Advanced Drug Delivery Reviews 236 (2026) 115915



Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr



Editorial

Gas delivery systems in biomedical applications☆



In recent years, therapeutic gases have emerged as active agents for the treatment of a broad range of diseases. Endogenous gasotransmitters, including nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S), together with other biologically relevant gases such as oxygen (O_2) and hydrogen (H_2), regulate vascular tone, mitochondrial metabolism, redox homeostasis, inflammation, immune activation, and tissue repair. Their small molecular size and high diffusivity enable rapid penetration into tissues and subcellular compartments. However, their clinical translation remains constrained by fundamental delivery challenges. Precise control over gas concentration, exposure duration, and spatial distribution is difficult to achieve, while short half-lives lead to rapid clearance and insufficient accumulation at target sites. These limitations narrow the therapeutic window and reduce efficacy. Accordingly, a main challenge in gas-based medicine is the development of efficient and precise delivery strategies. This Special Issue brings together recent advances in materials, devices, engineered living systems, and disease-specific platforms that address these challenges and broaden the therapeutic potential of gas-based therapeutics.

Building on these delivery challenges, therapeutic gas delivery is increasingly developed in a disease-specific context, moving beyond formulation-centered approaches toward pathology-guided design. In cancer immunotherapy, **Dr. Yunching Chen** and **Dr. Chieh-Cheng Huang** describe how gases such as NO, CO, H_2S, and O_2 act as immunomodulatory signals that reshape the tumor microenvironment by relieving hypoxia, enhancing immune-cell infiltration, and promoting immunogenic cancer cell death when integrated with targeted and stimuli-responsive delivery systems [1]. In oral diseases, the work by **Dr. Jonghoon Choi** and **Dr. Tagbo H.R. Niepa** highlights a distinct setting in which localized gas delivery addresses biofilm persistence, antimicrobial resistance, and impaired tissue repair through minimally invasive platforms, including gas-generating nanomaterials and hydrogel-based systems [2]. In central nervous system injuries, **Dr. Nikolaus Plesnila** focuses on gases such as H_2, NO, CO, xenon, and argon as modulators of oxidative stress, inflammation, and excitotoxicity, while emphasizing the importance of delivery timing and dose control across evolving injury cascades [3]. Together, these reviews indicate that effective gas-based therapeutics depend on matching gas selection, release kinetics, and delivery route to the dominant biological barriers of each disease.

Another theme emerging from this Special Issue is the concept of gas-specific delivery, in which each therapeutic gas defines its own biological rationale, limitation, and delivery design logic. These reviews move beyond a generalized view of gas therapy and instead treat each gas as a distinct pharmacological modality with unique constraints on dose, timing, and spatial distribution. For oxygen, **Dr. Jinhui Wu** highlights its role in tissue regeneration, where delivery must dynamically adapt to the evolving metabolic demand of healing tissues while avoiding excess oxygen that can disrupt redox balance [4]. For nitric oxide, **Dr. Won Jong Kim** and **Dr. Jihoon Kim** describe a highly context-dependent immunomodulator, where both delivery and scavenging strategies are required to regulate opposing effects on inflammation and immune activation [5]. For hydrogen sulfide, **Dr. Liang Cheng** emphasizes its narrow therapeutic window in cancer, where small variations in concentration can shift its role from cytoprotection to cytotoxicity, requiring tumor-responsive and precisely tunable systems [6]. For molecular hydrogen, **Dr. Hsing-Wen Sung** and **Dr. Yu-Jung Lin** address the intrinsic challenge of rapid diffusion and poor retention, which drives the development of systems that prolong local residence and enable sustained bioavailability [7]. For carbon monoxide, **Dr. Lorenz Meinel** focuses on balancing potent cytoprotective signaling with systemic toxicity, favoring localized and controlled release strategies that minimize off-target exposure and carboxyhemoglobin formation [8]. Together, these gas-specific perspectives indicate that delivery is not only a technical barrier but a central determinant of therapeutic outcome. Effective gas therapy therefore depends on aligning donor chemistry, release kinetics, and delivery architecture with the intrinsic biology of each gas, advancing toward a more precise and mechanism-informed design paradigm.

