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The potential of magneto-electric nanocarriers for drug delivery

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Abstract

Introduction—The development and design of personalized nanomedicine for better health quality is receiving great attention. In order to deliver and release a therapeutic concentration at the target site, novel nanocarriers (NCs) were designed, for example, magneto-electric (ME) which possess ideal properties of high drug loading, site-specificity and precise on-demand controlled drug delivery.

Areas covered—This review explores the potential of ME-NCs for on-demand and site-specific drug delivery and release for personalized therapeutics. The main features including effect of magnetism, improvement in drug loading, drug transport across blood-brain barriers and on-demand controlled release are also discussed. The future directions and possible impacts on upcoming nanomedicine are highlighted.

Expert opinion—Numerous reports suggest that there is an urgent need to explore novel NC formulations for safe and targeted drug delivery and release at specific disease sites. The challenges of formulation lie in the development of NCs that improve biocompatibility and surface modifications for optimum drug loading/preservation/transmigration and tailoring of electrical–magnetic properties for on-demand drug release. Thus, the development of novel NCs is anticipated to overcome the problems of targeted delivery of therapeutic agents with desired precision that may lead to better patient compliance.

Keywords

drug delivery; magneto-electric nanocarriers; nanocarriers; therapeutic agent

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Declaration of interest

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1. Introduction

The challenges in favorable drug delivery include the attainment of tunable release profiles, biocompatibility and the confinement of therapeutic action to diseased sites. Recently, attention has been focused toward the nanoscale manipulation of drug-delivery systems offering unique properties for navigation of drug-vehicle and controlled drug release, which is often not achievable in conventional- (e.g., free-form) and microscale-drug carriers. Since the advent of drug-nanotechnology, nanomedicine is continuously seeking a targeted drug delivery approach that can possess maximum therapeutic capabilities with minimum side effects. Thus, the design and development of drug carrying nanoparticles (NPs) (nanocarriers [NCs] ~ 100 nm) is the central focus for therapeutic application [1–9]. The NCs are surface-engineered nanostructures that are used for single and multiple drugs loading and safe delivery in a controlled way [10,11]. Efforts are being made to understand higher drug-loading mechanism with on-demand controlled release at disease-specific site with fewer adverse effects [2,12]. Such engineered NCs are capable of carrying the drug safely in a precise way during the course of therapy for the effective treatment. However, the complexity of pathways and navigation tools limit their potentials for controlled delivery and the on-demand release of drug. These challenges open up novel methods for investigating NCs to achieve efficient drug delivery to cure diseases, referred to as Nano-Cure [3]. On the basis of advancements in science of NCs, Mitragotri and Lahann summarized the drug delivery prospects of NCs and proposed them as an innovative solution to address complex biological hurdles for drug delivery systems [13]. Figure 1 summarizes the types of NCs, for example, polymers [14–26], metal–metal oxide NPs [27–32], core–shell NPs [33], quantum dots NPs [34–36], hybrid nanocomposites [33,37], organic–inorganic frameworks [38–40] and novel structures like microneedles [41]. The advancements in the design of nanoscale stimuli-responsive systems that are capable of controlling drug bio-distribution in response to appropriate stimuli and controlled *via* exogeneous/endogenous mechanism are explained by Mura *et al.* [42]. Figure 2 illustrates suitable stimuli-responses NCs for drug delivery. However, the released drug from NCs–drug formulation in the bloodstream results in possible binding of the drug with unspecific sites. This causes drug concentration loss at active target site and leads to unwanted side effects and decrease in the efficacy of the formulation. These challenges can be overcome *via* designing multifunctional NCs of desired electrical, optical and magnetic properties to achieve target-specific delivery for on-demand drug release. NCs should possess good biocompatibility (immune-clearance) and ability to cross blood-brain barrier (BBB) for therapeutic application at CNS [43–46]. It has been proven that the choice of NC materials and its surface modification to architect the formulation are crucial in achieving high drug loading, proper navigation and controlled drug release with the proper selection of stimuli-response.

This review focuses on the design and development of novel magneto-electric (ME) NPs as potential drug delivery NCs to achieve above-mentioned undertakings. Recently, magneto-electric NCs (ME-NCs) have adopted for on-demand controlled drug delivery/release system because both magnetic and electric fields of ME-NCs can be coupled at body temperature and can be tuned/controlled in physiological condition. ME-NCs possess

potentials of on-demand and site-specific delivery of drug, proteins, genes and other compounds (small molecules) into the target cells and organs for therapeutic purposes. These NCs can be explored for *in vitro* diagnostic and monitoring tool for better health quality. The optimization of physical, chemical and molecular properties of ME-NCs helps in minimizing the side toxicity of payload drugs. Precise and on-demand localized drug release can be of great clinical importance to treat NeuroAIDS, cancer and other chronic conditions in CNS.

