

REVIEW PAPER

Recent advances in nanoformulations for co-delivery of curcumin and chemotherapeutic drugs

Maryam Hashemi^{1*}; Mahboubeh Ebrahimian²

¹Nanotechnology Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

²Division of Biotechnology, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran

ABSTRACT

The application of chemotherapy in cancer treatment has been limited due to cause side effects such as toxicity against normal cells and drug resistance. In recent years, numerous studies have been focused on using natural products with chemotherapeutic drugs to enhance therapeutic efficiency and reduce cytotoxicity. On the other hand, encapsulation of drugs into nanoparticles (NPs) can improve solubility of hydrophobic drug; circulation time in blood and the residence at the pathological site by enhance permeation and retention (EPR) effect. It has been shown that curcumin (CUR) has a wide range of pharmacological activities against many diseases such as cancer. CUR has been demonstrated to be a potent chemosensitizer that can induce additive or synergistic effects with chemotherapeutic drugs against different cancer cell lines. Recently, various types of nanocarriers have been investigated for CUR. In this review, different co-formulations containing Cur and chemotherapeutic drugs used in cancer therapy are discussed with emphasis on their pharmaceutical properties.

Keywords: Cancer, Curcumine, Co-delivery, Nanoformulation

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INTRODUCTION

The application of chemotherapy in cancer treatment has been limited due to cause side effects such as toxicity against normal cells and drug resistance [1]. In recent years, numerous studies have been focused on using natural products with chemotherapeutic drugs to enhance therapeutic efficiency and reduce cytotoxicity [2-4]. Turmeric (*Curcuma longa*) is a natural yellow spice that widely use in Asian countries for traditional medicines. Curcumin (diferuoylmethane) is the most potent content in turmeric derived from the rhizomes of *Curcuma longa*. Other analogues of curcumin such as demethoxycurcumin and bisdemethoxycurcumin also have same pharmacological effects with lower potency that suggests a critical role of the methoxy

groups on the phenyl rings (Fig. 1). Interestingly, the mixture of these analogues was found to be more active than individual compounds due to synergistic effect [5].

In recent studies, it has been shown that curcumin (CUR) has a wide range of pharmacological activities against many diseases such as type II diabetes, rheumatoid arthritis, multiple sclerosis, Alzheimer's disease and atherosclerosis (Fig. 2).

CUR has been demonstrated to be a potent chemosensitizer that can induce additive or synergistic effects with chemotherapeutic drugs against different cancer cell lines [6-8]. It is also noteworthy that CUR efficiently inhibits the expression of MDR1, BCL2 and bcr/abl gene in K562 cells [6, 9].

CUR can interfere with multiple cell signaling pathways, including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and down-regulation of anti-apoptosis gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/

*Corresponding Author Email: hashemim@mums.ac.ir
Tel: (+98) 37112470

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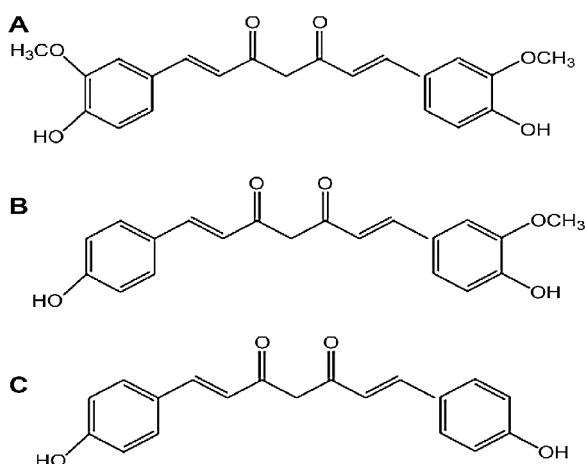


Fig. 1. A) Chemical structures of curcumin, B) demethoxycurcumin and C) bisdemethoxycurcumin

AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4) and inflammation (NF- κ B, TNF, IL-6, IL-1, COX-2, and 5-LOX) [10]. Many approaches have been

proposed to improve CUR solubility such as using nanocarriers. Encapsulation of CUR into NPs can also improve its circulation time in blood and the residence at the pathological site by enhances permeation and retention (EPR) effect. Recently, various types of nanocarriers, such as liposomes, polymeric nanoparticles and micelles, conjugates, peptide carriers, cyclodextrins, solid dispersions, lipid nanoparticles and emulsions have been investigated for CUR [11, 12]. In this review, different co-formulations containing CUR and chemotherapeutic drugs used in cancer therapy are discussed with emphasis on their pharmaceutical properties.

