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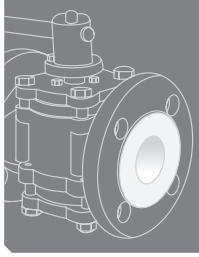

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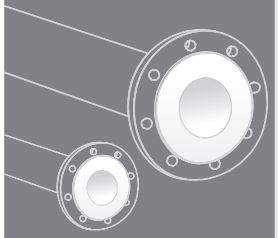

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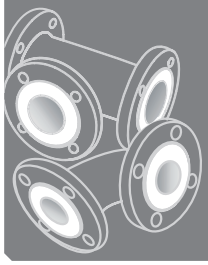

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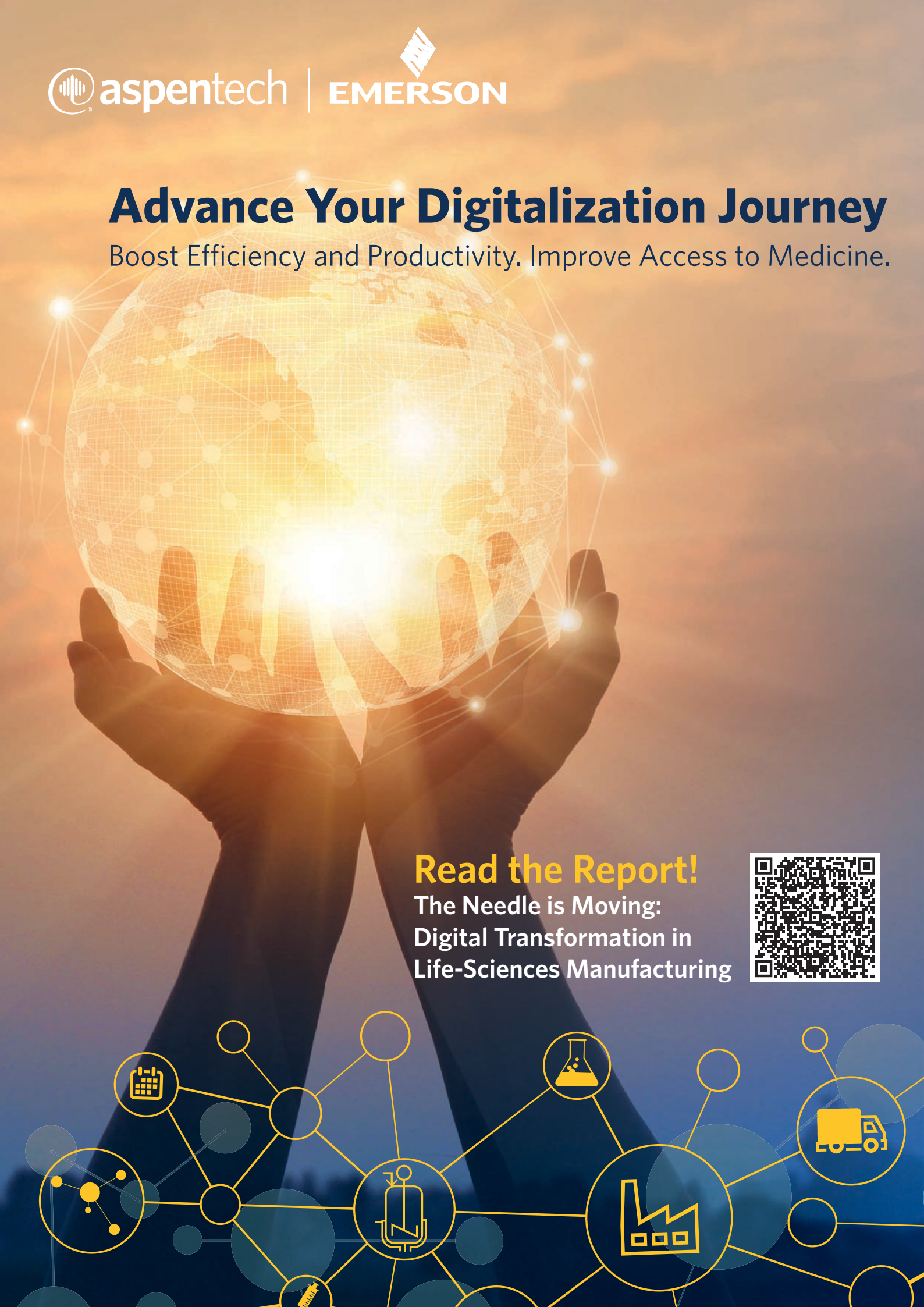

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Being the world's first intra-nasal COVID19 vaccine, this marks a glorious tribute to the call for Atmanirbhar Bharat: Dr. Mansukh Mandaviya

New Delhi, India: Dr. Mansukh Mandaviya, Union Minister of Health & Family Welfare unveiled the iNNCOVACC COVID19 vaccine today in the presence of Union Minister of State (IC) for Science and Technology, Dr Jitendra Singh. iNNCOVACC is the world's first intranasal COVID19 vaccine to receive approval for the primary 2-dose schedule, and as a heterologous booster dose. It is developed by Bharat Biotech International Limited (BBIL) in collaboration with Biotechnology Industry Research Assistance (BIRAC), a PSU under the Dept of Biotechnology, Ministry of Science and Technology.

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MeitY's R&D Institute SAMEER signs MoU with Siemens Healthineers on India MRI technology - a milestone in creating a Deeptech health care R&D and Supply Chain ecosystem

MoS Shri Rajeev Chandrasekhar witnessing the signing of MoU between SAMEER & Siemens

New Delhi, India: SAMEER, India's premier R&D Institute of Ministry of Electronics and IT (MeitY) signed a memorandum of understanding with Siemens Healthineers that will contribute towards the development of new, improved and innovative technologies for advancing healthcare and diagnostic access in India, in Bengaluru today. Welcoming the strategic agreement, the Minister of State for Electronics & Information Technology and Skill Development & Entrepreneurship, Shri Rajeev Chandrasekhar, who was present on the occasion, said it will make available low-cost MRIs as part of Prime Minister's vision of providing quality, and affordable healthcare

and diagnostic access for every Indian.

Emphasising that Digital India Programme launched by Prime Minister in 2015 has paved way for India to move from being a consumer of technology to a producer of technology, devices, and products, the Minister said, "The MoU today is a significant step in this direction."

Stating that healthcare sector in India represents a big market, the Minister said that the Government is prepared to partner with global companies who are willing to set up manufacturing bases in India. "We are also supportive of R&D model based on co-development between Global companies and India's vast network of academic institutions."

Citing the example of how the Government is working closely with industry leaders and academicians in the Semiconductor sector, the Minister said, "The Government is willing sit with experts from the healthcare sector to chart out the curriculum for grooming the next gen talent in India."

SAMEER, which is the acronym for Society for Applied Microwave Electronics Engineering & Research, specializes in RF Microwaves Radar and Communication Systems, E3 testing and Medical Electronics a strategic partnership.

Aardex and Cambridge Cognition announce collaboration to increase adherence oversight to hybrid and decentralized clinical trials

Liege, Belgium: Aardex Group's Adherence Specialists team and Cambridge Cognition's Remote research platform experts in the Clinpal team at Cambridge Cognition have announced collaboration to provide increased adherence monitoring during hybrid and decentralized clinical trials (DCTs). A seamless Adherence Management tool will be developed resulting from this collaboration by integrating Aardex Group's MEMS dosing capture and analytics system with Cambridge Cognition's Clinpal DCT platform, including a video consultation, electronic Informed Consent and the research database provides sponsors and contract research organizations (CROs).

MEMS-connected medication adherence packaging and interrogated by the MEMS AS enables digital dosing capture and can flag concerning medicine-taking behaviour in real-time. The collected data is synched directly to the Clinpal research database, which also registers data from participants, sites, and laboratories. The integration allows sites to access all study data, including adherence information, in one place. Clinpal manages the patient creation and linking, and participants can access adherence data through the Clinpal app. The result is an integrated, easy-to-use system that provides an optimal understanding of patient medicine-taking behaviours during the study while placing no additional burden on sites or participants.

The approach has been adopted by Trials@ Home, a centre of excellence for DCTs whose members include Sanofi, J&J, and Pfizer, and deployed in the project's RADIAL study. The phase IV clinical trial comprises around 600 people with type 2 diabetes across 63 sites. Of these, 150 are site-based, 150 are hybrid, and up to 300 are participating fully remotely.

Qurient and TB Alliance announce an agreement to develop and commercialize new anti-tuberculosis agent- telacebec

Seongnam-si, South Korea: Qurient Co. Ltd announced that they have entered into a license agreement to develop and commercialize telacebec (Q203), a first-in-class orally available cytochrome bc1 inhibitor for the treatment of tuberculosis (TB) and other non-tuberculosis mycobacterium infections.

Under the terms of the license agreement TB Alliance obtains the exclusive worldwide license (except for South Korea, Russia and the Commonwealth of Independent States (CIS) countries) to develop and commercialize telacebec for the treatment of tuberculosis and some non-tuberculosis mycobacteria (NTM) infections.

"As telacebec's unique mechanism of action of blocking energy metabolism of the Mycobacterium can address all types of TB, including drug-resistant TB, we expect telacebec to potentially become an essential component of drug combination regimens for the treatment of TB. We believe telacebec will greatly contribute to the global efforts to combating the TB pandemic, which remains a serious public health challenge worldwide. Our partnership with the TB Alliance will accelerate the widespread availability of telacebec and bring it to those in need", said Kiyean Nam, Ph.D., CEO of Qurient.