The salient features of ME-NCs such as site-specific delivery and on-demand controlled drug release on external magnetic and electric stimulation across the BBB are also highlighted in this review. The future prospects of ME-NCs to develop a robotic platform system-based compartmentalization needed for personalized dosage on disease requirement are also highlighted. Next section explores potential applications, advancement and limitations of magnetic NCs (M-NCs) in the fields of drug delivery.

2. Magnetic NCs for brain delivery

Nanomedicines for therapeutics have opened exciting prospects for drug delivery systems due to their ability of target (cells/organs) specific delivery and release. Among NCs, magnetic NPs (M-NPs) are extensively utilized drug delivery NCs due to their unique properties such as magnetic hyperthermia, and controllable movements and MRI contrast agent [47–53]. The favorable drug delivery properties of M-NPs are their stealth surface chemistry, high drug-loading capacity, multiple functionalities and optimal particle sizes (10 – 100 nm). Sagar *et al*. have explained the possible drug release mechanism of drug-loaded M-NCs upon external stimulation such as thermal responsive, optical responsive, pH responsive, enzymatic catalysis and acoustic activation [2]. M-NCs-based molecular transport has been adopted as modern approach to increase delivery with reduced toxicity in many fields that is, cardiology, ophthalmology and oncology. As recent advancements, efforts are being made to deliver drug at neuronal level across the BBB. The delivery of therapeutic agents across the brain is very limited and until now technologies to adjust their pharmaco-distribution have remained restricted. Hence, there is a need to develop the novel strategies for site-specific delivery of therapeutic agents across the intact BBB with minimal toxicity remains a challenge in the field.

Advances in material science for controlling magnetic properties, size and shape of M-NCs *via* adopting novel synthesis routes expand the protocol toward developing efficient therapeutic agent to cure diseases. The introduction of external magnetic force-based trigger for drug delivery and controlled release in the brain is the recent investigation. In this approach, the speed and time for drug delivery is estimated on applying external magnetic field. Several experts reported the potentials of M-NCs for the advance drug delivery and proposed M-NCs as excellent personalized nanomedicine carriers. Pilakka-Kanthikeel *et al.* showed an *in vitro* study using M-NCs for targeted brain-derived neurotropic factors (BDNF) delivery across the BBB. Delivering BDNF helps in preventing the HIV-related neurotoxicity and disease progression in case of NeuroAIDS [54]. Authors developed Fe_3O_4-NCs for binding with BDNF and assessed efficacy and ability to transmigration across the BBB using an *in vitro* BBB model. The outcomes of this study suggested that

transmigrated BDNF is effective in suppressing the morphine-induced apoptosis, inducing response element-binding expression and restoring the spine density. Such developed NCs may provide a potential therapeutic approach to treat opiate addiction, protect neurotoxicity and synaptic density degeneration [54]. Ding *et al.* developed a novel transferrin-embedded fluorescent multifunctional liposomal magnetic NCs formulation to enhance BBB transmigration [55]. A dual mechanism that includes receptor mediation combined with external noninvasive magnetic force incorporated into homogenous magneto-liposome (~ 100 nm) was used to improve delivery across BBB. The magnetic-liposome formulation demonstrated improves delivery across BBB than traditional methods [55]. Authors also suggested the need of *in vivo* studies to clarify the related mechanism of dual transportation for the successful application of these NCs in various CNS diseases [56].

An integrated mircorobotic system based on functionalized M-NCs for on-demand and targeted therapeutic intervention is developed by Fusco *et al.* [57]. This robotic system consists of drug-loaded magnetic alginate microbeads encapsulated by near-infrared responsive (NIR-785 nm) hydrogel. Protective hydrogel layer provides protection to magnetic–alginate compartment and also rapidly opened on NIR exposure (~ 40°C). This protocol is based on controllable trigger mechanism for on-demand release of biomolecule at specific target, wherein NIR penetrates body tissue without side effect at repeated doses. The utilized magnetic carriers help in navigation in the body, and developed prototype can be used for drug delivery [57]. The assembly, design and manipulation of nanorobotics for medicine applications using NCs have been explored [58–60].

