response phospholipids. By mixing various lipids with various gel-to-liquid transition temperatures could design liposomes with the favorite gel-to-liquid transition. For example, liposomes composed of dipalmitoylphosphatidylcholine (DPPC) as primary lipid and distearoylphosphatidylcholine (DSPC) as a co-lipid undergo phase-transition from gel-to-liquid crystalline and lamellar-to-hexagonal transition resulted in the release-loaded elements during such transitions [50]. Using of temperature-sensitive liposomes in combination with localized hyperthermia can increase the temperature-dependent effects and particularly releases the trapped drug in the heated tumor tissue. In a study [51], a 1.2-dipalmitoyl-*sn*-glycero-3-phosphoglyceroglycerol (DPPGOG)-based liposomal formulation was synthesized that enabled long circulation time with durable and effective drug release under moderate hyperthermia (41–42°C) and DPPGOG facilitates temperature-triggered drug release from these liposomes. The researchers declared that grafting PEG to lipids can possibly be used for clinical applications and the mean area under the curve for tissue drug concentration was raised more than sixfold by these liposomes compared with nonliposomal drug delivery.

Integrating stimuli-responsive polymers and liposomes together to obtain triggerable, targetable and theranostics capabilities nanoscale platforms can fulfill all the disadvantages of these structures when used lonely, such as lack of drug-release triggers and the instability of naked liposomes. Polymers can rapidly experience a phase transition to a gel which triggers conformational variations in the chains of polymer and a coil-to-globule transition in response to external stimuli including variations in temperature. Polymers having LCST could be applied to prepare thermosensitive liposomes. Below the LCST, polymers stabilize the liposomes in their hydrated form, but above the LCST, polymers destabilize the liposomal due to temperature transition behavior and liposomal integrity structural starts to disintegrate and resulting in the release of its cargo. Using NIPAAm copolymers as LCST polymers in the structure of the thermoresponsive liposome has been reported in many studies [52–54]. The liposomes membrane could be simply modified with the triggered response polymers and small molecules to facilitate releasing of cargo by stimuli. Through a postsynthesis modification strategy, a network of stimuli-responsive polymers can be integrated onto the liposomes surface to produce a multifunctional nanoscale DDSs that allows for multidrug loading, triggered drug, release targeted delivery, and theranostic abilities.

5. HYPOXIA-RESPONSIVE DRUG DELIVERY SYSTEMS

The penetration of drugs to tumors is an important issue therefore, designing carriers that are able to deliver drugs efficiently, has been a challenging matter forever. The cancerous matrix is a heterogeneous environment composed of irregular blood vasculature and raised interstitial fluid pressure prevents penetration of drugs to the solid cancerous matrix and resulted in weak therapeutic effects. One of the promising nanocarriers, to acquire satisfactory efficacy, is hypoxia-responsive DDSs that exploit features of the cancerous environment and could assist as an important therapeutic target [55]. Based on our knowledge of cancerous tissues, tumor metabolizing is based on glycolytic pathways that provide oxygen and food. Cancerous tissue always faces a shortage of oxygen (less than 5 vs 40–60 mmHg in healthy tissues [56]) and food because of its high metabolization leads to an acidic condition that could be exploited by hypoxia-responsive DDSs to deliver drugs efficiently.

The zeta-potential of the nanocarrier surface could be increasingly altered by replying to the hypoxia gradient therefore hypoxia-responsive nanocarrier could enhance the positive surface charge by responding to hypoxia gradients and resulted in deep penetration in the cancerous matrix. Studies have shown that positively charged nanocarriers have a better penetration capability due to overcoming the hydraulic pressure gradient and exhibit efficient binding plus internalization to angiogenic endothelial cells (Fig. 6) [57]. Given that, the reticuloendothelial system removes positively charged nanocarriers from circulation but stimuli-responsive nanocarrier could produce positive charge on the carrier surface in the cancerous site by the response to cancerous condition such as lack of oxygen (hypoxia) and acidic condition (refer to part 2 in this chapter).

Nitroimidazoles [58], nitrobenzyl alcohols [59], and azo linkers [60] are used in nanocarrier structures as a hypoxia-responsive group which can reduce under hypoxic conditions and result in variations in surface charge and hydrophobicity or hydrophilicity of the nanocarriers (Fig. 7).

In a study [59] anticancer theranostics FDU-DB-NO_2 drug delivery system designed for solid tumors treatment that can specifically be activated by hypoxia. This prodrug has investigated to deliver an anticancer drug floxuridine (FDU) and a fluorescence dye precursor 4′-(diethylamino)-1,1′- biphenyl-2-carboxylate (DB) for selective two-photon imaging and a hypoxic trigger 4-nitrobenzyl group that can track real-time drug release in hypoxia condition of solid tumors. 4-Nitrobenzyl group of FDU-DB-NO_2 reduces by NTR/NADH under