"TB Alliance is excited to partner with Qurient to bring about the next generation of TB cures. New drugs like telacebec are urgently needed in the fight against TB as well as certain NTM infections – compounds with potentially impactful novel mechanisms of action can have a significant benefit in combating the TB pandemic. If we expect to regain ground lost to Covid-19, we need to use every tool we have to give patients the best possible treatment and save lives. We look forward to advancing this new compound as part of combination regimens that could yield a short, simple, safe, and highly effective cure for all forms of TB" said Mel Spigelman, MD, president and CEO of TB Alliance.

bioMérieux launches MAESTRIA, a new generation middleware for microbiology laboratory

Paris, France: bioMérieux launches MAESTRIA a new generation middleware for the microbiology laboratory aims at providing a central software tool for the workflow management of all routine activities. Automation and digitalization of diagnostic solutions is a key need of the Clinical Analytics industry as clinical microbiology laboratories need to handle more and more medical data along the healthcare pathway. They require specific software solutions to help manage the growing needs for workflow optimization, biological expertise and data management. Managing workload in a timely manner and ensuring the quality of the testing workflow are everyday challenges in order to assist the various health professionals in their decision-making process for optimizing patient care.

MAESTRIA is the new generation microbiology middleware from bioMérieux,

managing specimens from the moment they are logged into the laboratory workflow until the final testing results are available. This software with a state-of-the-art graphical user interface covers various workflow steps including staining results or manual input of offline Antimicrobial Susceptibility Testing (AST) results, in addition to all connectable instruments. MAESTRIA also allows to define customer-specific AST interpretation rules, merging results from multiple methods - either online or manual - to consolidate one final antibiogram. Thanks to the additional CLARION Lab Analytics module, a data visualization feature, MAESTRIA transforms data into real-time, easy-to-access and actionable insights.

Already available for a number of pilot sites, MAESTRIA is being progressively launched globally through 2023. Customer feedback helps demonstrate the value of MAESTRIA in the lab routine and also provides broader workflow coverage and new features through continuous improvement.

US FDA approves GSK's Jesduvroq to treat anaemia of CKD in adults on dialysis

London, United Kingdom: GSK plc announced that the US Food and Drug Administration (US FDA) has approved Jesduvroq (daprodustat), an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), for the once-a-day treatment of anaemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least four months. Jesduvroq is the first innovative medicine for anaemia treatment in over 30 years and the only HIF-PHI approved in the US, providing a new oral, convenient option for patients in the US with anaemia of CKD on dialysis.

The FDA approval is based on results from the ASCEND-D trial, assessing the efficacy and safety of Jesduvroq for the treatment of anaemia of CKD in patients on dialysis. Results were published in the New England Journal of Medicine with additional results published in the New England Journal of Medicine supplementary appendix.

Jesduvroq, a HIF-PHI, belongs to a novel class of oral medicines for the treatment of anaemia of CKD in adult patients on dialysis. Inhibition of oxygen-sensing prolyl hydroxylase enzymes stabilises hypoxia-inducible factors, which can lead to transcription of erythropoietin and other genes involved in the correction of anaemia, similar to the physiological effects that occur in the human body at high altitude. Jesduvroq provides an oral treatment option for adult patients with anaemia of CKD on dialysis. Jesduvroq is a tablet available in 5 dosage strengths: 1mg, 2mg, 4mg, 6mg, 8mg.

"Over the last several decades, there has been little innovation in anaemia of CKD. We are proud to have developed Jesduvroq as a new oral treatment where there is a patient desire for more options", said Tony Wood, President and Chief Scientific Officer, GSK.

CKD is an increasing global health burden affecting 700 million patients worldwide, with an estimated one in seven patients also developing anaemia. When left untreated or undertreated, anaemia of CKD is associated with poor clinical outcomes and leads to a substantial burden on patients and healthcare systems. There is an unmet need for oral treatment options with efficacy and safety comparable to current treatments.

Gerresheimer displays new Clinical Trial Kit to accelerate drug development

Paris, France & Düsseldorf, Germany: Gerresheimer displays its new Clinical Trial Kit at Pharmapack in Paris. This kit consists of sterile Gx RTF vials in nest and tub or tray

with matching closures and is tailored to requirements to support the development of new drugs, vaccines and biologics in early phases.

The Clinical Trial Kit is suitable for small batch manufacturing from first line trials to validation and clinical batches. It can be ordered in six different configurations of Gx RTF Glass Vials. Kits including Gx Elite and Gx RTF COP vials will follow soon. It is currently offered in six different configurations with nest and tub or tray for filling volumes 2R RTF, 6R RTF and 10R RTF. Customers may receive a tailored kit made from a range of stopper and closure options selected using expertise advice. Each kit offers tried-and-tested product features, such as the integrity of the container system.

The Gerresheimer Clinical Trial Kit simplifies the clinical development of drugs by offering pre-tested and validated solutions that are readily usable for small batch sizes to replace commercial production. The major advantage of this concept is that companies can benefit from the exact same performance of the containers during commercialization as during research and development. This helps to shorten time to market and bring life-saving drugs to patients faster.

"There are currently more than 3,000 injectable drug programmes in pre-clinical and clinical phases. With our clinical trial kits and supportive services, we want to proactively support our customers by providing them with first-class primary packaging solutions," said Jean-Edouard Rabier, Sales Development Manager and Director (Project Management and Pharmaceutical Services).

US FDA approves Natco Pharma's anti-cancer drug azacitidine

Maryland, United States: Natco Pharma Limited has received final approval from the US Food and Drug Administration (FDA) for azacitidine injection used in the treatment of cancer.

According to the Press Release, Natco Pharma Limited is pleased to announce final approval of abbreviated new drug application (ANDA) from the US FDA for azacitidine for injection, 100 mg per vial, single-dose vial - a generic version of Vidaza by Celgene Corporation.

Natco and its marketing partner Breckenridge Pharmaceutical Inc (BPI) plan to launch this product in the US market in the near future. ■

Will Quantum Computing Transform Biopharma R&D?

Of the many industries in which quantum computing is expected to have a far-reaching impact, biopharma is among the most promising. Quantum computing has the potential to significantly accelerate, enhance the quality of, and reduce the costs of data-rich R&D processes. The earliest uses are likely to involve the early stages of R&D (drug discovery and design), but the impact will extend into the later stages of R&D, thanks to higher clinical success rates from better early design.

Authors

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Quantum computing is still very much an emerging technology, and the pathway to practical application remains under construction. However, the technology is graduating from the lab and heading for the marketplace. Google announced that it had achieved "quantum supremacy" in October 2019, IBM has committed to doubling the power of its quantum computers every year, and numerous other companies and academic institutions are investing billions toward making quantum computing a commercial reality. Biopharma companies have the potential to benefit significantly from this technology—and those that begin taking

"Biopharma companies that take the right approach to quantum computing now may gain a lasting advantage."

the right steps now may gain a lasting advantage.

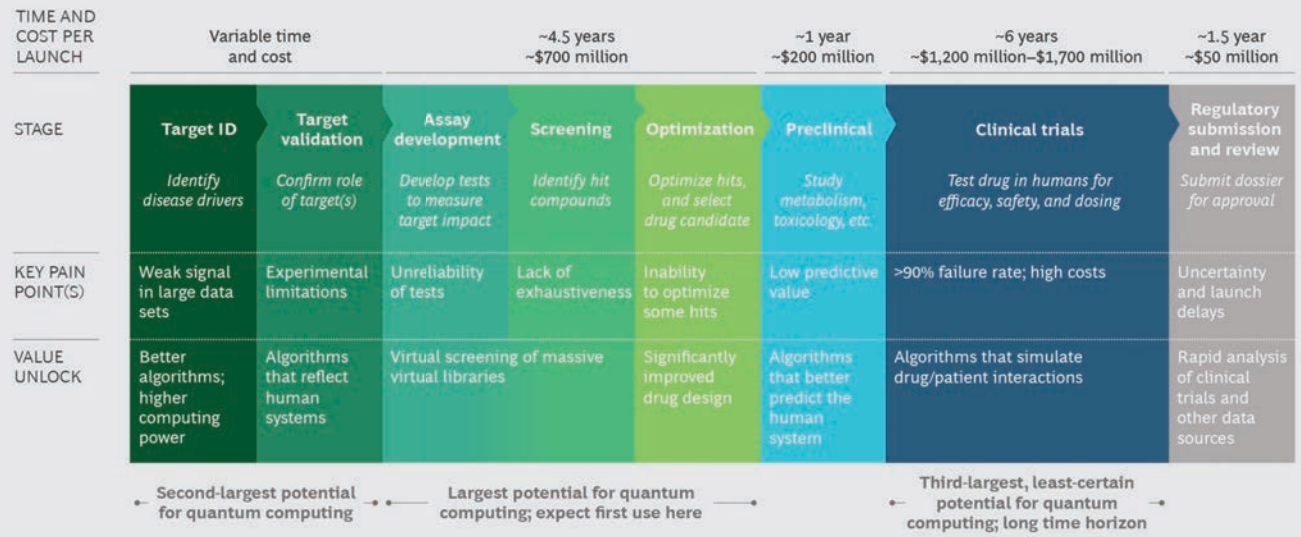
As with any emerging technology, much of the potential value lies in how commercial enterprises apply new capabilities to improve core processes. We believe that quantum computing is very likely to transform the early stages of pharmaceutical R&D over the coming decades—and that it will provide near-term benefits as the technology matures. But its actual impact will depend in large part on how biopharma companies learn to use it. Aside from quantum computing hardware and software, keys to success will include talent, new ways of working, and partnerships. Early movers will almost certainly gain advantages that followers will have a tough time matching.

Current Challenges in Pharmaceutical R&D

The biopharma R&D process—from drug discovery to development—is a costly, lengthy, and risky endeavor. A new drug typically takes 10 to 15 years to progress from discovery to launch, and the capitalized costs exceed $2 billion. The success rate is less than 10% from entry into clinical development to launch. For these reasons, biopharma companies count on a few blockbuster drugs to realize payback of the more than $180 billion that the industry spends each year on R&D.

