interactions, resulted in the endosomal escape. The researchers declared that DC-liposomes have the potential to break the endosomal barriers to improve the therapeutic efficacy of encapsulated cargoes. Also, it was investigated that DOX-loaded DC-liposome presented higher cytotoxicity than the free DOX because of DC-liposomes' endosomal escape capability.

Another class of nanocarriers is micelles which have been developed pH-responsive DDSs [27]. Copolymers can form micelles and by protonation of the groups such as carboxylic or amines on the surface of the water-soluble copolymer, micelle can response to the pH variation and able to start degradation and release own payloads [28]. For example, poly(L-lactide)-*b* poly (2-ethyl-2-oxazoline)-*b*-poly(L-lactide) (PLLA-PEO-PLLA) triblock copolymers and diblock copolymers such as (PEO-PLLA) have been used in the pH-responsive micelle's systems [24].

Dendrimers are another class of nanomaterials that have been investigated to develop pH-responsive DDSs [29,30]. Dendrimers composed of pH-responsive monomers such as 2,2-*bis*(hydroxymethyl)propanoic acid or by modifying of terminal ends with acid-sensitive groups including hydrophobic acetal groups that are conjugated to desired cargo to produce a pH responsive delivery system that able to cleave off the dendrimer structure in acidic situation resulting in the cargo release [31,32]. In a study [13], The 3.5th generation of dendritic chitosan-coated silica magnetic (DCSM) NPs with a lot of amino and carboxylic acid groups on the surface were synthesized and two different anticancer drugs, DOX and methotrexate (MTX) were loaded to DCSM NPs by electrostatic interactions and simultaneously intracellular delivery of these drugs was investigated. The amino functional groups in the chitosan polymeric chain are responsible for its solubility owing to the protonation in acidic media, moreover, NPs with chitosan coating is biodegradable and biocompatible. At low pH rates, the amine functional groups ($-NH^{3+}$) and carboxylic acid (–COOH) on the nanocarrier surface were protonated, and at high pH rates, Fe-OH, carboxylic acid, and Si-OH groups are deprotonated ($Fe\text{-}O^{-}$, COO^{-}, and $Si\text{-}O^{-}$) resulting negatively charged zeta potential and results in DCSM NPs act as a pH-responsive nanocarrier. The scientists reported that DOX@MTX@nanocarrier has shown high drug release at cancerous conditions (pH 5.4 and 4.0) while having a low drug release in the simulated bloodstream at physiological circumstances (pH 7.4) and co-delivery of MTX with DOX to MCF7 cell lines can generate synergistic anticancer effects and enhance the treatment efficacy and decrease toxic side effects of drugs.

3. REDOX-RESPONSIVE DRUG DELIVERY SYSTEMS

It is important to develop types of block copolymers that are able to respond to dual redox (both oxidants and reductants) responses under mild conditions. The redox-responsive polymer through a disulfide (S—S) or diselenide (Se—Se) bonds that are embedded in liposomes, micelles, and dendrimers structures can be exploited as glutathione (GSH)-triggered drug release at a high GSH level environment. Relying on this fact that there is a redox potential change between the oxidizing intracellular space and the reducing extracellular area which can be potentially used to deliver the redox-sensitive DDSs into the cells that are prone to redox reactions due to components including S—S or Se—Se linkages [5,33].

Redox-sensitive DDSs after entering the cancer cell by endocytosis or other entrance ways, disulfide linkage in their structures start to disrupt in the late endosomes environment rich of GSH and resulted in facilitating their payload releasing. GSH is a small tripeptide derived from three amino acids: glutamate, cysteine, and glycine that synthesized naturally in the cell cytosol and within the cell, above 98% exists in the thiol-reduced form (GSH). GSH is present inside specific intracellular sections such as mitochondria and endoplasmic reticulum and acts as a coenzyme, cofactor, and/or substrate for some of the enzymes, and participate in some of the redox reactions [34]. In normal cells, low GSH concentrations make stable disulfide bonds of proteins but cancerous cells demand high levels of GSH (more than three times higher) due to rapidly cells proliferating [33]. A certain level (1–10 mM) of the presence of GSH has been regarded as an important distinction between normal and cancerous tissues. The GSH pathway plays a key role in the reduction of the disulfide linkage in the reducing intracellular environment by maintaining an elevated level of GSH [35]. The disulfide crosslinking also guarantees the stability and integrity of the redox-sensitive DDS and limits the possibilities of early release of the payload until reaching to a rich environment of GSH.

A stimuli-responsive system such as redox-sensitive DDS could be used as a reliable delivery biosystem for nucleic acid-based therapeutics such as ASN, pDNA, siRNA, and miRNA or other biomolecules such as proteins and peptides for the treatment of various genetic diseases. Since these biomolecules are highly prone to degradation, therefore, the successful delivery of them is a great challenge and requires many efforts. One of the most used approaches to exploit the redox stimuli systems is applying positively charged groups such as polyaspartamide in the polymer backbone that entrap