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Supramolecular lipid nanoparticles as delivery carriers for non-invasive cancer theranostics

Syeda Zunaira Bukhari [a], Kornelius Zeth [b], Maryam Iftikhar [a], Mubashar Rehman [c], Muhammad Usman Munir [d], Waheed S. Khan [a], Ayesha Ihsan [a,*]

[a] National Institute for Biotechnology and Genetic Engineering College, Pakistan Institute of Engineering and Applied Sciences (NIBGE-C, PIEAS), Faisalabad, Pakistan
[b] Department of Science and Environment, Roskilde University Center, DK-4000 Roskilde, Denmark
[c] Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan
[d] Department of Pharmaceutical Chemistry, College of Pharmacy, Jouf University, Sakaka, Aljouf, 72388, Saudi Arabia

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ABSTRACT

Nanotheranostics is an emerging frontier of personalized medicine research particularly for cancer, which is the second leading cause of death. Supramolecular aspects in theranostics are quite allured to achieve more regulation and controlled features. Supramolecular nanotheranostics architecture is focused on engineering of modular supramolecular assemblies benefitting from their mutable and stimuli-responsive properties which confer an ultimate potential for the fabrication of unified innovative nanomedicines with controlled features. Amalgamation of supramolecular approaches to nano-based features further equip the potential of designing novel approaches to overcome limitations seen by the conventional theranostic strategies, for curing even the lethal diseases and endowing personalized therapeutics with optimistic prognosis, endorsing their clinical translation. Among many potential nanocarriers for theranostics, lipid nanoparticles (LNPs) have shown various promising advances in theranostics and their formulation can be tailored for several applications. Despite the great advancement in cancer nanotheranostics, there are still many challenges that need to be highlighted to fill the literature gap. For this purpose, herein, we have presented a systematic overview on the subject and proposed LNPs as the potential material to manage cancer via non-invasive approaches by highlighting the use of supramolecular approaches to make them robust for cancer theranostics. We have concluded the review by entailing the future perspectives of lipid nanotheranostics towards clinical translation.

1. Introduction

1.1. Nanotechnology: a dynamic approach for cancer theranostics

Despite of the advances and a huge progress which has been made in clinical technologies and drug discoveries, cancer is still the second leading cause of death worldwide after cardiovascular diseases (Nagai and Kim, 2017). According to the global cancer statistics 2020, GLOBOCAN estimated 19.3 million new cancer cases and about 10 million deaths have been caused by cancer (Sung et al., 2021). The complex multifactorial etiology makes the treatment of disease more complex. In addition, acquisition of the multidrug resistance feature is the cause of failure of many anticancer therapies. Therefore, a single treatment is not effective in all cases. In many cases, recurrence can occur as cancer may develop resistance to previously effective treatments.

Taking cancer as the most challenging and complex disease and to design the most effective cure, concerned scientific community has realized to involve the association of different research disciplines including organic and supramolecular chemistry, nanotechnology, oncology, and pharmacology. Nano-based therapeutics bring the concept of utilizing nanotechnology in medical and clinical applications (Norouzi et al., 2020). A variety of different nanostructures (NSs) are being synthesized and employed for diagnosis, treatment, monitoring, and control of biological systems. During past five years, different NSs (Lim et al., 2015) including magnetic (e.g. spherical, crystal-like, ring, disk, and rod-shaped) (Liu et al., 2019), (Busquets et al., 2015), (Hobson et al., 2019), polymeric (e.g. linear, spherical, star-shaped, and highly branched) (Wenet al., 2019), (Gálisová et al., 2020), (Wang et al., 2015a), metallic (e.g. gold nanorods (Shah et al., 2020), (Ishtiaq et al., 2020), (Moroset al., 2020), carbon nanotubes

* Corresponding author.
E-mail address: aishaehsan@nibge.org (A. Ihsan).

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(CNTs) (Shaoet al., 2018), carbon dots (CDs) (Boakye-Yiadom et al., 2019), (Du et al., 2019), quantum dots (QDs) (Wang et al., 2016), (Liet al., 2019) etc., are gaining interest in cancer theranostics due to their unique chemical, mechanical, electrical, optical, magnetic, electro-optical, magneto-optical properties. NSs possess multiple intrinsic anticancer therapeutic attributes and are capable of targeting surface-bound molecules on tumor cells or can be used as delivery carriers to incorporate a variety of drug molecules. Furthermore, NSs can also incorporate multiple contrast agents, providing enhanced sensitivity, multiplexing ability, and flexibility of design. Assuredly, for several imaging modalities, NSs are now not only auxiliary imaging agents, but are instead the original and solo source of image signal that empower the modality's existence (Smith and Gambhir, 2017). One of these NSs, the multimodal theranostic are nanoparticles (NPs) comprise/describe architecture allows us to monitor the therapeutic response and to improve drug efficacy and safety (Lee et al., 2012), (Yasun). Several NSs have been designed and engineered in attempts to address the above-mentioned problems regarding cancer treatment.

Versatile nanosystems with multifunctional abilities can respond to the different mechanisms of carcinogenesis. In this scenario, nanotheranostics is an emerging frontier of personalized medicine research particularly for cancer. Theranostics is a hybrid of therapeutics and diagnostics. The field of cancer theranostics has been gradually coming up and comprehensive knowledge of it could be beneficial for targeted therapeutics and tumor imaging in order to successfully examine cancer and monitor therapeutic effects (Lymperopoulos et al., 2017), (Palekar-Shanbhag et al., 2013). The idea of personalized cancer nanotheranostics is based on the approved nanomedicines which can provide the treatment at the right time and in the right dosage with more efficiency and with minimized expenditures. The real meaning of personalized nanotheranostics employ the use of consistent and new crucial theranostic molecular biomarkers (Jo et al., 2016). In this regard, clinical translation of bioinspired NPs has shown promising potential in personalized cancer diagnostics and therapeutics (Rao et al., 2017, 2018, 2019).

Nanotheranostics open up the possibilities of utilizing a single regimen to assist precise cancer diagnosis and therapeutics with several non-invasive diagnostic approaches including optical imaging, computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), X-ray radiography, single photon emission computed tomography (SPECT), and positron emission tomography (PET). These diagnostic modalities aimed at optimizing the therapeutic procedures in a personalized way via real time *in vivo* visualization of tumor cells (Jo et al., 2016).

Nonetheless, the field of nanotheranostics is an emerging frontier of nanomedicine research, it however has not yet meet the clinical standards. This is due to the intricacy and the synergy of nanotheranostic systems. For example, even if some of the systems possess potential diagnostic ability, but they deprived of therapeutic efficacy. On the contrary, some of the systems have shown significant therapeutic index but with poor imaging capabilities. Another important cause of interruption in clinical translation is the biodistribution and biosafety concerns of nanotheranostics when used in humans. Scientists are putting much efforts to transform these novel nanotheranostic treatments to be available to clinicians by investigating different NSs. Precise and well-designed research concerning eternal safety as well as effectiveness in inventive medical assessment is still demanding, the crucial part of this journey (Min et al., 2015).

In view of the rapid advancements in the field of nanotheranostics over past years, periodic update on the development of novel products is required. Herein, this review focuses on summing up the recent advances in lipid-based nanotheranostic platforms for cancer management that could assist medical oncologists on providing additional progress in this field.

1.2. Why lipid nanocarriers for cancer theranostics!

Among several nanotheranostic systems, the *in vivo* fate and biodegradability of CNTs (Negri et al., 2020) and metallic NPs (Sharma et al., 2018) are still a matter of concern. The idea of surface coating of these NSs with biocompatible materials (e.g. poly-ethylene glycol (PEG)) can be realistic to make them suitable for clinical translation. Alternatively, nanotheranostic systems can be fabricated using biocompatible or biodegradable agents which have been clinically approved for other pharmacological uses e.g. lipids (See section 4 for clinical translation of lipid-based therapeutics). Therefore, the alteration or conjugation of already approved therapeutic entities with targeting ligands which will enhance their diagnostic index, could be beneficial.