Computational tools are already key components of drug discovery and development. In many instances, they have significantly shortened the time companies spend on drug optimization. Researchers rely on high-performance computing—using powerful supercomputers or massive parallel processing—to perform in silico modeling of molecular structures, mapping of the interactions between a drug and its target, and simulations of the drug's metabolism, distribution, and interactions in the wider human system. For example, computational chemistry algorithms aim to predict how a potential drug molecule will bind to specific target proteins, by modeling the binding energy of interaction. Because many of these algorithms do not scale well with the number of atoms, however, they are often limited to relatively simple molecular structures. For example, IBM has estimated that fully and accurately modeling the base-state energy of the penicillin molecule, which is composed of 41 atoms, would require a classical computer with more transistors than there

EXHIBIT 1 | The Potential for Quantum Computing's Impact on the Drug Discovery and Development Process



Sources: Paul et al., "How to improve R&D productivity: The pharmaceutical industry's grand challenge," *Nature Reviews Drug Discovery* 9(3):203–214 (2010); BCG experience and analysis.

are atoms in the observable universe.

How Quantum Computing Can Reshape Drug Discovery

Quantum computers work fundamentally differently than classical computers, and these differences give them the power to solve certain classes of problems that classical computers cannot. Classical computers are built on bits that have values of zero or one. In contrast, a quantum computer uses quantum bits (or qubits), which can be overlays of zeros and ones (meaning part zero and part one at the same time). Rather than working in isolation, qubits become entangled and act as a group, which helps enable quantum computers to achieve an exponentially higher information density and computing speed than classical computers. This gives them an advantage over classical computers in solving four types of problems: combinatorial optimization, differential equations, linear algebra, and factorization. Whereas modeling penicillin on a classical computer would take 1086 bits, it could take as few as 286 qubits on a quantum computer.

Quantum computers provide powerful tools for studying complex systems such as human physiology and the impact of drugs on biological systems and in living organisms. We believe that quantum computing will have numerous uses in pharmaceutical R&D, especially in the early phases of drug discovery and

"Quantum computers can achieve exponentially higher information density and computing speed than classical computers."

development. Take optimization. Currently, the process of modifying the physio-chemical properties of hit compounds to produce lead compounds and, ultimately, drug candidates still mostly relies on expensive and time-consuming experimental methods. The biopharma industry already applies quantum mechanics for energy calculations and structural optimization, especially in molecular docking and quantitative structure-activity relationship analyses. Quantum mechanics–enabled synthetic chemistry gives researchers the tools to preclude potentially inactive compounds and to support the synthesis of more challenging compounds. As quantum-based virtual screening and optimization leverage molecular simulations, it is possible that researchers will someday be able to combine both into a single in silico workflow.

Or consider screening. Virtual screening tools tend to be cheaper and faster than chemical processes for screening large compound libraries against a target of interest. But the usefulness of virtual tools depends on their ability to accurately predict hits, especially for complex molecules. Quantum computing has the potential to transform virtual screening through physically precise modeling of drug-target interactions and efficient screening of massive virtual libraries. Another complication is that building a tool to test compounds for the desired impact on a target during screening is a slow, labor-intensive lab process. By improving in silico screening and compound validation, quantum computing could reduce the need for costly and time-consuming in vitro testing. Eventually, quantum computing could permit end-to-end in silico drug discovery.

Quantum computing may also be useful in the target identification phase by enabling deeper exploration of complex multifactorial diseases that require the modulation of multiple targets. In addition, there could be applications in clinical development.

The possibility of step changes in capability is not a distant dream. Hybrid quantum-classical approaches that can predict molecule structure should be available within the next five years, allowing more-effective structure-based drug design of small molecules. A number of startups are developing virtual screening tools that use 3D representations of molecules derived from quantum mechanics to determine interactions between drugs and their targets.

How Biopharma Can Get Ready for Quantum Advantage

While the long-term promise of quantum computers may be transformative, the machines available today have serious shortcomings related to capacity, stability, and reliability. These issues must be overcome before companies can put quantum computers into practical service. We expect this journey to develop through four distinct phases, during each of which capabilities, applications, and business income will steadily increase over time.

The earliest uses involve the computer-aided drug discovery (CADD) applications described above. The next decade will be defined by so-called noisy intermediate-scale quantum (NISQ) devices, which increasingly will be able to perform useful, discrete functions, but will also be plagued by high error rates that limit their functionality. In three to five years, error mitigation techniques, along with better hardware and algorithms, should begin to support useful business applications.

Error-corrected machines will achieve true quantum advantage, outperforming classical computers in time, cost, or quality for the applications we have outlined. But error correction is still at least a decade away. The next milestone after that is full-scale fault tolerance, at which point quantum computers could enable full in silico drug discovery and design.

Harnessing technology during the NISQ decade requires mastery of four areas: quantum hardware- and software-based solutions, talent, new ways of working, and partnerships.

EXHIBIT 2 | The Journey Toward Quantum Drug Discovery

Quantum computing era

Near term

	Quantum-inspired CADD[1]	NISQ[2]	Broad quantum advantage	Full-scale fault tolerance
	0–3+ years	3–5+ years	10+ years	20+ years
Technical milestones	Quantum-inspired software and classical machine learning	Error mitigation and circuit optimization	Error correction	Modular architecture
Quantum computing enabled or advanced	Faster, more-accurate CADD	Improved CADD speed, scope, and accuracy	Virtual screening and optimization	End-to-end in silico drug discovery
Hardware	Classical	Quantum[3]	Quantum	Quantum

Source: BCG experience and analysis.
[1]CADD = computer-aided drug discovery.
[2]NISQ = noisy intermediate-scale quantum.
[3]Gate-based and annealing.

"Makers of quantum computing hardware aim to develop circuits optimized to solve problems such as molecular docking."

Quantum Hardware- and Software-Based Solutions. In addition to the hardware advances that large end-to-end providers such as Google, IBM, and Honeywell are pursuing, emerging companies such as D-Wave, Rigetti, and Xanadu are active. As happened in the early days of the semiconductor industry, quantum computing hardware manufacturers are aiming to develop circuits optimized to solve particular problems, such as molecular docking. For example, IBM is taking this approach to produce specialized circuits for "hidden shift" and quantum Fourier transform algorithms. "When it comes to near-term applications, the beautiful work will happen at the cross-section of business needs and quantum circuitry so that the circuit itself determines the application," IBM's head of quantum computing, Jay Gambetta, told us.

Because they work differently from classical computers, quantum computers require new software and algorithms. Specialists such as ProteinQure, GTN, Rahko, Menten AI, and Qulab are pioneering quantum drug-discovery algorithms. By partnering with these and larger companies, biopharma companies may be able to shape optimized circuit-to-application solutions and realize value more quickly.

In the meantime, the massive classical computing industry continues to deliver performance improvements (through supercomputers, HPC, and GPUs) and better algorithms that will help bring value to biopharma companies even sooner. Quantum computing has introduced new ways to approach problems, inspiring new algorithms that run on classical hardware. Microsoft, which has dubbed these new techniques "quantum-inspired," has just released a quantum-inspired chemistry library with 1QBit to run on Azure Quantum. Companies such as Silicon Therapeutics, XtalPi, Qubit Pharmaceuticals, Atomwise, Turbine, and Benevolent AI are using quantum-inspired approaches, often in combination with machine learning, and aim to achieve quicker and more-accurate drug discovery. Proven quantum computing algorithms boost machine learning training, so this approach will accelerate as NISQ machines become more powerful.

Talent. How companies decide to tackle specialized software development—internally, externally, or with a combination of the two—will have major implications for

their talent needs and their organizations. Companies will need skilled scientists and technicians, including hardware and software experts, to handle these tasks. Such talent is in short supply—and the supply is shorter still for jobs that require quantum computing knowledge or experience. Early movers have the opportunity to establish a skills advantage by becoming recognized centers of commercial advances in quantum computing. Companies such as Airbus already offer quantum training programs to prepare their engineers for the future.

New Ways of Working. In order to derive value from new approaches such as quantum computing, companies may need to change their processes. Building internal quantum computing capabilities requires not only relevant quantum skills but also collaboration between research scientists and pharma businesspeople and, work with talent in other technical fields such as artificial intelligence and machine learning. The new solutions promise a step change over current CADD tools in both accuracy and speed (for example, Atomwise claims a 10,000x improvement in hit rates and 100 times faster screening times, and other players point to similar improvements) that will open up radical new ways to design drugs. But to capture the value, companies must change their processes and, potentially, their organizational structure, as well as adopting agile ways of working. An agile approach enables faster and more efficient testing and iteration of promising therapeutic candidates and technological advances. In other industries, early leaders that have adopted agile have seen as much as a doubling of the speed of their new product development.

Partnerships. Innovation is a much more fragmented and varied endeavor today than ever before. More young companies in more places are pursuing more new avenues. One result of this fragmentation and diversity of effort is that although knowledge, skills, and information are much more accessible, they are also harder to harness because they reside in more numerous and more disparate places—geographically, industrially, and functionally. Investing in partnerships dedicated to building custom solutions that address the most crucial drug discovery challenges is an effective way to gain a foothold in the emerging quantum computing ecosystem. As BCG has observed before, deep technologies require a more thorough analysis of the

"Quantum computing solutions promise a step change over current CADD tools in accuracy and speed."

"Computing may encourage tech players to enter drug discovery, competing with pharma companies."

stakeholders' interdependencies and more precise value creation models in order to accurately determine how to align goals, set strategies, and organize for interaction with others.

How to Get Started

Quantum computing is likely to have a profound impact on biopharma R&D, potentially changing the competitive set and dynamics of drug discovery. A quantum-advantaged world will probably witness a race to find and patent the best molecules for a given target. This in turn will set off a "landgrab" of the most promising molecules, targets, and biological or clinical mechanisms for subsequent exploration. It's also possible that tech players will enter drug discovery, competing with pharma companies. In an extreme scenario, biopharma companies risk being relegated to focusing mainly on clinical development, medical affairs, and sales.

Biopharma should take the necessary steps now to prepare for quantum computing's role in R&D. A sensible first step would be to conduct an assessment of the probable impact of quantum, featuring a workflow analysis to identify key friction points and solution mapping to determine whether these challenges fall into quantum-advantaged problem archetypes. Companies can then identify "lighthouse" use cases and build out early.

