Smart Nanomaterials Technology

Santosh Kumar Rath · Vagish Dwibedi ·
Azamal Husen · Nadeem Akhtar *Editors*

Nanomaterials for Drug Delivery and Neurological Diseases Management

Springer

Smart Nanomaterials Technology

Nanotechnology is a rapidly growing scientific field and has attracted a great interest over the last few years because of its abundant applications in different fields like biology, physics and chemistry. This science deals with the production of minute particles called nanomaterials having dimensions between 1 and 100 nm which may serve as building blocks for various physical and biological systems. On the other hand, there is the class of smart materials where the material that can stimuli by external factors and results a new kind of functional properties. The combination of these two classes forms a new class of smart nanomaterials, which produces unique functional material properties and a great opportunity to larger span of application. Smart nanomaterials have been employed by researchers to use it effectively in agricultural production, soil improvement, disease management, energy and environment, medical science, pharmaceuticals, engineering, food, animal husbandry and forestry sectors.

This book series in Smart Nanomaterials Technology aims to comprehensively cover topics in the fabrication, synthesis and application of these materials for applications in the following fields:

- Energy Systems—Renewable energy, energy storage (supercapacitors and electrochemical cells), hydrogen storage, photocatalytic water splitting for hydrogen production
- Biomedical—controlled release of drugs, treatment of various diseases, biosensors,
- Agricultural—agricultural production, soil improvement, disease management, animal feed, egg, milk and meat production/processing,
- Forestry—wood preservation, protection, disease management
- Environment—wastewater treatment, separation of hazardous contaminants from wastewater, indoor air filters.

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ISSN 3004-8273 ISSN 3004-8281 (electronic)
Smart Nanomaterials Technology
ISBN 978-981-97-0307-4 ISBN 978-981-97-0308-1 (eBook)
https://doi.org/10.1007/978-981-97-0308-1

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

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Preface

World Federation of Neurology (WFN) has shown keen interest in the environment and its relation to neurological diseases. In 2018, WFN promoted the awareness of environmental challenges with the slogan 'Clean Air for Brain Health' on World Brain Day. A survey made by the collaboration of WHO and WFN noticed that neurological disorder in the world is a global burden of disease and environmental pollution is a major threat in increasing neurological diseases burden in the world. Several drugs as used in Oncology, Neurology and Psychiatry in recent times but none of them can promise the complete curing of Epileptic, Alzheimer or Parkinson's diseases. However, the side effects seem to be more day by day. Epilepsy and seizure disease is the most common serious chronic neurologic disease, affecting more than 50 million people of all ages, genders, ethnic backgrounds, and geographic locations worldwide. Hence to improve therapeutic effects and reduce their side effect active drug molecules accumulate in the disease site for a prolonged period with high controllability. Drug delivery approaches and nanoformulation technologies are much more acceptable for transporting therapeutics in the body safely and can achieve the desired therapeutic effect. At present, the nanomaterial-based drug delivery vehicles are really helpful in finding new routes of administration by diverse nano-based formulation techniques as targeted therapy for the treatment and management of neurological disorders.

This book aims to provide necessary information on the current scenario of different neurological diseases and is also well focussed to depict how the present nano-drug delivery approach is the best alternative solution of treatment to specific neuro or brain diseases. This book also intends to motivate researchers and the general public to align themselves towards sustainable growth through modern delivery techniques.

This collective work is distinct because of our focus on diverse nano-based drug delivery technologies which are high-throughput, reliable, pioneering, and applicable to researchers of different countries despite their socio-economic conditions. Our book will enliven the up-to-date technologies and ideas, and should invoke researchers and innovators to take ahead the current inter-disciplinary knowledge

for more advancement and effective management of various neurological problems which is a serious global issue. This Book will improve the current state of knowledge and should invoke researchers and innovators to take ahead the current inter-disciplinary knowledge into technologies that are readily available and effectively minimize hazards associated with neurological disorders. Chapters have been divided into three main sub-sections.

(A) A fundamental study on nanomaterial-, nanocarrier- and nanoformulation-based drug delivery in neurological diseases management.
(B) Nano-drug delivery therapy—a novel approach towards common neurological disorders.
(C) Novel nano-delivery strategies in targeted neurological diseases management.

