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Review

항암제의 치료 효율성을 높이기 위한 다양한 자극 응답성 물질이 개질된 키토산 마이셀의 응용성 고찰

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Application of Stimuli-responsive Chitosan Micelles for Improved Therapeutic Efficiency of Anticancer Agents

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초 록

현재 항암제의 낮은 치료 효율과 부작용을 해결하기 위해 고분자 기반의 약물전달체의 연구가 활발하게 진행되고 있다. 기존의 고분자기반의 약물 전달체는 우수한 결과를 보이는 등 상당한 진전이 있었음에도 불구하고, 대부분 혈중에서 안정성이 감소하여 표적 부위에 도달하기 전에 약물이 방출될 뿐만 아니라 오랜 시간 동안에 약물을 방출함으로써 부작용 및 낮은 치료 효율을 초래한다는 문제점을 가지고 있다. 본 총론에서는 이러한 비효율적인 약물 방출의 문제점을 개선하기 위한 방법으로 독성이 없고 생체 적합한 천연 고분자 키토산에 자극 응답성 물질을 도입하여 혈중에서 안정성을 높이고 표적 부위에서 약물을 과다 방출하여 치료 효율을 극대화할 수 있는 방법을 제시하고자 한다.

Abstract

Currently, to overcome low therapeutic efficiencies and side effects of anticancer agents, the study of drug carrier based on polymers have been consistently investigated. Although the traditional drug carrier based on polymers displayed an excellent result and significant progress, there has been a problem with the side effect and low therapeutic efficiency because of the premature drug release before reached to the targeted region by the low stability in blood stream and sustained drug release. In this review article, to improve the problem of inefficient drug release, methods were suggested, which can maximize the therapeutic efficiency by increasing the stability in the blood stream and triggering drug release at the target site by introducing a stimuli-responsive substance to the non-toxic and biocompatible natural polymer chitosan.

***Keywords**: chitosan, stimuli-responsive system, selective drug release, anticancer effect*

1. Introduction

Chemotherapy, one of cancer treatment methods, have been utilized to infection patients for decades[1,2]. In generally, anticancer drugs are administrated by intravenous injection or oral route to prevent diffusion whole body of tumor cells and progressive tumor growth[3-6]. However, utilization of only anticancer drugs has been limited due to poor solubility against water, lack of stability, rapid degradation, and non-selective drug distribution, which may lead to side effects and inefficient therapy[7,8]. To overcome these obstacles, many of researchers have used to nanotechnology of polymeric micelle based on drug delivery system (DDS).

The nanotechnology in biomedical field could offer new opportunities for diagnosis and therapy against various cancers due to its a prolonged circulation time in blood stream, improved solubility and high stability from enzyme[9-11]. Selection of nanocarriers are an important in nanotechnology to solve various defects of traditional chemotherapy. As compared with traditional drug delivery systems, drug delivery systems using nanotechnology have shown potential ability such as high solubility, bioavailability, prolonged circulation time, systemically controlled drug release, and active/passive or multiple targeting[12-14].

Polymeric micelles, one of nanocarriers based on drug delivery system using nanotechnology, have received attention in biomedical field