As they move forward, biopharma companies should look for early wins that will demonstrate the value of new approaches (such as a speed-up over previous, nonprobabilistic algorithms) to the rest of the organization. Quantum-inspired algorithms that emulate quantum concepts on classical hardware or specialized NISQ-era quantum circuits are good places to start.

Ultimately, quantum computing is likely to yield greater speed and efficiency in drug discovery, improvements in existing drugs, and faster development of new drugs. It should also accelerate time to market. The technology's long-term potential is vast, but quantum computing also offers biopharma companies tangible benefits in the near term. Companies that want to play need to prepare for a quantum future now. ■

Lipid-based drug delivery systems are paving the way for effective healthcare therapies.

Arun Kedia
Managing Director, VAV Life Sciences

Pharmaceutical breakthroughs today are coming from targeted drug delivery systems based on lipids. Lipid nanoparticle (LNP) technology is an emerging area of biopharmaceutical science that offers a wide medicinal platform. It can potentially deliver a whole range of therapeutics, encompassing genes, RNAs, peptides, and diagnostic imaging agents. It can also help improve the therapeutic index, pharmacokinetics, and pharmacodynamics of several drugs.

Such lipid-based drug delivery systems are being studied extensively for their ability to deliver drugs and nutrients through various administrative routes due to their biocompatibility, slow-release rate, high stability, and low toxicity. Some of them like Solid Lipid Carriers (SLC) and Nanostructured Lipid Carriers (NLC) are among the most widely studied. These systems are based on phospholipids.

However, working with phospholipids extracted from natural sources is not easy. Due to the presence of unsaturated fatty acids in natural phospholipids, they produce a variety of components in mixed ratios that could vary from batch to batch. The resulting differences in physical, chemical, and biological properties make it difficult to develop robust, controlled-release drug delivery systems.

Thankfully, innovations in lipid science have led to the development of modern synthetic phospholipids. These can help overcome this hurdle. They are easier to standardize. Under suitable conditions, they permit a controlled adjustment of physical, chemical, and biological properties, especially where more physically stable liposomes with increased stability in blood plasma or phospholipids with more powder-like properties are desired. Because they lack antigenic

properties they can also be metabolized easily in the body. They are less toxic and have a higher degree of solubility, thus making them better candidates for liposomal-based drug delivery systems, especially for parenteral administration and inhalation dosage forms.

Lipids-based drug delivery systems can be quite robust.

Progress in LNP delivery systems has led to the development of robust drug delivery systems. As seen in the technology used in the mRNA-based Covid-19 vaccine delivery systems, synthetic lipid nanoparticles provide stability throughout the delivery process, helping generate a stronger immunogenic response. The mRNA strand is extremely fragile and susceptible to degradation but when this strand encoded with the key protein is encapsulated in synthetic lipid nanoparticles and used in the vaccine, it is delivered much more efficiently.

Nucleic acid drugs encapsulated in synthetic LNP (Lipid Nanoparticles) are being extensively researched for their potential to be used for replicon-based therapeutics in oncology, protein replacement therapy, and to aid in gene-editing techniques. The use of ionizable lipids which is the critical component of the LNP helps in determining the potency of the LNP towards target sites and allows for enhanced penetration in the target tissues such as the liver and solid tumours.

Lipid-based drug delivery systems are used across therapies. Some of these include:

- **Cancer therapy**

Lipid-based drug delivery systems have brought about a radical change in the biomedical and therapeutic fields. Active molecules used for the treatment of cancer can be encapsulated into liposomes and delivered efficiently to the target cancer cells. Liposomes up to 100 nanometres easily penetrate tumours and are stable for longer periods. Liposome-bound antibodies can target tumour-specific antigens and deliver drugs to the tumour. Their biostability helps deliver the drug to the specific cancerous cell, with minimal side effects to surrounding cells and tissues. These nanoparticles can target cancer cells by overcoming the blood-brain barrier. They are therefore considered extensively while treating brain tumours. Doxorubicin encapsulated in a closed lipid sphere (liposome) is the first clinically approved PEGylated nanoliposome for the treatment of cancer.

- **Cardiovascular disease**

The therapeutic index of certain cardiovascular drugs is known to be increased by liposomes. More recently the use of long-circulating liposomes is also gaining importance in the treatment of cardiovascular disease. For

example, during myocardial infarction, and atherosclerosis, platelets get accumulated. Here, platelet-targeted liposomal drug delivery offers potential therapeutic applications in the treatment of atherosclerosis. Liposomes coated with a biocompatible molecule help in preventing the destruction of the liposome drug carrier, thereby ensuring it stays for a longer time in the system for increased effectiveness.

- **Antibiotic therapy**

Antibiotics-loaded lipid nanoparticles can be used in the treatment of drug-resistant bacterial infections specifically in ocular, pulmonary, and topical bacterial infections. The use of drug delivery agents offers several advantages like better protection of the antibiotics from degrading while enhancing the biodistribution of the medicine within the system. These liposomes can selectively target and penetrate bacterial colonies despite all repulsive forces. This technique is also useful in eliminating intracellular bacterial growth within infected tissues due to enhanced antibiotic retention and drug release in a controlled manner with fewer side effects.

Emerging technologies using cationic lipids as siRNA delivery agents.

The use of synthetic cationic lipids like oxime ether lipids containing hydroxylated head groups is known to be superior siRNA delivery agents. They offer hope in the treatment of breast cancer using Small Interfering RNA (siRNA) based gene silencing therapy. Due to their small size, they can easily penetrate the tumour and release the drug in the intracellular space. This target cell site delivery mechanism using LNPs helps in reducing side effects to the surrounding healthy tissues. As the optimum size ranges from 80 nm to 100nm, these nanoparticles can tide through several bioavailability barriers that are encountered during the treatment phase.

Challenges in lipid-based drug delivery systems

Synthetic phospholipids with different polar head groups and fatty acid compositions can be manufactured using various synthesis routes. By varying fatty acids incorporated in the phospholipids, differences in the liposome's physical properties can be studied. But this involves complicated chemistry, complex characterisation as well as an expensive process. However, the advantages of using synthetic phospholipids with relatively high purity, are that the delivery system is relatively more stable with a predictable release pattern and improved targeting abilities.

Government support is needed to unlock the potential of lipid-based drug delivery systems.

Modifications to lipid-based drug delivery systems are constantly investigated to minimize toxicity, increase efficacy, and reduce rapid clearance from the bloodstream. Experimental studies focused on complex multi-functional liposomal formulations are in progress to develop more efficient drug delivery systems.

However, there still exist bottlenecks in the clinical translation of lipid-based drug delivery systems owing to pharmaceutical manufacturing, government regulations, and IP. Quality assurance and cost remain the major challenge. This complex system can be affected by the scalability of the process, the reliability and reproducibility of the final product, stability of the product and lack of in-house expertise. IP of liposomal based drug delivery systems is quite a perplexing challenge and costly as well. Clinical trials of liposomal formulations are more complex and time consuming than chemical formulations.

In India, the government needs to consider introducing schemes and incentives for companies that manufacture lipids. State-funded research on the effectiveness of liposomal nanotechnology will go a long way in positively providing support to industry and academia as well. With proper support and awareness, there is no doubt that the pharmaceutical industry's use of lipids will grow rapidly in the next decade worldwide. ■

Exosomes and Exosome-Inspired Vesicles for Targeted Drug Delivery

The similarities between exosomes and liposomes, together with the high organotropism of several types of exosomes, have recently prompted the development of engineered-exosomes or exosome-mimetics, which may be artificial (liposomal) or cell-derived vesicles, as advanced platforms for targeted drug delivery. In this review, we provide the current state-of-the-art on the development of exosomes, as well as artificial nanoparticulate systems that aim to mimic their properties as innovative nanocarriers with high drug targeting efficiency.

The most recent discoveries in the field of extracellular vesicles are unravelling exciting concepts on intercellular communication pathways. The fast growing literature in this field is showing that nano to micron sized vesicles budding from cells and named exosomes display specific organotropic behavior as part of their active role in cell-to-cell communication and material (protein and/or nucleic acid-cargo) transfer pathways. Besides local cell-to-cell communication, in some cases, the secreted factors play a key role in the interactions between cells located far apart from each other. The tremendously high and specific organotropism of some types of exosomes is one of the major goals of all the types of nano-based drug delivery systems (DDSs) that have been screened to date, which remains unmet. By providing important insights into the key elements that dictate the biological fate of vesicles and their ability to interact and be taken up by specific cells, the novel and fast-growing field of exosomes is now inspiring the design of ex-novo nanovesicles as targeted drug carriers for therapeutic applications.

Due to the numerous similarities between liposomes and exosomes, the application of liposome engineering technologies to engineer exosomes has been proposed as a way to overcome their limitations. The many similarities between the two systems is also the reason why liposomes are of the nanoparticle type, which is preferentially used for the construction of artificial

exosomes or EX-mimetics as drug carriers.