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Editors and Contributors

About the Editors

Santosh Kumar Rath is a medicinal and natural product chemist with more than 10 years of experience in research, academia, and industry. Rath received his doctorate from AcSIR at CSIR-Institute of Minerals and Materials Technology (CSIR-IMMT), Bhubaneswar, India. Presently he is working as Assistant Professor in Pharmaceutical Chemistry at the Department of SoPPHI, Faculty of Pharmacy, DIT University, Dehradun, Uttarakhand, India. Formerly, he worked as an Associate Professor and Research Head at the Department of Pharmaceutical Chemistry, Danteshwari College of Pharmacy, Jagdalpur, Chhattisgarh, India (2020–2022). He also worked as Research Associate (CSIR-RA) in the School of Chemistry & Biochemistry at Thapar Institute of Engineering & Technology, Patiala, India (2018–2020). He received Research Associateship from CSIR in 2018 and Senior Research Fellowship (ICMR-SRF) from ICMR, New Delhi, India in 2013. He did research at the CSIR-Indian Institute of Integrative Medicine (CSIR-IIIM), Jammu, India. He has many publications to his credit, published more than 32 research papers in highly reputed international journals, as well as 10 book chapters three edited books, and 2 Indian patent. His area of research is Natural Product Chemistry and Organic Synthesis, in which he is expertise in the isolation, identification, and characterization of bioactive secondary metabolites, and structural modification of major chemical constituents

from plants as well as fungal sources. He is acquainted with various chromatographic techniques such as column, Preparative TLC, and HPLC for separating and purifying compounds. He is well aware of the interpretation of spectroscopic data, viz., 1D and 2DNMR, MASS, IR, etc. His research involves multistep synthesis of biologically active synthetic and/or natural product-based hybrid scaffolds for lead identification in special targets for neurological disease, cancer, HIV, Covid-19, and infectious diseases. His research mainly focuses on synthesizing novel P-gp and bacterial efflux pump inhibitors, besides synthetic modifications of the bioactive natural products for better activity/minimize toxicity profiles. Currently, he is developing new synthetic methodologies for the C-H functionalization of heterocycles and other medicinally relevant molecules. He contributed substantially to many research projects and is also having collaborative research work with many other research groups. The contributions, dedication, and brilliance of Dr. Rath in the area of natural product drug discovery and organic synthesis are truly commendable. His contributions aim to serve as an inspiration to all scientific fraternity and inculcate scientific temperament to others to think innovatively.

Vagish Dwibedi did his B.Sc. from Lucknow University, Lucknow, Uttar Pradesh, and Ph.D. from Thapar Institute of Engineering and Technology, Patiala, India. Dwibedi is an academician and researcher with more than 8 years of experience in biotech research and development. He has carried out research projects and consultancy work in the areas of plant-microbe interaction/bioassay-guided drug-discovery and development, food security/sustainable agriculture and waste water treatment. Presently he is working as Assistant Professor at University Institute of Biotechnology, Chandigarh University, Gharuan Mohali, Punjab. Formerly, he was worked as Research Scientist at Agpharm Bioinnovations LLP incubated at Thapar Institute of Engineering & Technology, Patiala, India. He was also Winner in Down select competition-DST-Lockheed Martin-Tata Trust_IIGP 2.0 (2k18) (India Innovation Growth Programme 2.0) Innovation ID: IIGPUIBSUNB (The award carries financial support up to 25 Lac INR.). His work is directed towards the development

of screening platforms for different biological activities such as anti-microbial, anti-oxidant, anti-cancer, or finding novel molecules that interfere in the mechanism of development of diseases such as Alzheimer Dementia (AD), Parkinson disease (PD), Obesity, Anti-gout (arthritis) and type 2 diabetes. He is also interested in food security, which predominantly involves the exploitation of plant-microbe interaction to combat abiotic stress and post-harvest preservation to enhance the shelf life of fresh crop/horticulture produces. He has published more than 25 research papers in various national and international journals and published 2 Indian patent.

Azamal Husen is presently working as a Professor at Sankalchand Patel University, Visnagar, India; and Adjunct Professor at Graphic Era (Deemed to be University), Dehradun, Uttarakhand, India. He is also working as an Invited Professor at University Putra Malaysia, Selangor, Malaysia. Previously, he served as Professor and Head of the Department of Biology, University of Gondar, Ethiopia; and worked as a Foreign Delegate at Wolaita Sodo University, Wolaita, Ethiopia. He also worked as a Visiting Faculty of the Forest Research Institute and the Doon College of Agriculture and Forest at Dehradun, India. His research and teaching experience of 25 years encompasses biogenic nanomaterial fabrication and application; plant responses to nanomaterials; plant adaptation to harsh environments at the physiological, biochemical, and molecular levels; herbal medicine; and clonal propagation for improvement of tree species. He has conducted research sponsored by the World Bank, the National Agricultural Technology Project, the Indian Council of Agriculture Research, the Indian Council of Forest Research Education, and the Japan Bank for International Cooperation. Husen has published extensively (over 250) and served on the Editorial Board and as reviewer of reputed journals published by Elsevier, Frontiers Media, Taylor & Francis, Springer Nature, RSC, Oxford University Press, Sciendo, the Royal Society, CSIRO, PLOS, MDPI, John Wiley & Sons, and UPM Journals. He is on the advisory board of Cambridge Scholars Publishing, UK. He is a fellow of