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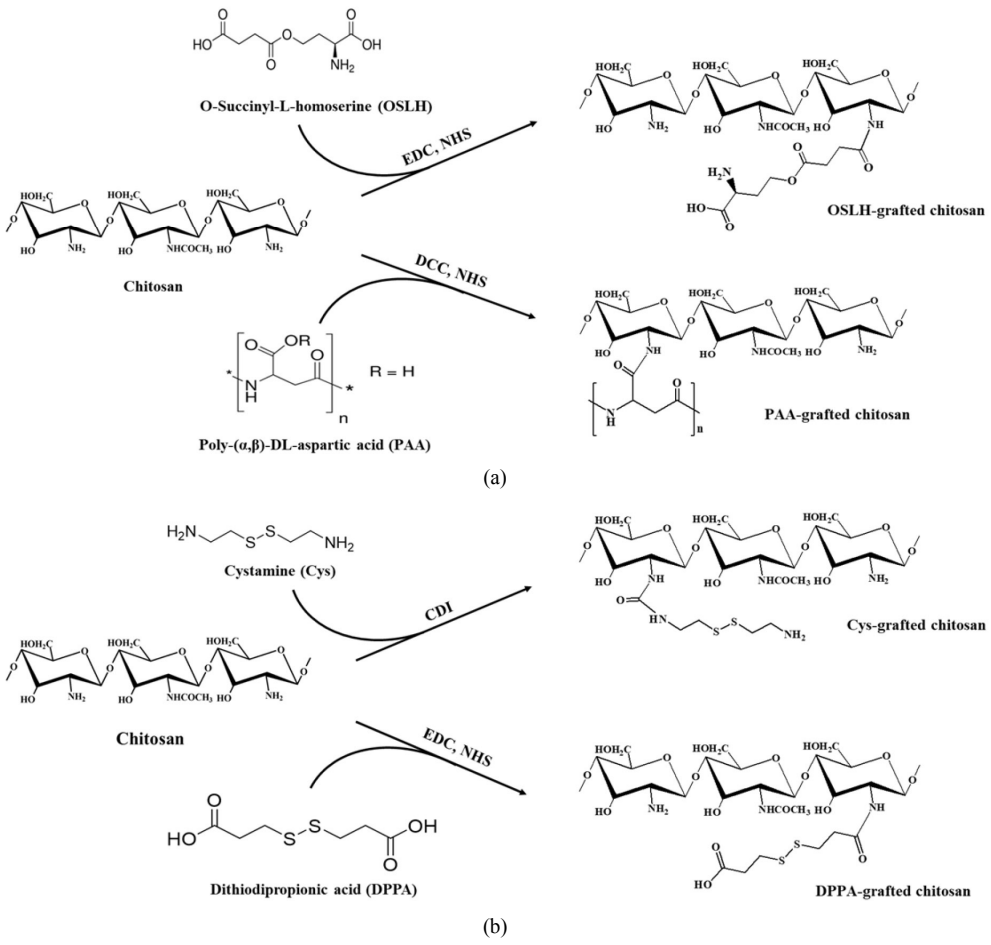


Figure 1. Synthetic scheme of stimuli-responsive drug carrier based on chitosan. (a) pH-responsive linker-grafted chitosan, (b) Redox-responsive linker-grafted chitosan (*Abbreviation : EDC, N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide; NHS, N-Hydroxysuccinimide; DCC, N,N'-Dicyclohexylcarbodiimide; CDI, 1,1'-Carbonyldiimidazole).

for the past decade because they have a lot of advantages such as solubilization of hydrophobic anticancer drugs, favorable biodistribution and excellent biocompatibility[15-17]. However, polymeric micelles as drugs nanocarrier should satisfy such as non-toxicity into body, non-immunogenicity, and positive charge for excellent endosomal escape in intracellular environment[18-20]. For these reasons, many researchers have tried to drug delivery using polymeric micelles based on chitosan as a natural polymer.

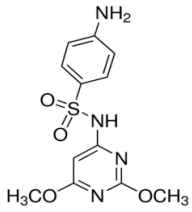
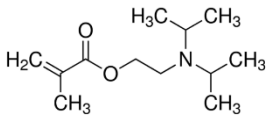
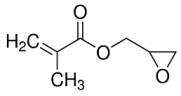
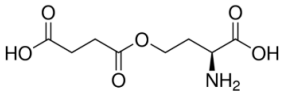
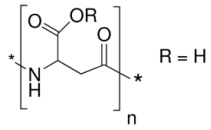
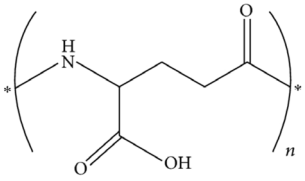
Chitosan, a linear-natural polysaccharide, is derived by alkaline deacetylation of chitin, which is composed of 2-amino-2-deoxy-(1-4β)-D-glucopyranose residues and *N*-acetyl-D-glucosamine units[21-23]. Chitosan is regarded as a non-toxic, biocompatible, and biodegradable macromolecule[24,25]. In addition, chitosan as carrier of drug and gene delivery system have been applied due to many free amine groups ($-NH_2$), which can induce excellent interaction with anionic molecules and enhanced mucosal absorption[26-29]. Moreover, the pKa value of chitosan is approximately 6.0~6.5, which can induce to protonation of amine group at the tumor site of acidic-pH environment[30-32]. Chitosan with these properties has been used as a main substance in drug and gene delivery system.