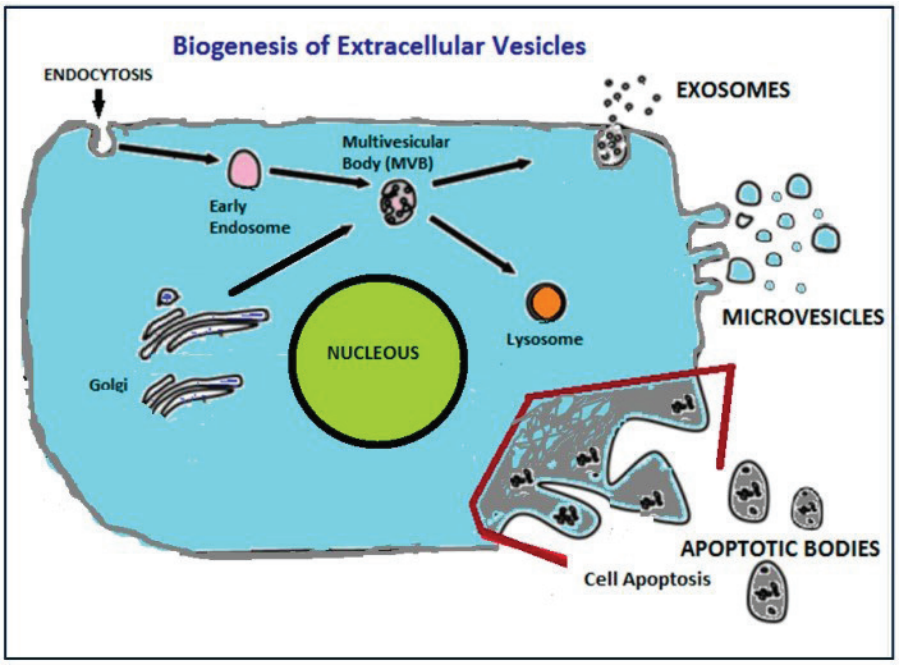
In order to understand why exosomes can be used as targeted drug carriers, we need to initially clearly define what they are, and additionally, review their basic functions. Exosomes are one of the types of a broader category of cell-derived vesicles characterized as extracellular vesicles (EVs).

In more detail (Figure 1): Representation of the biogenesis of extracellular vesicles from eukaryotic cell.

(i) Apoptotic bodies are released during cell death and are heterogeneously shaped vesicles with sizes between 50–5000 nm. They are formed from the plasma membrane, and they contain DNA, RNA, histones, and signalling molecules.

(ii) Micro vesicles are formed by blebbing of the cell membrane with concurrent incorporation of cytosolic proteins, and their sizes range between 20–1000 nm, depending on the origin cells and the method applied for their isolation from cell media. Their formation can be triggered through Ca2+ influx, phorbol esters, ATP, etc.

(iii) Finally, exosomes include a more homogeneous population of vesicles compared to microvesicles, with sizes that range from 50 nm up to 120 nm. Their biogenesis is initiated by inward budding of the plasma membrane which results in the formation of intermediate endosome-vesicles, the multivesicular bodies (MVBs).



Microvesicles and exosomes are smaller compared to apoptotic bodies. They differ from apoptotic bodies in their content, since they rarely contain DNA. Although these two vesicle-types, microvesicles, and exosomes, are separate classes of vesicles, due to the fact that they overlap in size, and since the commonly used non-specific protocols for exosome isolation and purification rely solely on the vesicle size differences. Because of this, it has been proposed

that the term "extracellular vesicles" (EVs) be used as a general term for all small vesicles/particles, including both vesicle types, and excluding only apoptotic bodies.

As a result of the above-mentioned functions, extracellular vesicles may serve as novel tools for various therapeutic and diagnostic applications, such as (a) anti-tumour therapy, (b) pathogen vaccination, (c) immune-modulatory and regenerative therapies and (d) drug delivery.

Indeed, in the last 5 years, extracellular vesicles were proven to have high targeting potential for specific cell types, but in most cases, following systemic administration, they failed to demonstrate the anticipated therapeutic results. It is well-known today that the main pre-requisites for using any type of vesicle for the targeted delivery of drugs are that: (i) they can be loaded with a sufficient amount of drug, in order to elucidate a therapeutic response; (ii) they are stable during circulation in the blood stream before reaching their therapeutic target in the body; (iii) they can avoid uptake by the macrophages and circulate for prolonged time periods so that they can reach their cellular targets; and (iv) they are biocompatible, or else non-toxic and non-immunogenic. In accordance to these requirements, the main problems identified for the successful translation of extracellular vesicles into targeted drug carriers are the following: (i) drug loading and/or retention of drugs in exosomes is not sufficient; (ii) the poor pharmacokinetics of natural extracellular vesicles when loaded with bioactive agents, and (iii) the fact that a big problem for such systems to be included in industrial roadmaps still remains, giving very low yields of isolation from biological media or cell cultures.

Due to the aforementioned shortcomings, other approaches are currently being exploited, such as the use of exosomes- or extracellular vesicle-mimetics, which are, in most cases, liposomes constructed after appropriate selection of their components in order to mimic the composition (and hopefully) the structure of organotropic extracellular vesicles.

Current Bottlenecks in Nanoparticle-Assisted Targeted Drug Delivery and Liposomes

Several types of nano-based drug delivery systems (DDSs) have been, over the last 4 decades, and are currently being considered for drug targeting applications. Among all the nano-based DDSs, liposomes—that first reached clinical approval—are the most biocompatible and least toxic artificial systems, which is logical since they are constructed by phospholipids and cholesterol, the main components of cell membranes.

Liposomes have made great impact on therapeutics due to their advantages

as DDSs. Indeed, in addition to their non-toxic and biocompatible nature that can accommodate high payloads of drugs, they have the capability of loading multiple drugs in order to provide protection of drugs from degradation, and to enhance drug endocytosis into cells. It is well known that Liposome-assisted drug delivery has a major impact on many biomedical areas, and that several liposomal formulations are proven to stabilize therapeutic compounds, overcome cellular/tissue uptake obstacles, and improve biodistribution, enabling thus the effective delivery of encapsulated drugs to target sites and minimizing their systemic toxicity.

In addition to the bottlenecks of insufficient targeting efficiency and translation difficulty due to their complexity, which have been identified for ligand-targeted liposomes, other types of targeted nanoparticles also suffer from poor biocompatibility and biodegradability, as well as immunogenicity, factors that could be resolved by exosome-based drug delivery systems. Currently, the need for superior targeted-drug carriers is further increased due to the fact that the tremendous therapeutic potential of biopharmaceuticals will become available only after formulation and delivery issues are resolved.

Additionally, the development of drugs that act on the central nervous system is presently severely hampered by the lack of efficient methods to deliver the drugs into the brain. It is well known today that only a very small fraction (<1%) of injected antibodies enter the brain by passive diffusion, while other large molecule-drugs can be only administered by peripheral injection or invasive intra-cranial procedures, approaches that failed in the clinic. The extremely challenging issue of blood-brain-barrier (BBB) crossing is an urgent need, taking into consideration the worldwide rise in neurodegenerative disorders, as well as the yet unsolved problem of treating brain cancers, both situations having at present no recognized therapeutic solution.

In addition to the approaches mentioned above, other advanced methodologies have been exploited with the aim of further increasing the targeting potential of ligand-targeted-liposomes. In this context, phage display methodologies have been utilized for the selection of high affinity ligands. Additionally, multi-targeted liposomes which can target two of more receptors simultaneously have been constructed, with the aim of increasing liposome targeting efficiency. Other approaches employ the use of physical stimuli to further increase the targeting efficiency of ligand-targeted-liposomes, such as magnetic- or ultrasound-enhanced targeting. Nevertheless, in addition to other potential problems, the multifunctional systems may be too complicated for translation into drug products, a factor that should also be

seriously taken into account when seeking solutions to the bottelnecks of actively-targeted liposomes, or nanoparticles in general.

Similarities and Differences between Exosomes and Liposomes

Exosomes have many similarities with small unilamellar, vesicle-(SUV)-type liposomes (Figure 2), which explains why most types of artificial exosome-mimetics are mainly based on liposomes. These similarities could allow researchers to engineer exosomes, using the methodologies developed in the liposome technology field. Indeed, both exosomes and SUV-liposomes, are vesicular structures consisting of one lipid bilayer, with mean diameters ranging from 50 nm to 120 nm. The major difference between SUV-liposomes and exosomes is the complex surface composition of exosomes, and more specifically, the characteristic array of membrane proteins such as tetraspanins, which are present on the membrane of exosomes, whereas SUV-liposomes do not usually have proteins in or on their lipid bilayer. These exosomal proteins are required for facilitation of their efficient targeting and uptake by recipient cells.

When comparing the advantages and disadvantages of exosomes and liposomes, with respect to their applicability as targeted-DDSs, it

