

Particle Size Effect of Curcumin Nanosuspensions on the In-vitro Anticancer Activity, Cellular Uptake and In-vivo Pharmacokinetics

by

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Master of Science



State Key Laboratory of Quality Research in Chinese Medicine

Institute of Chinese Medical Sciences

University of Macau

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A thesis submitted in partial fulfillment of the
requirements for the degree of

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Supervisor

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碩士學位論文

不同粒徑薑黃素納米混懸液的體外抗腫瘤活性、細胞攝取及大鼠體內藥動學研究

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澳門大學中華醫藥研究院
中药质量研究国家重点实验室

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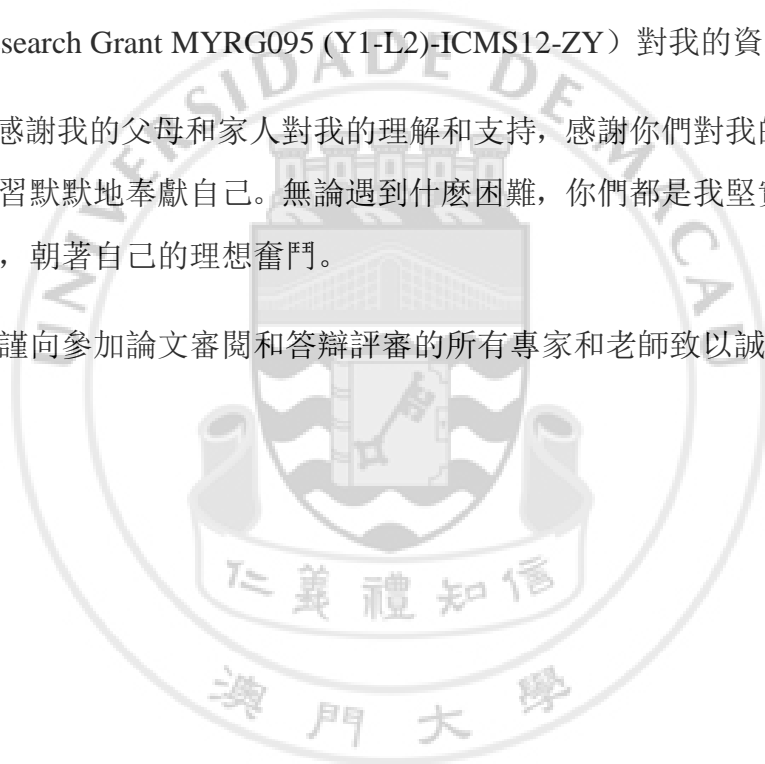
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澳門大學

摘 要

不同粒徑薑黃素納米混懸液的體外抗腫瘤活性、細胞攝取及大鼠體內藥動學研究

畢 超

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薑黃素是從薑科植物薑黃等的根莖中提取出的一種多酚類化合物，廣泛用於食品添加劑及染料中。薑黃素具有多種藥理作用，例如抗氧化，抗炎，抗腫瘤等活性。雖然薑黃素的使用前景廣泛，但是由於它的穩定性差，水溶性差，體內生物利用度低等缺點而限制了其的推廣使用。

如今，納米製劑技術的出現為這些易降解，生物半衰期短的藥物提供了有效保護，納米給藥系統已經成為現代製劑學研究的熱點。納米混懸液是一種通過表面活性劑/高分子材料的電荷效應和/或立體效應的穩定作用，將納米尺度的純藥物粒子分散在水中形成的穩定體系。它在增加藥物溶解度，生物利用度和給藥靶向性等方面發揮著重要的作用。

目的：製備 20~200 nm 範圍內三種不同粒徑的薑黃素納米混懸液(CUR-NS)，研究粒徑大小對 CUR-NS 的體外抗腫瘤活性、細胞攝取及大鼠體內藥動學行為的影響。

方法：採用普通反溶劑沉澱法製備~70 nm 和~200 nm CUR-NS；採用反溶劑沉澱法以新型多通道快速混合儀（multi-inlet vortex mixer, MIVM）製備~20 nm CUR-NS。採用透射電子顯微鏡（TEM）和原子力顯微鏡（AFM）對 CUR-NS

進行形態學考察。採用 MTT 法，利用人乳腺癌細胞 MCF-7 考察薑黃素原藥溶液以及不同粒徑 CUR-NS 的體外抗腫瘤活性。通過螢光顯微鏡對薑黃素原藥溶液以及不同粒徑 CUR-NS 的細胞內藥物攝取進行定性研究；通過螢光分光光度法對薑黃素原藥溶液以及不同粒徑 CUR-NS 的細胞內藥物攝取進行定量研究。最後，研究還比較了靜脈注射薑黃素原藥溶液和不同粒徑 CUR-NS 後大鼠體內的藥動學行為。