However, phase change of M-NCs on interaction with biological moieties causes drug loss during transport and limits its applications of on-demand drug release in *in vivo* model. M-NCs-based delivery methods release drug in uncontrolled manner in response to patho-physiological changes (pH, temperature, etc.) or *via* body defense mechanism (exocytosis of drug-enclosing intracellular vesicle). Hence, there is a significant scope to develop new M-NCs of properties that can be controlled using external magnetic or electric forces, and are capable of on-demand drug release at target organ. Next section explores ME-NCs and their application in the field of on-demand controlled drug delivery and release for personalized nanomedicine.

3. Magneto-electric nanocarriers

The challenges and future prospects related to M-NCs-based drug delivery systems are the motivation to design and develop novel materials, and such of one is ME NCs. ME-NCs exhibit dual effect (magnetic and electronic) and therefore possess both ferroelectric and ferromagnetic parameters in a single phase and unable to couple with other parameters to exhibit novel properties, that is, ME effect [61]. This phenomenon allows the control of magnetization and electrical polarization in a single phase. Energy conversion from magnetic to electric takes advantage of piezoelectric properties of the ferroelectric phase and piezomagnetic properties of the ferromagnetic phase [61–63]. Key advantages of ME-NCs over M-NCs are structurally compatible, high stability (chemical, thermal and mechanical) and easy preparation. In general, ME-NCs are core shell structures, wherein a magnetic core is preserved with a shell of desired electrical properties [64–66]. The control on core size

and thickness of the shell enables the fine adjustment of the structure and phase fraction of the ME-NCs formulation, ensuing in materials with tunable properties and reproducible features. The synthesis of core–shell NPs is conventionally carried out in two successive steps: i) the precipitation of the ferrite NPs; and ii) the creation of a shell around each NP. Along with drug delivery, ME nanostructures due to above-mentioned unique properties have been used in transduction, spintronics, optical devices and sensors. Moreover, ME-NCs are dissipation-free, energy-efficient and low-field on-demand targeted drug release can be achieved by applying low remote ME field [64,65]. However, ME nanostructures can be of inorganic–inorganic nano-composite and organic-metal oxide frameworks [37,52]. ME-NCs enable a new dissipate ion-free mechanism to force a high-efficacy externally controlled drug release process at the subcellular level using remote low-energy direct current and/or alternating current (a.c.) [67].

The non-zero magnetic moment of ME-NCs can be controlled on applying an external magnetic field that offers an energy-efficient control of the intrinsic electric fields within the NPs. Our group at Center of Personalized Nanomedicine @FIU explored ME-NCs for safe delivery and on-demand controlled release of anti-retroviral (ARV) drug across BBB using low energy a.c. magnetic field to control the a.c. electric signals [56] and also for noninvasive artificial stimulation of the neural activity deep in the brain for Parkinson's disease [68].

For the first time, Dr. Nair's group in collaboration with Dr. Khizroev explored the use of computational technology in predicting the artificial stimulation of neurons using the ME-NCs in deep inside the brain [68]. Yue *et al.* demonstrated this concept and proposed this noninvasive technique that couples neuronal electric signals to the magnetic dipoles of ME-NCs. The established protocol is of use for noninvasive stimulating the patient brain with Parkinson's disease to bring the pulsed sequences of the electric field to the levels comparable to those of healthy people. Simulation results predicted that ME-NCs concentration of 36×10^6 particles/cc with size of 20 nm and frequency (80 Hz) of the externally applied magnetic field (300 Oe) can give us the desired effects [68]. Field-controlled ME-NP drug formulation showed a unique capability of field-triggered release across BBB due to intrinsic magnetoelectricity. On applying external magnetic field, the electric forces in drug-NCs bonds enable remotely controlled delivery due to coupling of ME properties [68]. The application of ME-NCs for filed-controlled site-specific and on-demand drug delivery with possible delivery and release mechanism is discussed in next section.

4. Potentials of ME-NCs in drug delivery

ME-NPs are exploring for field-controlled drug delivery and on-demand release application. ME-NCs can be synthesized in different size and shape depending upon the use and target organ that is, spherical core–shell NPs (magnetic core and an electric shell) or rods with a piezoelectric coating (concentric magnetic/piezoelectric tubes) or composite sphere (piezoelectric ceramics or piezopolymers with surrounded M-NPs). Only few reports are available on ME-NCs-based drug delivery and other biological-related applications.

Researchers explore the electromagnetic property of ME-NPs for learning the voltage-gated ion channels. Ion channels are primary targets for pharmacological agents for therapeutic purposes, and cellular responses to various chemical stimuli, for example, drugs, can be investigated in relations of their influence on ion channels [69]. There is a need of highly specific and targeted delivery of anti-neoplastic drugs for cancer therapeutics or CNS disease.

