



**NANO-IN-MICROPARTICLES FOR THE  
PULMONARY DELIVERY OF CURCUMIN IN LUNG  
CANCER**

**Toshtemirov Shukhrat**

*Development of Drugs and Health Products (D2HP)  
University of Paris-Saclay*

**ARTICLE INFO:**

*Received:10.10.2026*

*Revised: 11.10.2026*

*Accepted:12.10.2026*

**KEY WORDS:**

*Curcumin; nano-in-  
microparticles;  
pulmonary drug  
delivery; lung cancer;  
dry powder inhaler;  
nanoparticle  
formulation; spray  
drying; aerosol  
performance.*

**ABSTRACT**

*Lung cancer remains a major global health challenge, and the effectiveness of anticancer treatment can be limited by systemic toxicity, inadequate drug accumulation at the tumor site, and the development of treatment resistance. Curcumin, a naturally occurring polyphenolic compound derived from *Curcuma longa*, has demonstrated anticancer activity in preclinical research. However, its poor aqueous solubility, limited bioavailability, and chemical instability restrict its pharmaceutical application.*

**Introduction.** Lung cancer is one of the leading causes of cancer-related mortality worldwide. Its treatment may involve surgery, chemotherapy, radiotherapy, targeted therapies, immunotherapy, or combinations of these approaches, depending on the tumor type and disease stage. Despite improvements in diagnosis and treatment, the management of lung cancer remains challenging because of tumor heterogeneity, acquired drug resistance, and treatment-associated adverse effects.

Conventional systemic administration of anticancer agents exposes both tumor and healthy tissues to the administered drug. Pulmonary drug delivery offers an alternative strategy for investigating whether drugs can be deposited more directly at the site of lung disease. Inhalation-based systems may potentially increase local pulmonary exposure while limiting unnecessary systemic distribution. However, this benefit depends on the drug's properties, aerosol characteristics, regional deposition, absorption, and clearance from the respiratory tract.



Curcumin is a naturally occurring polyphenol found in turmeric. Experimental studies have investigated its potential effects on cancer-associated biological processes, including cellular proliferation, apoptosis, oxidative stress, inflammatory signaling, and tumor-related molecular pathways. These findings have generated interest in curcumin as a potential component of future anticancer formulations. However, preclinical activity should not be interpreted as proof of clinical effectiveness in patients with lung cancer.

The pharmaceutical development of curcumin is complicated by its poor aqueous solubility, limited systemic bioavailability, and susceptibility to degradation under certain conditions. Nanotechnology-based delivery systems, including liposomes, polymeric nanoparticles, micelles, and nanosuspensions, have therefore been investigated to improve its dispersion, stability, cellular uptake, and delivery to target tissues [1–3].

One promising strategy is the development of nano-in-microparticles, in which curcumin-loaded nanoparticles are incorporated into larger microparticles suitable for inhalation. The larger structures can facilitate powder handling and aerosolization, while the incorporated nanoparticles may redisperse after contact with pulmonary fluids. This design seeks to combine the advantages of two particle-size scales within a single formulation. Baghdad and colleagues demonstrated the feasibility of this approach in a study of inhalable curcumin-loaded nano-in-microparticles for bronchoscopic photodynamic therapy. Their formulation was prepared by nanoprecipitation followed by spray drying with mannitol as a stabilizer. The study reported favorable aerosol properties and nanoparticle redispersion, supporting further investigation of the platform [1].

The purpose of this article is to examine the formulation principles, characterization methods, potential biological benefits, and remaining challenges associated with nano-in-microparticles for pulmonary curcumin delivery in lung cancer.

**Curcumin as a potential anticancer agent.** Curcumin has attracted considerable research interest because of its reported effects on several biological pathways involved in cancer development and progression. Depending on the experimental model and concentration, studies have investigated its influence on apoptosis, cell-cycle regulation, inflammatory signaling, oxidative balance, and tumor-cell proliferation.

