# Synthesis of Micro-nanostructured $TiO_2$ Sphere with Homogeneous Precipitation assisted by MicrowaveIrradiation and its Drug Loading Capacity

Di Liu, Shi-ting Deng, Hong Yu, Yong-guang Bi*

College of Pharmacy, Guangdong Pharmaceutical University, Guangzhou, Guangdong, China

*Corresponding author:biyongguang2002@163.com

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**Abstract.** Nanoparticulate titanium dioxide were synthesized via homogeneous precipitation assisted by microwave irradiation.The powder was characterized by X-ray diffraction(XRD), Scanning Electron Microscopy(SEM), Differential scanning calorimetryand thermogravimetric analysis(TG-DSC), Roman spectra and Transmission electron microscopy(TEM). The results showed that obtained $TiO_2$ were pure-phase anatase with BET Surface Area of 53.9445m²/g and the average pore diameter of 9.3439nmand 800°C is the crystal phase transformation temperature, exhibited high drug loading capacity towards sorafenib of 5.65% while the $TiO_2$/sorafenib ratio at 15:5 for 6h under stirring condition. Micro-nanostructured $TiO_2$, as a drug delivery system, has great potential in the treatment of cancer diseases.

## Introduction

Titanium dioxide ($TiO_2$) received numerous attention due to its advantages of high activity, non-toxicity, long-term stability, high catalytic efficiency and good biological compatibility [1], has been widely used in the field of photocatalysts, solar cell electrodes and environmental protection[2,3].

Sorafenib (SF), a novel oral antieoplastic drug, has been approved by Food and Drug Administration (FDA) to treat renal cell carcinoma in 2005, and then has a wide applications in treating liver cancer, renal cell carcinoma and hypothyroid [4,5]. However, its serious side effects such as diarrhea, hypertension and hand foot skin reaction and so on which negatively affect the patient's quality of life, greatly limit its application [6]. Many efforts have been paid to investigate the relation between plasma concentration of SF and its curative, adverse effects. Mai H et al have found that Plasma concentration of sorafenib was >10,000 ng/mL in patients with severe Major adverse reactions (ADRs), which decreased with reduction in dose or discontinuation of treatment. In conclusion, plasma concentration of sorafenib was associated with its safety and efficacy in Chinese patients with metastatic renal cell carcinoma (mRCC) [7]. Therefore, controlling SF dosage in an appropriate range is still a challenge.

In this paper, anatase was synthesized through the method which has been investigated before. Taking titanium oxysulfate sulfuric acid complex hydrate ($TiOSO_4 \cdot xH_2SO_4 \cdot xH_2O$) and urea as raw materials. The reaction time was as short as 20min and discussed the drug loading capacity of $TiO_2$ toward SF.

## Materials and Methods

**Synthesis of Anatase.** Firstly, 12.24g urea, 2% Span 20 and 5% PEG600 were added into titanium oxysulfate sulfuric acid complex hydrate (272g/L). Then, the mixture solution was transferred into three-necked flask and placed in microwave field at 90°C for 20min, the resulting solution was washed by deionized water and absolute ethanol, the white precipitate was dried in a vacuum at 80°C for 2h and calcined in muffle at 600°C for 2h. Finally, the obtained powders were anatase.

**Characterization.** The crystal phase was identified by X-ray diffraction (XRD) D8 Advance Diffractometer (Bruker, Germany) with $CuK_\alpha$ radiation source at 40kV and 30mA, the analysis was performed at 2θ(°) ranging from 10 to 80 at a scanning speed of 10°/min. And the crystallite size can be calculated by Debye-Scherrer formula from XRD patterns:

$$D = \frac{K\lambda}{\beta Cos\theta} \quad (1)$$

where λ is the wavelength (0.154nm), β is the full width at half maximum intensity, θ is the half diffraction angle and K is a constant equal to 0.89.

The morphology and the size of samples were observed by Scanning Electron Microscopy (SEM) using a ZEISS 500 microscope (Germany) operating at an accelerating voltage of 1kV.

High Resolution Transmission electron microscopy (HRTEM, FEI Tecnai G2 f20 s-twin) and field-scanning electron microscopy with 200 kV accelerating voltage (FESEM, SU8010) were employed to observe the structure and morphology of $TiO_2$ which was pretreated with ethanol by ultrasonic. Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were performed with STA409PC apparatus (NETZSCH, Germany) in nitrogen flow of 50ml·min$^{-1}$ and heating rate of 10 k·min$^{-1}$ from 25°C to 1000°C.

## Results and Discussion

**Characterization of $TiO_2$.** Fig. 1shows XRD patterns of synthesized $TiO_2$. The sample showed no peak shift and other new crystalline phase, clearly existed six characteristic peaks indexed to (001), (004), (200), (105), (211), (204) diffraction planes which are matched well with JCPDS file No. 21-1272, indicating that calcined sample is phase-pure anatase. The particle size calculated by Scherrer equation is 21.24nm.