the Plantae group of the American Society of Plant Biologists, and a member of the International Society of Root Research, Asian Council of Science Editors, and International Natural Product Sciences. He is Editor-in-Chief of the *American Journal of Plant Physiology*, and a Series Editor of *Exploring Medicinal Plants* (Taylor & Francis Group, USA); *Plant Biology, Sustainability, and Climate Change* (Elsevier, USA); and *Smart Nanomaterials Technology* (Springer Nature, Singapore). He has been achieved the distinguished honour of being recognized as one of the "World's Top 2% Scientists" for the year 2022, and again for the 2023 by Stanford University, USA. This recognition has also been prominently featured in the Elsevier Data Repository.

Nadeem Akhtar a scientist, is currently making significant strides in the animal health and longevity sector for a leading Canadian company, CBS Bio Platforms Inc. His impressive background demonstrates that he has held a variety of important positions in academia and research throughout his career. Akhtar was a Research Associate at the University of Guelph, Canada, where the objective of his work was to improve companion animal's health in order to promote a superior and more health-conscious lifestyle. Prior to assuming this position, he excelled as a postdoctoral researcher at the Department of Chemical Engineering, University of Waterloo, Canada (2019–2021) and the Department of Animal Biosciences, University of Guelph, Canada (2015–2019). His accomplishments in the National Eligibility Test (NET-2010) and Graduate Aptitude Test (GATE) in Life Sciences (2010) and Biotechnology (2011) further emphasize his academic excellence. He earned his Ph.D. from the esteemed Department of Biotechnology at the Thapar Institute of Engineering and Technology in India. His scientific contributions are nothing short of remarkable, with over 27 articles published in peer-reviewed international journals as well as 12 book chapters and two edited books. His abilities extend to patent accomplishments, as he has one granted patent to his name. In addition to his research, he has shown his dedication to knowledge advancement by serving as a reviewer for prestigious journals such as RSC Advances, the Journal of Applied Microbiology, Scientific Reports, and Poultry Science. His career exemplifies dedication and

excellence, demonstrating his invaluable contributions to the fields of animal science and biotechnology. His journey continues to motivate and shape the global scientific landscape.

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Abbreviations

AChE	Acetylcholinesterase
ALS	Amyotrophic Lateral Sclerosis
APIs	Active Pharmaceutical Ingredients
APP	Amyloid Precursor Protein
ASOs	Antisense Oligonucleotides
AuNPs	Gold Nanoparticles
BBB	Blood-Brain Barrier
BCSFB	Blood-Cerebrospinal Fluid Barrier
BM NPs	Biogenic Magnetic Nanoparticles
BMP	Bone Morphogenetic Protein
CAA	Cerebral Amyloid Angiopathy
CDR	Controlled Drug Release
ChAT	Choline Acetyltransferase
CNS	Central Nervous System
CPP	Cell-Penetrating Peptide
DDS	Drug Delivery Systems
DMTs	Disease-Modifying Treatments
DWCNTs	Double-Walled Carbon Nanotubes
ECM	Extracellular Matrix
EGCG	Epigallocatechin-3-Gallate
EGFR	Epidermal Growth Factor Receptor
EOF	Ease of Functionalization
GABA	Gamma-Aminobutyric Acid
GSS	Gerstmann-Straussler-Scheinker Syndrome
IONP	Iron Oxide Nanoparticle
LCST	Lower Critical Solution Temperature
LFS	Large and Functional Surfaces
MAPT	Microtubule-Associated Protein Tau
MBP	Myelin Basic Protein
MPS	Mononuclear Phagocytic System
MSNs	Mesoporous Silica Nanoparticles

MWCNTs	Multi-Walled Carbon Nanotubes
NFAT	Nuclear Factor of Activated T Cells
NFTs	Neurofibrillary Tangles
NMDAR	N-Methyl-D-Aspartate Receptor
NMR	Nuclear Magnetic Resonance
NTB	Nose-to-Brain
PEG	Polyethylene Glycol
PICALM	Phosphatidylinositol-Binding Clathrin Assembly Protein
PNIPAM	Poly(N-isopropylacrylamide)
PPMS	Primary Progressive Multiple Sclerosis
PTDs	Protein Transduction Domains
RMT	Receptor-Mediated Transcytosis
SAVR	Surface Area-to-Volume Ratio
SLNs	Solid Lipid Nanoparticles
SORL1	Sortilin-Related Receptor 1
SPIONs	Superparamagnetic Iron Oxide Nanoparticles
SPMS	Secondary Progressive Multiple Sclerosis
TDD	Transdermal Drug Delivery
TfR	Transferrin Receptor
TLE	Temporal Lobe Epilepsy
TLR9	Toll-Like Receptor-9
TREM	Triggering Receptor Expressed on Myeloid Cells
TRH	Thyrotropin-Releasing Hormone
VEGF	Vascular Endothelial Growth Factor
αSN	α-Synuclein
β-CD	β-Cyclodextrin