PLGA

Poly (d, l-lactide-co-glycolide) (PLGA) is one of the most widely used polymeric nanoparticle with biodegradability and biocompatibility properties which has been approved by the Food and Drug (FDA) for drug delivery. As a result of PLGA hydrolysis, two monomers, poly lactic acid (PLA) and poly glycolic

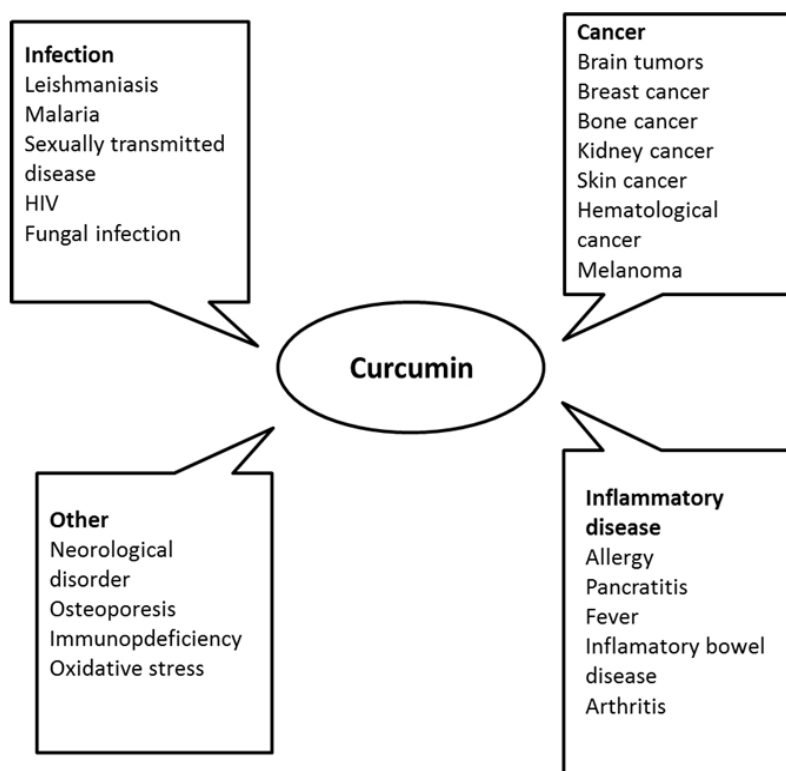


Fig. 2. Therapeutic applications of curcumin

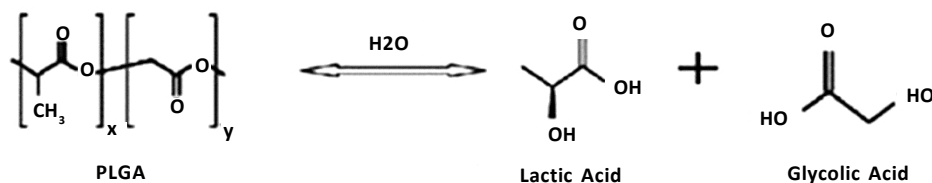


Fig. 3. Metabolic pathway of PLGA

acid (PGA), produced which metabolized readily in the body via Krebs cycle (Fig. 3).

PLGA copolymer with different molecular weights (from 10 kDa to over 100 kDa) is comprised of different molar ratio of monomers. For example, the common PLGA copolymer 50:50 contains 50% lactic acid and 50% glycolic acid. Copolymer molar ratio and molecular weight of PLGA could influence the degradation process and release profile of the encapsulated drug [13]. PLGA copolymer as delivery vehicle has several privilege in comparison with other polymeric vehicles including the enhancement of the solubility, stability, circulation half-life, biodistribution and controlled release of the encapsulated agents. Another advantage of PLGA is that it can be modified with different agents to improve its properties such as cytotoxicity, delivery efficiency and targeting to specific tissues/cells [14].