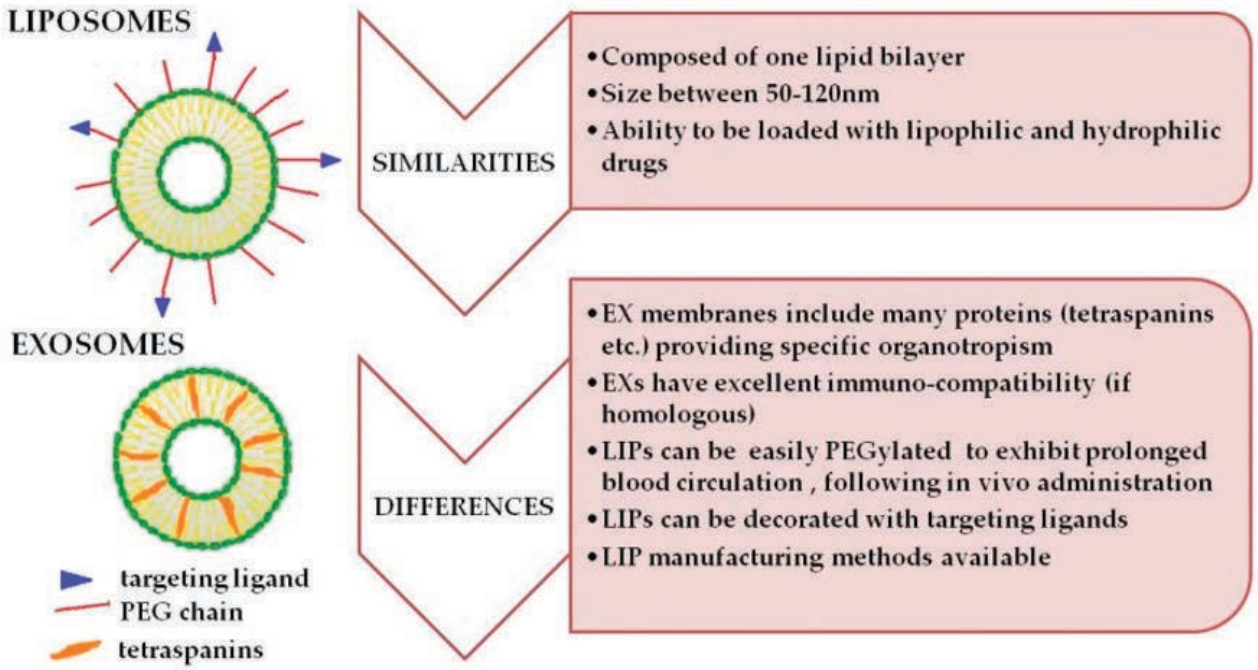
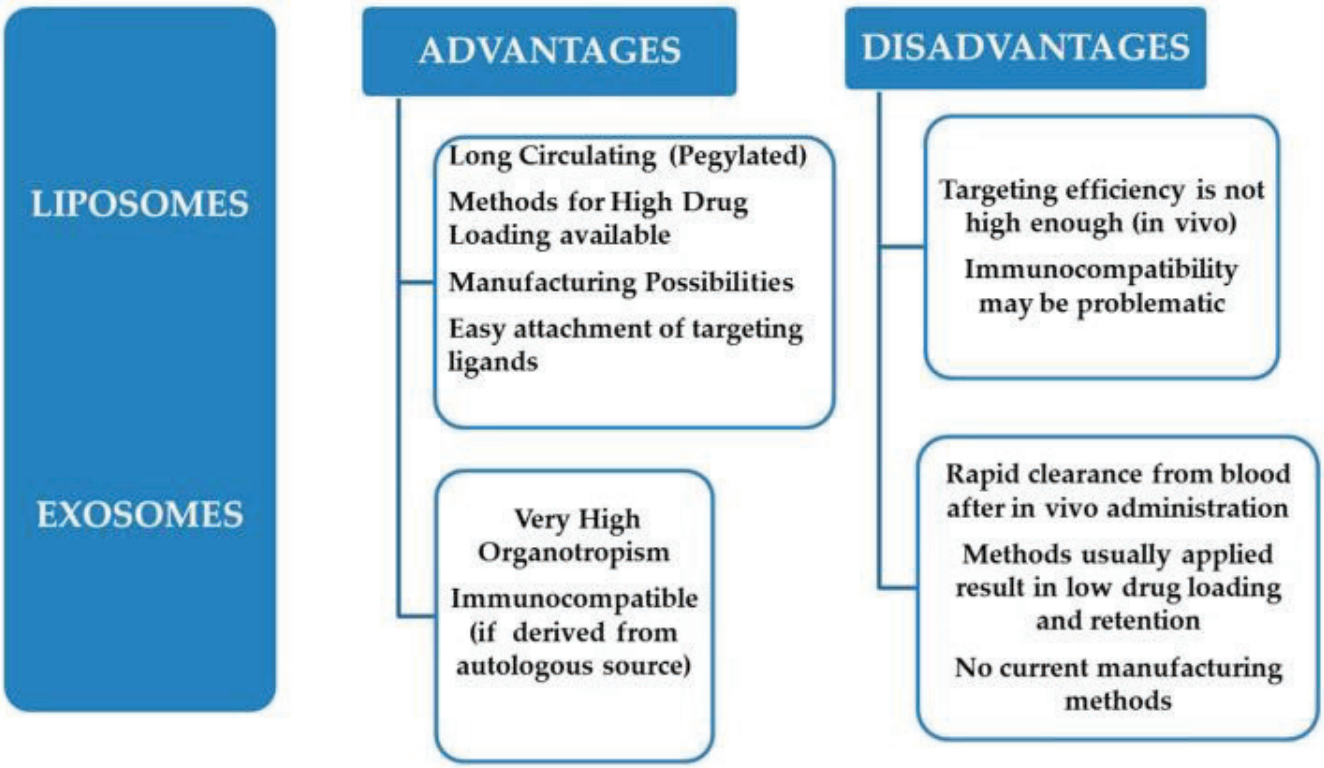


Figure 2: The basic structural characteristics, as well as the main similarities and differences of liposomes and exosomes are presented.



Scheme 2: Advantages and disadvantages of liposomes and exosomes.

becomes evident that the two systems are complimentary, since the advantages of the one system are disadvantages of the other and vice-versa (Scheme 2). Thereby, the incorporation of the advantageous features of the two vesicle types into one hybrid vesicle, if possible, would most probably result in the realization of an advanced system for drug targeting applications.

Sources, Methods of Isolation and In Vivo Clearance of Unmodified Exosomes

Sources of Exosomes

Most cell types have been demonstrated to be able to release exosomes. Most of the in vivo-detected circulating exosomes (about 80%) are derived from platelets. Mesenchymal stem cell (MSC)-derived exosomes are currently being exploited for numerous applications since they have been shown to play a role in cell-free therapy of many diseases, including myocardial infarction, drug addiction, and status epilepticus. They are also thought to be able to ameliorate liver injury, inflammation-induced preterm brain injury, and various types of cancer. Exosomes are also found in many physiological fluids.

The cellular origin of exosomes strongly determines their contents, and as a consequence, also their functions.

Exosomes which are produced by B lymphocytes contain functional MHCI, MHCII, and T cell co-stimulatory molecules, and can thus stimulate T cell proliferation. Alternatively, exosomes from cancer cells contain cell adhesion related molecules, such as gelatinolytic enzymes, and thus, they have the ability to enhance the progression and metastasis of tumors. Cancer cell-derived exosomes are actively incorporated by mesenchymal stem cells (MSCs) (in vitro and in vivo), since the transfer of exosomal proteins and miRNAs depends on the physical and functional characteristics of tumor-supporting fibroblasts.

Isolation Methods

Several methods have been developed to efficiently isolate exosomes from cells and biological fluids. Each method exploits a specific trait of exosomes, such as their size, shape, density, or surface antigens to aid isolation. However, the most challenging task of all methods employed is to specifically purify exosomes from the wide spectrum of extracellular vesicles, cellular debris, and interfering molecular components. For this reason, the quality of each batch of isolated exosomes should be examined before any further application is pursued.

In all the exosome isolation methods, the first general step is to culture parental cells in serum-free media and allow the cells to condition the media. Conditioned media is then collected and processed in different ways based on the specific isolation method applied. For bodily fluids or other types of fluids, the principle for exosome isolation is the same as when starting from cell culture conditioned medium, but because of the vicosity of some fluids, it is necessary to dilute them, and in some cases, to pre-clean them from large bioparticles, as well as to spike them with protease inhibitors in order to prevent potential degradation of the exosome proteins.

Ultracentrifugation: Ultracentrifugation (U/C)-based exosome isolation is considered as the gold standard, and is one of the most commonly used and reported techniques for exosome isolation. There are two types of methodologies based on the principles of separation: differential and density-gradient U/C.

Immunoaffinity: Immunoaffinity capture-based techniques exploit interactions between antibodies and selective exosome surface proteins in order to isolate them. Higginbotham et al. recently demonstrated the feasibility of using fluorescence-activated vesicle sorting to analyze and sort individual exosomes from DiFi cells (human colorectal cancer cells).

Other Size-Based Isolation Methods: The most popular size-based exosome isolation technique is ultrafiltration. Based on their size, exosomes can be isolated with sequential filtration using membrane

filters with defined size-exclusion limits (specific membrane pore sizes). Another size-based separation technique is size-exclusion chromatography that uses a column packed with beads that have smaller pores to those of the exosomes. Fractions are eluted sequentially in order of decreasing sizes, and exosomes can be thus isolated, from larger and smaller particles.

Precipitation: Exosomes can be isolated from biological fluids by altering their solubility. Various methods use polymers that can precipitate exosomes according to their surface characteristics.

Yield of Common Isolation Methodologies: A common aspect among isolation methods is that they all involve multistep procedures, and thus, they finally provide a low production yield and/or a low purity of exosomes. The U/C method for instance, which is currently the most classical and reliable isolation technology, can isolate only a small portion of extracellular vesicles (~20–25%). On the other hand, immune affinity methods require expensive antibodies and matrices, but finally lead to similar yields to those acquired when using U/C. Size-exclusion methods are often used in combination with U/C or other techniques, but the complex-methods finally realize low yields due to the fact that a large fraction of the (extracellular vesicle) sample is lost due to its adhesion to the gel materials or the filters. Polymeric precipitation instead might achieve a higher yield than the other methods, but cannot purify the exosomes from the polymeric material used. Altogether, the very low production yield of exosomes imposes a tremendous impediment to their utility in research, thus delaying their potential clinical translation for any type of therapeutic application.

