules. Among these nanocarriers, liposome is largely studied nanoscale delivery systems and offers more advantages than others due to their unique structural properties. This review will highlight theranostic concept as well as some examples of theranostic liposomal formulations in clinical or preclinical stages. We briefly reviewed approaches to formulate theranostic liposomal formulations. Key Words: liposomes, drug delivery, imaging, diagnosis, (Nano)theranostic

Introduction:

Liposomes are lipid bi-layered vesicles with inner aqueous core. Most commonly preferred nanocarrier to deliver therapeutic agents is used in the form of liposomes[1]. Liposome based drug delivery is clinically most accepted to deliver anti-tumour, anti-fungal drugs, genes, vaccines and imaging components as well. Liposomes were the first therapeutic nanoparticles in the market approved by FDA as DOXIL in 1995[2].'

'Nanotheranostics' is a term reflecting therapeutics and diagnostics with nanotechnology which is expected to give improved patient outcomes and increased safety by more personalized approach to medicine[3]. It is a novel approach to produce integrated and biocompatible formulations containing

therapeutic as well as imaging agents in a single formulation. Combination of chemotherapeutic, radio-diagnostic or gene therapeutics is made possible by theranostic formulations. In comparison with other vesicular carrier systems, liposomes offer less toxicity, biocompatibility and biodegradability. Ability to withstand surface modifications and various size ranges with consistency is the most considerable aspects for using liposomes in theranostic applications [4]. Theranostic concept is described in figure below which shows difference between conventional liposomal formulation and theranostic liposome.

Fig. 1

Combination of liposomes with other nanoparticulate systems is at the developmental stages, such hybrid nanoscale architects provide tremendous opportunities to modify these nanotheranostic drug delivery systems. Lots of different nanoparticles are being made worldwide with various chemical compositions to offer biocompatibility in vitro & in vivo and stability with varying bio-physicochemical properties [5]. These are highly suitable nanoparticles for simultaneous diagnostic and therapeutic purpose. These nanoscale delivery systems offer large surface area which allows covalent and non-covalent surface manipulations. Generally during surface manipulations, it was observed that these modified hybrid nano-architects loose the theranostic properties and becomes less stable. Here, liposomes offer various structural properties to make theranostic nanoparticles more biocompatible and hence liposomes offer clinically accepted multiutility platform for enhancing diagnostic & therapeutic ability of nanoparticles. With the advancement of nanoengineering technologies improved liposome

formulations were formulated having wide size distribution ranges, composition & functionality. Cancer therapy is profoundly being benefited by theranostic formulations. Non-invasive imaging techniques (such as MRI, SPECT, Surface Plasmon Resonance) offer better understanding of drug delivery process, drug release and site specific accumulation of therapeutic and imaging components[6]. Iron oxide, gold nanoparticles and quantum dots are continued to be used for diagnostics and imaging agents.

Liposomes in clinical drug delivery:

Liposomes were first used for medical applications in 1960[7]. Various different types of targeted nanoparticles have been studied since years for clinical applications based on liposomes, micelles, antibodies, polymers. These nanoscale (size range from 5- 200 nm) carriers have potential to improve therapeutic index of low molecular weight drugs [8]. Liposomes offer space to both hydrophilic & hydrophobic chemotherapeutics for encapsulation in its aqueous core and phospholipid bilayer respectively. Poor pharmacokinetics with large bio-distribution is the main obstacles in delivery of low molecular weight drugs. PEGylation of liposomes can improve 2-10 fold circulation time from uptake by RES [9]. Figure given below explains one of such example of theranostic liposomal formulation.

Fig. 2

Encapsulated Doxorubicin (DOXIL) in aqueous core of liposome has been used in AIDS associated Kaposi's sarcoma, Myocet for multiple myeloma and Caelyx for ovarian cancer therapy [10, 11]. Sustained release multivesicular liposome formulation containing Cytarabine have been approved for cancer

treatment [12]. Also, targeting with liposomes is well established by means of active and passive manner (ex. passive accumulation of stealth liposomes in solid tumour due to its leaky vasculature). On-going research on liposomal drug delivery includes long circulation time [13] and stimuli sensitivity (i. e. temperature, pH, enzymes etc.) to release the drug at specific pathological site & controlled manner. Example, temperature responsive ThermoDox is recently in clinical trials for oncology related hyperthermia treatment [14].

Liposomes in nanomedicine:

To study the aspects related biological cell membrane, lipid bilayer vesicles (liposomes) were used as a model to mimic membrane properties in vitro [15]. Liposomes offer greater flexibility while engineering its size, surface, composition and hence used to mimic the living cells to study the physiological processes, such as diffusion across membrane, interaction of membrane with various biologics & therapeutic agents in vitro. Surface receptors on the plasma membrane can be studied with the new generation biosensors designed by reconstructing the proteins from lipid membrane. Liposomes have been explored to study the chemical kinetics of remotely controlled reactions. Very small reaction volumes offer rapid diffusional mixing [16].