A Fundamental Study on Nanomaterials, Nanocarriers and Nanoformulation-Based Drug Delivery in Neurological Diseases Management

Nanocarriers for Drug Delivery: General Characteristics

Devendra Sillu, M. Sudhakara Reddy, and Shekhar Agnihotri

Abstract The escalating pace of disease transmission has prompted scientists to embark on innovative approaches to enhance the therapeutic efficacy of modern drugs. Several barriers present in the human body limit the overall efficiency of directly administrated therapeutics. The heterogeneous nature of these barriers across patient populations presents another crucial obstacle to designing a universal solution. The concept of precision therapeutics, which involves tailoring interventions based on the individual patient's pathology, has gained considerable attention but lacks practical affordability on a global scale. Nanomaterials have gained significant attention as potential drug delivery systems owing to their exceptional properties, including high drug loading capacity and ease of administration. However, the administration of any foreign materials, including nanomaterials, may activate the inherent immune response to clear out them. To bypass the defence system and deliver drug molecules at specific target sites, nanomaterials with specific physicochemical properties have been utilised. An in-depth understanding of physicochemical characteristics of nanomaterials is imperative for developing effective nanocarriers capable of surmounting both physical and biological hurdles, ultimately leading to enhanced therapeutic outcomes. The present chapter provides a comprehensive overview of the most frequently encountered barriers in utilizing nanomaterials as drug carriers, ranging from physical to biological hindrances. The chapter elucidates how manipulating the physicochemical attributes of nanocarriers can serve as a powerful tool to circumvent these barriers, leading to improved drug delivery efficacy. Finally,

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S. K. Rath et al. (eds.), *Nanomaterials for Drug Delivery and Neurological Diseases Management*, Smart Nanomaterials Technology,
https://doi.org/10.1007/978-981-97-0308-1_1

the future prospects of employing nanocarriers in drug delivery applications are discussed.

Keywords Nanocarriers · Drug delivery · Barriers · Physicochemical properties · Modifications

1 Introduction

Multiple factors such as lifestyle changes, environmental degradation, aging population, and genetic predisposition have contributed to an unprecedented surge in life-threatening diseases. This has concomitantly increased the demand for active pharmaceutical ingredients (APIs), leading to a significant rise in the production of drugs [1]. Drugs are employed for diagnosis, prevention, cure, or mitigation of harmful diseases to restrict the causalities incurred. Drugs can be designed to affect the structure or functions of the body part affected by these diseases in a target specific manner. The direct administration of drugs however pose many challenges e.g. limited solubility, uncontrolled release rate, lower viability, and low tissue/cell specific actions [2]. Advanced therapeutics based on peptides, proteins, oligonucleotides, and DNA constitute an important class of APIs to treat life-threatening diseases due to their ability to target specific cellular pathways, exhibit high potency, and low toxicity. These APIs too exhibit low bioavailability and are prone to degrade in biological fluids [3]. Conventional drugs used widely for oral or injectable administration have a critical drawback in terms of optimal formulation [3]. The general approach to improve their bioavailability is through increasing the surface area per particle. The size reduction process, however reduces the API's performance especially in case of biomolecules. In addition, smaller drug particles are extremely difficult to stabilize and isolate. Moreover, this strategy does not prevent biomolecules from enzymatic and acid-catalyzed degradation.

The use of non-therapeutic structures as delivery vehicles for drugs is a viable strategy to improve their bioavailability and shielding from body fluids-led degradation [4, 5]. These carriers are biocompatible tools assisting the transport of molecules for pharmaceutical, cosmetic, and nutraceutical applications to specific targeted sites [6]. These carriers provide controlled drug release, enabling the dose precision as per the respective medical need. Specific drug delivery systems are designed which are capable of targeted and regulated release of drugs, hence improving the overall effectiveness of the drug for intended tissues/cells [6]. The delivery of specific therapeutic concentration of drug to the disease causing cells while preserving its biological viability is of utmost importance when selecting any drug carrier. Commonly investigated drug carriers include liposomes, niosomes, polymeric micelles and microparticulates [7, 4].