These biological effects are complex and may vary across cancer types, cell lines, experimental conditions, and formulation systems. Curcumin should therefore be regarded as an investigational anticancer compound rather than an established standalone treatment for lung cancer.

Several physicochemical properties complicate the development of curcumin formulations:

- **Poor aqueous solubility:** Curcumin has limited solubility in water, which can restrict its dispersion and availability in biological fluids.
- **Chemical instability:** Its stability depends on environmental conditions, including the composition and pH of the surrounding medium.



- **Limited bioavailability:** Conventional formulations may not provide adequate or sustained exposure at the intended target.

- **Formulation challenges:** Maintaining a reproducible drug concentration, preventing aggregation, and achieving consistent delivery can be difficult.

Nanoparticle encapsulation may help address some of these challenges by modifying the drug's physical environment and facilitating its dispersion. The degree of improvement depends on the carrier material, encapsulation process, and final formulation characteristics. Pulmonary administration is being investigated as a means of delivering therapeutic agents directly to lung tissues. For lung cancer, this route may offer the possibility of increasing local drug exposure while reducing some forms of systemic exposure.

However, deposition in the lungs does not automatically result in delivery to tumor cells. The drug must be released from the carrier, traverse the relevant biological barriers, and reach tumor tissue at an effective concentration. In addition, inhaled particles may be removed through mucociliary clearance, uptake by alveolar macrophages, or absorption into the circulation.

Consequently, the development of an inhalable curcumin formulation requires both pharmaceutical characterization and biological assessment. Nano-in-microparticles are composite delivery systems in which nanoparticles are incorporated into microparticles. In pulmonary applications, the microparticles are designed to support aerosol generation and deposition, while the nanoparticles provide the drug-carrier structure after redispersion.

A typical formulation may consist of curcumin-loaded polymeric or lipid-based nanoparticles combined with a suitable stabilizing or bulking excipient. The nanoparticle suspension can be converted into a dry powder through spray drying or another appropriate drying technique.

Following inhalation, the microparticles are deposited within the respiratory tract according to their aerodynamic properties. Upon contact with pulmonary fluids, a successful formulation should release or redisperse its nanoparticle components without excessive aggregation.

The formulation must balance several requirements:

1. Adequate powder flow and physical stability.
2. Efficient aerosolization from the selected inhaler or delivery device.
3. Appropriate aerodynamic properties for the intended lung region.
4. Reproducible nanoparticle redispersion after deposition.
5. Sufficient drug release and acceptable pulmonary compatibility.

Nanoparticles and microparticles serve different functions. Nanoparticles can provide a matrix for drug incorporation, influence drug release, and modify interactions with cells. Microparticles can improve the physical handling and dispersibility of nanoparticle-containing powders. The combined system may therefore offer advantages over administering an