Theranostic concept:

Fig. 3

Theranostic concept is simplified in above mentioned figure. The term theranostic can be better described as simultaneous diagnosis and therapy to pathological site or particularly targeted organ. Formulation with

nanocarrier systems offers improved target specific accumulation and bio-distribution of i. v administered chemotherapeutics. Animal as well as clinical studies showed the ability of nanomedicines to improve the balance between efficacy and toxicity. Along with therapeutic applications these nanocarriers are also employed for imaging purpose in past few years. Theranostics is the new area of interest in diagnostic imaging & targeted therapeutic drug delivery. Theranostic formulations will be the most suitable tools in near future to conquer the challenges of disease diagnosis and pharmacological drug delivery. Theranostic nanomedicines can provide valuable information of target site & off-target accumulation of pharmacologically active agents. This information will be very useful to understand and optimize the basic properties of drug delivery systems.

Liposomal carriers in theranostic formulations:

Liposomes can act as a microreservoir system by dissolving or dispersing molecules in its hydrophilic or hydrophobic compartments and exhibit controlled leakage characteristics. Drug encapsulation with liposome can largely reduce its side effects to heart, kidney or nervous tissues by avoiding drug bio-distribution in tissues of such organs [17]. It is considered that, liposome uptake by macrophages is initiated by surface adsorption of plasma macromolecules, mostly protein molecules of immune system. This opsonisation is minimized by modifying liposome surface properties with polyethylene glycol (PEGylation) [18, 19]. This is called steric stabilization approach, which is due to osmotic and entropic effects of polymer coating [20, 21, 22]. PEG offers inert, non-ionic, hydrophilic and flexible polymer

coating that increases repulsive forces above the liposome surface and consequently PEGylated liposome shows reduced interaction & protein adsorption [23]. These parameters are very useful in long circulation time of liposomes to achieve better localization in desired tissues for imaging and therapy.

Liposome-nanoparticle hybrids:

Ringsdorf had described early forms of liposome-polymer hybrids [24]. As nanotechnology is growing rapidly; various novel nanomaterials have been developed in recent years. Nanoparticles of such as Gold, superparamagnetic iron oxide (SPIOs) and semiconducting nanocrystals (quantum dots, QD) shows magnetic & optical properties that can be exploited as imaging probes [25]. Encapsulation of these nano-sized imaging agents within liposome gives improved biocompatibility, stability in plasma and better pharmacokinetic profile. Three different types of methods have been used for merging imaging probes into liposomes. These approaches are explained in figure given below.

Fig. 4

These approaches are- 1. Hydrophobic materials can be embedded/adjusted in lipid bilayer [26]. 2. Hydrophilic nanoparticles can be encapsulated into inner aqueous compartment of liposome [27, 28] 3. Different nanoparticles can be adsorbed over the liposome surface on the basis of their physical & chemical properties [29, 30]. Magnetoliposomes (iron oxide nanoparticle-containing liposome) can be used for inducing hyperthermia to a desired tissue in response to a magnetic field [31]. Theranostic liposomal formulation

containing doxorubicin and MRI contrast agent (manganese sulphate, $MnSO_4$) was used by Grang et al in Kaposi's sarcoma model in vivo [32]. MRI imaging was exploited to check liposome tissue distribution as well as to monitor drug delivery and release. To treat oncology related hyperthermia, encapsulated doxorubicin and MRI contrast agent in temperature sensitive liposomes allowed non-invasive imaging of drug release [33, 34]. By this way, the liposome-nanoparticle hybrids can be applied for both therapeutic and imaging purposes.

Liposome-quantum dot hybrids for diagnostic imaging and therapy:

Quantum dots (QDs) are generally described as fluorescent semiconductor nanocrystals QDs offer unique optical and electronic properties so that QDs could be explored as a promising tool for imaging based disease diagnosis and targeted drug delivery[35, 36, 37]. Quantum dots are 10 to 20 times brighter [38] and 100 to 1000 times photo stable than traditional organic dyes [39, 40] because of these properties QDs are greatly suitable for long term tracking and imaging[41, 42]. QDs are hydrophobic nano-crystals and insoluble in water [43, 44]. These hydrophobic quantum dots can be incorporated into phospholipid bilayer of liposomes to improve their safety, biocompatibility and targeting ability for diagnostic imaging. If therapeutic drug molecule is formulated in liposomes along with imaging agent, simultaneous diagnosis and therapy can be achieved.

Conclusion and future perspectives:

Theranostic formulations can be applied for various purposes such as for understanding key important aspects of drug delivery, improving disease diagnosis & more specific target oriented drug delivery. To achieve the objectives of theranostic formulations it is desired that the carrier system should be unique in its properties. Liposomes or lipid bi-layered vesicles offer unique physicochemical & structural properties with reduced toxicity and biocompatibility. Liposomal drug delivery is most successfully translated delivery system at clinical and pre-clinical stages. Currently, some of theranostic liposomal formulations are in clinical use for different types of cancers, inflammatory and dermatological diseases. Drug delivery systems can be optimized by with theranostic formulations by non-invasive assessment of different parameters like tissue localization, bio-distribution and drug release etc. With the help of theranostic formulations and medical imaging, basic kinetics of carriers in vitro can be correlated to their in vivo ability. Liposomes can be widely applied in future theranostic formulations because they offer low size range, capability to surface modifications and responsiveness to external stimuli such as pH, temperature and ultrasound. Safety and efficacy of targeted drug delivery systems can be improved by non-invasive visualization of drug localization in targeted area and normal healthy tissues. Cancer therapy will be more benefited with theranostic nanomedicine formulations in near future.