Different methods have been used for PLGA nanoparticle formation. Among them, the emulsification-solvent evaporation (single and double emulsion) is the oldest and most common technique. However, the main limitation of single emulsion technique is to encapsulate water soluble therapeutic agents [15, 16]. PLGA has been widely used as co-delivery system. In double emulsion method which is a water in oil in water (w/o/w) emulsion, the oil phase cause loading of hydrophobic drugs and the aqueous phase contains hydrophilic drugs [17, 18].

Misra and et al synthesized PLGA NPs containing DOX and CUR for enhancement of efficacy of DOX and reduce drug resistance in K562 cells. The results showed encapsulation of CUR and DOX in NP could increase the cytotoxicity compared to DOX + CUR in solution or DOX alone. This NP also inhibited more downregulation of MDR1 and BCL-2 expression in K562 cells [19].

In another study, paclitaxel and CUR was co-encapsulated into the transferrin receptor-binding peptide T7-modified magnetic PLGA nanoparticle to

overcome the blood-brain barrier (BBB) obstacle. The synthesized NP showed more inhibition of tumor growth and less cytotoxicity compared to single use of each drug. Dual targeting resulted in enhancement of cellular uptake and brain delivery compared to the non-targeting NPs [20].

Two anticancer agents Cur and H₂S-releasing prodrug SH-aspirin (SH-ASA) co-encapsulated into mPEG-PLGA NPs via an optimized oil-in-water single-emulsion solvent evaporation method. Synthesized vectors showed synergistic anticancer effects on ES-2 and SKOV3 human ovarian carcinoma cells in *in vitro* by activation of the mitochondrial apoptosis pathway[21].

Xiao and et al synthesized several type of camptothecin (CPT)/CUR-loaded chitosan-functionalized PLGA polymeric NPs at different weight ratios of CPT to CUR. Chitosan was used to increases the cellular uptake and tumor accumulation of NPs. Co-delivery of CPT and CUR in a single NP with a CPT/CUR weight ratio 4:1 showed the highest anticancer activity [22].

lipopolymeric micelles

lipopolymeric micelles are considered as one of the appropriate carriers for poorly water-soluble drugs which can be encapsulated into the hydrophobic core of a micelle. Most lipopolymeric micelle structures are constructed from conjugates of polyethylene glycol (PEG) and diacyllipids, such as phosphatidy lethanolamine (PE). PEG-PE lipopolymeric micelles have displayed small size (10-100 nm) with improved pharmaceutical properties such as low toxicity, controlled drug release, and high stability. In *in vivo* studies, these micelles showed their extended half-life in plasma circulation (typically >36 hours in mice) and effective accumulation in tumorous tissues [23, 24]. Recent studies were done based on the investigation of potential therapeutic application of lipopolymeric

micelles in co-delivery systems. Accordingly mixed micells, composed of the polyethylene glycol-phosphatidyl ethanolamine (PEG-PE) and vitamin E containing CUR and paclitaxel (PCL) was investigated in SK-OV-3 human ovarian adenocarcinoma and multi-drug resistant version SK-OV-3-paclitaxel-resistant (TR) cells. No significant changes were observed in the cytotoxicity of PCL along with different concentration of CUR on sensitive cell line. But in resistant cell line, micelles containing CUR (10 μ M concentration) and PCL resulted in the improvement of the PCL cytotoxicity. The *in vivo* data showed that CUR in high dose (25 mg/kg) could not significantly inhibit the tumor growth. However, an increase in tumor inhibition was observed with CUR and PCL in single formulation compare to the PCL-treated group[25].

In another study, cytotoxicity and cellular uptake of PEG-PE polymeric micelles co-encapsulated with PCL and CUR and targeted with transferrin (TF) was investigated into monolayer and deeper layers using multicellular 3D cancer cell culture (spheroids). All formulations have displayed hydrodynamic diameter between 15 – 20 nm. It was found that higher doses of drugs was needed to create same level of cytotoxicity in spheroids model in comparison with monolayer

due to changes in the cellular pathways, overexpression of P-gp and limited penetration. TF-targeting formulation showed more cytotoxicity compare to non-targeted in single agent-loaded micelles. However targeting of micelles co-loaded with CUR and PCL had no effect on increasing the cytotoxicity. Similar results were obtained in *in vivo* tumor inhibition which suggested that the spheroid model can be used as an intermediate model for evaluation of co-delivery formulations [26].