To impart anticancer effect more effectively, anticancer drugs should be released exclusively in tumor tissue or inside tumor cell. However, excessively stabilized polymeric micelles may prevent to their drug releasing when they are reached to the tumor site, which can cause to poor therapeutic efficacy[33-35]. Therefore, stimuli-responsive polymeric micelles have been developed due to their smart response with selective drug release. The design of stimuli-responsive polymeric micelle may be possible because of property of tumor tissues such as including acidic pH, altered redox potential, and overexpressed proteins and enzymes. Aim of this review article is to summarize recent study in the utilization of stimuli-responsive polymeric micelles based on chitosan.

2. Stimuli-responsive Polymeric Micelles Based on Chitosan

Although polymeric micelles as carrier of chemotherapeutic drugs was successfully achieved the therapeutic effect in vitro, they in vivo and clinical trials have some problems that polymeric micelles composed of hydrophilic and hydrophobic chain have a particular critical

Table 1. Type of pH-sensitive Linker with Ionize or Degradation of Linkage

Name	Chemical structure	Reference
Sulfadimethoxine		[56]
2-(Diisopropylamino)ethyl methacrylate		[57]
Glycidyl methacrylate		[58]
O-Succinyl-L-homoserine		[59]
Poly-(α , β)-DL-aspartic acid		[60]
poly(γ -glutamic acid)		[61]

micelle concentration (CMC) in aqueous solution, which may cause to destabilization of hydrophobic inner-core polymeric micelles in blood stream[36,37]. From this phenomenon, therapeutic effect can be reduced by premature drug release before reached to the tumor site[38]. The premature drug release can be prevented by enhancing drug interaction with the copolymer block through appropriate micellar stabilization or specific binding effects such as hydrogen bonding or cleavable covalent bonds[35,39,40]. Regarding tumor-targeted drug delivery and achieving adequate release, a highly effective method is the introduction of stimuli-responsive polymeric micelles (SPMs). According to reported articles related to cancer therapy, tumor tissues possess a lower pH at the tumor site with endosome/lysosome than normal cells, overexpressed specific enzymes, and high levels of glutathione (GSH) in the cytoplasm[41-43]. These unique microenvironments can be utilized as internal triggers along with external stimuli such as pH-environment at the tumor site and redox potential in cytoplasm[38]. Furthermore, to achieve successful clinical trials, SPMs should be non-toxicity, biodegradable, and biocompatibility[18,19]. For these reasons, SPMs based on chitosan as natural polymer have been developed and they have an advantage that stimuli-responsive functional moieties can easily be introduced to free amine group of chitosan by various coupling agents and organic reactions (Figure 1). The strategies for the development of chitosan SPMs used in cancer therapy will be reviewed individually below.

2.1. pH-responsive polymeric micelles based on chitosan

The pH-responsive polymeric micelles (PPMs) have widely been used as nanocarrier for anticancer drug/imaging agent delivery. The around pH value of tumor tissue is acidic (pH 6.5~7.2) by improved metabolic rates and enhanced glycolysis, while the pH value in blood stream and normal tissue is almost neutral pH (7.4)[44,45]. In addition, pH values of intracellular endosome (pH 5.5~6.5) and lysosome (pH 4.5~5.0) are displayed a lower pH value than extracellular around pH value[46]. These pH properties of these tumor tissues have been utilized to PPMs for selective drug release at the tumor site. In addition, the pKa value of chitosan is about 6.0~6.5, which can induce to protonation of amine group at tumor site of acidic-pH environment[30,32]. Therefore, PPMs based on chitosan (CPPMs) may contribute to selective drug release at the tumor site of acidic-pH environment. To maximize a pH-responsive effect of CPPMs, various pH-sensitive moieties have introduced to amine group of chitosan back bone (Figure 1) and their structure summarized in Table 1. The pH-sensitive moieties