The controlled electric field of ME-NCs *via* external magnetic field can be explored to exploit the intrinsic properties of the cell membrane. Ion channels present on cell membrane are kind of electrically polarized medium that can be affected by the applied electric field. This property explored to open up the pores of cell membrane on applying electric field. The porosity of the cell membrane is found to be dependent of applied electric field. Guduru *et al.* used this field-controlled nano-electroporation (the scale down of electroporation to nanoscale is referred as nano-electroporation) technique for drug delivery using magnetic filed activated ME-NCs loaded with anticancer drug inside the tumor cell. Drug-loaded ME-NCs are capable of to generate enough localized field needed to open up the cell membrane pores for the penetration of NCs and drug release on changing field without causing heat. Authors explored nano-electroporation *via* using $CoFe_2O_4@BaTiO_3$ (30 nm) ME-NCs for controlled and targeted drug delivery to eradicate ovarian cancer. A physical concept is explored based on the differences in the electrical properties of tumor cell membrane, healthy cells membrane and the capability of ME-NCs converters of remote magnetic field energy into the ME-NCs intrinsic electric field energy. An *in vitro* model on human ovarian carcinoma cell (SKOV-3) and healthy cell (HOMEC) lines was used for the proof-of-concept using electroporation technique (cell membrane-dependent electrical method to trigger drug delivery into the cells). Results showed that an electric field > 1000 V/cm creates pores of appropriate size for the penetration of nanoformulation through the cell membrane. Drug-loaded ME-NCs ($CoFe_2O_4@BaTiO_3$) penetrated through the membrane on applying 30 Oe to trigger highly specific uptake of paclitaxel and completely eradicated the tumor within 24 h without any side effect [64]. A field-controlled gate generated on interaction between ME-NCs and the electric system of the membrane allows the drug-loaded ME-NCs into the tumor cells as depicted in Figure 3. Proposed scheme highlights the nano-electroporation methodology using ME-NCs and drug release pattern. The potential of cancer cell is lower than that of healthy cell, likewise the threshold field (H_{th}) for drug-loaded ME-NCs is lower in case of cancer cell than healthy one. Using simple isotropic expression that is, DP (induced electric dipole field) = αH (external magnetic field), the ME coefficient (α) is calculated as~ 100 mV cm^{-1} Oe^{-1}, which can be obtained at small magnetic field (~ 100 Oe). On applying appropriate magnetic field (100 Oe), the drug-loaded ME-NCs penetrate the cell membrane via electroporation and further drug can be released from ME-NCs on increasing field to critical value that is, $H_{r.}$ To achieve the high-efficacy uptake, H_r should be higher than H_{th}. For the specificity of uptake to the cancer cell, the value of applied external field H_A should be higher than H_{r_cancer} and lower than that of $H_{th\_healthy}$.

Another potential application of ME-NCs was explored by Nair *et al.* for anti-HIV drug delivery. Authors used ME-NCs for successful on-demand delivery of ARV drug across the

BBB for the prevention of NeuroAIDS [65]. The proposed mechanism of drug loading and on-demand release under the effect of external magnetic field is illustrated in Figure 4. Results of using *in vitro* model demonstrate on-demand release of azidothymidine 50-triphosphate (an anti-HIV drug) using $CoFe_2O_4$@$BaTiO_3$ (30 nm) NPs was achieved *via* application of low a.c. magnetic field across the BBB. Authors proposed that this platform technology of on-demand drug delivery can be used for other CNS diseases treatment, where deep tissue high efficacy at subcellular level is needed [65].

The main principle of drug release lies in the breaking of all bonds between drug and ME-NCs formulation uniformly and efficiently on applying an a.c. magnetic field. AZTTP binds *via* electrostatic interactions to the ME-NCs, which have an original ionic bond (zero fields with charge Q ionic). On applying non-zero field, a non-zero electric dipole moment ($\Delta P = \alpha H$, where α-first-order ME coefficient and H-magnetic field) is generated within ME-NCs. The value of the dipole charge surface density on each side of ME-NCs would be of the order of $\sigma_{ME} \sim \pm H$ (opposite sides of the dipole). This modulated dipole moment results in breaking of the original symmetry of the charge. On increasing the magnetic field more threshold value, the dipole charge density of each side of ME-NCs becomes comparable that is, $\sigma_{ME} \sim Q_{ionic}/\pi d^2$, that is, $\sigma_{ME} \sim Q_{ionic}/\pi d^2 \alpha$ (d = diameter). In this way, the bond in the direction of applied field is broken and bond at the opposite side got strengthened [65]. For the next-generation on-demand drug released technology, an array of coils can be used to generate a.c. fields with nonzero phase shifts with respect to each other. The proposed schematic of ME-NCs-based drugs delivery across the BBB is shown in Figure 5. The salient features and capabilities of ME-NCs for safe and on-demand target-specific drug release in comparison of M-NCs are summarized in Table 1.