Co-delivery of sorafenib and CUR was performed using directed self-assembled nanoparticles (SCN) to enhance the therapeutic effects. SCN was fabricated by hydrophobic interaction among the lipophilic structures of compounds and polyethylene glycol derivative of vitamin E succinate (PEG-VES) which formed uniform spherical nanoparticles with the size of 84.97 ± 6.03 nm (Fig. 4).

This co-formulation showed an enhancement of *in vitro* cytotoxicity and cell apoptosis in BEL-7402 cells and Hep G2 cells, antiangiogenesis activities in tube formation and microvessel formation in HMEC-1 cells in comparison to sorafenib, CUR and the free combination (Sora + Cur). The same results were observed in BEL-7402 cells induced tumor xenograft models [27].

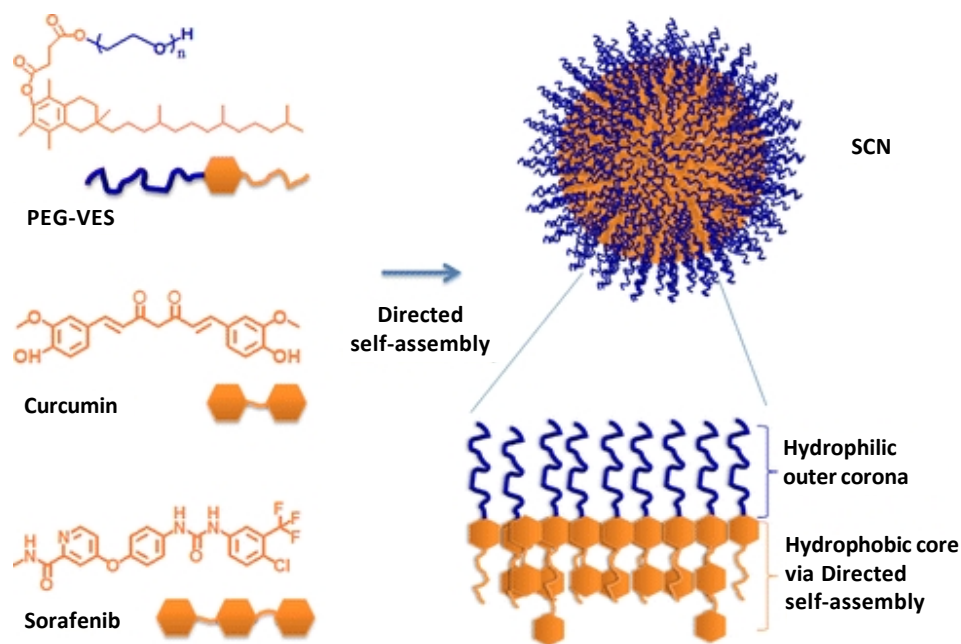


Fig. 4. Co-delivery of sorafenib and curcumin using PEG-VES[27]

Lipid NPs

Lipid NPs have been demonstrated to be a good candidate for anticancer drug delivery due to biocompatibility, high encapsulation efficacy (EE), sustained drug release and high stability. Zhao et al synthesized lipid NPs to co-deliver of DOX and Cur using a high-pressure microfluidics technique. Compared with free DOX, higher cell cytotoxicity was observed with DOX-NPs and DOX/Cur-NPs at different ratios in HepG2 cells. The highest cell growth inhibition was obtained for the weight ratio 1:1 (DOX/CUR). In *in vivo* studies, DOX/Cur-NPs (1:1) showed more growth tumor inhibition compared with DOX-NPs ($P < 0.05$) [28]. In another study, DOX and Cur were co-delivered by lipid NPs (weight ratio DOX/Cur was 1:1) using high pressure microfluidics technique and examined the inhibitory effect of this formulation on diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) in mice. The results showed that nodule number and size were significantly decreased with DOX/Cur-NP, compared to DOX-NPs. Also DOX/Cur-NPs could decrease the mRNA and protein levels of MDR1, bcl-2 and HIF-1 α more than those in DOX-NPs might reverse multidrug resistance (MDR) through these pathways [29].