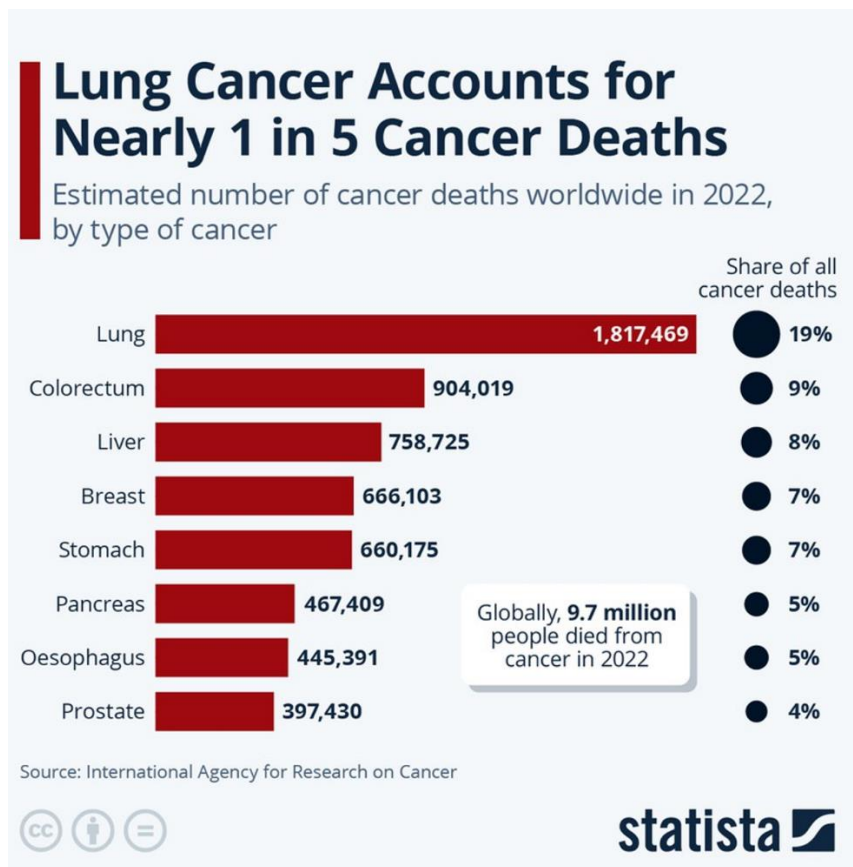
unprocessed nanoparticle suspension as an aerosol or using conventional drug microparticles alone.

Nevertheless, these advantages must be demonstrated experimentally. Drying may cause nanoparticle aggregation, alter the crystalline state of the drug, or reduce the ability of the particles to redisperse. The selection of excipients and drying conditions is consequently critical. Curcumin-loaded nanoparticles may be produced using a suitable method such as nanoprecipitation, solvent evaporation, emulsification, or self-assembly of amphiphilic materials. The choice depends on the carrier composition, drug solubility, required particle characteristics, and intended route of administration.

Nanoprecipitation is particularly relevant when the drug and carrier can be dissolved or dispersed in compatible solvent systems. Under controlled conditions, the addition of an appropriate nonsolvent promotes particle formation. The resulting dispersion can then be purified to remove unencapsulated drug and residual solvent.

Polymeric nanoparticles, liposomes, and micelles have each been investigated for curcumin delivery. Each system has distinct advantages and limitations concerning drug loading, stability, release, and compatibility with pulmonary fluids.

After nanoparticle preparation, the suspension may be converted into an inhalable powder using spray drying or freeze drying, depending on the formulation objectives.





“High mortality → need for better therapies”

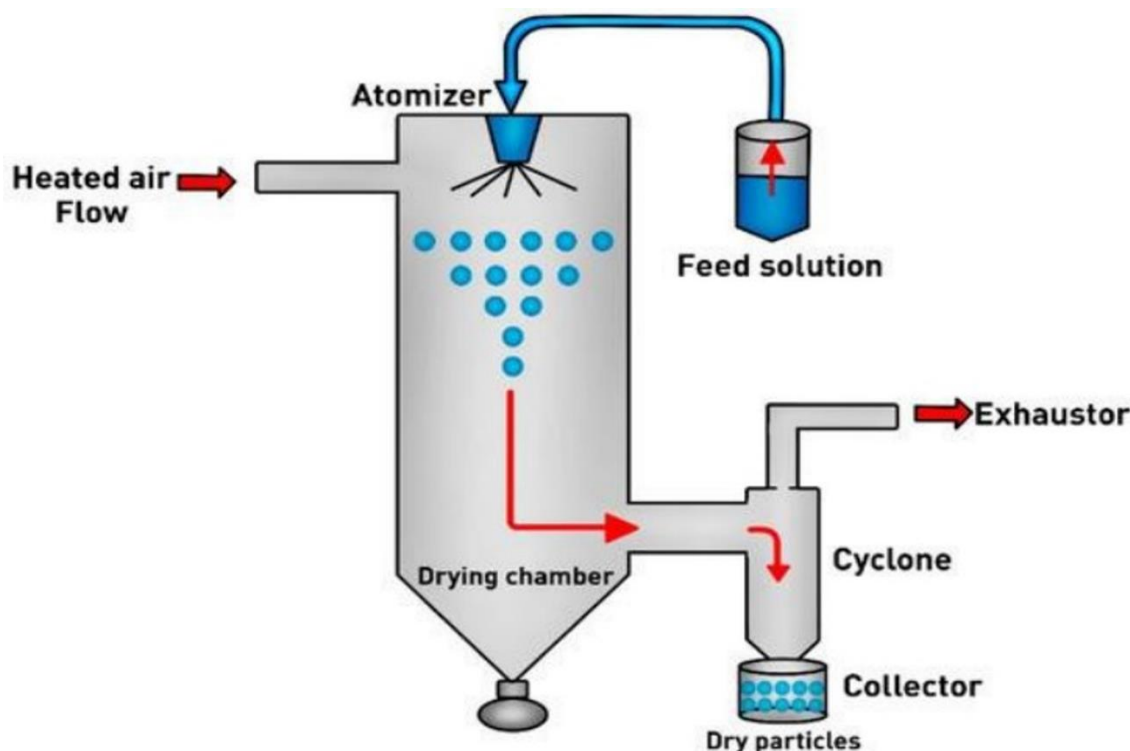
World Health Organization (WHO) – Lung Cancer Fact Sheet (16 April 2026)