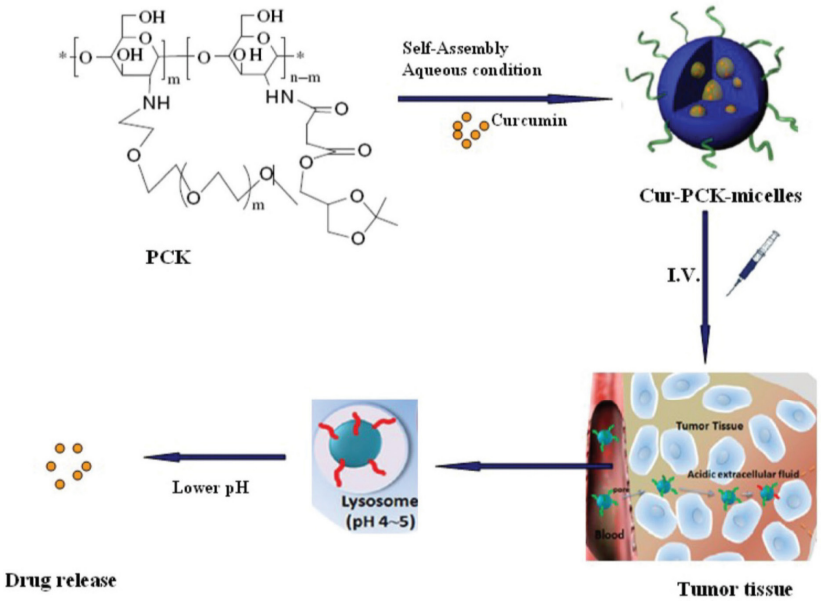


Figure 2. Schematic illustration of pH dependent on drug release from anticancer durg-encapsulated pH-sensitive chitosan micelle[68].

