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# Evaluation of radiolabeled curcumin-loaded solid lipid nanoparticles usage as an imaging agent in liver-spleen scintigraphy

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ABSTRACT

Curcumin-loaded solid lipid nanoparticles (C-SLNs) were prepared using micro emulsion and ultrasonication methods in the first stage of this study to determine the role of C-SLN on liver-spleen scintigraphy. It was concluded that the curcumin that was encapsulated in solid lipid nanoparticles had a β′ polymorph structure according to the X-ray diffraction (XRD) analysis. İt was concluded that these particles were at nano scale according to the laser diffraction (LD) analysis. Fourier transform infrared spectroscopy (FT-IR) analysis suggested an interaction between the curcumin and the solid lipid matrix, and the curcumin was loaded on the solid lipid nanoparticles. Moreover, the particles were concluded to be spherical and at nanoscale according to the scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images. On the other hand, thermogravimetric analysis (TGA) suggested that the curcumin loaded solid nanoparticles were stable against the temperature.
C-SLNs were labeled with Technetium-99 m ($^{99m}$Tc) radioisotope in the second stage of the study, then using scintigraphic methods in-vivo studies were performed on New Zealand rabbit and made a comparison with Phytate colloid, routinely used in liver-spleen scintigraphy. After analyzing the images and the biological distributions obtained from the experiments, uptake was observed in the liver and the spleen.
Following from the experiment results, $^{99m}$Tc-labeled C-SLNs was concluded to be a possible imaging agent. In particular, it could be a new radiopharmaceutical alternative to $^{99m}$Tc-labeled compounds that are used in liver and spleen imaging in colloid scintigraphy.

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## 1. Introduction

Nuclear medicine facilitates the understanding of various physiological and functional events in the human body. In nuclear medicine, imaging is done by ensuring the uptake of radioactive material in the target organ. High quality of imaging depends on high uptake of the radioactive material in the target organ and low background activity. The high quality of imaging is correlated with the accuracy of diagnosis. Compounds that are labeled with radioactive materials and administered in the body for diagnosis and treatment purposes are known as radiopharmaceuticals. In other words, they are generated by combining a radioisotope with a bioactive compound. The bioactive agent should be appropriate for getting localized in the target organ and the radioactive agent should radiate in the organ where the compound is localized in order to enable detection [1]. Therefore, it is of great importance to identify and develop alternative radiopharmaceuticals in nuclear medicine.

Curcumin (Diferuloylmethane) is a yellow hydrophobic polyphenol with low molecular weight and is obtained from the roots of Turmeric (*Curcuma longa*, Zingiberaceae) plant. The chemical structure of curcumin is [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] and is demonstrated in Fig. 1 [2,3].

The activity of a molecule that shows bioactive properties is dependent on its bioavailability, stability, absorption, and solubility. Curcumin has a wide spectrum of pharmacological and biological activities and it has been shown to have anti-oxidant, anti-carcinogenic, anti-inflammatory, and anti-bacterial activities. Moreover, in previous preclinical and clinical studies curcumin has been indicated to have a therapeutic effect against many chronic diseases such as hepatic and biliary. In various animal models and human studies it was proven to be considerably safe even at high doses [4–6].

Despite the variety of bioactivities of curcumin and its potential to prevent and treat diseases, it has low bioavailability because of its low solubility, instability in water-based solutions, insufficient tissue absorption, degradation in alkaline pH, and rapid systemic elimination. Therefore, these issues constitute the most important problem that prevents the use of curcumin as a therapeutic agent [4,7].

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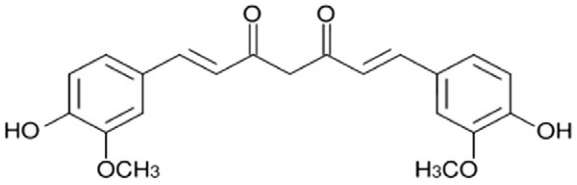


**Fig. 1.** The chemical structure of curcumin.

Numerous approaches have been tried to improve the bioavailability of curcumin. Various carrier systems such as micelles, nanoparticles, liposomes, phospholipid complexes, nanogels, microsponges, micro emulsions, chitosan nanoparticles, cyclodextrin complexes, and self-microemulsifying drug delivery systems (SMEDDS) have been developed [8–10].

One of the solution approaches to minimize the limiting effects of curcumin has been the solid lipid nanoparticle formulations. Solid lipid nanoparticles emerged as an alternative carrier system to existing colloidal carrier systems (emulsions, liposomes, polymeric nanoparticles) in 1990s. Since the SLNs are composed of physiological lipids, they have a high level of bioavailability and biodegradability while a low level of systemic toxicity and cytotoxicity. Moreover, the interest in SLNs is increasing significantly because of their advantages such as the following: they do not contain organic solvent residues, they can be mass produced, they have a simple preparation process, they are physically stable, they protect unstable drugs against chemical degradation, and they allow a controlled release of drugs [11–14]. Implementation of these systems in the radiopharmaceutical medicine is considered a promising avenue for developing new diagnosis and treatment methods.