This issue also highlights externally triggered gas delivery platforms, in which the therapeutic effect arises not only from the delivered gas but also from the trigger mechanism that determines when and where gases or gas-derived reactive species are generated. **Dr. Yu-Kyoung Oh** reviews cold atmospheric plasma as an in situ gas-generating modality that produces reactive oxygen and nitrogen species for gas therapy and gas-activated drug delivery [9]. In this setting, plasma acts as an energy-to-chemistry interface. It converts externally applied electrical energy into reactive species through gas-phase ionization, while subsequent plasma–liquid–tissue interactions shape the composition, concentration, and lifetime of these species. **Dr. Hyuncheol Kim** and **Dr. Kwangmeyung Kim** further examine ultrasound-responsive nanomaterials for cancer therapy, in which ultrasound provides a non-invasive and deeply penetrating physical trigger for local gas generation or release [10]. Through thermal effects, structural disruption, phase transition, or sonodynamic activation, ultrasound-responsive systems can control the delivery of gases such as O_2, NO, CO_2, CO, and H_2S with spatial and temporal precision. Together, these reviews define a distinct class of gas

☆ This article is part of a Special issue entitled: 'Gas Delivery' published in Advanced Drug Delivery Reviews.

https://doi.org/10.1016/j.addr.2026.115915

Available online 9 June 2026
0169-409X/© 2026 Published by Elsevier B.V.

delivery systems in which therapeutic precision depends on how external energy is translated into controlled gas generation or release. Their translational potential will ultimately depend on whether these physical triggers can be standardized to produce predictable, reproducible, and safe therapeutic effects.

Extending this emphasis on control, a further advance highlighted in this Special Issue is the development of carrier architectures that give therapeutic gases more controllable pharmacological behavior. Because therapeutic gases diffuse rapidly and remain difficult to retain or control, the carrier must define how a transient signal is positioned and sustained. **Dr. Xian-Zheng Zhang** develops this concept through living materials, in which the carrier is not only a passive vehicle but also a biological system that can participate in gas production and respond to the disease environment [11]. This approach changes the logic of delivery, as pathological tissues are no longer treated only as passive targets but as biological contexts that can help regulate gas generation and release. Therefore, living materials shift gas delivery from simple payload transport toward disease-responsive therapeutic devices. **Drs. Leo Otterbein** and **James D. Byrne** address the same challenge from a materials and formulation perspective [12]. Their review of gas entrapping materials shows how foams, hydrogels, and solid matrices can convert gases into practical dosage forms with distinct release behaviors and routes of administration. In these systems, architecture serves as the basis for dose control. Foams provide high gas loading and rapid local exposure. Hydrogels support conformal tissue contact and prolonged release at barrier sites. Solid matrices offer implantable depots for localized reoxygenation or sustained gas delivery. Together, these reviews point to a carrier-centered future for gas therapeutics. The key question is no longer only which gas to deliver, but how carrier design can make gas therapy stable, localized, and matched to disease dynamics.

Overall, this Special Issue brings together current advances and challenges in gas delivery systems for biomedical applications. The collected reviews show that therapeutic gases are no longer viewed only as small diffusible molecules with biological effects. Instead, they are increasingly being developed as programmable therapeutic signals. Their activity depends on disease context, donor chemistry, carrier design, and external control. Their therapeutic value is therefore defined not only by intrinsic gas biology, but also by how precisely they can be generated and retained within complex tissues. Despite this progress, clinical translation remains challenging. Many gases are difficult to dose precisely because they diffuse rapidly, clear quickly, and often act within a narrow therapeutic window. Safety also remains a key concern, particularly when local therapeutic effects must be balanced against systemic toxicity. Further progress will require a deeper understanding of gas behavior in diseased tissues and more standardized preclinical evaluation frameworks.

Addressing these challenges will require sustained collaboration across gas biology, materials science, device engineering, imaging, pharmacology, and clinical medicine. We would like to thank all contributors, reviewers, editors, and the editorial team for their time and expertise in supporting this Special Issue. We hope this collection will serve as a valuable resource for understanding the mechanisms, delivery principles, and translational opportunities of gas based therapeutics. We also hope it will stimulate the development of more precise, safe, and clinically relevant gas delivery systems for future biomedical applications.

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