Review Article ISSN: 2996-3893

Trends in General Medicine

NARRATIVE REVIEW: Vesicular Delivery of Precision Drugs

Karel Petrak*

Matrx Pharmaceuticals, Inc., 555 Fifth Avenue – 17th Floor, New York, NY 10017, USA.

***Correspondence:**
Karel Petrak, Matrx Pharmaceuticals, Inc., 555 Fifth Avenue – 17th Floor, New York, NY 10017, USA.

Received: 21 Feb 2025; **Accepted:** 24 Mar 2025; **Published:** 31 Mar 2025

Citation: Karel Petrak. NARRATIVE REVIEW: Vesicular Delivery of Precision Drugs. Trends Gen Med. 2025; 3(1): 1-3.

ABSTRACT

Precision medicine considers individual variability in genes, environment, and lifestyle for each person to treat diseases. Precision drugs are needed to act on the identified disease targets to achieve this. Exosome properties are very relevant when considering the delivery of therapeutic agents to disease sites. This narrative review examines using exosome-based delivery systems to treat solid tumors.

Keywords

Precision drugs, Disease targets, Exosome delivery, CART-cell therapy.

Introduction

Pharmacokinetics (PK) describes drugs' behavior after administration. It considers how medications are presented to the body, e.g., intravenous, oral, topical, and others, and evaluates drug distribution, concentrations in circulation and at the location of the intended pharmacological action, drug metabolism, and elimination. It documents the passage of drugs from administration to complete elimination from the body [1]. The phases of drug presence in the body include absorption, distribution, metabolism, and excretion (ADME). The active ingredients, drug compounds, are generally manipulated by adding excipients to formulate drugs into pharmaceutical products. Hence, "liberation" is sometimes included, referring to the drug release from its formulation (LADME). Ultimately, drug efficacy is determined by the concentration of the active ingredient at the intended biological target of the disease to be treated. The drug's steady state is reached when the overall intake of a drug is in a dynamic equilibrium with its elimination, usually 3–5 times its half-life. The fraction of the active ingredient in the systemic circulation gives a drug's bioavailability. It is determined mainly by the physical properties of the active ingredient, somewhat modified by the formulation. The intravenous administration provides the maximum possible bioavailability, i.e., of 1 (or 100%).

A drug's bioavailability reports the level that must be reached to achieve the required blood plasma levels. Bioavailability is, therefore, a mathematical factor for each drug that influences the administered dose. Blood plasma levels need to be maintained to support the drug's pharmacodynamics, i.e., the biochemical and physiological effect of a drug and its mechanisms of action at the tissue, cellular, subcellular, and molecular levels. In other words, pharmacodynamics describes the drug's effects on the body, both beneficial and undesirable. The body distribution of conventional drugs is decided entirely by their physicochemical properties; it is not related to the molecular targets of the diseases to be treated. Much effort has been made to target drugs to their intended site of action. For example, particles have been used to carry medications to desired disease target locations; however, the success is minimal. Drugs released from particles close to the intended target follow their PKs and consequently distribute throughout the body.

Drug delivery systems (DDS) aim to facilitate the uptake of therapeutic agents at the desired site of action if free active agent's pharmacokinetics and biodistribution are not optimal or to reduce off-site toxicities. The clinical success of DDS depends on its in vivo behavior. However, after the drugs have been released at the targeted site, the fate of the drug is determined entirely by its physical properties; the pharmacokinetics of the classic active ingredients and DDSs are very different. Poor understanding of the mechanisms controlling pharmacokinetics, biodistribution, and the kinetics of each process in the context of disease targets has hampered the successful use of drug delivery systems in clinical medicine [2].

Formulating conventional drugs could moderately improve treatment efficacy. For example, combining drugs with microparticles can modify their solubility, increase bioavailability, and enable controlled release, leading to enhanced pharmacodynamics and reduced frequency of administrations and drug adverse effects [3]. It can also improve permeability, enabling access to intracellular targets. When applied to already-marketed drugs, such formulations have a commercial impact. None of this, however, provides features required by precision medicine treatments.

The Challenges of Meeting the Precision Drug Requirements

The definition of precision medicine requires the following for disease treatment: "…an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." The existing drugs' "one-size-fits-all" approach will not work [4].

Chimeric antigen receptor (CAR) T-cell therapy has emerged as one of the most rapidly evolving immunotherapy modalities. It has successfully treated hematological malignancies, raising hopes for positive outcomes in solid tumors.

A real-world study from the French DESCAR-T registry confirmed previous efficacy data from the pivotal ELARA trial, showing that with a median follow-up of 9.8 months, CD19 CAR-T therapy with tisagenlecleucel in 129 cases of R/R follicular lymphoma achieved a 98.2% ORR, including 85.8% best CR, with only 1.8% experiencing progression as the best response, 12-month PFS and OS rates of 62.6% and 84.9%, respectively (both medians were not reached), and < 1% grade 3–4 CRS and/or ICANS [5].