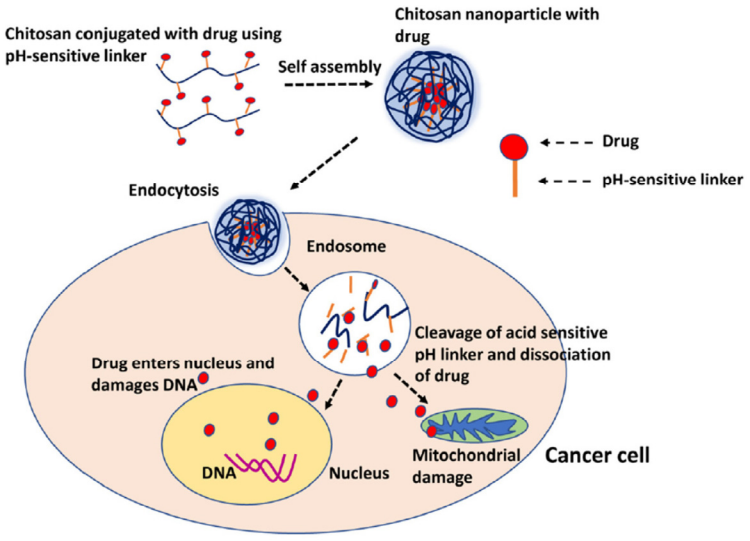


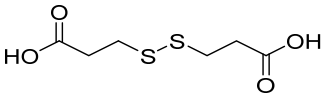
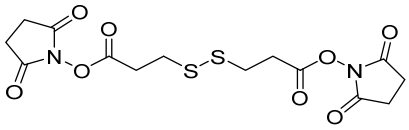
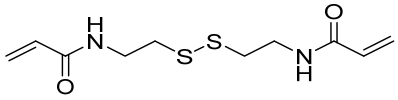
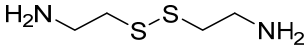
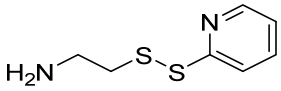
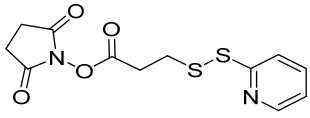
Figure 3. Schematic illustration and apoptotic pathway of pH dependent on drug release from anticancer durg-encapsulated pH-sensitive chitosan micelle[69].

mainly result from the protonation of ionizable groups or the degradation of pH-sensitive linkages. Therefore, approach to impart the pH-sensitive effect to polymeric micelles based on chitosan is to introduce of ionizable functional groups or pH-sensitive linkage into chitosan that can be used to facilitate polymeric micelles to ionize or dissociate at tumor extracellular or intracellular acidic pH (Figures 2, 3). The CPPMs with ionizable group or pH-sensitive linkage are lead to triggered drug release by protonated cationic charge or destabilization of CPPMs from dissociation of linkage in the tumor site of acidic-pH environment, while their formation can intactly be retained in blood stream with neutral-pH environment (Figures 2, 3). Therefore, CPPMs with enhanced stability in blood stream can expect to high anticancer effect by selective drug release at the specific tumor site.

2.2. Redox-responsive polymeric micelles based on chitosan

Redox-responsive drug delivery system has been applied to selective drug release at the tumor site due to the difference in glutathione (GSH) concentration of extracellular, intracellular, tumor, and normal tissue [47,48]. The GSH concentration (2~10 mM) in cytoplasm of intracellular environment could be 100~1,000 times higher than that in the extracellular environment (2~10 μM)[49,50]. As compared with normal tissue, GSH concentration in cytoplasm of tumor tissues was a higher at least 4 times than that in cytoplasm of normal tissues[50]. Over the past decade, the presence of high concentrations of GSH in tumor or intracellular environments has led to tremendous advances in the development of redox-responsive nanocarriers for targeted drug delivery or gene transfer, because the redox reaction is highly fast and

Table 2. Type of Disulfide Bond-containing Redox-responsive Linkers

Name	Chemical structure	Reference
Dithiodipropionic acid		[62]
Dithiobis(succinimidylpropionate)		[63]
Cystamine bisacrylamide		[64]
Cystamine		[65]
2-(pyridyldithio)-ethylamine		[66,67]
N-succinimidyl 3-(2-Pyridyldithio)propionate		

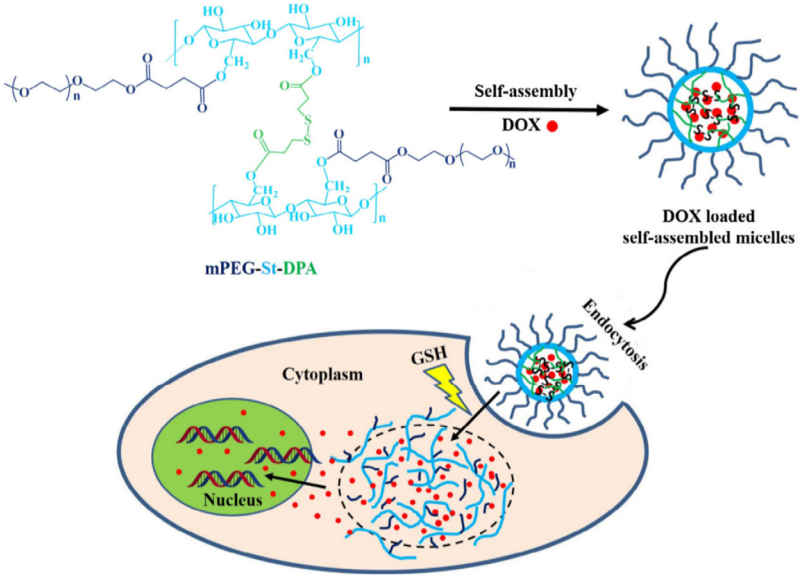


Figure 4. Schematic illustration and apoptotic pathway of intracellular drug release using redox-responsive chitosan micelle in tumor cell with high GSH[70].

