Pain management using nanotechnology approaches

Siavash Beiranvand and Mohamad Masud Sorori

ABSTRACT

The proper treatment of pain is yet a major medical challenge. To obtain a long-term analgesia action, opioid therapy is the gold standard therapy for overcoming a chronic pain. Nanotechnology focus on formulating therapeutic agents encapsulated in a biocompatible nanocarriers (∼10–200 nanometer), these include but not limited to nanoparticles, liposomes and nanocapsules, micelles, dendrimers and nano-tubes. This review gives an overview of current strategies of pain treatment with the help of the knowledge of nanotechnology. In addition, the applications of nano-innovation in oxidative therapy, genotoxicity and immunogenicity, are elucidated.

Introduction

The development in nanotechnology field and its applications to the field of medicines and pharmaceuticals in the twentieth century has led to the provision of a solution to most problems. Nanotechnology deals with materials at the nanometer scale, which brings about a standard class of materials with enhanced properties for an extensive variety of utilization [1]. Their utilization offered extraordinary favourable circumstances over common materials in assorted territories which have been tremendously investigated as of late.

Nanomaterials design have been broadly inspect for biomedical applications, including advancement of new demonstrative instruments, for example, novel therapeutics for targeted drug delivery, nanobiosensors and technique modalities and platforms for tissue regeneration [2–4]. Biocompatibility, have been taken into account to avoid their toxicity on entering into the blood stream. Nanotoxicology addresses the danger potential of nanomaterials. Although, there is a vast application of nanomaterials cutting across various fields, yet, there is are issues that are needed to be addressed for more insight on the treatment of human disease, biocompatibility and strength of nanomaterials. Materials used for synthesizing nanomaterials include but not limited to carbon, metals and silica in various shapes (i.e. bars tubes and spheres) [4–6] (Figure 1).

This review gives an overview of current strategies of pain treatment with the help of the knowledge of nanotechnology. In addition, the applications of nano-innovation in oxidative therapy, genotoxicity and immunogenicity, are elucidated.

Current treatment of pain in human

Bisphosphonate therapy in RA

Bisphosphonates are chemical analogues of inorganic pyrophosphate [10]. It can likewise increase both bone formation and bone-to-implant contact and bone resorption which represent an effective strategy for improving bone-implant integration, especially in the case of osteoporotic patients [11]. Osteoclast; a large multinucleate bone cell that absorbs bone tissue during growth and healing, is critical in the repair, maintenance and remodelling of skeletal bones.

Application of nanotechnology ophthalmology medicine

With the help of nano devices and nanostructures that work extremely in parallel at the unit cell level and with the intention of medical benefit achievement, the purpose of medical nanotechnology is to screen, check, create, renovate, protect and improve human biological systems at the nanostructure
levels, [12]. Nanotechnology has been applied in ophthalmology through nano-prescription, like pseudo-intelligence and bio-mimicry. Among the utilization of nanotechnology in ophthalmology are incorporate estimation of intraocular weight; treatment of oxidative pressure; theragnostics; application of nanoparticles for the treatment of choroidal new vessels, treatment of retinal degenerative malady utilizing quality treatment; prosthetics; anticipate scars after glaucoma surgery and regenerative nano-medication. The present remedial difficulties in drug delivery, postoperative scarring will be altered with the assistance of nanotechnology and will help in different unsolved issues, locate reestablishing treatment for patients with retinal degenerative sickness [13]. From this development, field medicines for ophthalmic infections are normal. A novel nanoscale-scattered eye salve (NDEO) for the treatment of extreme evaporative dry eye has been effectively designed.

**Gene therapy applications of nanotechnology**

Gene modification and therapy involving RNA interference, which aiming at directing and impairing the posttranscriptional expression of undesirable genes and disease-related signalling pathways. Most diseases start from the malfunctioning or deficiency of endogenous genes inside the body. The primary defense against attacking foreign materials and pathogens is the immune system, which is complicatedly organized by specific molecular genetic pathways [14,15].

Treatment of diseases of the central nervous system, drug addiction, lung injury, stroke, asthma, obesity, chronic pain and infectious diseases are examples of nanoparticle delivery of genetic materials in medicine.

Pain treatment is not only related to retinoic acid (RA) [16,17], the effect of IL-35 drug delivery in an immune system and extreme RA model have been demonstrated [18]. A non-tissue-specific cationic protein transduction domain (PTD-5) was joined to a peptide (KLAK) that destroy organisms [19] to create two pro-apoptotic peptides named DP2 and DP1 (G-protein–coupled receptors, DP1 and DP2 (CRTH2)).