Spray drying offers the possibility of producing a dry powder in a relatively continuous process. The drying conditions, feed composition, and excipient selection influence particle morphology, residual moisture, redispersibility, and aerosol performance. Mannitol, lactose, and L-leucine are examples of excipients investigated in inhalable powder formulations. Their suitability depends on the specific formulation and intended inhaler. The use of any excipient for pulmonary administration requires consideration of its concentration, quality, and respiratory tolerability.

A systematic formulation-development program should examine the variables that influence the performance of the final product. These include:

- Nanoparticle composition and concentration.
- Curcumin-to-carrier ratio.
- Initial nanoparticle size and polydispersity.
- Type and concentration of stabilizing excipients.
- Drying method and processing conditions.
- Residual moisture and powder storage conditions.
- Redispersibility and post-drying particle characteristics.

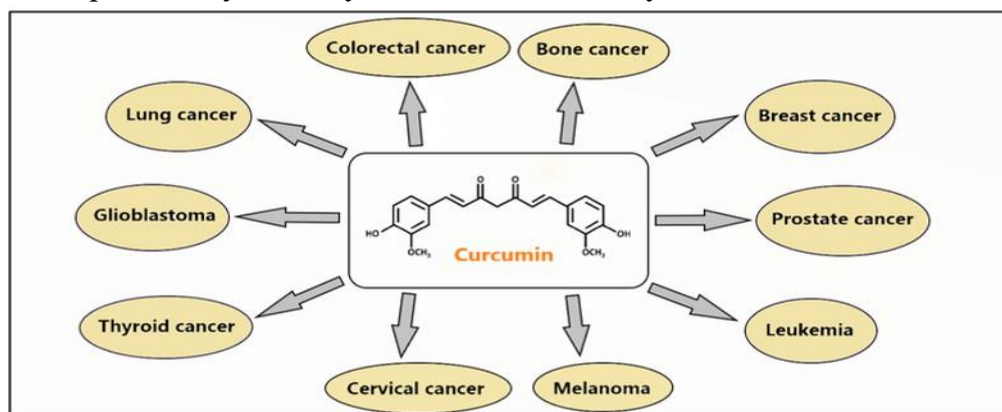
Optimization should use predefined quality attributes and an appropriate experimental design. A formulation should not be considered optimal solely because it produces small nanoparticles or a high encapsulation efficiency; aerosol performance and biological suitability are also essential. Dynamic light scattering can be used to determine the hydrodynamic diameter and polydispersity index of nanoparticles before drying and after redispersion. Electron microscopy may provide complementary information about particle morphology.