5. Conclusion

In summary, this review highlights the contribution of ME-NCs for specific and targeted drug delivery toward the development of nanomedicine. The ease of surface modification and tuneablilty of electric/magnetic properties of ME-NCs make them suitable for high drug loading, desired navigation and on-demand release, proven their advantages toward the development of nanomedicine for therapeutics. To retain magnetic and electrical properties of ME-NCs during transport and release deemed to explore new materials chemistries such as core–shell ME and metal–organic frameworks-based NCs. Also, these modified NCs have the potential to transport the drug across the BBB and thus can be used to deliver therapeutic agent in the brain. As concluding remark, we purpose that the potential therapeutic and diagnostic impact of innovative and novel ME-NCs is highly significant not only for HIV, cancer, Parkinson’s disease and Alzheimer’s disease but also in other CNS diseases, where the ability to remotely controlled drug release and diagnostics is the key.

6. Expert opinion

The ability of NPs to precisely control the release of payloads externally (on-demand) without depending on the physiological conditions of the target sites has the potential to enable patient and disease-specific nanomedicine. Important characteristics including particles size, surface engineering, toxicity and BBB transmigration ability of ME-NCs need

further development for better navigation and precise drug release on-demand at target location without loss of drug payload for personalized nanomedicine. Further, ME-NCs can be used for development of noninvasive deep brain stimulation toward the treatment of many neurological disorders such as Parkinson's, Alzheimer's, dementia and so on. But to achieve these tasks, there is a need to develop better understanding of intrinsic electrical/ magnetic property of ME-NCs on application of external magnetic and electrical field and the effects of ME-NCs interactions with blood/tissue/organ during navigation. The highlighted features to formulate drug delivery nanosystem are feasible *via* exploring novel chemical/ physical synthesis routes for desired surface functionalization or modification to achieve efficient target-specific on-demand delivery and release without drug loss.

As proof-of-concept, ME-NCs have shown on-demand drug release at disease target location. For example, ME-NCs-based therapeutic agent has been demonstrated to cure HIV and ovarian cancer. However, these studies are limited to *in vitro* model and must be explored for real application. Therefore, efforts should be accelerated to prove the potential of ME-NCs as therapeutic agent utilizing *in vivo* model. For further developments, the interrelated challenges to improve the potentials of ME-NCs-based drug delivery both *in vivo* and *in vitro* include better biocompatibility and less cytotoxic-ity. Many *in vitro* and *in vivo* studies already have been conducted to evaluate the toxicity of several types of metal-oxide NPs for example, TiO_2, Fe_3O_4, MoO_3 and so on, have been studied [70]. Results showed that lower doses (10 – 50 μg/ml) have found no significant toxicity effect on the cells *in vitro*, while there was a profound effect at higher levels (100 – 250 μg/ml). Literature shows that the toxicity effect is a function of concentration and chemical composition of NPs. In case of ME-NPs to date, no studies have been performed that address the possible toxic effects of these multifunctional NPs. Nonetheless, our results showed that low concentration on ME-NPs does not show any toxicity *in vitro*; however, the complete profile of toxicity is still underway using different *in vitro* and *in vivo* cytotoxicity models. Intensive studies are being carried out for evaluating the effect of physiochemical properties (e.g., surface area, surface composition, ionic charges, roughness and surface area) of ME-NCs with respect to peripheral and CNS toxicity. Also, additional investigation needs to be carried out for: i) assessing internalization and intracellular distribution of NPs that may contribute to the toxic effects observed in mice model; ii) studying target organelles (e.g., brain and gut) involved with neurotoxicity; and iii) evaluating the neuro-behavioral studies to understand the toxic effect. However, evidence around toxicity of metal oxide and heavy metals NPs continues to increase, a significant knowledge gap still exists on a complete toxicological profile of these NPs. Hence, there is a need to develop novel nanomaterial with magnetic and electric properties without the use of toxic heavy materials to have better biocompatibility and lower cytotoxicity.