Lipid nanoparticles (LNPs) are well-explored carriers for imaging and therapeutic agents for cancer theranostics (Yue and Dai, 2018), (Miller, 2013). While considering the perspectives of cell biology, cancer cells have a better uptake of lipid-based formulations with excellent biocompatibility (Butler et al., 2020), which is an important prerequisite to engineer a theranostic system. Being highly biocompatible and even biodegradable, lipid-based theranostic systems provide advanced delivery of therapeutic and imaging agents, thus improving pharmacokinetic profile, and safety (Valetti et al., 2013). Moreover, LNPs can overcome many biological obstacles (Kim et al., 2018), thus attracting increasing attention of the researchers day by day (García-Pinelet al.), (Tang et al., 2018). In addition to their potential to cross various physiological barriers, these nanocarriers can be functionalized with several targeting moieties to enhance penetration across the barriers (Olusanya, Haj Ahmad, Ibegbu, Smith, Elkordy), (Riaz et al., 2018). Furthermore, temperature dependent self-assembly of lipid molecules, termed as thermo-responsive LNPs (TLNs), have served to enhance the drug permeability across the blood brain barrier (BBB) with potential to target glioblastoma cells (Rehman et al., 2017a). (See section 2 for suitability of lipid nanotheranostic system).

Among several LNPs, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid nanocapsules (LNCs), liposomes, and core-shell lipid nanoparticles (CLNs) have been widely explored in recent years. Specifically, SLNs and NLCs have shown promising potential as oral drug carriers anticipated to help the scientists planning to conduct studies on lipid-based nanocarriers (Okur et al., 2020). Ample studies aren't present regarding *in vivo* analysis of different aspects of NLCs as they have recently joined the plethora of lipid nanocarriers (Feitosa, Geraldes, Beraldo-de-Araújo, Costa, Oliveira-Nascimento).

SLNs corresponding to the colloidal drug delivery method comprise of a solid-lipid core that retains its solid phase at both, room and body temperatures. The solid core is hydrophobic covered by single layer of phospholipids, while the drug is normally dissolved or dispersed in the core. These nanocarriers are in a size range between 50 and 1000 nm and are usually sphere-shaped (known as nanospheres) (Fig. 1A) (Mishraet al., 2018). Different types of lipids are used for SLNs formulation including fatty acids (e.g. stearic acid), triglycerides (e.g. tristearin), steroids (e.g. cholesterol), waxes (cetyl palmitate), and partial and complex glyceride combinations. This medium is stabilized by different surfactants or polymers (Battaglia and Ugazio, 2019). However, SLNs have some limitations; owing to their perfect crystalline structure, these possess low drug encapsulation efficiency and undesired leakage of loaded drug because of the crystallization process under storage conditions (García-Pinel et al.), (Silva, Pinho, Lopes, Almeida, Gaspar, Reis), (Ghasemiyeh and Mohammadi-Samani, 2018). Another downside is early outburst (Makwana et al., 2015). In SLNs, drugs positions between the fatty acid chains or glycerides. Moreover, during storage times and polymorphic changes in these structures, there is a tendency of leakage of formerly dissolved drug in SLNs. NLCs were designed to solve the SLNs limitations (Ghasemiyeh and Mohammadi-Samani, 2018). SLNs contain solid lipids while NLCs are actually a fusion of liquid and solid lipids that make distinctive NSs (Fig. 1B), which similar to SLNs are solid at both, room and body temperatures. The lipid medium of NLCs possesses

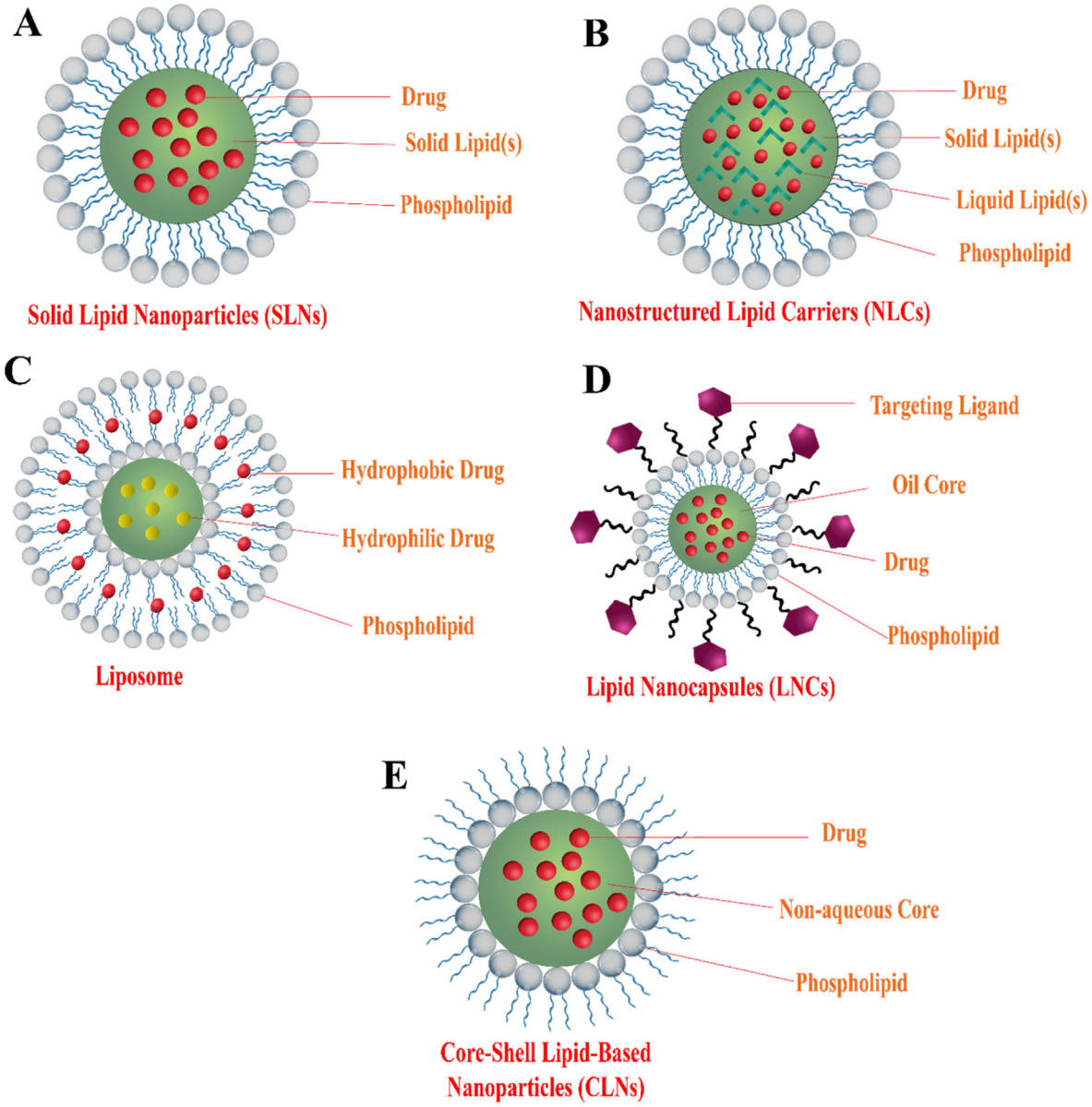

Fig. 1. Schematic designs of proposed models of various types of LNPs structures loaded with drugs. (A) Structure of SLN comprising hydrophobic solid core carrying the drug covered by single layer of phospholipids. (B) Structure of NLC comprising liquid and solid lipids, while core carrying the drug covered by single layer of phospholipids. (C) Structure of liposome self-assemble into a bilayer structure, carrying hydrophilic and hydrophobic drugs. (D) Hybrid structure of LNC with an oily core comprising medium chain triglycerides covered by a lipophilic and hydrophilic surfactant shell, functionalized by targeting ligands. (E) Core-shell structure of CLN comprising non-aqueous core carrying drugs, enclosed by a lipid shell.

specific properties with an amorphous structure of the solid lipid, thus unlike SLNs, NLCs show maximum drug loading ability, enhanced drug release, and biocompatibility. NLCs can also avoid undesired leakage of loaded drug during storage by avoiding lipid crystallization because of the presence of liquid lipids (Ghasemiyeh and Mohammadi-Samani, 2018), (Mussi and Torchilin, 2013). NLCs and SLNs are considered as excellent delivery systems as they are biodegradable and non-biotoxic. They have shown promising pharmacological worth that have resulted in significant theranostic potential (Duanet al., 2020).