Drug delivery systems are generally classified based on the interaction between drug and carrier or their release style. For instance, in the matrix drug delivery system, the drug is released through pores of matrix [8]. The semipermeable membrane acts

as key controller in case of reservoir systems [9], while degradation of the material is the major drug releasing mechanism in degradable drug delivery systems [10]. The release of drug under the influence of osmotic pressure change instigates the unloading of the concerned drug in osmotic pump systems [11]. The type of drug delivery system is dictated via the choice of material used for design of drug delivery system. The selection of an appropriate material with unique physicochemical properties presenting it as a biocompatible and efficient carrier for drugs is the most crucial step for the system to move on to the implementation techniques and clinical trials steps.

The conventionally used drug carriers often have associated implications such as limited biodistribution, and intracellular trafficking issues [12]. Nanotechnology could help overcome the limitations of conventional drug delivery systems in a systematic manner [13, 12]. Engineered nanomaterials have demonstrated noteworthy potency to improve disease diagnosis and treatment specificity [14]. A wide range of nanomaterials (Inorganic, Organic and Polymer-based) have been investigated for designing of drug delivery systems [12]. This chapter focuses on the key aspects associated with nanomaterials that help them to overcome different physical and biological barriers, presenting them as a viable option instead of conventional drug delivery systems.

2 Nanomaterial as Drug Carriers

Efficacy of drugs delivery systems is directly correlated with the particle size; therefore nanomaterial carriers with appropriate size can easily enhance their effectiveness. Nanomaterials owing to their unique intrinsic properties such as high surface to mass ratio, high loading capacity, and quantum properties have been employed for designing of drug delivery systems [15]. The primary goal for using nanocarrier systems is to attain the following goals in drug delivery:

- Faster delivery of drug
- High specificity for disease causing cells/tissues
- Reduced toxicity
- Superior biocompatibility and viability.

Owing to their small size and large surface area, nanocarriers demonstrate increased solubility resulting in enhanced bioavailability. The small size of nanocarriers facilitates the transportation of these carriers through various barriers [16].

Taking into consideration that nanomaterials, be it synthetic or natural, are considered as foreign particles by the human body, hence understanding how the body reacts when nanoparticles comes in contact with the cells/tissues is most important [17, 15]. Effective biodistribution and targeted delivery is a difficult task as drug carriers have to clear both physical and biological barriers which include shear forces, protein adsorption and clearance by the immune system [18]. These barriers restrict the efficacy of the carriers to reach the targeted therapeutic site and release of drug. The

state of these barriers is often different in healthy and ill individuals as well as for different individuals, further making it difficult to generalize the carrier.

2.1 Barriers in the Way

The barriers faced by nanocarriers depend on various factors such as the route of administration, physicochemical properties of nanocarriers, disease type, and disease stage [19]. The administration route of nanocarriers is a major factor that can influence the biodistribution. This may also amend the final fate and efficacy of nanocarriers. Numerous studies in the recent past have explored the role of administering means on the overall impact of nanocarriers. Local delivery method though can overcome some of the key barriers; however, their on ground execution is limited due to the involvement of invasive procedures and complex techniques. Moreover, local delivery methods are generally preferred in diseases where the exact target sites are known such as solid cancers or traumatic injuries. Systematic administration on the other hand is a preferred approach where pathology is unable to detect the exact target site [20].

The nanocarriers can be introduced in the human body via direct injection, inhalation or oral intake. Oral delivery methods are widely used for drug administration, however, in case of nanocarrier based targeted delivery the gastrointestinal tract acts as a barrier limiting their efficiency [21]. In case of oral administration, nanocarriers generally rely on endocytosis and subsequent exocytosis to cross the gastrointestinal tract. Nanocarriers with passive diffusion act as a major releasing mechanism, and the passage through the endothelium is limited by concentration gradients and P-glycoproteins.

Inhalation has also been reported to improve delivery of nanocarriers. Different types of pulmonary administration such as intratracheal instillation, intratracheal spraying and intranasal instillation, result in different rates of nanocarrier accumulation and heterogenous distributions [22]. These administration methods avoid exposure to systematic circulation, thus bypassing hepatic first-pass metabolism and accumulating effectively in lung and lymph node as compared to intravenous delivery [23]. Despite their advantages, inhalation of nanocarriers is not considered as a full proof administration method as it is affected by the physical barriers such as mucus and pulmonary surfactants. The unpredictable levels of these physical barriers across patients depending upon the concerned disease also restrict the application of this approach [24, 25]. Intranasal administration has been explored for nanocarriers loaded drug delivery to the brain, as it bypasses the blood–brain barrier (BBB) and limitation associated with systematic administration [26]. Factors including dose volume, patient condition, and mucus are some of the key obstacles to the intranasal route [27, 28]. There is a dire need to further optimise these methods to formulate proper administration route with consistency and accuracy.