In another combinatorial therapeutic protocol, DOX and DOX-SLN (2.5 mg/body weight/week) was administrated intravenously for five weeks with oral administration of CUR and CUR-SLN (50 mg/kg body weight/day) for 28 days in a mammary carcinoma (MC) rat model. Different parameters such as oxidative stress levels, cardiac and kidney function tests, TNF- α expression and histopathological examination were evaluated for therapeutic efficiency of CUR-SLN and DOX-SLN combination. The results showed that CUR-SLN could exhibit a potential significant protective effect in DOX-associated toxicity [30].

Other nanoformulations

Duan and et al co-encapsulated DOX and CUR in poly (butyl cyanoacrylate) nanoparticles (PBCA-NPs) as an excellent biocompatible and biodegradable polymer. In this formulation, chitosan was used as a stabilizing agent. The results showed that the CUR-DOX loaded PBCA-NPs system had the similar cytotoxicity to co-administration of single-agent loaded PBCA-NPs, free drugs or one free drug/another agent loaded PBCA-NPs in MCF-7/ADR human breast cancer cell. However, the lowest level of the P-gp expression was observed with CUR-DOX-PBCA-NPs in MCF-7/ADR cells [31]. A

core-shell drug-carrier was also designed for co-encapsulation of CUR and DOX. In this research, CUR was loaded into hydrophobic poly (L-lactide) (PLLA)-grafted polyethylenimine core and DOX was absorbed on hydrophilic heparin shell. DOX-Cur NPs showed higher cellular uptake and cytotoxicity in 4T1 tumor cells than either DOX or Cur alone at the same concentrations. After intravenous injection of DOX-Cur NPs, more growth inhibition of 4T1 breast carcinoma was observed [32].

In another study, poly (ethylene glycol)-block-poly(lactide) (PEG2k-PLA5k) micelles was synthesized for co-delivery of DOX and CUR to overcome multidrug resistance. (DOX + CUR)-micelles showed higher cytotoxicity in MCF-7/ADR cells compared to free DOX, free drug combination (DOX + CUR), and DOX-loaded micelles. In addition, this NP had an increased tumor accumulation and inhibitory effect on tumor growth in the xenograft model [33].

Methoxy poly(ethylene glycol)-poly (caprolactone) (MPEG-PCL) micelles was also used for co-delivery of DOX and CUR for lung cancer treatment [8].

One of the new effective drug delivery system is pH-sensitive prodrug nanoparticle to improve efficiency and cytotoxicity of anti-cancer agents. For example, PEG-DOX-Cur prodrug NPs was formulated by conjugation of DOX to PEG with Schiff's base reaction and encapsulation of Cur into the core by nanoprecipitated technique. In the acidic environment of tumors, PEG-DOX-Cur would be disassembled and the Schiff's base linker between PEG and DOX would break. The IC₅₀ value of PEG-DOX-Cur NPs was much lower than free DOX and DOX/Cur combination in HepG 2 cells and Hela cells. In BALB/c nude mice bearing HepG2 xenografts, the PEG-DOX-Cur NPs also showed higher tumor inhibition compared to other groups [34].

Barui and et al synthesized pegylated RGDGWK-lipopeptide containing CUR and ceramide for targeting tumor endothelial cells. In *in vitro* and *in vivo* analysis, the liposomal co-formulations with homoserine based C8-ceramide analogue containing oleyl chain showed more antitumor activity compared to the liposomal formulations of commercially available C8-ceramide. The mechanism of growth tumor inhibition was determined via PI3K-Akt signaling pathway [35].

CONCLUSION

Chemotherapy has been limited due to cause side effects such as toxicity against normal cells and drug resistance. Using natural products with chemotherapeutic drugs is a potential strategy to enhance therapeutic efficiency and reduce cytotoxicity. On the other hand, encapsulation of drugs into NPs can improve solubility of hydrophobic drug; circulation time in blood and the residence at the pathological site by enhance permeation and retention (EPR) effect. CUR has been demonstrated to be a potent chemosensitizer that can induce additive or synergistic effects with chemotherapeutic agents against different cancer cell lines. It is also noteworthy that CUR efficiently reduces drug resistance. This review shows different co-formulations containing Cur could significantly enhance tumor growth inhibition and reduce cytotoxicity of chemotherapeutic drugs. *In vitro* and *in vivo* analysis demonstrated that CUR has efficient role to reduces multidrug resistance. Therefore, this combinational strategy has significant promise in the clinical application for cancer treatment.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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