結果：本研究成功製備出三種不同粒徑的 CUR-NS，納米混懸液中藥物終濃度均為 0.5 mg/mL；其平均粒徑分別為 19.90 ± 0.23 、 69.65 ± 0.50 、 188.23 ± 8.98 nm；多分散係數分別為 0.37 ± 0.01 、 0.34 ± 0.03 、 0.25 ± 0.07 ；zeta 電位分別為 -8.21 ± 1.68 、 -8.67 ± 0.26 、 -9.52 ± 0.21 mV。短期物理穩定性研究表明，在 4 °C 下避光保存一個月後，三個製劑的平均粒徑分別為 20.73 ± 0.67 、 69.89 ± 1.57 、 195.93 ± 15.47 nm；多分散係數分別為 0.39 ± 0.01 、 0.26 ± 0.02 、 0.17 ± 0.09 ；zeta 電位分別為 -8.08 ± 1.17 、 -8.39 ± 0.58 、 -9.28 ± 0.42 mV，基本保持穩定。透射電子顯微鏡和原子力顯微鏡下觀察發現，CUR-NS 中粒子基本呈類球形，粒徑與粒度分析儀所測結果基本相符，且分散性良好，無聚合粘連。細胞毒性實驗表明，薑黃素原藥溶液，~20 nm，~70 nm，~200 nm CUR-NS 24 h 的半數抑制濃度 (IC₅₀) 分別為 44.09 ± 0.93 、 38.63 ± 2.55 、 36.23 ± 0.58 、 31.44 ± 0.79 μmol/L；48 h 的 IC₅₀ 分別為 33.24 ± 2.18 、 30.93 ± 2.26 、 25.61 ± 2.15 、 25.50 ± 2.32 μmol/L；結果提示當 CUR-NS 平均粒徑越小時，體外抗腫瘤活性越接近薑黃素原藥溶液；而當 CUR-NS 平均粒徑越大時，對人乳腺癌細胞 MCF-7 的增殖抑制作用越明顯，明顯強於薑黃素原藥溶液。同樣，細胞內藥物攝取的定性和定量研究結果表明，~20 nm CUR-NS 具有與物理混合物相似的攝取行為；而~70 nm 和~200 nm CUR-NS 的細胞內藥物攝取量明顯高於原藥溶液組；尤其是 6 h 後，與原藥溶液相比，~70 nm 和~200 nm CUR-NS 的細胞內藥物攝取量分別增加至 14.97 倍和 14.78 倍。給予大鼠靜脈注射薑黃素原藥溶液和不同粒徑 CUR-NS 後，~20 nm CUR-NS 表現出與原藥溶液相似的藥動學行為，從血液循環中快速消除，其藥動學參數和原藥溶液相比無顯著性差異 ($p > 0.05$)；而與原藥溶液組相比，~70 nm 和~200 nm CUR-NS 的藥時曲線下面積 (AUC) 分別增加至 1.53 倍和 2.25 倍；清除率 (CL) 分別降低至 1.51 倍和 2.24 倍；結果提示 CUR-NS 的平均粒徑越小，藥動學行為

與藥物越相似；平均粒徑越大，CUR-NS 的 CL 越慢，AUC 越大。

結論： 通過三種不同粒徑的 CUR-NS 的體外抗腫瘤活性、細胞攝取以及大鼠體內藥動學行為之間的比較發現，~20 nm CUR-NS 表現出與薑黃素原藥溶液相似的藥動學行為，而 CUR-NS 平均粒徑越大時，對腫瘤細胞的增殖抑制作用越明顯，細胞內藥物攝取量也越高，同時大鼠體內的清除率越慢，血藥濃度曲線下面積越大。

關鍵詞： 納米混懸液；薑黃素；粒徑；抗腫瘤；細胞攝取；藥物代謝動力學



University of Macau

Abstract

Particle Size Effect of Curcumin Nanosuspensions on the In-vitro Anticancer Activity, Cellular Uptake and In-vivo Pharmacokinetics

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Curcumin is a natural polyphenol derived from the rhizomes of *Curcuma longa* Linn.. It possesses many pharmacological activities, such as anti-oxidant, anti-inflammatory, anti-cancer, and anti-depressant properties. However, its poor solubility and stability in aqueous systems, as well as its rapid metabolism and systemic elimination, have limited its clinical application.