For quality monitoring, novel signaling transduction/ imaging pathway can be introduced with drug delivery systems. These ME-NCs have potentials to be used as contrasting agent for MRI and M-NP imaging to map neuronal activities of the brain (irrespective of its origin, i.e., superficial or deep tissue). However, existing techniques (electroencephalogram and magneto-encephalogram) only record the neuronal activities in the superficial tissue (cortex) but not in the deep brain tissues. ME-NCs-based development can be integrated with a

robotic system to develop an on-demand and site-specific controlled drug release technology using above-mentioned external stimulus. *In vivo* experiments to perform intramuscular and intravenous or oral delivery using novel formulation of ME-NPs as nanovehicles will be of great significance. The presented review explores the delivery and release of disease-specific medicine through an innovative cross-disciplinary exploration in the fields of therapeutics and nano-engineering. The capabilities of novel ME-NCs enable distinctive blend of significant functions such as energy-efficient/dissipation-free magnetic-field-controlled targeted drug delivery and on-demand release with high-specificity three-dimensional diagnostics toward the development of personalized nanomedicine.

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Article highlights

- On-demand controlled release of sufficient drug at disease target site is needed to develop personalized nanomedicine for better health quality.
- Magneto-electric nanocarriers (ME-NCs) can be used for energy-efficient field-controlled targeted drug delivery and on-demand release with no heat dissipation and unprecedented high efficacy.
- ME-NCs can be used for application of neuronal activation in the brain and also as contrasting agents (for MRI and MNI modalities) to capture molecular information of the surrounding tissue/microenvironment.
- ME-NCs can be used as nano-stimulators for noninvasive treatment of patients with CNS diseases.
- Intrinsic coupling between electric and magnetic fields within ME-NCs provides molecular composition specificity that can enable an entirely new dimension even to the conventional diagnostic methods such as MRI and positron emission tomography-computed tomography.

This box summarizes key points contained in the article.

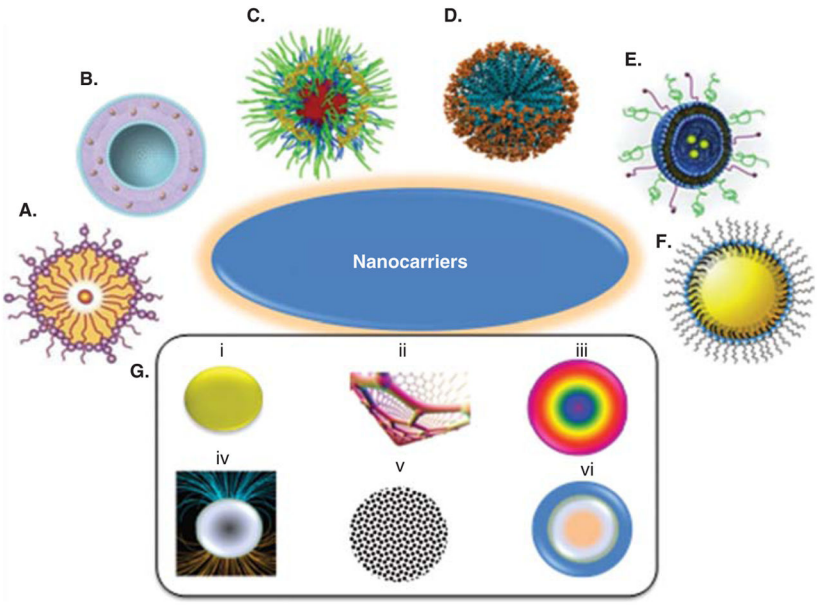

Figure 1. Illustration of various NCs utilized for drug delivery

A) Polymeric nanoparticle [17,71,72], **B)** dendrimers nanoparticle [73], **C)** polymeric micelle [19,25], **D)** non-polymeric micelle [25], **E)** lipid nanoemulsion [74], **F)** lipid nanocapsules [75–77] and **G)** inorganic NCs including: (i) metal nanoparticles [3,78–81], (ii) carbon nanotubes [82,83], (iii) quantum dots [34,36,84,85], (iv) magnetic nanoparticles [27–30,67,86–89], (v) silica nanoparticles [90–92] and (vi) core–shell nanoparticles [33,93,94].

NCs: Nanocarriers.