Most of the clinically approved nanocarriers are either intratumourally or intravenously administered, however alternative routes must be explored to deliver better

efficacy [29, 17]. In a nutshell, knit picking an optimal administration route might result in more desirable distribution which would definitely improve the targeting ability and specificity of nanocarriers.

After entering the systemic circulation, nanomaterial-protein interaction is the forefront line of defence system before movement to different body parts [30]. Clearance of nanocarriers from blood circulation happens by interaction with the mononuclear phagocytic system (MPS) or reticuloendothelial system [19, 31]. The phagocytic cells i.e., macrophages take up nanocarriers and accumulate them in the spleen and liver [32, 18]. Interaction with MPS, apart from resulting in clearance of nanocarriers can also cause toxicity as these cells trigger immune response resulting in inflammation or tissue damage [33, 34]. During circulation mechanistic parts such as excretion, blood flow, and coronas also have significant impact on the overall efficacy of the nanocarrier [14]. The impact majorly depends on the physiochemical properties of the nanocarrier used.

Once in circulation, extravasation is the first step for a nanocarrier to reach the intended target site [35]. Extravasation can be altered by changing the physicochemical properties of the nanocarriers. Adsorption via blood capillaries facilitates the distribution of nanocarriers in the lymphatic system. The key functions of this process include fluid recovery which involves filtration of fluids from blood capillaries. Another function is to impart immunity via eliminating dangerous entities. While recovering the excess fluid, the system also picks up foreign objects (cells, chemicals, drugs etc.), and when these fluids are introduced into the blood stream, the lymph nodes detect foreign objects, and macrophages will engulf and clear it from the body. This function tends to be a critical issue while administrating drug via nanocarriers.

The haemodynamics experienced by nanocarriers also significantly influence the distribution and drug delivery. After entering the human body, nanocarriers experience fluctuating flow rates of bloodstream which might induce shear stress [36, 37]. This could result in damaging the carrier structure and releasing drug abruptly before reaching the target site. These strong forces can also strip the surface coatings/functionalities and prevent nanocarriers from interaction with vessel walls, thus eliminating the chance to reach the target site [19, 35].

Local distribution of nanocarriers is gravely affected by the additional barriers such as biofilms and mucus [21, 38]. Mucus is basically a polymeric slimy substance, where the distances between the neighbouring polymer links control the mesh pore size. The mesh size can vary from 10 to 1000 nm, hence size selection of nanocarriers becomes a key aspect while intending for specific applications [38]. The characteristic features such as composition, mesh size, hydration thickness of the mucus barrier and viscoelasticity fluctuate throughout body depending on its physiological location making it a complex environment for nanocarrier delivery. In addition to filtration based on size, mucus can also trap nanocarriers via non- specific interactions, resulting in rapid clearance from epithelial surfaces [21].

Physical barriers which limit the efficiency of nanocarriers for drug delivery include tight junctions among the endothelial and epithelial cells of the BBB (in intravenous delivery) and the gastrointestinal tract (in oral delivery) [39]. To influence

central nervous system (CNS), nanocarriers need to use receptor-mediated endocytosis by endothelial cells of the BBB [40, 31, 34]. However, heterogeneity of plasma membrane transporters on endothelial cells, present a hurdle for nanocarriers to cross BBB [41]. Some of the highly expressed transporters such as glucose transporters help nanocarriers transport to attain some common target sites [42]. However their efficiency to deliver appropriate dose of drug loaded varies. Overall, the BBB is seen as a great obstacle for systemically administered nanocarriers to reach targeted cells of CNS [43].

Even after reaching the target site, nanocarriers have to face the local microenvironment, where change in chemical conditions or formation of physical barriers could influence their physical properties and the drug release profile. For example, the gastrointestinal tract has areas of extreme pH and presence of specific enzymes that might induce the degradation of nanocarriers [21]. The gastrointestinal microenvironment depends on the diet, disease states, and patient pathologies, resulting in unpredicted reaction with the nanocarriers in different individuals [44]. Variation of pH in case of tumours also hinders the general formulation of universal nanocarriers [45]. Specific nanocarriers have been developed in recent times that are environment responsive [39, 46]; such nanocarriers can be used after earlier contemplation of the local microenvironment.

Apart from the general barriers, cellular heterogeneity also has impact on the overall efficacy of the nanocarrier [47]. The cellular variations within different organs/target sites and among patients depend on the characteristics of an individual. Younger cells are capable of anchoring high concentration of nanocarriers as compared to older cells. Furthermore, drug-resistant cells add on to the cellular heterogeneity that makes nanocarrier delivery even complex. Both cell type and phenotypes results in cellular heterogeneity creating diverse barriers for nanocarriers. The innovative nanocarriers design approaches can assist in surpassing these unavoidable barriers.