Particle size, polydispersity index, and zeta potential values of SLNs were investigated in a study on biodistribution of radioactively labeled SLNs which were administered on rats through inhalation [15]. Videira et al. [15] used D,L-hexamethylpropyleneamine oxime (HMPAO) with lipophilic properties as the chelating agent and $^{99m}$Tc as the radionuclide in their study. They labeled the SLNs by incubating them with $^{99m}$Tc–HMPAO, reaching a labeling efficiency of 97%. The authors reported that SLNs that were administered through inhalation accumulated in lymph nodes at high amounts and concluded that SLNs could be used to target the lymph. This result means that SLNs could be used in lymphoscintigraphy or as an effective colloidal carrier system for the treatment of the pulmonary system.

In a previous study, experiments were conducted on rats to investigate the effectiveness of curcumin against cerebral ischemia reperfusion damage. Micro emulsion technique was used to prepare curcumin, which was then encapsulated in the SLNs and administered orally on rats with cerebral ischemia reperfusion damage. When the control (rats that were administered empty SLNs orally) and the test (rats that were administered curcumin solution orally) groups were compared, curcumin-loaded SLNs were found to inhibit lipid peroxidation and to decrease nitrite and acetylcholinesterase levels while they were concluded to significantly increase the activities of superoxide dismutase, catalase, glutathione, and mitochondrial enzymes [16].

In a study on nanoparticle biodistribution, paclitaxel loaded SLNs (P-SLNs) were radioactively labeled with $^{99m}$Tc. In this study, instead of routinely used tin salts, sodium borohydride was used to reduce sodium pertechnetate ($Na^{99m}TcO_4$) and then P-SLNs formulation was compared with the paclitaxel formulation. Labeling efficiency of P-SLNs was determined using thin layer silica gel plates and a gamma counter and concluded to be higher than 95%. P-SLNs were smaller than 100 nm and concentrated in the brain at high levels. Besides, scintigraphic studies supported the uptake of P-SLNs in brain cells, which were concluded to have reached the brain following the analysis of planar and tomographic images taken with a gamma camera [17].

A study on the applicability of liposomes for tumor diagnosis reported the injection of pegylated (Polyethylene glycol (PEG)-coated) liposomes radiolabeled with $^{111}$In-DTPA to 17 patients with various cancer types where the evaluation of scintigraphic images suggested that radiolabeled liposomes could be used as diagnostic agents for tumors [18].

Another study which focused on the biodistribution of SLNs after intravenous (IV) injection into the living organism used SLNs radiolabeled with $^{64}$Cu for imaging. PET and a gamma counter were used to investigate the biodistribution and the pharmacokinetics of $^{64}$Cu-SLNs. The study concluded that solid lipid nanoparticles could be used for diagnosis purposes [12].

This study investigated the feasibility of using C-SLNs radiolabeled with $^{99m}$Tc in liver-spleen scintigraphy, which is a diagnostic imaging test in nuclear medicine, and made a comparison with routinely used Phytate colloid.

## 2. Experimental

### 2.1. Materials

Compritol® 888 ATO (glyceryl behenate) was purchased from Gattefossé (Lyon, France). Tween 80, soy lecithin and stannous chloride dihydrate were purchased from Merck (Germany). Curcumin, chosen as drug model, was purchased from Sigma-Aldrich (St. Louis, MO). Xylazine was obtained from Bioveta (Turkey). Ketamine was obtained from Pfizer (Turkey). Phytacis® was purchased from CIS bio international, RADMED, (Turkey). $^{99}$Mo/$^{99m}$Tc kits were obtained from ELUMATIC-III® CIS bio international, RADMED, (Turkey). $^{99m}$Tc extraction was performed in Ataturk University Faculty of Nuclear Medicine, Erzurum, Turkey. All other solvents and reagents were of analytical grade.

### 2.2. Preparation of C-SLNs

Initially, the lipid was melted at 80 °C. Then the curcumin was added into the melted lipid. A calculated amount of surface-active substances with water at the lipid melting temperature was dripped into the lipid phase in the magnetic stirrer [19].The resulting emulsion was then homogenized by ultrasonication. The hot micro emulsion was dripped into cold water at 3–4 °C in a magnetic stirrer operating at 1000 rpm and the curcumin-loaded SLNs were produced. The resulting C-SLNs were placed inside glass vials and stored at predetermined temperatures. For control purposes, empty solid lipid nanoparticles were prepared without curcumin but in line with the method briefly mentioned above.

Moreover, the prepared C-SLNs were frozen in vials at −86 °C for a day to powder the C-SLNs in lyophilization. The C-SLNs were kept in the freezer for 24-h and then they were placed in the lyophilizator. The lyophilization process was performed for 24 h at 0.011 mbar and −60 °C. The lyophilized powder obtained at the end of this process was stored at +4 °C.

### 2.3. Characterization studies

Particle size and distribution, particle shape, FT-IR, TGA, and XRD analysis of the prepared solid lipid nanoparticles were examined.

#### 2.3.1. Studies for determining the particle size and the surface charge

Particle size and distribution of the prepared C-SLNs as well as the zeta potential values and the polydispersity index were measured using a Malvern Zetasizer Nano ZS device, which is based on the dynamic light scattering (DLS) principle. The sample of dispersion was diluted 1:1000 v/v with deionized water and subsequent analysis was performed. All measurements were taken at 25 °C and repeated three times.

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