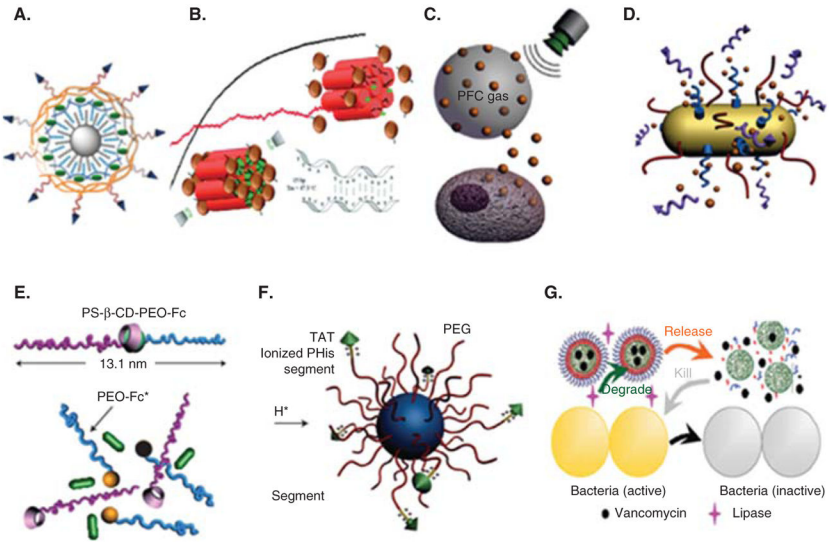

Figure 2. Presentation of stimuli-responsive NCs in drug delivery [42]

A) Temperature-based actuation mechanisms for liposomal drug delivery [95], **B)** Stimulation is heat generated by an alternating magnetic field, which lead on-demand drug release from nanocarriers [88], **C)** Ultrasound stimulated drug delivery from nanoemulsions via droplet-to-bubble transition [74], **D)** Near-infrared-triggered release of drug [78], **E)** Voltage-responsive controlled assembly and disassembly of carriers for drug delivery [96], **F)** pH-sensitive NCs for efficient drug release [97] and **G)** Enzyme-sensitive drug delivery [98].

A. Figure reused with permission of [95].

B. Figure reused with permission of [88].

C, D and **F.** Figures reused with permission of [42].

E. Figure reused with permission of [96].

G. Figures reused with permission of [98].

NCs: Nanocarriers.

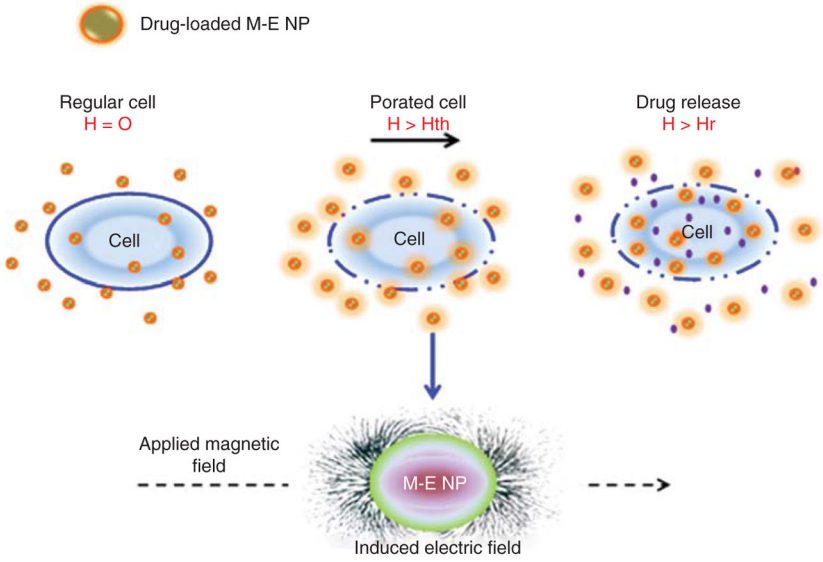

Figure 3. Schematic representation of ME-NCs as field-controlled nano-electroporation for drug transport across the cell membrane

ME-NC: Magneto-electric nanocarriers.

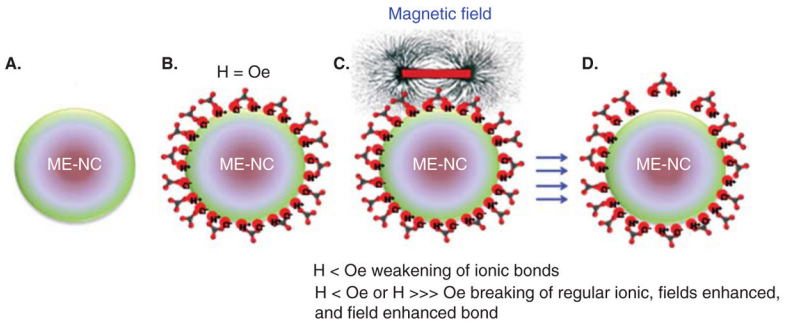

Figure 4. Schematic representation of drug loading onto ME-NCs and on-demand-controlled drug release under the influence of external magnetic field

A) Surface functionalized superparamagnetic ME-NCs, **B)** Binding of drug onto ME-NCs via electrostatic interaction, **C** and **D)** On-demand drug release by ME-NP stimulated by a uniform a.c. magnetic field.

a.c.: Alternating current; ME-NC: Magneto-electric nanocarriers.