Nowadays, nanotechnology has been increasingly employed to provide effective protection for easily degraded or short half-life drugs. Nanosuspensions are sub-micro colloidal dispersion system; typically, pure drug particles ranging in size from a few nm to 1,000 nm are stabilized by surfactants or polymeric materials. The 100% drug loading makes them efficient in transporting drug to or into cells, reaching a sufficiently high therapeutic concentration for the pharmacological effect.

Purpose: The aim of this study was to investigate the particle size effects of curcumin nanosuspensions (CUR-NS) on the in-vitro anticancer activity, cellular uptake and in-vivo pharmacokinetics.

Methods: CUR-NS were prepared by anti-solvent precipitation using a conventional method for samples with particle sizes of ~70 nm and ~200 nm, and a specially fabricated multi-inlet vortex mixer (MIVM) with rapid and effective micromixing for

highly reproducible samples of smaller particle size (~20 nm). Characterisation of CUR-NS was investigated by transmission electron microscopy (TEM) and atomic force microscope (AFM). Cancer cytotoxicity was evaluated by MTT assay in MCF-7 cells. Fluorescence microscopy and spectrophotometry were used for qualitative and quantitative cellular uptake of curcumin. Comparison of the pharmacokinetic profiles of curcumin solution and CUR-NS was conducted in Sprague-Dawley (SD) rats after intravenous administration.

Results: CUR-NS of three different sizes have been consistently prepared. The mean particle sizes (19.90 ± 0.23 , 69.65 ± 0.50 , and 188.23 ± 8.98 nm) were measured by dynamic laser light scattering, which conformed to the TEM and AFM images. The final drug concentration of all three formulations was 0.5 mg/mL (0.05% drug content). A short-term stability study showed that all three formulations were physically stable after storage at 4 °C for over one month. Cell growth inhibition studies on the nanosuspension samples indicated that the IC₅₀ values of curcumin solution, ~20 nm, ~70 nm, and ~200 nm were 44.09 ± 0.93 , 38.63 ± 2.55 , 36.23 ± 0.58 , and 31.44 ± 0.79 μmol/L at 24 h; and 33.24 ± 2.18 , 30.93 ± 2.26 , 25.61 ± 2.15 , and 25.50 ± 2.32 μmol/L at 48 h, respectively, suggesting that the smaller the particle size, the more similar to curcumin solution on the antitumour activity. CUR-NS with the smallest particle size (~20 nm) showed similar cellular uptake to that of physical mixture. Whereas nanosuspensions of larger particle size (~70-200 nm) displayed much higher cellular uptake compared to the solution; especially at 6 h, the uptake amount of ~70 nm and ~200 nm was 14.97-fold and 14.78-fold of curcumin solution, respectively. Following intravenous administration to SD rats, the ~20 nm formulation exhibited similar pharmacokinetic profiles to those of curcumin solution with rapid elimination of the drug from the blood circulation. In addition, the area under the curve (AUC) of ~70 nm and ~200 nm was increased by 1.53-fold and 2.25-fold; and the clearance rate was decreased by 1.51-fold and 2.24-fold, respectively, indicating that CUR-NS with larger particle size afforded significantly higher AUC, higher peak concentration and slower clearance rate.

Conclusions: For the three different size groups of the nanosuspension preparations studied, the smallest CUR-NS (~20 nm) are comparable to curcumin solution in pharmacokinetic behavior while the larger CUR-NS are superior to curcumin solution in terms of both in-vitro anticancer activity and in-vivo pharmacokinetics after intravenous administration.

Keywords:

Nanosuspensions, Curcumin, Particle size, Anticancer, Cellular uptake, Pharmacokinetics



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HPLC	High Performance Liquid Chromatography	高效液相色譜法
CUR-NS	Curcumin Nanosuspensions	薑黃素納米混懸液
PVP	Polyvinylpyrrolidone	聚乙烯吡咯烷酮
MIVM	Multi-Inlet Vortex Mixer	多通道快速混合儀
TEM	Transmission Electron Microscope	透射電子顯微鏡
AFM	Atomic Force Microscope	原子力顯微鏡
FBS	Fetal Bovine Serum	胎牛血清
PBS	Phosphate Buffer Solution	磷酸鹽緩衝液
MTT	Methyl Thiazolyl Tetrazolium	四甲基偶氮唑鹽
IC ₅₀	Half Maximal Inhibitory Concentration	半數抑制濃度
AUC	Area Under the Curve	血藥濃度曲線下面積
T _{1/2}	Half Life Time	消除半衰期
CL	Clearance	清除率
MPS	Mononuclear Phagocytic System	單核吞噬細胞系統