Liposomes are among few nanocarriers which are considered suitable for different drug delivery applications particularly to deliver functional molecules to cellular systems (Sercombe et al., 2015). Phospholipids are the major component of liposome-based NPs that can self-assemble into a bilayer structure via hydrophilic and hydrophobic interactions (Fig. 1C). Liposomes form vesicles in the presence of water, enhancing the stability and solubility of loaded drugs. They can encapsulate and deliver either hydrophilic or hydrophobic drugs (Fig. 1C). There are different types of liposomes including small uni-lamellar vesicles (SUVs) with size range of 10–100 nm, large uni-lamellar vesicles (LUVs) having a single bilayer with sizes exceeding 100 nm, and multi-laminar vesicles contain a multiple bilayer with size range between 0.5 and 10 μm (Yingchoncharoen et al., 2016a), (Pawar et al., 2012).

LNCs are biomimetic nanocarriers with a hybrid structure of liposomes and polymeric NSs and have an oily core comprising medium chain triglycerides covered by a lipophilic and hydrophilic surfactant shell (Fig. 1D). Currently, LNCs are significantly applied as carriers for lipophilic and hydrophilic drugs (Umerska et al., 2015), (Valcourtet al., 2016). LNCs present several advantages, for instance, they offer physical stability of up to one and half years under which conditions LNCs have small particle size ranges between 20 and 100 nm, and can be used by different administration applications including oral delivery (Mouzouvi et al., 2017).

Furthermore, lipids have been used to fabricate NPs that can be characterized by a core-shell structure, in which a shell intermingles with a core, termed as CLNs. These NPs consist of a lipid shell and a non-aqueous core of different biomaterials. Core carries the drugs, which is then enclosed by a lipid shell (Fig. 1E). This approach has shown much potential in order to enhance the NPs' stability and drug loading capacity as well as controlled drug release. A variety of drugs can be loaded in these NPs that can provide improved pharmacokinetics (Campani et al., 2018), (Yang, Merlin).

2. Required attributes of lipid-based theranostic system

LNPs can be used as robust biocompatible carriers for other theranostic tools including bioimaging, drug/gene co-delivery, diagnostic modalities, and laser-mediated therapeutics (such as photothermal therapy (PTT) and photodynamic therapy (PDT)) (Nabil et al., 2019), (Ma and Zhao, 2015). The purpose of using nanocarriers in theranostic applications is to get optimum systemic circulation, escaping host defenses, monitoring and treating the diseases at cellular and molecular level with enhanced efficacy and minimized side effects (ud Dinet al., 2017). To achieve these targets, these nanoplatforms can be functionalized with several targeting moieties such as PEG, antibodies, ligands, peptides, proteins, aptamers, small molecules, and carbohydrates (Yu et al., 2012). These targeting moieties bind to receptors specific for the surface of cancer cells. However, these cellular receptors are (often) also located on healthy cells, for example, for the generally used targeting moieties such as folic acid, transferrin,and sugars (Villaverde and Baeza, 2019). Targeting moieties on NPs must be capable of targeting only the cancer cells, thus, prevent non-specific toxicological issues to other healthy cells.

2.1. LNPs: superiority over other nanocarrier systems

Lipid-based formulations are known for better uptake efficiency at cellular level. Physiological aspects of lipid-cell interaction are vital to understand the therapeutic distribution and ultimate fate of carrier system (Xing et al., 2016). LNPs exhibit many advantages as delivery carriers over other nanocarrier systems (such as polymers, CNTs, metallic NPs etc.), and have seen extensive usage in drug delivery. In addition to the above mentioned concerns of CNTs and metallic NPs, it has been observed that metallo-supramolecular polymers, that can provide the functionality of the metal ion along with the processability of a polymer have some limitations when used in drug delivery processes. For example, the introduction of metal ions in the body can disturb the ion balance and limit certain medical applications (Rowan and Beck, 2005), (Dong et al., 2015). Furthermore, dendritic polymers exhibit many drawbacks which limit their usage in theranostic applications, for instance, several complex and highly expensive synthetic and purification procedures can lead to imprecise or nonspecific structures with low quantifiability. Moreover, these polymers show poor reproducibility and certain biosafety concerns due to their possible toxicity and unexpected removal, which restrict their clinical translation (Jain et al., 2010), (Shcharbin et al., 2014). The development of LNPs paves the way for resolving above stated limitations.

Advantages of LNPs may include: (1) ease of engineering processes, (2) up-scaling feasibility, (3) excellent biocompatibility and biodegradability, (4) negligible toxicity, (5) controlled and targeted drug release potential, (6) improved drug solubility and stability, (7) enhanced bioavailability, (8) potential of encapsulating both lipophilic and hydrophilic drugs, (9) less expensive, (10) encapsulation of high drug content, (11) potential to cross various physiological barriers, (12) easy validation, and many others which could be favorable for specific delivery route or nature of the payload (Ghasemiyeh and Mohammadi-Samani, 2018), (Attama et al., 2012).

Owing to the charm of their multi-lamellar structures and potential benefits, LNPs have been owed to the fact that in addition to drug delivery, nucleic acid delivery by them is also a matter of interest to the nanomedicine community. This interest in LNP research has been driven by emerging mRNA-based therapies for several diseases, the execution of which depends on the availability of safe and effective carrier systems. Furthermore, lipid type, size, morphology, and surface charge influence the behavior of LNPs *in vivo*. It was a long way to optimize LNP fabrication to deliver nucleic acids, which is now probably best characterized by the development of lipid-based mRNA vaccines for COVID-19. Moderna's mRNA-1273 and BioNTech/Pfizer's BNT162b2 vaccines both use LNPs as delivery vehicles of mRNA, expecting to have a significant descending trend of COVID-19 incidence and mortality. mRNA vaccines deliver mRNA into the cytoplasm of host cells, where it can be transcribed into spike proteins to trigger the immune response. However, negative charge of mRNA electrostatically resists the anionic cell membrane, thus preventing its uptake. For that reason, mRNA vaccines require a carrier that not only protects them from degradation but also allows them to enter cells ("Let's talk about lipid n, 2021). In light of the above, it is of great interest to extend LNP-based technology to deliver nucleic acid-based drugs as well. As these systems can load ample amount of mRNAs, they can potentially enable different approaches regarding nucleic acid-based therapies. For example, LNP-based short interfering RNA (siRNA) drug named Patisiran (trade name Onpattro) is being used for the treatment of polyneuropathies prompted by hereditary transthyretin amyloidosis, hence paving the way for a novel group of medicines based on nucleic acid-based therapies assisted by nano-particulate delivery systems (Akinc et al., 2019).

2.2. Size of LNPs

The size of LNPs is of pivotal concern while designing a lipid-based theranostic system. The size of NPs plays a crucial role in NP cellular adhesion and NP-cell interaction. Principally, owing to their smaller size, LNPs are taken up/internalized by cells via endocytosis and are responsible for enhanced oral uptake. It has been evidenced that decrease in size with an increase in surface area leads to sufficient and consistent absorption in the gastrointestinal tract (GIT) (Poovi and Damodharan, 2018). However, NPs sizes can be tuned depending upon their route of administration and target tissues. For intravenous administration, the recommended particle size is in the range of 100–300 nm (Albuquerque et al., 2015). Whereas for oral administration, NPs of varying size ranges have been reported depending on the fabrication procedures and mechanisms for NPs to pass through various physiological barriers including GIT (Poovi and Damodharan, 2018), (Yin Win and Feng, 2005). It has been proven that buffer used in NPs fabrication procedures with pH 1–7 did not affect the size of the LNPs (i.e. 140 nm). However, when LNPs were incubated in buffer of pH 9, a slight increase in particle size (i.e. 150 nm) was observed (Ball, Bajaj, Whitehead). Some of the recent advances in the field of lipid-based theranostic system and the particle size range preferred for this purpose are described here. Recently, a lipid-based theranostic system labeled with gadolinium (Gd) has been developed. Gd is an important contrast agent for MRI. Liposomal bilayer thickness was reported to be 4.6 ± 0.3 nm and 6.68 ± 0.3 nm with and without labeling of the contrast agent, respectively (Šimečkováet al.). In another study, a dendrimers-based lipid nanotheranostic platform has been developed for *in vivo* mRNA delivery and cancer imaging. For this purpose, they reported their LNP average size as 138 nm and a narrow PDI value of 0.102 (Xiong et al., 2020). Thus, the size of LNPs employed in theranostic platform may vary according to their function or intended destination *in vivo*.