### Spray Drying Technique

These measurements can help determine whether the drying process preserves the nanoparticle structure. A substantial increase in particle size after redispersion may indicate aggregation or incomplete recovery of the original dispersion.

Encapsulation efficiency describes the proportion of the initial drug associated with the carrier, while drug loading expresses the drug content relative to the recovered carrier formulation. Both parameters should be measured using a validated analytical method, such as high-performance liquid chromatography (HPLC). The method should distinguish curcumin from potential degradation products and formulation components. High encapsulation efficiency may improve the efficiency of formulation development, but it does not independently establish effective pulmonary delivery or anticancer activity.



Cancers 2024, 16(8), 1554; <https://doi.org/10.3390/cancers16081554>



Aerodynamic diameter is a key parameter for inhalable powders because it influences where particles are likely to deposit in the respiratory tract. It differs from geometric diameter because it incorporates the effects of particle density and shape.

The aerodynamic performance of dry powders can be assessed using an appropriate impactor system, such as a Next Generation Impactor, under validated testing conditions. Important measurements include mass median aerodynamic diameter and fine particle fraction. The optimal values depend on the delivery device, formulation, and intended deposition region. Aerodynamic characterization should therefore be interpreted in the context of the complete inhalation system rather than as an isolated particle measurement.

An important requirement for nano-in-microparticles is their ability to redisperse after deposition in an aqueous environment. Redispersibility can be evaluated by comparing nanoparticle size and distribution before drying with those measured after reconstitution. Powder stability should also be assessed during storage. Relevant parameters include moisture content, drug content, visible aggregation, particle morphology, aerosol performance, and changes in the nanoparticle dispersion after reconstitution. These measurements help determine whether the powder maintains its intended characteristics throughout its proposed shelf life.

Baghdan et al. developed curcumin-loaded nanoparticles using nanoprecipitation and subsequently converted them into microparticles through spray drying with mannitol. The study reported a nanoparticle hydrodynamic diameter of approximately 181 nm. The resulting powder exhibited a fine particle fraction of approximately 65% and a mass median aerodynamic diameter of approximately 3.02  $\mu\text{m}$ . The particles also demonstrated redispersibility and compatibility with a model of pulmonary surfactant [1].

The study investigated photodynamic therapy, in which curcumin was activated by light. In vitro experiments using A549 human lung cancer cells showed light-dependent, dose-related photocytotoxicity. These findings support the feasibility of the formulation approach but should not be interpreted as evidence of established clinical efficacy or as proof of successful treatment following routine inhalation. Another study developed a liposomal curcumin dry powder intended for pulmonary administration. The formulation showed aerosol characteristics considered suitable for lung delivery and demonstrated greater cellular uptake in A549 cells than free curcumin. The investigators also evaluated cytotoxicity in cancer cells and normal bronchial epithelial cells, as well as therapeutic effects in an animal model [2].

This research illustrates how lipid-based nanocarriers can be converted into inhalable powders while retaining measurable formulation and biological properties. However, liposomal powders and nano-in-microparticles are not identical systems, and their performance cannot be assumed to be equivalent.

Research published in 2023 investigated the aerosol performance of curcumin and quercetin nanoparticles for pulmonary delivery. The findings supported the feasibility of aerosolizing



nanoparticle formulations and investigating their effects on A549 cells. Subsequent work examined cellular uptake and toxicity-related outcomes [3,4].

These studies highlight the importance of evaluating formulation stability and biological activity alongside aerosol characteristics. They also suggest that combination formulations may warrant further investigation, although the benefits of any drug combination require appropriate experimental confirmation.

Cellular uptake studies can help determine whether a formulation changes the amount or rate of curcumin entering lung cancer cells. Suitable analytical or imaging techniques may be used, with free curcumin and blank-carrier controls included in the experimental design.