4. Types of Systems

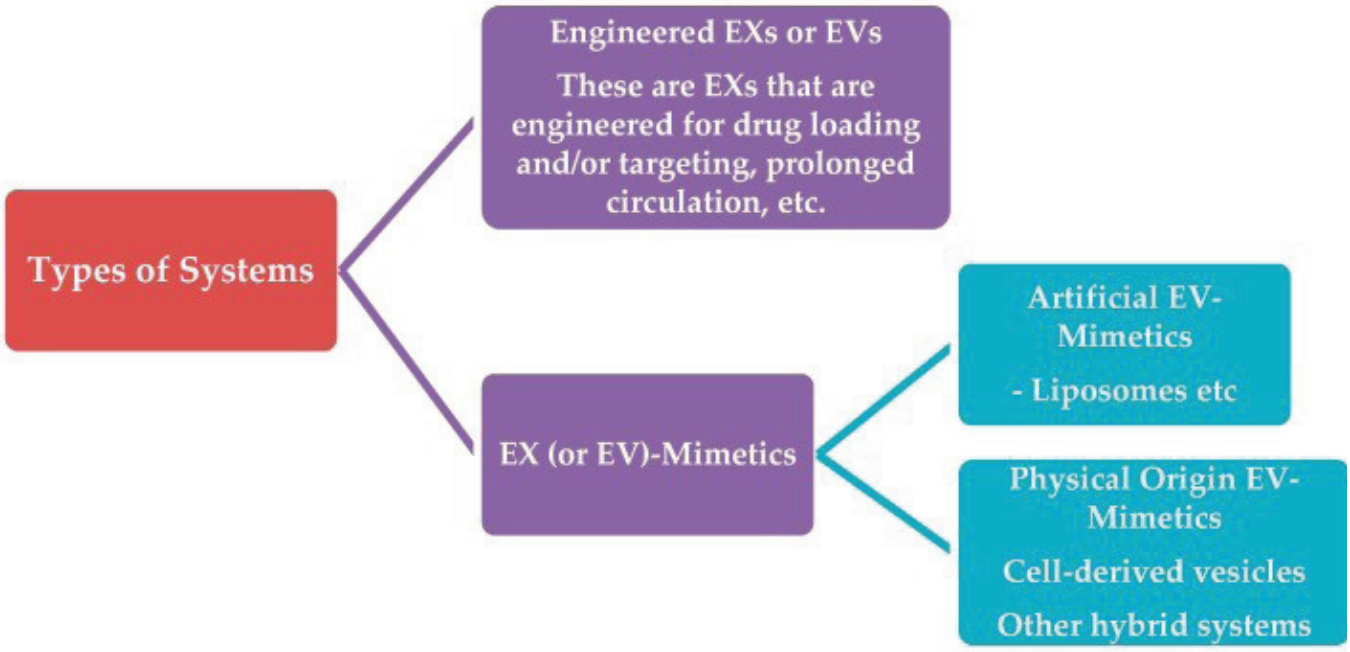
In this review, we will use the following categorization and naming for the various types of exosome-like systems which have been tested to date as drug carriers (Scheme 3).

The two main categories of exosome-evolving-vesicles that are being currently used for drug delivery will be defined as:

(1). Engineered-Exosomess or Extracellular Vesicles: This first category will include vesicles derived from isolated and purified exosomes or extracellulat vesicles.

(2). Exosome or Extracellular Vesicle-mimetics: This second category of vesicles includes all the vesicle-types that are not formed using exosomes or extracellular vesicles as their starting material. Such approaches have been explored in order to overcome the low yields of exosome isolation/purification methodologies, or to develop drug carriers for broader applicability.

Artificial Exosome-mimetics, when the starting material is of synthetic or semi-



Scheme 3: Classification of EV-like vesicles used for drug delivery applications.

synthetic origin. In most cases, artificial exosome-mimetics are actually liposomes with or without specific proteins in their membrane.

Engineered-Exosomes or Extracellular Vesicles

Several studies have exploited the potential use of extracellular vesicles for drug delivery/targeting, or, in general, for theranostic applications, after being engineered for drug loading, surface modification, or both.

Exosome (or Extracellular Vesicle)-Mimetics

As mentioned above, there are two types of Extracellular Vesicle-mimetic systems: (a) Artificial exosome-mimetics and (b) Physical-origin Extracellular Vesicle-mimetics. The main theoretical basis, and some examples of the potential applications for drug delivery of the two different types, are presented below.

Artificial Extracellular Vesicle-Mimetics

While pure populations of exosomes can be isolated from exosome-secreting cell lines, these exosomes, unlike those released from autologous primary cells, have immunogenic and oncogenic potential, inhibiting their broad use as drug delivery systems. Moreover, extracellular vesicles play multifaceted roles in health and disease, including the intercellular transfer of pathogens and disease-associated proteins, introducing major barriers for the translation of

naturally secreted exosomes to the clinic. Extracellular vesicle-mimetics may help circumvent these barriers.

Physical-Origin Extracellular Vesicle-Mimetics

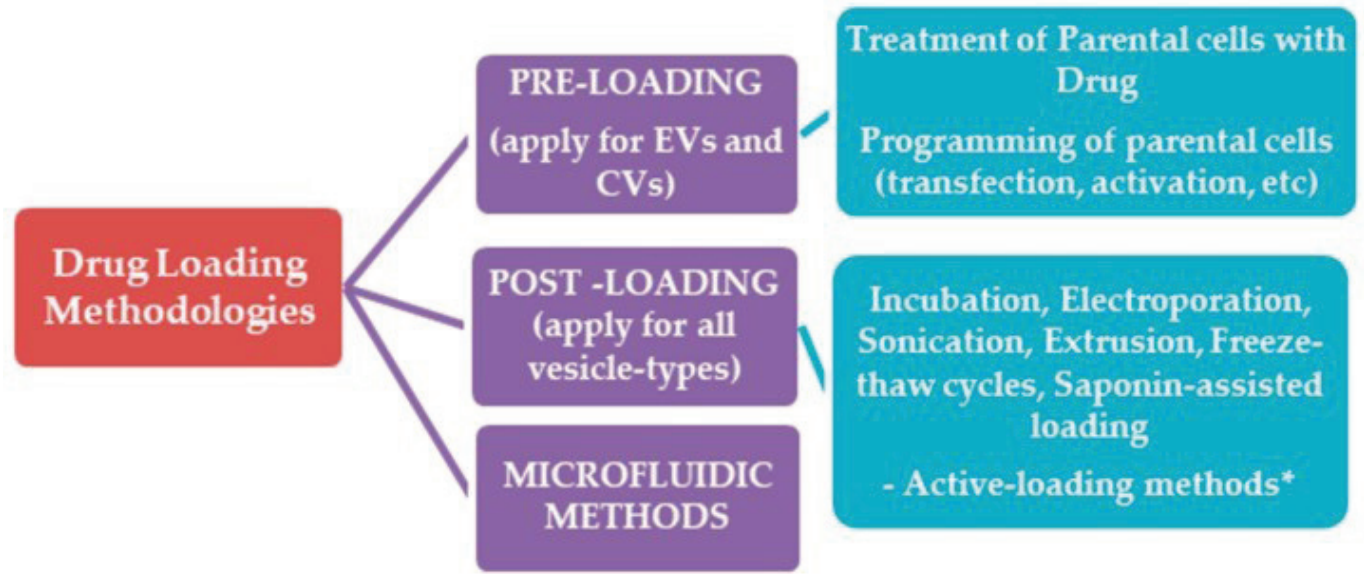
Due to the low yield of extracellular vesicle isolation from cell media or other sources, extracellular vesicle-mimetics have also been composed by using other types of physical-origin media as starting material. Most of the physical-origin extracellular vesicle-mimetics studied to date are derived from whole cells.

Cell-derived vesicles or cellular vesicles (CVs) are a new and rapidly evolving class of biological drug delivery systems. Cellular vesicles retain the surface characteristics of their parental cells, and are thus highly biocompatible with efficient intrinsic targeting ability; additionally, they don't need any further surface functionalization. This offers a clear advantage over other (synthetic) drug delivery systems. Cellular vesicles are obtained by subjecting cells to physical processes producing vesicles of nano-dimensions. Cellular vesicles are derived from the cell plasma membrane. They are composed of a lipid bilayer and have a final size between 50 and 200 nm. They are closed vesicular structures that incorporate many cellular contents from the parental cells, such as membrane proteins, intracellular proteins, and RNAs.

Methods of Preparation and Engineering of Engineered Exosomes and Exosome-Mimetics

Drug Loading Methodologies

The drug loading methodologies applied to date in the case of exosomes, and their physical mimetics (Cellular Vesicles),



Scheme 4: Categories of methods used for loading drugs into EXs and EX-like vesicles.

are categorized in two main groups, the pre-loading methods and the post-loading methods. The recently-developed microfluidic approaches are separately discussed (Scheme 4).

In pre-loading methods, the drug is initially produced or loaded in the parental cells, and thus, the extracellular vesicles or cellular vesicles isolated or produced by them are already pre-loaded with the desired drug. Such methodologies are particularly useful when oligonucleotides or proteins are to be loaded in the vesicles, in which case the cells can be programmed to produce "a-la-carte" extracellular vesicles or cellular vesicles (after applying particular cell engineering techniques).

In post-loading methods, the drug is loaded in the extracellular vesicles after their isolation. In recent years, scientists have been trying to apply high yield drug loading methods that have been used for liposome engineering, and in some cases, the loading efficiencies acquired are significantly improved

Incubation with Drug: The simplest way to incorporate any cargo into exosomes is their co-incubation, simply by mixing the isolated vesicles with the drug. The driving force for the loading is the different concentration of the drug in and out of the vesicle membrane. Hydrophobic drugs interact with the vesicles lipid layers, and the drugs diffuse into the exosome cavity along the concentration gradient.

Electroporation: By this technique, an electrical field disturbs the phospholipid bilayer of vesicles, creating small pores in their membrane, and thus allowing the passage of the drug into the vesicles. The integrity of the vesicle membrane is then recovered, resulting in the formation of drug-loaded vesicles.

Sonication: In this method, exosomes derived from donor cells are mixed with drugs and subsequently sonicated by a probe sonicator which allows the drug to flow into the exosomes due to the sonication-induced deformation of their membrane.

Extrusion: In this method, exosomes are mixed with a drug, and the mixture is loaded into a syringe-based lipid extruder and extruded through membranes with 100–400 nm porous size, at controlled temperature. During the extrusion, the exosome membrane is disrupted and vigorously mixed with the drug, resulting in drug loading into the exosomes.

Freeze/Thaw Cycle Method: In this method, drugs are mixed and incubated with exosomes at RT, and the mixture is subsequently frozen at −80 °C or in liquid nitrogen, and re-thawed at RT. This process is repeated for at least 3 cycles to ensure drug encapsulation. However, by this method exosomes, may aggregate, while the drug loading efficiency is generally lower than that of sonication or

extrusion.

Saponin-Assisted Loading: Saponin is named from the Latin "sapo" which meaning "soap"; it is a surfactant molecule that, upon incubation with exosomes, generates pores in their membrane through interactions with cholesterol, leading to increased exosomes-membrane permeability. Saponin can also assist in loading other hydrophilic molecules into exosomes.