2.3. Supramolecular design of lipids/lipid bilayers

Supramolecular chemistry focuses on non-covalent interactions that are weak and reversible and are not only important in understanding the molecular mechanisms, self-assembling processes, and biological phenomenon but also for the engineering of complex materials (Li et al.,

2019). Non-covalent forces are the fundamental forces in living organisms in different physiological phenomena related to growth and reproduction. Thus, supramolecular structures are considered to be the best candidates to mimic biological processes (Yu and Chen, 2019), (Song et al., 2019). In theranostics, the active nature of non-covalent interactions provide the prerequisite for NSs with unique characteristics, offering captivating potential (Yu and Chen, 2019). Scientists have made attempts to assimilate supramolecular structures to medicines to formulate innovative drugs for theranostic purposes (Dong et al., 2015).

Supramolecular nanotechnology approaches have shown encouraging potential to efficiently solve the limitations of chemotherapeutic drugs such as instability, non-specificity, inefficiency, less solubility and enhanced toxicity, which can lead to certain side-effects. In attempts to address toxicological problems, supramolecular theranostic approaches aiming at specifically "switched on" merely in tumor cells, circumventing issues of cytotoxicity in non-cancerous cells (Cheng et al., 2019).

Lipids are playing a predominant role in engineering lipid-based supramolecular structures and function as building blocks to assist the stabilization or delivery of a molecule or structure. In contrast with covalently bonded liposomes, liposomes built on supramolecular approaches exhibit additional advantages such as quick response to exteriors and successful release of payloads (Jin et al., 2019). Since liposomes can be used to encapsulate a variety of theranostic agents, they are considered as potential nanocarriers for cancer nanotheranostics. In addition to encapsulation, the lipids can also be chemically modified to allow the integration of theranostic agents into liposomes. Lipids can encapsulate photothermal agents, photosensitizers, radiosensitizers, and immunotherapeutic agents in order to recognize synergistic anticancer therapeutics to prevent resistance, tumor decline, and cancer metastasis. Moreover, fluorescent dyes, MRI contrast agents, and PET radiotracers can also be grafted for real-time imaging (Zhou et al., 2021).

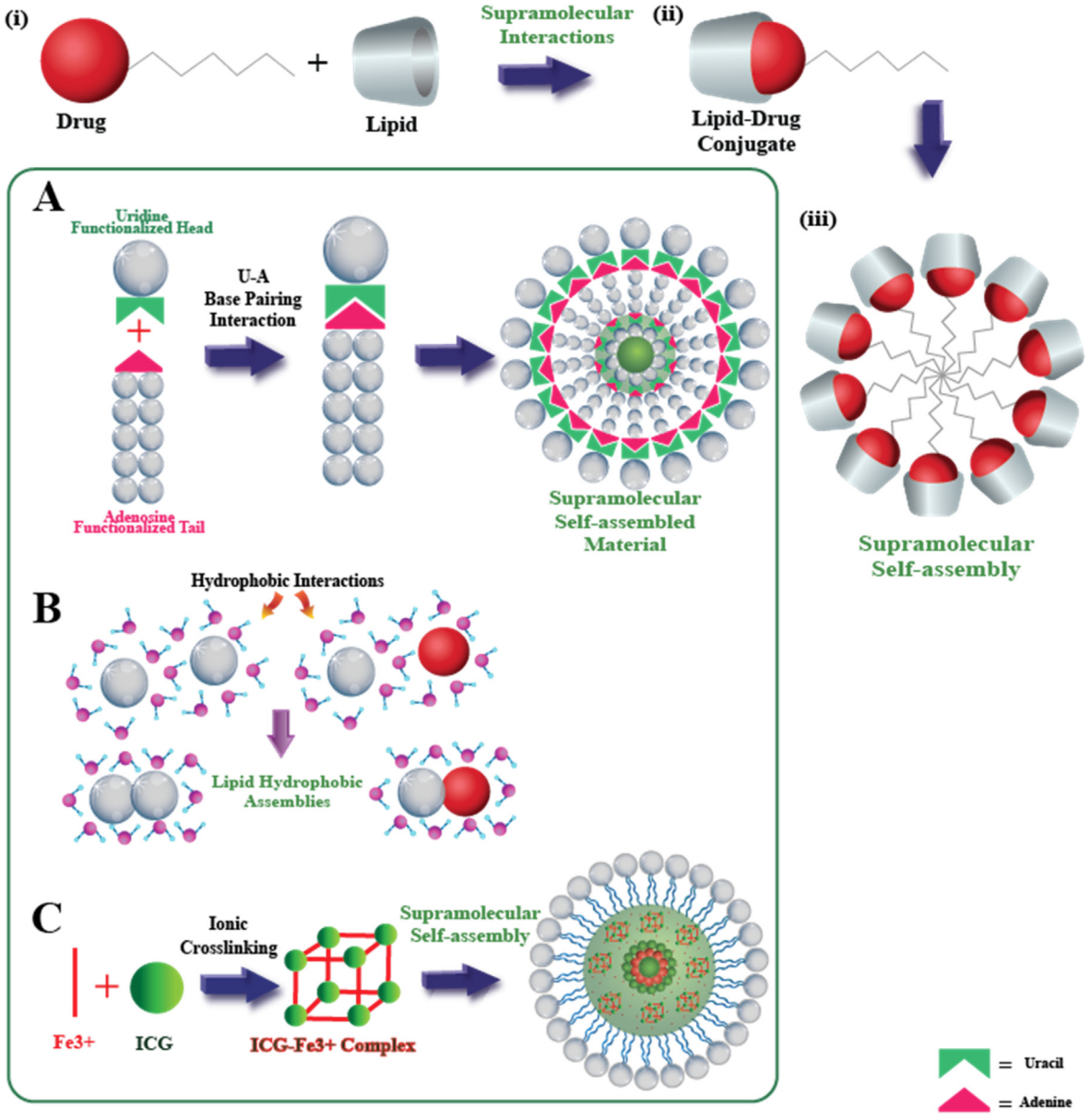

Fig. 2. Conceptual schematic of supramolecular structures of LNPs showing three main stages of the self-assembly process, (i) Structural units, (ii) Initial configuration via supramolecular forces, (iii) Final Stage: Supramolecular self-assembly. (A) Formation of supramolecular lipids based on the base-pairing interaction between A and U (Based on the concept given by (Wang et al., 2015)). (B) Formation of lipid hydrophobic assemblies via hydrophobic effects among lipids, and between lipids and its payloads. (C) Demonstration of metal-coordination interaction via ICG-metal ion (Fe^{3+})-mediated ionic crosslinking self-assembly (Based on the theory reported by (Lin et al., 2019)).

Among several supramolecular forces, hydrophobic interactions, base-pairing interactions, and metal-coordination interactions among lipids lead to supramolecular structures of lipids (Jin et al., 2019). Self-assembly processes of nanotechnology have certain common attributes that can adopt a conceptual scheme based on some general steps. Self-assembly process of supramolecular structures of LNPs can be comprehensively explained by the following main steps, starting from the construction of structural units, which is then followed by the initial configuration of lipid and drug molecules to make lipid-drug conjugate via supramolecular forces. Final step involves the making of the self-assembled structure of supramolecular conjugate (Fig. 2).

2.3.1. Base-pairing interaction: nucleosides functionalized lipids self-assemble into bilayer nanocarrier

Base-pairing interactions have shown the ability to form supramolecular structures of phospholipids and liposomes, however, merely little research has been performed in this regard. Supramolecularly engineered phospholipids could be a key development as compared to conventional covalent-bonded phospholipid structures. Phospholipids can self-assemble to make supramolecular structures in which hydrophobic tails and hydrophilic heads are functionalized with a pair of nucleobases such as Adenine (A) and Uracil (U). Base-pairing interactions based on complementary hydrogen bonding of nucleosides can engineer the supramolecular phospholipids by self-assembling them into liposome-like bilayer structures in aqueous media (Fig. 2A) (Wang et al., 2015). Due to the hydrogen bonding, these supramolecularly engineered structures could reveal fast stimuli-responsive behaviors. Owing to the stimuli-responsive behavior, supramolecular liposomes from nucleoside phospholipids could efficiently deliver drug to tumor site, which will be taken up by tumor cells, and lead to the controlled release of their cargo, thus resulting in an improved antitumor activity *in vivo* and *in vitro* (Wang et al., 2015). Conclusively, a variety of nucleobases and phospholipid structures could serve to fulfill several therapeutic requirements.