Increased cellular uptake does not necessarily indicate greater anticancer efficacy. The intracellular distribution of the drug, its release from the carrier, and the biological response must also be considered. In vitro studies may compare the effects of the formulation on lung cancer cells and relevant nonmalignant respiratory cells. Viability assays, apoptosis measurements, and other validated endpoints can provide information about cellular responses. A formulation that reduces cancer-cell viability may still be unsuitable if it causes unacceptable damage to healthy pulmonary cells. Consequently, both efficacy-related endpoints and toxicity-related outcomes should be considered.

Photodynamic applications require particular attention to the light source, wavelength, irradiation conditions, and delivered light dose. Results obtained after controlled laboratory irradiation cannot be generalized to ordinary inhalation without evaluating how the required light reaches the relevant tissue. Pulmonary compatibility is essential because the respiratory epithelium and alveolar structures are sensitive to irritants and particulate exposure. Studies should assess the effects of the formulation and its excipients on relevant cellular models and, where appropriate, tissue integrity and inflammatory responses.

Future research should focus on improving the reproducibility and biological relevance of inhalable curcumin formulations. Formulation optimization may investigate alternative carrier materials, excipients, drying conditions, and methods for controlling drug release. More comprehensive studies should compare nano-in-microparticles with other inhalable systems under standardized conditions. Such comparisons should consider not only particle size and encapsulation efficiency but also aerosol performance, redispersibility, pulmonary compatibility, drug exposure, and tumor response.

The role of curcumin as a photosensitizer also warrants careful investigation where photodynamic therapy is intended. The delivery system, irradiation method, and light distribution must be considered together to determine whether the proposed treatment is practically feasible.

Finally, successful translation will require scalable manufacturing, validated quality-control methods, appropriate toxicological evaluation, and evidence from relevant preclinical studies.



Clinical use cannot be justified on the basis of formulation properties or cell-culture results alone.

**Conclusion.** Nano-in-microparticles represent a promising formulation strategy for investigating the pulmonary delivery of curcumin in lung cancer. By combining nanoparticles with inhalable microparticles, this approach seeks to improve the handling and aerosolization of a poorly water-soluble compound while retaining the potential benefits of nanoscale drug carriers.

The next stage of development should integrate pharmaceutical characterization with biological evaluation and appropriately designed preclinical studies. This approach will help determine whether nano-in-microparticles can provide a meaningful advantage over existing pulmonary drug-delivery systems for curcumin.

### **References**

1. Baghdan E, Duse L, Schürer JJ, Pinnapireddy SR, Pourasghar M, Schäfer J, Schneider M, Bakowsky U. Development of inhalable curcumin loaded Nano-in-Microparticles for bronchoscopic photodynamic therapy. *European Journal of Pharmaceutical Sciences*. 2019;132:63–71. <https://doi.org/10.1016/j.ejps.2019.02.025>
2. Inhalation treatment of primary lung cancer using liposomal curcumin dry powder inhalers. *Acta Pharmaceutica Sinica B*. 2018;8(3):440–448. <https://doi.org/10.1016/j.apsb.2018.03.004>
3. Loo CY, Traini D, Young PM, Parumasivam T, Lee WH. Pulmonary delivery of curcumin and quercetin nanoparticles for lung cancer—Part 1: Aerosol performance characterization. *Journal of Drug Delivery Science and Technology*. 2023;86:104646. <https://doi.org/10.1016/j.jddst.2023.104646>
4. Loo CY, Traini D, Young PM, Parumasivam T, Lee WH. Pulmonary delivery of curcumin and quercetin nanoparticles for lung cancer—Part 2: Toxicity and endocytosis. *Journal of Drug Delivery Science and Technology*. 2023. <https://doi.org/10.1016/j.jddst.2023.104375>
5. Ghodke SS, Taylor KMG, Somavarapu S. Spray-dried micellar dry powder inhalation of curcumin for lung-targeted delivery in non-small cell lung cancer therapy. *Journal of Microencapsulation*. 2025;42(5):459–471. <https://doi.org/10.1080/02652048.2025.2495246>