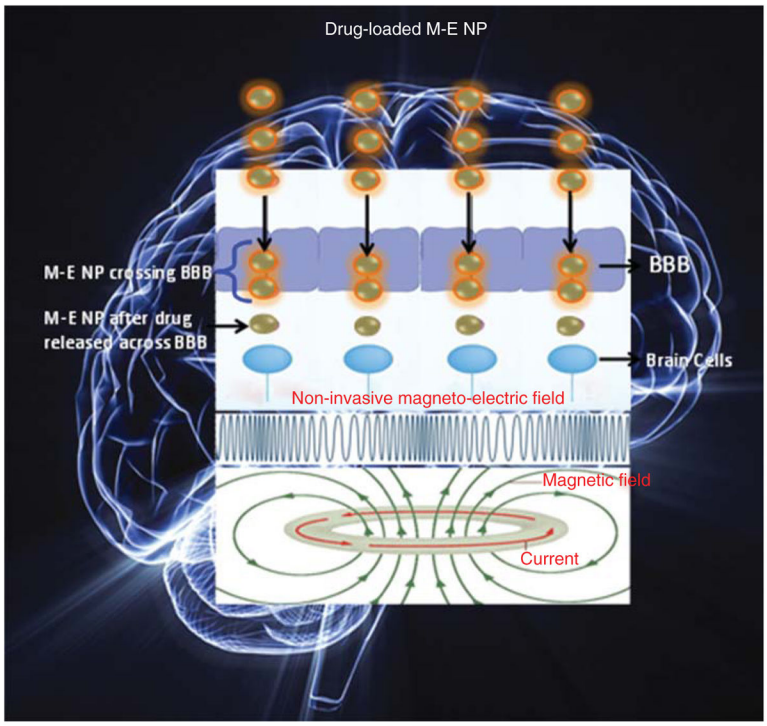

Figure 5. Proposed schematic of ME-NCs-based ARV drugs delivery across the BBB

ARV: Anti-retroviral; BBB: Blood-brain barriers; ME-NC: Magneto-electric nanocarriers.

Table 1

A summary of magnetic and ME nanoparticles-based delivery systems for transportation of drugs across the BBB [2].

Nanocarriers	M-NCs	ME-NCs
BBB transmigration potentials	These NCs could be hybridized with liposomes as 'magneto-liposomes,' which can behave as 'Trojan magneto-liposomes' residing in monocyte/macrophage. Externally magnetic force-mediated movement helps in escape of nanocarriers uptake from reticuloendothelial system and accelerates active targeting. Increased transmigration of ARV drugs across *in vitro* BBB model	Unlike M-NCs, ME-NCs possess unique combination of magnetic and electric properties. While externally magnetic force-mediated movement helps in speedy transport to tissue target resulting escape of NCs' uptake from reticuloendothelial system, noninvasive electric force mediates release of bound drugs Increased transmigration of ARV drugs across *in vitro* BBB model
Drug release mechanism	Drug release from this carrier relies on tissue/organ-specific response such as change in temperature, pH, intracellular Ca^{2+} concentration and so on. External stimulus such as mild hyperthermia may also affect the drug uploading	AC field triggers the dipole moment uniformly in all orientation, which breaks the intrinsic pattern of positive/negative charges on atoms. When dipole moment goes above the threshold value (more than the ionic bond strength between particles and drugs), a homogenous release of drugs from particles could be achieved
Limitations	Although many *in vivo* studies show site-specific targeting and lab to on-field and on-site transfer ability for non-HIV drugs, the same for ARV drugs are very limited	Although few initial *in vivo* studies show site-specific targeting and lab to on-field and on-site transfer ability, the same for other drugs have to be verified
Remark	More *in vivo* studies based on mouse, rat or monkey models must be performed	More *in vivo* studies based on mouse, rat or monkey models must be performed

ARV: Anti-retroviral; BBB: Blood-brain barriers; ME: Magneto-electric; ME-NC: Magneto-electric nanocarriers; M-NCs: Magnetic nanocarriers.