Potential Clinical Applications of EXs and EXs-Mimetics

To date, most of the reports related with the use of exosome-like vesicles for drug delivery concern the use of exosomes derived from cells, such as cancer cells, dendritic cells, from biological fluids or from other types of sources such as milk of fruits. Most of the studies are actually early preclinical proof-of-concept studies, to prove: (i) the possibility of exosome-like vesicles being loaded with sufficient amount of drugs; (ii) their capability to retain the drug under in vivo simulating conditions; and (iii) their potential to deliver the drugs in a functional state to the target cells of interest, at higher amounts compared to the free drug or other types of nanocarriers. In several cases, in vivo studies have also been carried out in appropriate disease models, verifying the in vitro findings. The pre-clinical studies performed to date concerning the usage of exosome-like vesicles for drug delivery aim to treat several potential diseases such as different types of cancers, cardiovascular diseases, Parkinson's and Alzheimer's disease, as well as other neurodegenerative diseases, musculoskeletal diseases, kidney and diabetes-related pathologies, and others.

Challenges and Future Perspectives

The main challenges towards unlocking the potential of exosome-like vesicles, regardless of their type, towards the development of novel targeted drug delivery systems with enhanced targeted efficiency, are related to the following factors: (i) the abundance of starting material for their construction and their preparation yield; (ii) the loading efficiency of drugs; (iii) the blood circulation time, assuming that this determines their targeting efficiency; (iv) the inherent targeting efficiency of the selected system, and how this may be affected by various engineering methodologies; (v) methods/roadmaps for scalable, repeatable manufacturing.

Between exosomes and cellular vesicles, the latter seem to have several advantages for clinical applications, the most important of which are: (i) the high yield, and (ii) the simple purification processes required for their production. These two advantages may be the ones that will perhaps facilitate the construction of a roadmap for the rapid manufacturing

of engineered cellular vesicles from autologous sources for drug targeting systems.

Finally, several other issues have not yet been considered, such as the stability of engineered-exosomes, engineered-cellular vesicles, and artificial-exosomes, since it is not straightforward to predict how stable the protein parts of their membrane will be during storage. Furthermore, nothing is known about the potential to lyophilize such vesicle dispersions.

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How drug delivery can impact treatment

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The human body is complex, and while we are still learning about the impact various drugs can have on it, the search for more effective treatments for common ailments to more complex diseases is ongoing. Researchers are studying how medicines interact with and move through the human body, how much time the medicine can take to reach the affected cells and the impact those drugs may have on the surrounding healthy cells. Mr Alagu Subramaniam, Managing Director, West India, in the article expounds on how drug delivery can impact treatment.

Not every medicine will react the same way for everyone, and certain drug combinations may react with healthy tissues leading to serious side effects. In fact, this is a concern that is limiting the ability of pharma researchers as they work to develop suitable treatments for a variety of diseases. Additionally, the quantity, the time/frequency of dosage, the rate at which the drug is administered into the body, the location where it is administered and the distance it needs to travel to reach the affected area – are additional concerns faced when designing a drug. The more targeted a drug is, the lower its chance of triggering any adverse reaction or resistance, which is a serious concern surrounding the use of broad-spectrum antibiotics.

Additionally, when bringing a new injectable drug product to market, the packaging is quite important, especially considering the potential problems that can result with stability, manufacturing,

or use. In today's regulatory climate, it is essential to have a heightened awareness of all the risks that can occur, from development through lifecycle.

Keeping the above in mind, it is no surprise that over the last couple of decades, science has been focused on developing better and more effective drug delivery mechanisms.

Evolution in the landscape

As the healthcare landscape evolves and technology continues to play a greater role in both drug discovery and drug delivery, patient care is increasingly becoming an area of collaboration between healthcare professionals and the patients themselves. Other key trends in the landscape include digitization of healthcare, innovation in healthcare devices, greater reliance on data analytics, remote care becoming a reality and precision treatments.

As digital technologies find more pervasive application in the healthcare space, researchers and medical professionals find themselves in possession of valuable data not just about the patient but also about the treatments, recovery patterns and other key metrics. Artificial Intelligence and Machine Learning are making it possible to derive valuable insight from these datapoints. Innovation in design of healthcare devices is making heavy machinery portable, making it possible to take treatment to the patient's doorstep. Remote care and online consulting are now possible too, as with patients being treated at-home this would take some of the burden off the shoulders of the

overworked healthcare professionals in a country like India, where the last mile is still a challenge for healthcare services.

Patient-centric care

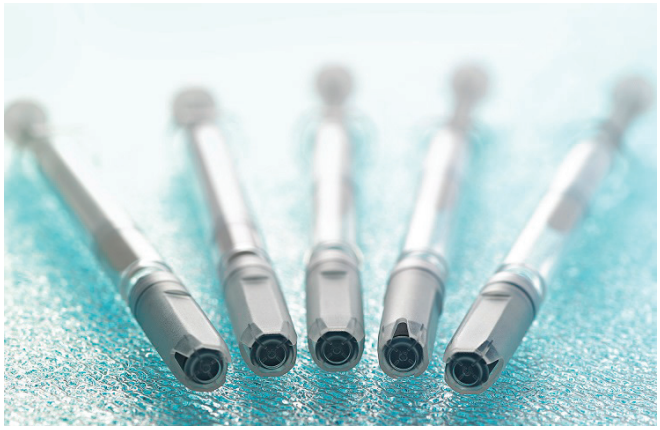
Innovations in interactive applications and technology have made it possible to provide information about health concerns and care literally at the patient's fingertips. This has led to greater participation of the patients in their own treatments.

As patients become more knowledgeable and play a greater role in their own care decisions, there is need for the drug delivery mechanisms to be simple and self-administrable. The delivery mechanism should also be designed in a way that it does not cause unnecessary discomfort to the patient and does not require extensive medical or technical knowledge to use so that the patient finds it easy to adhere to the prescribed therapeutic routine.

Improving the efficacy of delivery mechanism

Developing a new drug is an expensive and time-consuming exercise. The current thinking is that by improving the efficacy of the existing drugs, better results can be achieved from the same treatment at a much lower investment and time cost. As a result, pharma industry is giving equal importance to different means of drug delivery, that can then have a marked impact on the treatment cycle such as dose titration as well as therapeutic drug monitoring. Delivering the dose at a controlled rate and targeted delivery are goals that are being pursued by the pharma packaging manufacturers.

In fact, there are many drugs that are capable of effectively treating various health concerns. However, it may be possible that these drugs are limited by delivery issues or bring with them side effects that need to be mitigated. This is exactly what has been driving the researchers to find better and more effective delivery mechanisms. For example, at present the drug delivery routes that are garnering increasing amount of interest include nasal and pulmonary routes. They are being explored to see if they can provide promising alternatives to drug delivery compared to routes such as parenteral, that require the use of a needle, syringe, or an intravenous infusion set. Parenteral route is usually taken when the medication is poorly absorbed internally by the body or when enzymes deactivate it as it passes through the digestive tract.



Additionally, for treatments that require regular injections, manufacturers are evaluating alternative injection platforms that reduce the need for use of IV in large volume doses. Case in point being the SmartDose® Platform. Drug therapies are only effective when patients follow a prescribed treatment. For those suffering from chronic conditions, daily or even weekly injections can cause pain and fatigue, resulting in patient non-adherence. New options in biologic therapies have enabled single-dose options, but those options require higher dose volumes administered over a long period of time. Such was the case with a cholesterol-lowering drug offered by one of West's customers. While a once-a-month dose could work, effective delivery of the large-volume dose posed a challenge.

The SmartDose® platform of wearable injectors allows patients to self-administer large volumes of medication in accordance with their prescribed treatment over a longer period of time. Extensive human factors testing and analysis was undertaken to understand the interaction between the patient and the delivery system while designing this platform. The SmartDose injector adheres to the patient's body, usually on the abdomen, so the patient can be hands off during administration. The injector comprises of a silicone-free Daikyo Crystal Zenith® cartridge and a FluroTec ® coated piston containment system.

Delivery challenges faced when it comes to new drugs

The legacy challenge

In the case of new drugs coming to the market, in particular biologic drug products, many manufacturers use legacy components for packaging, i.e., components they have used over time and with other drug products. This is based on the assumption that packaging components are inert, or that issues can be overcome by reformulation. These legacy components appear to offer the benefits of known performance and supply chain and resultant smooth production with minimal downtime. But legacy components may not meet the quality and regulatory standards of today, which require understanding of potential risks for each individual pairing of drug product and Container Closure System (CCS). In particular, an understanding of the factors that impact protection, compatibility, safety, and performance, is required.

Pace of innovation adoption

Although the industry is very interested

in innovations, its ability to adopt them is quite slow.

One might argue that the barriers to innovation adoption lie in the drug R&D process itself, particularly in the way that scientists and engineers relate to supporting functions such as information technology, intellectual property, legal, procurement/supply chain, operations, regulatory and quality assurance. This challenge, coupled with the frequent lack of clarity as to decision making ownership, and the normal risk aversion due to potential regulatory challenges, is central.

Components may be part of a combination product

Historically, the industry has been focused on the drug product and package – not the delivery device. Therefore, there was limited understanding of the technical, developmental, and regulatory requirements to meet current combination product best practices, which means combining both the drug and device CGMP regulations. Failure to do so can put many products at risk from the standpoint of regulatory approval.

Failure to Understand Special Challenges of New Molecular Entities

There is a growing complexity to the molecular entities in the industry's pipeline. Many manufacturers, who had focused on small molecule drug products, are expanding into large molecule biologics, such as monoclonal antibodies (mAbs). mAbs comprise the majority of biologics both in development and already commercialized. This pipeline is becoming more diverse, with the emergence of therapies based upon technologies such as gene, siRNA, oligonucleotides or stem cells. There may be unique needs for these new drug products, and packaging/delivery requirements (sensitivities, storage/delivery) may be quite different from those of small molecules or mAbs. Thus, it is essential that the starting point for all packaging be the needs of the molecular entity – to ensure suitability and ultimately safe delivery to the patient.

Manufacturers today are paying greater attention to delivery mechanisms – be it for existing or new drugs – for the role they can play in drug impact on treatment. ■

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