2.3.2. Hydrophobic interactions: role of hydrophobicity in supramolecular lipid-nanocarrier

In addition to the base-pairing interactions, hydrophobic interactions among lipids also lead to their supramolecular structures that can facilitate the "link-up" or "plug in" formulation with payloads (Fig. 2B). The payloads can be integrated into the lipid bilayer via lipid hydrophobic interaction and the strategy is used to formulate multi-modular nanoplatforms (Huang et al., 2020). It has been observed that supramolecular construction of biomimetic high density lipoprotein (HDL)-like NPs via lipid-conjugated core scaffolds has potential to be used as therapeutic agents. These NPs are ~10 nm in diameter and mimic human HDLs in their physical and chemical characteristics and perform significant HDL functions such as suppression of inflammation (Henrich et al., 2019). These NPs can be loaded with different therapeutic payloads (such as chemotherapies) and ensure targeted delivery to cancer cells. In addition to drug delivery, these NPs could be therapeutically vital in particular tumor types (McMahon et al., 2015). Moreover, these imitated HDL nano-discs comprising apolipoprotein A1-mimetic peptides and phospholipids have been suggested as an anticancer vaccine approach for personalized cancer immunotherapy (Kuai et al., 2017). These vaccine nano-discs can incorporate antigens and adjuvants by simple mixing with antigen peptides. These nano-discs were shown to generate 47-fold higher frequencies of antigen-specific cytotoxic T-lymphocytes than soluble vaccines (Kuai et al., 2017). In the meantime, loading of antigens can be controlled easily, making this incorporation strategy suitable for personalized neo-antigen vaccination.

2.3.2.1. Porphysomes (porphyrin-lipids): lipid-based supramolecular structures. Porphysomes self-assemble into phospholipid bilayers to form supramolecular structures, which resemble liposomes. Porphysomes can form similar supramolecular structures as phospholipids owing to their amphipathic nature, resultant from the hydrophobic nature of the acyl chain and porphyrin, and the hydrophilic head. With high porphyrin loading, these lipids show fully quenched fluorescence and efficiently convert light into heat with exceptional photoacoustic (PA) and photothermal properties. This photonic property of lipids is sensitively reliant on their structures and can be used to furnish them with multimodal abilities for theranostic applications. This infers that porphysomes-based supramolecular structures can have potential applications in theranostics including fluorescence imaging, PA diagnosis, PTT, and PDT (Huynh and Zheng, 2014), (Lovellet al.).

2.3.3. Metal-ligand coordination interaction

Metal–ligand coordination NSs are based on the coordination interactions between inorganic metal ions and organic ligands. These NSs have shown the ability to form coordination-assembled supramolecular nanoplatforms for cancer theranostics (Fig. 2C). Recently, nanoscale metal−organic frameworks (NMOFs) are being used in cancer theranostics (Zhou et al., 2018a), (He et al., 2019). Notably, for medical diagnostics, NMOFs have shown superiority over other NPs such as they can be employed as contrast agents by coherent selection of metal ions and organic ligands. For instance, the integration of metal ions (e.g. Fe^{3+}) into the coordination complexes allows the execution of MRI and fluorescent organic ligands (e.g. dyes) enables the optical imaging (Li et al., 2020). In this regard, a versatile non-invasive supramolecular approach has been developed for US-assisted cancer theranostics that aimed at circumventing the major problems of sonodynamic therapy and to monitor the therapeutic activity *in vivo*. This system based on the self-assembly of theranostic dyes (i.e. indocyanine green (ICG)) was constructed by ICG-metal ion (Fe^{3+}) binding via metal-coordination mediated ionic crosslinking between anionic sulfonic groups and Fe^{3+} ions. This ICG-Fe^{3+}-complex was encapsulated by lipids to form supramolecular self-assembly (Fig. 2C), which was then employed for cancer sonotheranostics. ICG-Fe^{3+}@lipids can be used to obtain enough acoustic and optical signal intensities that permit imaging-assisted sonodynamic therapy against hepatocellular carcinoma (HCC). Because of non-invasive multimodal imaging, greater biocompatibility and better drug loading capacity, this system can be suitable for their applications in clinical settings against inherent cancers (Lin et al., 2019).

3. Focus of current lipid-based theranostic approaches

Detection and screening for cancer at an early enough stage is certainly a fundamental step towards successful treatment. Non-invasive diagnostic approaches seem to be beneficial over repetitive biopsies of tumor lesions, as biopsies can cause great trauma. However, precise and early diagnosis is challenging. Dual imaging approach can offer reciprocal advantages to attain early diagnosis. To this end, lipid-based nanocarriers are investigating for their potential use for diagnostic applications. On the other hand, being non-invasive, oral delivery of therapeutic agents has received increased compliance by patients, exclusively for the diseases such as cancer which require prolonged treatments (Krohe et al., 2016). However, oral delivery of chemotherapeutics is relatively problematic because of the biological barriers that hinder drug deliveries to blood stream, due to which their clinical usage may be obscured and may cause detrimental effects (Zhou et al., 2018b). For this reason, lipid-based nanocarriers can serve to improve oral drug delivery to ensure clinically feasible and time-controlled drug release, ultimately maximize the therapeutic efficacy (Pridgen et al., 2015), (Dilnawaz). Owing to their ability to penetrate the oral drug adsorption barriers, SLNs and NLCs have shown promising potential as oral drug carriers anticipated to help the scientists planning to conduct studies on LNPs (Okur et al., 2020). However, as mentioned above in Section 1, the systems that own potential diagnostic ability usually possess poor therapeutic efficacy, while systems with excellent therapeutic index usually hold poor imaging ability. Herein, we elaborate how most of the recent studies focus merely on diagnostics and therapeutics, and how the synergistic

mechanisms of theranostics reveal the potential of LNPs as delivery vehicles for cancer management (Fig. 3).

Some diagnostic applications are exemplified by self-assembled LNC carrying iodixanol in its cavity and labeled with ^{64}Cu for dual PET/CT imaging is effective to obtain high radiolabelling efficacy, stability, and successful targeting of lung cancer cells. This formulation confirmed the abilities of higher contrast CT imaging and sensitive PET imaging to endow excellent dual-mode imaging of lung cancer cells, hence showing promising potential for early, precise, and sensitive tumor diagnosis (Caiet al., 2020). Along the same lines, peptide functionalized superparamagnetic iron oxide nanoparticles (SPIONs) encapsulated by NLCs have been developed as a targeted MRI contrast agent for early, precise, and sensitive diagnosis of HCC (Luet al., 2020).

Alternatively, for therapeutic purposes, SLNs are being employed for oral delivery of angiogenesis inhibitors. Surface functionalized SLNs loaded with curcumin have shown significant anti-angiogenic activity (Perteghella et al., 2020). Anti-angiogenesis agents can combat cancer as they inhibit the growth of blood vessels that support cancer development instead of preventing the cancer cells to grow (Perteghella et al., 2020). Moreover, SLNs-based delivery systems have shown the potential to improve the delivery efficacy of different chemotherapeutic agents for several types of cancers, for example, 5-Fluorouracil for colorectal cancer (Smith et al., 2020), nutlin-3a and asiatic acid for glioblastoma (Garanti et al., 2020), (Grillone et al.), epigallocatechin gallate, docetaxel (DTX), letrozole, and variabilin for breast cancer (Radhakrishnan et al.), (Lee et al., 2019), (Ahmadifard et al., 2020), (Lerata et al., 2020), and morin hydrate for cervical cancer (Karamchedu et al., 2020). In addition, lipid-calcium-phosphate NP system ensures the sustained and combined release of doxorubicin (DOX) and paclitaxel (PTX) to human lung cancer A549 cells. This biocompatible phospholipid-based drug delivery system was developed by the integration of DOX into hollow calcium phosphate, which is covered by a lipid bilayer carrying PTX. The fusion of these two drugs verified their synergistic effect against A549 cells. This combined-therapeutic approach had proven to have anti-tumor properties, which were verified by apoptotic analysis, *in vivo* anti-tumor activity, and *in vitro* cytotoxicity analysis (Wu et al., 2017). Likewise, LNCs offer the combined breast cancer therapy by sufficient co-loading and co-delivery of DTX and thymoquinone (THQ) to enhance chemotherapeutic efficiency against drug-resistant breast cancer cells (Zafar et al., 2020), (Zafar et al., 2020). Furthermore, LNCs can be loaded with different chemotherapeutic agents to be used to enhance cancer treatment in the setting of immunotherapy for glioblastoma (Pintonet al.), colorectal cancer therapy (Fourniols et al., 2020), (Tsakiris et al., 2020), and breast cancer therapy (Zafar et al., 2020), (Zafar et al., 2020), (Vasconcelos et al., 2020), (Behdarvand, Bikhof Torbati, Shaabanzadeh), (Szwed et al.). This implies that synergistic effects of nanosystems had bestowed the co-delivery of various chemotherapeutic agents (such as anti-tumor and anti-angiogenesis agents) at the target site, thus offering combined therapeutics which signifies a well-established approach for cancer therapy. Moreover, as liposomal structures imitate the biological membranes, these structures can fuse with the cell membranes via phagocytosis. Undeniably, it is the most primitive nanosystem permitted for clinical applications by the US Food and Drug Administration (FDA) (Bulbake, Doppalapudi, Kommineni, Khan). From medical point of view, liposome-based NPs have presented enhanced pharmacokinetics and biodistributions of encapsulated drugs, thereby enhancing the drug's selectivity, providing sustained drug release and diminishing the toxicity to non-cancerous cells, making them ideal candidates in cancer therapeutics (Yang, Merlin). Liposomal nanocarriers have shown the potential to encapsulate various chemotherapeutic agents and deliver them via oral route of administration for cancer therapeutics (Liu et al., 2018), (Kim, Shin, Kim).