Chimeric antigen receptor (CAR)-T cell therapy has successfully treated hematological malignancies [6]. However, prolonging remission and reducing the recurrence of hematological malignancies and solid tumors' complex tumor microenvironment (TME) are challenges for CAR-T therapy [7]. This therapeutical approach provides a clear example of delivering drugs to well-defined disease drug targets that are physically available (e.g., in blood circulation) and challenges when they are not (e.g., in solid tumors).

Challenges such as suboptimal expansion and persistence, adverse events, a scarcity of ideal targets, high immunosuppression, and insufficient infiltration due to the intricate tumor microenvironment hinder the efficacy of CAR-T therapy and limit its application [8]. In hematological cancers, the disease target is relatively easy to identify, as individual associated antigens and disease markers, such as the B-cell marker CD19, are commonly expressed. Solid tumors express associated antigens on their surface and tissue; they are also found at low levels in normal tissues. There is heterogeneity between tumor types (primary vs. metastatic) and in same cancer diagnosed in different patients. Consequently, generating the relevant CAR-T cell type targeting antigen in solid tumors is challenging [9]. The issues of CART technology present a classic example of the importance of drug access and delivery to disease targets. Drug delivery systems driven not by their physicochemical but biological properties are needed.

Possible Solution: Vesicular Drug Delivery

Distributing drugs in the body is critical to enable their efficacy and safety. Although DDSs such as liposomes, micelles, dendrimers, and polymeric and inorganic nanoparticles can improve the effectiveness of the drug and reduce side effects, their clinical utility is hindered by several factors, including accessing the specific organs they target, pharmacokinetics and dynamics determined by physical properties, and related toxicity. The fundamental reason is that physicochemical properties govern the behavior of such DDSs, while their application aims to control biological behavior.

The transport and distribution, i.e.," the delivery" of functional components in cells, are performed by macromolecular transporters and several endogenous particles. For example, the vesicular acetylcholine transporter (VAChT) is an essential part of cholinergic neurotransmission, enabling the packaging and transporting of acetylcholine for exocytotic release. The loss of this function may lead to neurological disorders [10].

Lysosomal enzymes must be explicitly transported from the Golgi apparatus to lysosomes within vesicles that recognize and fuse only with the appropriate target membrane. The 2013 Nobel Prize in Physiology or Medicine has been awarded to James Rothman, Randy Schekman, and Thomas Südhof "for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells" [11]. Several types of extracellular vesicles, such as apoptotic bodies, microvesicles, and exosomes, have been identified depending on their intracellular origin and size. Apoptotic bodies ranging from 50 to 5000 nm contain cellular contents such as nucleic acids and histone proteins. Microvesicles range from 50 nm to 1000 nm and are formed by plasma membranes. Exosomes are extracellular nanosized membrane vesicles (30–100 nm) secreted by various types of cells found in blood, cerebrospinal fluid, urine, and saliva [12]. The properties of exosomes are very relevant when considering the delivery of therapeutic agents to disease sites. The main reason is their intrinsic involvement in cellular communications, transporting nucleic acids, proteins, and metabolites to designated cells. Every cell type in the human body secretes exosomes, distributed throughout the body by systemic circulations [13].

Exosomes, consisting of a lipid bilayer membrane, encapsulate proteins, nucleic acids, and lipids, transport bioactive molecules such as proteins and RNAs into recipient cells, affecting cellular functions and signaling pathways through such intercellular interactions. The feature that is especially important for developing DDSs is their ability to cross the blood-brain barrier, access the nervous system from blood circulation, and target specific cells or tissues to deposit uploaded active components. For DDSs, the exosome surface can be modified with ligands or antibodies to deliver to targeted cells or tissues. The methodology for producing exosomes on a commercial scale has been reviewed [15].

Exosomes and Diseases

An exosome-mediated drug delivery is likely to possess low toxicity and immunogenicity, promising cell-free therapies for

various diseases [16]. Endogenous exosomes transfer a range of molecules, such as proteins, RNA, DNA, and lipids, to regulate multiple pathways in recipient cells after depositing their load, such as surface, heat shock, fusion, lysosomal proteins, tumor-sensitive genes, and nucleic acids components to perform specific functions. Therefore, therapeutic agents have been loaded into exosomes to serve as DDS. However, insufficient knowledge of exosome properties and their overall involvement in health and disease makes therapeutic effects and long-term safety uncertain. Many challenges exist in understanding exosomes regarding therapeutic cargo loading [17].