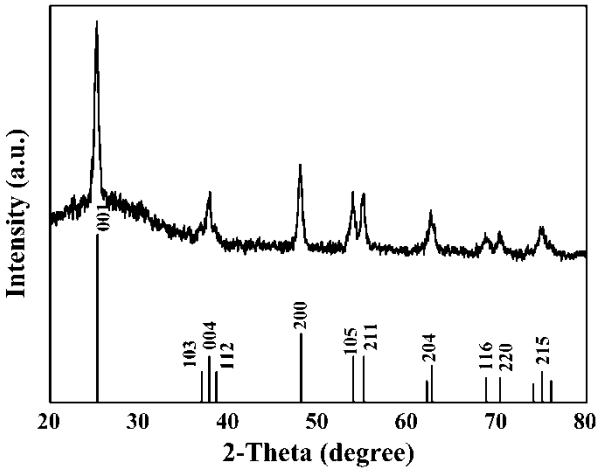


Figure 1. XRD Patterns of Synthesized $TiO_2$

Fig. 2 showed SEM and HRTEM images of product that sphere-like morphology with diameter

of 1μm is clearly observed and one of the spheres is enlarged with rough surface in 2b, the lattice spacing was 0.3689nm in 2d, assigned to the (101) lattice spacing of anatase structure (d101=3.52Å)which confirmed the XRD results.

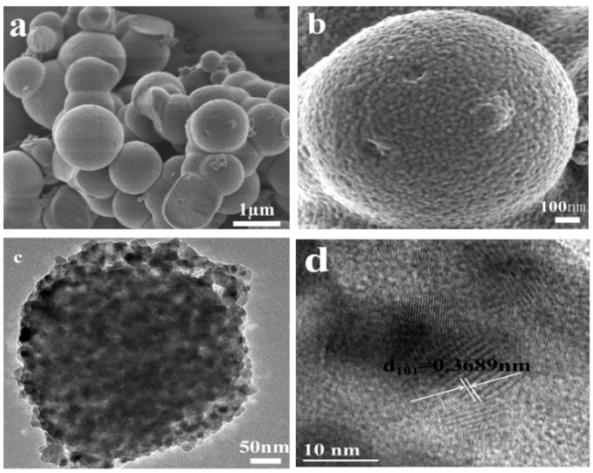


Figure 2.Characterization of product: (a) the low-magnification SEM image; (b) the enlarged SEM image; (c) TEM image; (d) the high-magnification TEM image

Raman spectra of the final product were shown in Fig. 3a. The vibration strong peak at 140-145cm$^{-1}$ is corresponding to anatase phase and the peak shifts to high wave-number due to a smaller particle size. A strong peak at 150cm$^{-1}$ and peaks at 398, 517, 640cm$^{-1}$ are observed, indicating that powder has good crystallinity of anatase with very small particle size, which is consistent with XRD results. TG-DSC curve were shown in 3b, an endothermic peak at 100°C in DSC curve was observed with a mass loss of 3% due to the desorption of water, another exothermic peak at 800°C is corresponding to the crystal phase transformation of $TiO_2$ from anatase to rutile with a mass loss of about 0.2% according to the TG curve.5c showed nitrogen adsorption desorption curve which has type IV like isotherm, indicating the existence of mesoporosity, and the specific surface area of antase is 53.9445 m²/g calculated by Brunauer-Eminett-Teller (BET) equation in the range of 0.05 and 0.35 ($p/p_0$), the pore diameter is 9.3439 nm calculated by Barrett-Joyner-Halenda (BJH) equation.

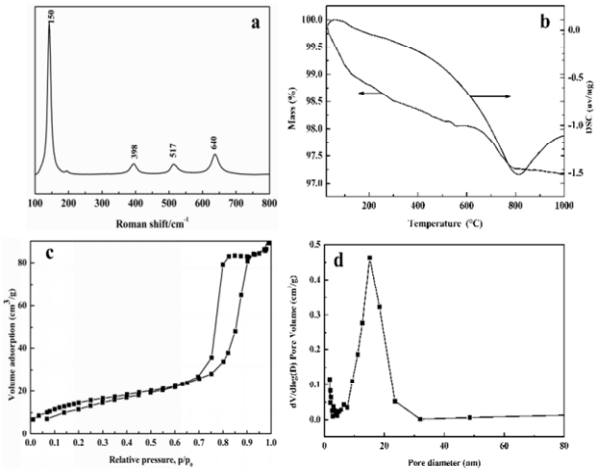


Figure 3. The characterizations of final product: (a) Roman spectra; (b) TG-DSC curve

**Drug Loading Capacity of $TiO_2$ toward SF.** To determine the drug loading capacity of nanostructured micro-spheres, an appropriate $TiO_2$/sorafenib ratio was diluted with 10mL methanol at 37°Cfor a period of time under stirring condition. The supernatant concentration can be measured

by UV-Vis spectrophotometer (752, ShangHai, China) after centrifugation at 5000r/min for 10min. The drug loading capacity was (5.65±0.04) % with entrapment efficiency of (17.97±0.13) % while $TiO_2$/sorafenib ratio was 15:5 with stirring for 6h.

## Conclusion

Combined homegeneous precipitation method with microwave irradiation, $TiO_2$ micro-spheres are easily obtained, and the conditions are moderate and easy to operate, the reaction time is as short as 20 min. Numerous nano-spheres with crystallite size of 21.24nm Constitute $TiO_2$ micro-spheres with diameters of about 1-2μm.The drug loading capacity and encapsulation efficiency of $TiO_2$ towards sorafenib increase with an increase of sorafenib concentration, when the $TiO_2$/sorafenib ratio is 15:5 under stirring condition for 6h, the drug loading capacity and encapsulation efficiency are (5.65±0.04) % and (17.97±0.13) %, respectively, indicating that $TiO_2$ micro-spheres have a wide applications to treat tumor diseases as a drug delivery carrier.

## Acknowledgments

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