As synergistic approach, LNPs are also shown to be potentially beneficial for non-invasive cancer theranostics. Evidence suggested that a novel liposome-based formulation carrying NIR-II dye (IR-1061), termed Polipo-IR NP, had shown promising potential for early diagnosis and treatment of HCC. This formulation not only diagnose tumor non-invasively and pre-operatively with a strong signal-to-noise ratio, but this also aid in precisely navigating tumor during course of surgical process. IR-1061 dye-based LNPs for PA diagnosis of HCC and effective

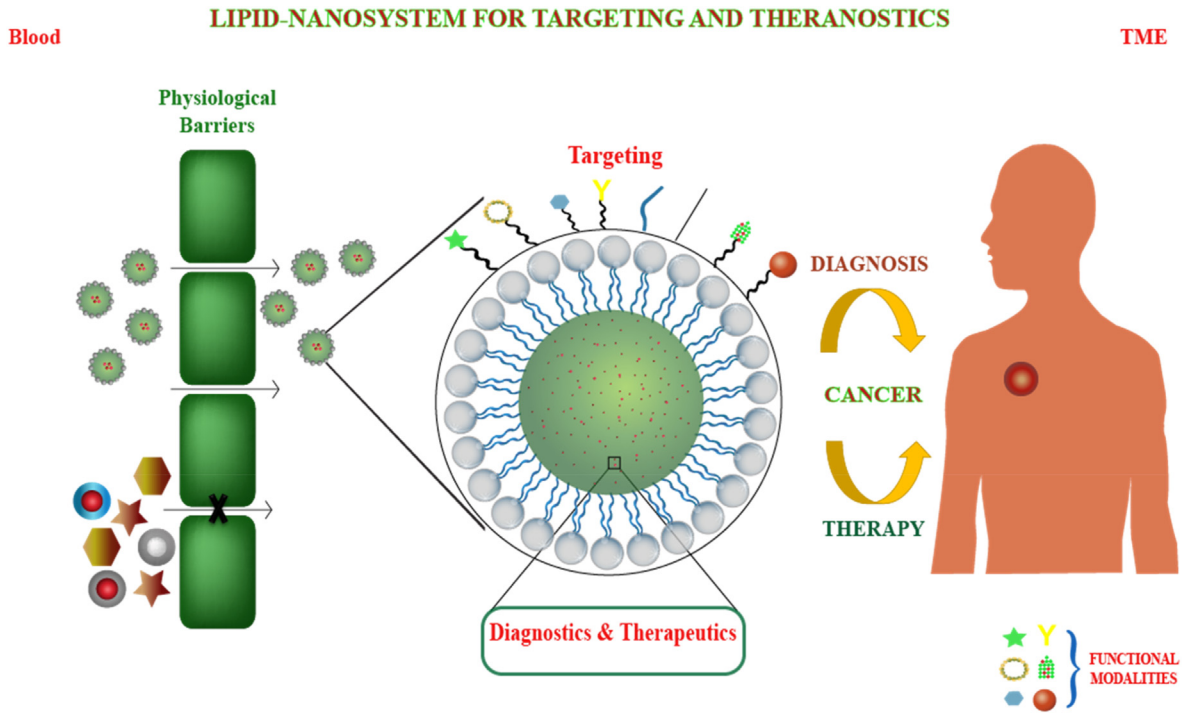

Fig. 3. A schematic illustration of lipid-based cancer nanotheranostic system exhibiting potential to cross various physiological barriers, functionalized with several targeting moieties to enhance penetration across the barriers, used for simultaneous release and imaging. The functional groups of nanotheranostics can be antibodies, peptides, proteins, aptamers and carbohydrates, while their core material are lipids.

PTT can provide state-of-the-art knowledge for understanding HCC theranostics (Chen et al., 2019). Furthermore, lipid-based complexes have shown much suitability for US-imaging and release of their payload when exposed to US. In this context, it has been suggested that US-mediated delivery system built on folic acid-conjugated lipid nanobubbles loaded with artesunate, is potent for imaging-assisted anticancer therapy. This complex showed an enhanced cellular uptake and enhanced and dosage-dependent apoptotic activity, thus exhibited greater anticancer efficacy *in vitro*. Furthermore, it showed long-term tumor retention, enhanced tumor suppression, and negligible systemic toxicity *in vivo* (Gao et al., 2019). Along the same lines, a complex comprising nanobubble-PTX-liposome has shown a non-invasive cancer theranostic strategy for US imaging and US-assisted drug release at tumor site. In presence of US, this formulation has shown 300-fold increase in antitumor activity in human pancreatic cancer, breast cancer, and tongue cancer cell lines, when compared to commercially available Abraxane. Moreover, this complex has shown to be echogenic when compared to the US contrast agents present in the market with echogenic stability of up to more than 7 days (Prabhakar and Banerjee, 2019). Besides liposomal nanobubbles, other types of echogenic liposomes are also used for drug delivery; including bubble liposomes, liposome-loaded microbubbles and CO_2 gas-generated liposomes (Ahmadi et al., 2020) (Fig. 4).

Furthermore, it has been proposed that cRGD peptide-conjugated SLNs carrying IR-780 dye exhibited potential for NIR-assisted PTT (Kuang et al., 2017). Likewise, NLCs are responsible for the NIR-assisted co-delivery of quantum dots and PTX, aimed at cancer theranostics (Olerile, 2020). Thus, in view of their unique advantages, LNPs have shown much potential in non-invasive cancer theranostics.

3.1. Targeting of tumor microenvironment (TME)

Although nano-based drug delivery approaches can considerably improve drug accumulation at tumor sites, but deficiency in concentration of released drug can be occurred due to some physiological barriers in TME. Even though nanocarriers offer passive release after cellular uptake, it is very encouraging to well define the TME to attain optimal and rapid payload release. NP-based strategies have developed apparent potential for diagnosis and drug delivery by active and passive targeting with extended blood circulation time. In order to improve anticancer therapeutic targeting, scientists are trying to define the TME, thereby crafting the most suitable and accurate setting for the accumulation of nanosystems at tumor sites due to the enhanced permeation and retention (EPR) effect (Silva, Pinho, Lopes, Almeida, Gaspar, Reis) (Fig. 5).

This is associated with the fact that EPR factor results in the diffusion of nanotheranostic agents. EPR effect accepts as one of the key phenomena affecting the diffusion of NPs in tumor tissues. Moreover, real-time *in vivo* visualization of tumor cells and their nearby TME can assist in providing valuable information for identifying cancer progression or suppression. Imaging agents can be used to label tumor cells to make them detectable. However, TME weakens the efficacy of cancer immunotherapy, which entails the remodeling of TME. For this purpose, NLCs are being employed for targeting tumors. NLCs have been developed for the co-delivery of DOX and sorafenib (Sfn), where Sfn was expected to remodel the TME, consequently enhance the immunotherapy, which was then stimulated by DOX for successful esophagus cancer therapy (Wang et al., 2020).

However, many scientists have explored the passive targeting of NPs in animals, as EPR effect may not be prominent in many human tumors. Hence, there is a need of suitable animal models while evaluating the nanotheranostics.