efficient[48,51-53]. Also, unlike pH-sensitive nanocarriers designed to release drugs in the lyso/endosome compartment, the redox-responsive system led to drug release by destabilization of nanoparticles in the cytoplasm (Figure 4). Disulfide bonds (-S-S-), one of responsive-functional group by GSH, are commonly used to obtain redox-responsive effect and their structure summarized in Table 2. Recently, redox-responsive polymeric micelles based on chitosan (CRPMs) have been received attention due to its non-toxicity and biocompatibility [54,55]. In addition, chemical reaction between chitosan and redox-responsive functional group with disulfide bond is a very simple (Figure 1). The micelle structure of CRPMs can be intactly retained in blood stream with GSH concentration of low level, while that can be quickly disassembled in cytoplasm with GSH concentration of high level, which can lead to high anticancer effect by rapid drug release (Figure 5). Therefore, CRPMs can expect to high anticancer effect by redox-responsive effect in cytoplasm with GSH of high level.

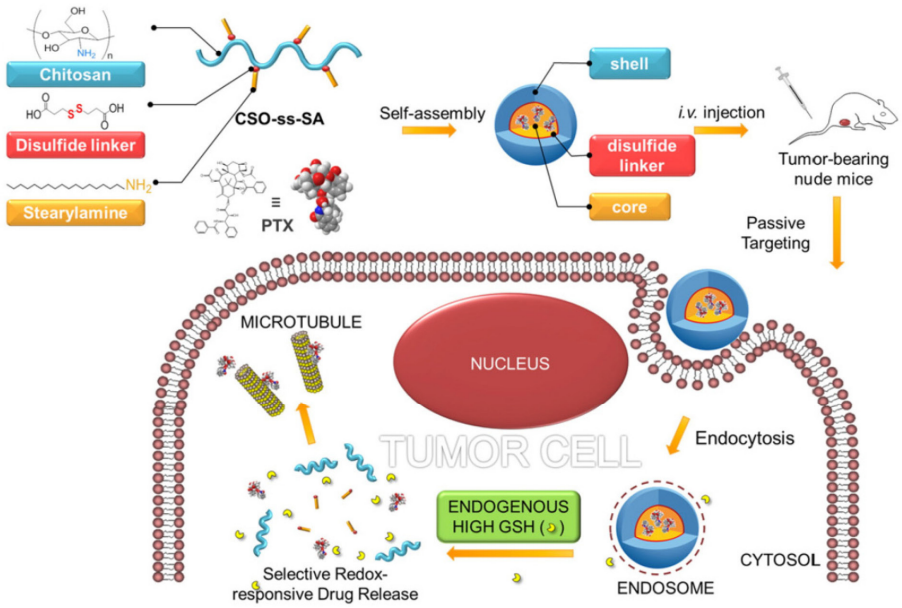


Figure 5. Schematic illustration of intracellular drug release from anticancer drug-encapulated redox-responsive chitosan micelle in tumor cell with high GSH[71].

3. Conclusion

To maximize efficiency of anticancer drug at therapeutic region, we suggested that drug delivery using stimuli-responsive polymeric micelles based on chitosan can expect to high anticancer effect by rapid drug release at the tumor site. They have an advantage that can induce to triggered drug release by ionizable or degradation of pH-responsive linkage at endo/lysosome with acidic-pH environment. In addition, they can lead to rapid drug release from destabilization of hydrophobic inner-core by dissociation of disulfide linkage in cytoplasm with reducing environment, while their micelle structure can be intactly retained in blood stream with neutral pH and GSH environment of low level. From these properties, stimuli-responsive chitosan polymeric micelles recommend as carrier to deliver anticancer drug at the tumor site.

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