In case of solid tumours, the vasculature, interstitial fluid pressure and extracellular matrix (ECM) density may act as barriers limiting the permeation and penetration of nanocarriers [19, 48, 49]. The microenvironment of the tumour dictates the final fate of nanocarriers, such as heterogeneous vasculature which might facilitate nanocarrier accumulation via the leaky vessels a phenomenon often referred to as the enhanced permeation and retention (EPR) effect [50]. The heterogeneity of vasculature depends on the individual patients' factors such as age, genetics, lifestyle and even previous antitumour treatments [50, 51, 34]. Hence to select an appropriate nanocarrier for the tumour, individual patient must be assessed for determining the potential of EPR effect. Reports have suggested that mechanisms such as immune cell interactions, protein coronas and molecular mechanisms also play important roles for nanocarrier accumulation in tumour [52]. Furthermore, tumour microenvironments might instigate cells' overproduction or generation of altered ECM components that result in a dense ECM which physically hinders nanocarrier delivery [49]. Specifically tagged nanocarriers can be used to assess the level of the EPR effect at the tumour site.

Additionally, decreased interstitial fluid drainage in tumour vasculature prevents nanocarrier perfusion. The increased intertumoural interstitial pressure in such cases

averts most tumour cells from interacting with nanocarriers [48, 33]. Limited perfusion is also an obstacle for nanocarriers used for delivery in brain, as even after crossing the BBB nanocarriers often fail to permeate the tissue because of the limited extracellular space and non-specific adherence to the ECM [53, 54].

Over the time, various modifications in the characteristic features of carrier nanomaterials have been investigated to improve the efficacy of nanomaterial based drug delivery [19]. The key characteristics having the most significant impact on the fabrication of efficient nanocarrier systems are discussed below.

2.2 Impact of Shape and Size

The morphological attributes i.e., size and shapes are the key parameters which influence the perspective of the defence system towards the nanocarrier used. The overall loading and release profile of drugs are directly influenced by the by the size; as particles' size get smaller, their surface area to volume ratio gets larger resulting in higher loading of drug. Moreover, in case of smaller particles the drug molecules would be closer to the surface of the particles that would lead to faster drug release [55]. Hence, utilizing nanoparticles with higher surface area to volume ratio are preferred as drug carriers; however, toxicological aspect of these carriers must be monitored. As discussed previously, the size of the nanomaterials dictates their biological fate, as the immune system (vascular and lymph systems) filters out the foreign particulates. Particles with size >200 nm activate the lymphatic system and are removed from circulation quicker [56]. Whereas, nanocarriers with overall size less than 10 nm are eliminated by the kidneys [57]. Hence, considering the reported literature nanomaterials of size around 100 nm are optimum carriers for high drug loading, passing the BBB and deliver sufficient amount of drug.

Previous studies have demonstrated that particles of 100 nm size have 2.5 fold higher uptake by the cell system as compared to particles with 1 μm diameter. The uptake gets even shortened with increase in particle size as a particle of 10 μm exhibits 6 times lesser uptake by the cells [58]. These parameters also affect the distribution, toxicity and targeting ability of the nanocarrier system inside the human body. For instance, it's because of their ultra-small size that they are capable to pass through the blood brain barrier (BBB), and deliver medication for diseases that were previously difficult to treat [43, 26]. These parameters can be easily moulded in case of nanomaterials providing an edge over other delivery methods. This also provides opportunity to realize new targets and more control over drug distribution.

Distribution of nanocarriers in organs is a size-dependent phenomenon, as small nanocarriers can easily cross capillary walls, contrary to large size nanocarriers [34, 18]. Highest accumulation of nanocarriers is often found in the liver and spleen [19, 57]. In some cases, size-dependent distribution of nanocarriers is also affected by the pathological environments. One such case is the presence of larger intracellular gaps in tumour vasculature, where even large nanocarriers can easily transport through

the gap [18]. Overall, extravasation results in a non-specific distribution of nanocarriers, and this presents a translational challenge for applications that require specific localization of nanocarriers.

With respect to the haemodynamics factor, large size particles (microscale) have rather high probability of localizing to the vessel walls, and non-spherical particles demonstrated greater margination with the adhesion of white blood cells to the walls of damaged blood vessels [35]. Shapes such as ellipsoids, discoid shapes and nanorods with higher aspect ratios have demonstrated superior localization to blood vessels than spherical shapes [35, 42, 59]. The key reason behind this phenomenon is flow-induced rolling of different shapes, which is equally affected by the aspect ratio of the particle [19]. This might seem as the appropriate choice at this point that non-spherical particles with high ratio can resolve all the issues; however architecture dependent drag forces can still rip nanocarriers from the cell membranes if they lack binding affinity [60].