3.2. Targeting metastasis

Metastasis is the ultimate challenging bottleneck for cancer cure for which more therapies are required. In many cancer cases, metastasis is the principal cause of death (Steeg and Theodorescu, 2008), (Wu et al., 2021). The development of targeted therapeutics aimed at the tumors and tumor-host interactions is reliant on understanding the keystones that manage the metastatic process from beginning to end. Metastatic process is a cascade of complex events which involves several consecutive biological mechanisms, for example, cancer invasion, tumor cell intravasation into the circulation via entry into lymphatic vessels or blood vessels, survival in circulation, spread to distant sites, extravasation, and eventually progression in different microenvironment to give rise to secondary tumors (Hapach, Mosier, Wang, Reinhart-King). Integrins and other cell adhesion molecules, extracellular matrix (ECM) components such as collagen and fibrin, and signaling molecules such as cytokines and growth factors etc. play a major role in metastatic cascade

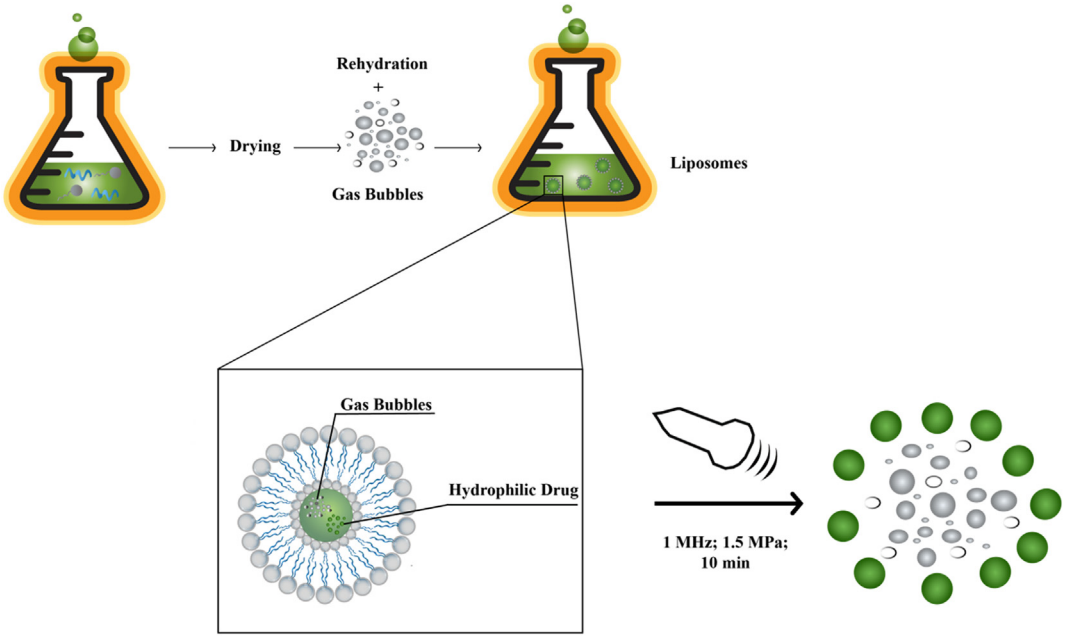

Fig. 4. Illustration of echogenic liposomes used for drug delivery. When ultrasonic waves expose these liposomes, they warmed, develop permeability, and release their payload. Modified with the consent from (Ahmadi et al., 2020).

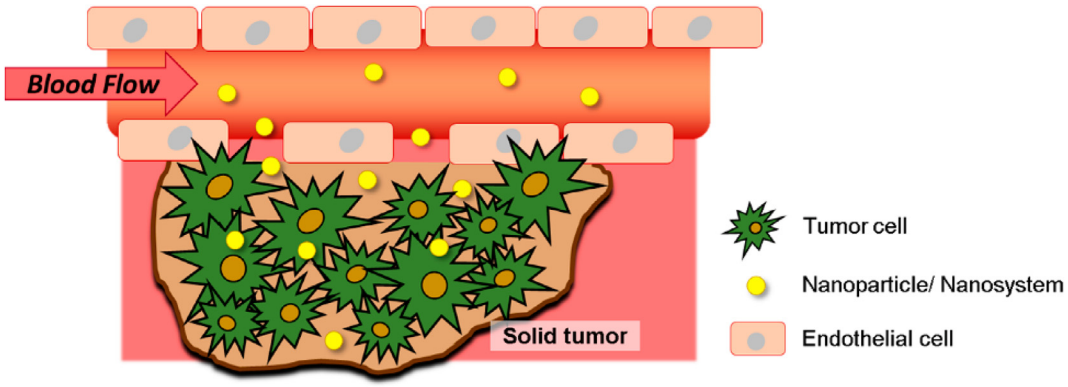

Fig. 5. Representation of the accumulation of NPs in solid tumors due to the EPR effect. Reused with the consent from (Silva, Pinho, Lopes, Almeida, Gaspar, Reis).

(Smart et al., 2021), (Eble and Niland, 2019), (Fares et al., 2020). Therefore, an approach aimed at targeting multiple factors may pave the way for cancer management. Moreover, various chemotherapeutic agents have short half-lives leading to poor bioavailability that curtail their efficiency (Yingchoncharoen et al., 2016b). Therefore, their targeted delivery in continuous mode is a precondition for clinical usage. For all these concerns, nanotheranostics have shown considerable potential for prevention of metastatic cancer (Prasad et al., 2020), (Israel et al., 2020). Biological processes that particularly drive each step of metastasis can be addressed using NPs. Owing to the stated earlier advantages of LNPs; these can increase the clinical therapeutic efficiency by increasing drug accumulation in tumor tissues while decreasing its accumulation in healthy tissues, to attain effective cancer treatment (Yingchoncharoen et al., 2016b). Moreover, NPs (<100 nm in size) can take the advantage of pathophysiological features in tumors and extravasate via leaky vasculature of tumor tissues and accumulate within the ECM due to impaired lymphatic drainage (EPR effect) (BAZAK et al., 2014).

It has been proposed that by employing berbamine loaded LNPs (BBM-LNPs), cancer metastasis can be targeted. In a recent study, therapeutic potential of BBM-LNPs was evaluated at the initial tumor site (i.e. mouse melanoma cell lines) by B16–F10 melanoma tumor model then metastatic activity was evaluated by hematogenous metastasis of melanoma cells to secondary tumor site (i.e. lungs). These BBM-LNPs have shown effective suppression of the initial tumor growth as well as lung metastasis in melanoma tumor model and signified as a potential candidate for metastatic cancer management (Parhi et al., 2017). We have shown in our previous work that SLNs can be used as a therapeutic approach in an effective manner than that of native drug for improvement of breast cancer therapy (Rehman et al., 2017b). Metastasis is the major cause of breast cancer-related mortalities in women. DTX and PTX are being used to target metastasis of breast cancer (Hammadi et al., 2017). Evidence suggested that the formulation of SLNs loaded DTX (SLN-DTX) exhibited an encouraging anti-metastatic as well as anti-cancer efficacy *in vivo*, for metastatic breast cancer. Treatment with SLN-DTX inhibited the spontaneous lung metastasis in tumor-bearing mice. This formulation holds great promise for metastatic breast cancer management and in metastasis inhibition (da Rocha et al., 2020). Moreover, it has been suggested that chemokine receptor CXCR4 and its related ligand SDF-1 (CXCL12) control the breast cancer invasion to some particular metastatic sites. It has been observed that CXCL12/CXCR4 axis together plays a major role in cancer invasion and metastasis (Jin et al., 2012). Several studies have shown that CXCR4 receptor positive tumors metastasize with high levels of SDF-1. Breast cancer cells express high levels of CXCR4, whereas the primary metastatic sites express high levels of SDF-1 (Krohn, Song, Muehlberg, Droll, Beckmann, Alt). In order to target metastasis, there is an effective strategy available to target the interaction between SDF-1 and CXCR4 (Wang et al., 2015b), (Li et al., 2012), either by downregulation of CXCR4 (Wang et al., 2020) or by CXCR4 antagonists (Ling et al., 2013). For example, CXCR4-targeted NLCs with a CXCR4 antagonist (AMD3100) and IR-780 exhibited great potential for prevention of metastasis and for photothermal anti-tumor efficacy *in vivo*, proposing breast cancer cure (Li et al., 2017). In addition, for triple-negative breast cancer, a study reported hybrid nanovesicles (hNVs) that comprise platelet-derived-NVs, M1 macrophage-derived-NVs, and cancer cell-derived NVs considerably stimulating macrophage activation against post-surgical cancer recurrence and metastasis. The hNVs can effectively accumulate in surgical incisions, interact with circulating tumor cells, repolarize tumor-associated macrophages towards M1 phenotype, and block the CD47-SIRPα interaction, hence stimulate macrophage mediated cancer cells phagocytosis (Rao et al.). Furthermore, visualization of tumors by PET, fluorescence and PA imaging can give inclusive information to assist image-guided therapy through PDT or PTT. Evidence suggested that, with multimodal porphysomes, primary or metastatic tumors can be visualized. ^{64}Cu having similar half-life as circulation half-life of porphysomes, can be used as a radiotracer. In PET imaging, the biodistribution of ^{64}Cu-porphysomes can be examined and measured (Liu et al., 2013).