Challenges in using exosomes for drug delivery

Contrasting conventional nanoparticulate systems such as liposomes or polymeric nanoparticles, exosomes might deliver therapeutic cargos directly into the cytoplasm [18]. However, an inefficient understanding of exosome nature and their role in overall disease and health conditions makes it difficult to foresee long-term safety and therapeutic effects. Practical challenges related to the exosome's stability, the production of sufficient amounts of exosomes with safety and efficacy, the efficient loading of drugs into exosomes, the clearance of exosomes from circulation, and the transition from the bench scale to clinical production may limit their development and clinical use [19]. For the clinical use of exosomes, it is essential to understand the molecular mechanisms behind the transport and function of exosome vesicles [20].

Conclusions and Outlook

The advent of exosomes and their functions in biology is one of the most exciting breakthroughs in the medical field in recent years. Exosomes, a nano-vesicle produced by most cell types, have a unique role in cell-cell communication, delivering various cargos to designated cells. This new DDS has a unique structure, distinct physiochemical characteristics, low immunogenicity, and toxicity. The challenges, such as modest efficiency, delivery, and off-target effects of precision gene editing concerning precision drugs, have yet to be resolved. Ultimately, after all the exosome challenges are resolved, unique molecular targets of diseases must be known for developing effective DDS.

References

1. Li Y, Meng Q, Yang M, et al. Current trends in drug metabolism and pharmacokinetics. Acta Pharm Sin B. 2019; 9: 1113-1114.
2. Glassman PM, Muzykantov VR. Pharmacokinetic and Pharmacodynamic Properties of Drug Delivery Systems. J Pharmacol Exp Ther. 2019; 370: 570-580.
3. Oliveira S, Converti A, Ádley L, et al. Microparticles in the Development and Improvement of Pharmaceutical Formulations An Analysis of In Vitro and In Vivo Studies. Int J Mol Sci. 2023; 24: 5441.
4. Petrak K. Precision medicine and drug targeting: The promise versus reality of target-specific drug delivery. In Nanostructures for the Engineering of Cells, Tissues, and Organs: From Design to Applications. 2018; 155–166. Elsevier. Available: https://doi.org/10.1016/B978-0-12-814732-4.00013-6.
5. Bachy E, Thieblemont C, Houot R, et al. 805MO real-world efficacy and safety of tisagenlecleucel (CTL019) for relapse or refractory follicular lymphoma patients included in the early access program through the French DESCAR-T registry. Ann Oncol. 2024; 35: 598-599.
6. Zheng R, Zhu X, Xiao Y. Advances in CAR-T-cell therapy in T-cell malignancies. J Hematol Oncol. 2024; 17: 49.
7. Zhang P, Zhang G, Wan X. Challenges and new technologies in adoptive cell therapy. J Hematol Oncol. 2023; 16: 97.
8. Huang H, Yu L, Weng H, et al. Advances in CAR-T cell therapy for hematologic and solid malignancies latest updates from 2024 ESMO Congress. J Hematol Oncol. 2024; 17: 120.
9. Martinez M, Moon EK. CAR T cells for solid tumors new strategies for finding, infiltrating, and surviving in the tumor microenvironment. Front Immunol. 2019; 10.
10. Qiao M, Kunpeng M, Yanli D, et al. Binding mechanism and antagonism of the vesicular acetylcholine transporter VAChT. Nat Struct Mol Biol. 2025; 1-10.
11. https://www.nobelprize.org/prizes/medicine/2013/rothman/facts/
12. Srijita S, Joyal X, Nitesh K, et al. Exosomes as natural nanocarrier-based drug delivery system: recent insights and future perspectives. 3 Biotech. 2023; 13: 1-25.
13. Maria I MH, Luis CM, Oscar MV, et al. Exosomes Potential Disease Biomarkers and New Therapeutic Targets. Biomedicines. 2021; 9: 1061.
14. Sharma V, Mukhopadhyay CD. Exosome as drug delivery system Current advancements. Extracellular Vesicle. 2024; 3: 100032.
15. Qing Q, Bin F, Yong L, et al. Current Strategies for Promoting the Large-scale Production of Exosomes. Curr Neuropharmacol. 2023; 21: 1964-1979.
16. Liang Y, Duan L, Lu J, et al. Engineering exosomes for targeted drug delivery. Theranostics. 2021; 11: 3183-3195.
17. Butreddy A, Kommineni N, Dudhipala N. Exosomes as Naturally Occurring Vehicles for Delivery of Biopharmaceuticals Insights from Drug Delivery to Clinical Perspectives. Nanomaterials. 2021; 11: 1481.
18. Patil SM, Sawant SS, Kunda NK. Exosomes as drug delivery systems A brief overview and progress update. Eur J Pharm Biopharm. 2020; 154: 259-269.
19. Yi-Fan C, Frank L, Yuan-Soon H, et al. Exosomes a review of biologic function diagnostic and targeted therapy applications and clinical trials. J Biomed Sci. 2024; 31: 67.
20. Duan L, Lin W, Zhang Y, et al. Exosomes in Autoimmune Diseases A Review of Mechanisms and Diagnostic Applications. Clinic Rev Allerg Immunol. 2025; 68.