Nanocarrier curvature and aspect ratio are also important features for selection of appropriate nanocarrier. Shape variation can be a viable approach for avoiding uptake by phagocytic cells as triangular and rod-shaped nanocarriers are frequently captured by phagocytic cells as compared to star shaped or spherical nanocarriers [61, 62]. On the other hand, rod shaped nanocarriers are reported to cause more inflammation in macrophages [63].

In case of oral administration, smaller nanoparticles might avoid transport across the epithelial barrier and perform intestinal permeation through tight junctions [64]. Nanocarriers with large surface area are considered for oral route as there are increased numbers of interactions with the gastrointestinal tract, which would facilitate the efficient delivery of the drug [65]. The nanocarriers with size around 100 nm are reported to be optimal for gastrointestinal applications as compared to lower or higher size [65, 66–69]. Rod shaped nanocarriers generally perform better than spherical shaped nanocarriers, credited to the fact that rods internalize into epithelial cells efficiently as compared to spheres [70, 71]. However, only this aspect does not ascertain effective delivery as only a small portion of these nanocarriers undergo exocytosis [72].

2.3 Impact of Surface Properties

Surface characteristics of the carrier can also influence the performance of nanomaterial-based drug carriers [73]. The interaction of drug molecules with the nanomaterial surface can be easily controlled by surface functionalization of nanomaterials, such as introduction of specific groups or targeting ligands. These functionalities prevent aggregation, improve biodistribution, increase stability, and instil efficient receptor binding, thus improving the overall pharmacological effects of the drug [74, 75]. Incorporation of reactive sites is another class of modifications that can improve the overall efficiency of the nanocarrier.

While selecting the surface properties, the first and foremost important aspect to consider is the safe entrance of the nanocarrier into the human body. Since, nanomaterials can be easily recognised by the defence system as a foreign entity, they will be flushed out as the body's natural immune response. Hydrophobic particles have high affinity towards blood components and are thus easily cleared out by the lymphatic system [76]. Considering this simple point, using hydrophilic particles for drug delivery is considered as a viable option, as they will remain in the human system for a longer period of time, thus increasing their chances to attain the set goals. Coating the nanomaterials with polymers or surfactants has been widely used technique to modulate the hydrophilic nature of the nanocarriers. Various polymers such as polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamine, and polysorbate 80 have been used for such applications [77, 78].

PEG is a relatively inert hydrophilic polymer which inhibits the binding of plasma proteins that may induce degradation, secretion and clearance. Furthermore, PEGylation prevents the drug leaching from the nanocarrier and improve circulation time by altering the solubility. This feature presents the PEGylated nanomaterials as relatively stealth, however this does not completely prevent recognition by macrophages or other cells of the immune system [79, 80, 14]. Prior PEG exposure can prompt the production of anti-PEG antibodies that can induce rapid flushing out of PEGylated nanomaterials [81, 82]. This means even the first dose of PEGylated nanocarriers might not be able to circulate for a long period [83, 84]. They are also reported to contribute to uncommon but severe allergic reactions [85, 86].

Although the safe entry of drug nanocarrier can be envisaged by practise of various approaches, however the aggregation of these nanocarriers inside the human body is yet another critical issue that requires undivided attention. Owing to their large surface area, nanomaterials tend to agglomerate under physiological conditions. As discussed before, the administration route of nanocarriers directly influences their final fate, for example polymeric nanocarriers injected intravenously accumulate primarily in the liver and spleen, whereas if subcutaneously or intranodally injected, they are more likely to accumulate in local lymph nodes [87]. These approaches can be used in several immunotherapeutic applications where there is an immediate need to deliver drug to the lymphatic system thus avoiding the systemic circulation [88]. Nanomaterials such as dendrimers, quantum dots, and micelles form agglomerates easily as compared to others. Scientists have developed strategies to restrict aggregation, such as coatings with capping agents, and alteration of zeta potential [51].

The overall charges on the nanocarriers also affect the clearance from blood circulation. The immune system tends to rapidly clear out cationic nanocarriers as compared to anionic or neutral nanocarriers [19, 41]. The cationic nanocarrier may anchor to the negatively charged tumour ECM, reducing the permeation of nanocarriers [89, 18]. Stiffer nanomaterials are highly prone towards the clearance mechanism associated with the mononuclear phagocytic system (MPS) or reticuloendothelial systems [90, 91].

While circulating in the blood stream the interaction between the nanocarriers and biomolecules present in the blood is inevitable. The interaction with these