Conclusively, exploring the metastatic progression and anti-metastatic strategies is essential to be able to develop improved therapeutics in the future and will certainly complement advancements in cancer nanotechnology. As per our understanding, anti-metastatic strategies should confront multiple biological events at once. These strategies may include: (1) targeting the primary tumor to inhibit its metastatic ability (i.e., targeting migration, angiogenesis and invasion), (2) targeting the TME, (3) targeting cancer stem cells, (4) targeting tumor cells in circulation before they migrate to new location, (5) targeting resting cells so as to bring them out of the dormancy so they might be sensitive to previous chemotherapeutics or otherwise, keeping the dormancy to inhibit the occurrence of metastatic process, and (6) targeting defined colonization and the secondary tumors (oligo-metastatic and poly-metastatic tumors) formation.

4. Clinical safety and translation of LNPs

Although several potential chemotherapeutics have been developed, the major problem to clinical translation is the failure of delivering drugs to the cancer cells without causing painful side-effects. In order to circumvent this issue, nano-based formulations promise the targeted delivery for enhanced cancer therapy. Many combined, targeted and triggered drug delivery systems have been established based on multiplexed particles and internal tumor triggers (such as pH) or external active triggers (such as US and hyperthermia) (Ingram et al., 2020). Moreover, intrinsic drugs ineffectiveness can be directed to their interruption in clinical applications. In this regard, supramolecular nanotechnology approaches offer alternative methods to the researchers to transform trash (ineffective drugs) into treasure.

An innovative drug that is proceeding to clinical translation acquires around 12 years to get approval by FDA (Van Norman, 2016). According to a recent survey, at present, around 50 different NPs are in clinical trials but only 2 of them have been approved from FDA or European Medicine Agency (EMA) from 2016 to 2019 (Anselmo and Mitragotri, 2019). Another survey reported that, at present, about 50 nanomedicines have been approved by FDA and are available for clinical usage and 77 are in clinical trials (Ventola, 2017), (Bobo et al., 2016). However, as mentioned above in introduction, despite of significant research work towards the design and improvement of theranostic nanoplatforms which has been already done, still no nanotheranostic formulations have been approved for clinical applications. Principally, translational criteria include a size range of 100 nm or less, suitable morphology, effective encapsulation, low surface charge, robustness, scalable synthetic procedures, ways of administration, specific binding, biodistribution, metabolism, sufficient stability of products, and removal and possible toxicity (Choi and V Frangioni, 2010). In this context, inherent features of nanomaterials can greatly serve to achieve success in clinical translation. Therefore, complete and broad understanding of all factors of NPs is considered to be obligatory to improve clinical translation. In a delivery system, if the excipients show toxicity, it would not be satisfactory to bring them into clinical settings. Opportunely, along with their potential as multifunctional nanomaterials for theranostics, LNPs have also been applied for advanced clinical applications due to their negligible toxicity. Lipids are generally regarded as safe (GRAS), because of their presence in the human body and in all the foodstuffs that humans take. However, the ultimate safety can be compromised due to the toxic surfactants used in lipid formulations. Therefore, surfactants of GRAS status should be used. Regarding lipids, usage of SLNs and NLCs for oral administration is completely safe (Siram et al., 2019). In addition, specific lipids from the food industry can also be used in pharmaceutical industry; though their direct usage for the preparation of pharmaceutical products is prohibited. However, the toxicity analysis of a lipid used in the food industry can be used for receiving approval from the pharmaceutical regulatory bodies (Wang et al., 2015c), (Zoubari et al., 2017). Moreover, lipids minimize the toxicity of various chemotherapeutic drugs and thus protect the healthy cells (Siram et al., 2019). Undeniably, liposomes were the first nanosystem to be used for clinical applications after getting approval from FDA because of their biodegradable and biocompatible nature (Bulbake, Doppalapudi, Kommineni, Khan). SLNs are considered as clinically safer as compared to other polymeric NPs. Several studies have reported the clinical safety of SLNs and NLCs by providing evidences of greater biocompatibility through *in vivo* and *in vitro* analysis of both (Doktorovová et al., 2016), (Reis et al., 2016). Clinical translation of other lipid-based delivery systems is sluggish. There is a need to explore their translation into optimistic approaches for the delivery of several medically dynamic particles in the clinic.

In a nutshell, lipids are absolutely biocompatible, show no toxicity due to their biological origin, and can be used to lessen the toxicity issues and thereby enhancing the safety of the nano-pharmaceuticals. Conclusively, lipid-based nanotheranostics will necessarily play a strategic role in developing nanotechnologies that can fulfill unmet clinical needs and give a fast approach towards translation.

5. Concluding remarks and future perspectives

Compared to conventional medicinal approach, NP-based systems have developed apparent prospective for diagnosis and drug delivery. Lipid nanocarriers based on divergent NSs displayed much potential in cancer theranostics. In addition, owing to the considerable potential of LNPs, demand for lipid-based drug and vaccine delivery is high, and has achieved considerable success for COVID-19 treatment as well. Moreover, for the past years, several advanced supramolecular systems have been broadly developed and functionalized in the area of nanotheranostics and further attained several fascinating advancements.

Along with promising advantages, the given challenges regarding nanotheranostics must also be taken into account: (1) Large-scale production of complex nano-platforms could be complicated. (2) No obvious FDA policies are there to give proper regulation to nanotheranostics. (3) Diagnostics and therapeutics both have different necessities for tumor targeting. Combined delivery of nanotheranostic components may not have major synergistic effect for clinical setting. (4) Nano-toxicity must also be taken into consideration. Toxic effects caused by NPs are not yet completely identified. Further research is required to explore on how to minimize the toxicity and elucidate the potential applications of NPs in the future.

Though the worth of nanoplatforms is getting bigger, there is yet a long journey to go for promising successful nanotheranostic platforms intended for targeted tumor imaging and delivery of therapeutics. This is particularly noteworthy in the area of personalized products, where no authorized personalized nanomedicine exists. A major attempt is needed in this area in the future. Though, the scientists are not only hopeful and confident but various organizations have also been working in collaboration with regulatory authorities to contribute to the transformation of nano-medicinal research outcomes from laboratories to the industrial level with the aim to exploit personalized novel nanomedicines for commercial use. By presenting the interpretation of the considerable analysis and research attempts being devoted, we hope that the mankind will significantly take advantage from supramolecular nanotheranostics subsequently.

Conclusively, it is the need of the hour to overcome certain challenges which are still unmet with respect to achieving higher efficacy of theranostic platforms employing lipids and other biomolecules.

CRediT authorship contribution statement

Syeda Zunaira Bukhari: Content curation, designed an outline of the main topics/subtopics, use supporting evidences, write first draft, editing what the co-authors have advised about, devise schematics conceptually, draw schematics, approval of final manuscript. **Kornelius Zeth:** Reread the entire article, critique the article through identifying gaps, point out some strengths and weaknesses, highlight the key points, pinpoint and support the article's main argument, approval of final manuscript. **Maryam Iftikhar:** Data curation, emphasize the constructive aspects and details, Writing – review & editing, spot grammatical errors/mistakes, notice any flaws, devise schematics. **Mubashar Rehman:** Critique the article for contradictions, disparities in the text, identify unanswered questions, summarize the article by revisiting what the first author has written about, give the second opinion on the article. **Muhammad Usman Munir:** Identify relevant facts and findings from the article, Writing – review & editing, approval of final manuscript. **Waheed S. Khan:** Took a standpoint of either supporting or not supporting the statements, back up arguments with facts and relevant theories, approval of final manuscript. **Ayesha Ihsan:** Conceptualization, writing title for reviewing, make an outline of the main topics/subtopics, engage co-authors, Supervision, take a standpoint of supporting the authors, analyze the article adequately, editing and approval of whole and final draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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