**Antimicrobial therapy**

Metallic nanoparticles such as silver, gold and platinum are outstanding for being toxic on a large group of pathogenic organisms [20]. Silver antimicrobial treatment holds a great promise to reduce wound contaminations [18], and restore a normal wellbeing of 50% in patients [21]. Metallic nanoparticles utilization for example, applications of Ag in antimicrobial therapies, produce a range of beneficial effects [22], for instance, the multilevel antibacterial ability to decrease the probabilities of low systemic toxicity, effectiveness against multidrug-resistant organisms and increasing resistance [23].

**Nanoparticles**

Metal nanoparticles have been employed for synergist interaction lately [19,24,25]. Among the different NPs, nano-sized silver is especially attractive because of its high surface area to volume ratio when compared to metals [26,27].

Noble metal nanostructures have been used by scientist in removing toxic organic pollutant which includes gold nanoparticles [28], silver nanoparticles [29] and noble metal nanoparticles (Au, Ag and Pt) stabilized with varying substance. NPs can be applied in tumor photodynamic treatment, in which the nanoparticles should be introduced inside the tumor and will be illuminated from the outside [30].

For delivery in the biological milieu, NPs additionally allow constant aqueous diffusions of active, but poorly water-soluble molecular agents. Degradation of NP-encapsulated agents can be prevented by numerous endogenous defense mechanisms which include mucociliary clearance in the lungs, acid hydrolysis in the stomach, sequestration by the reticuloendothelial system (RES) in the bloodstream, immuno-degradation and enzymatic degradation [31]. NPs are used in
cancer photodynamic therapy, wherein the particle is inserted within the tumor in the body and is illuminated with photo light from the outside [32]. Metal nanoparticles absorb light and it will become heated owing to energy from the light. Thus, NPs are favourable tools for the development of drug delivery, as bio-imaging and diagnostic sensors [33].

Polymeric nanoparticles

Polymeric NPs allow encapsulation of promising drugs inside the polymeric matrix, which will defend them from hydrolytic and enzymatic degradation [34]. They possess many benefits in drug delivery for several kinds of pharmaceutical substance (proteins, peptides, small interfering ribonucleic acids [siRNA] and small molecules) (Table 1) [35–39]. These benefits include prolong duration of action, multiple available routes of administration, controlled discharge and high stability during storage. Once the polymeric NPs reaches the target tissues, the drug will be released by desorption, diffuse through the polymer matrix or polymer wall, or eroded. There is a development in pain therapy, using combine polymeric NPs with biodegradable bearers loaded with pain-killers. Polymeric nanoparticles loaded docetaxel have been employed in extracellular milieu of prostate-particular region antigen [40]. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles loaded with tramadol hydrochloride (TrHC) were synthesized by Lalani et al. [41] and conjugated with the glycoproteins lactoferrin and transferrin for brain targeting. An improved pharmacological effect was shown with these composite, at a controlled TrHC release and augmented times of circulation. They observed that the PLGA nanocomposite showed enhanced performance, as regards imparting antinociceptive effects, compared to those with transferrin [41]. An additional type of polymeric nanoparticles was fabricated and targeted to the brain, intranasally, showing an elevated uptake of the drug [42], and several imprinted polymeric nanoparticles that exhibiting better selectivity, binding capacities and controlled release of TrHC [43,44].

Toxicity of nanomaterials on human

Many in vitro and clinical investigations have discovered that numerous nanoparticles present minor to major hazardous/toxicological effects [45]. Researchers have concentrated on the expulsion of lethal organic contaminations using NPs which effects human health [46]. As compared to their larger counterparts, nanomaterials have unique biological and physicochemical properties, which can great impact on their connections with cells and biomolecules, because of their unique properties like shape, chemical composition, charge, size, agglomeration, surface structure and solubility [47].

### Nanotoxicity and toxicokinetics

NPs immunologically collaborate with organic shapes, prompting modification in their structure and capacity, which may bring about carcino genesis and hypersensitivity. NPs may diffuse unreservedly in organic matters and localized inside various cells, tissues and other subcellular compartments. This type of toxicity might be activated through the congestion of these biological compartments. Toxicity might be activated through the accumulation of these organic compartments. For instance, severe lung toxicity has resulted under exposure to inorganic NPs in mines, in which many mechanisms have participated such as the production of carcinogenesis, inflammatory cytokines, fibrosis and so on [48].

### In vitro toxicity

#### Oxidative stress

The generation of reactive oxygen species (ROS) within cells can be the result of oxidative stress, which can be both non-radical (singlet oxygen and hydrogen peroxide) and radical (hydroxide radicals, nitric oxide). Small amounts of generated ROS are well tolerated by the body [49]. Body presented with organic pressure, which incorporates attack by foreign substances; pathogens and NPs; lead to the build-up of ROS. A very high level of ROS may result in lethal effects, known as oxidative pressure [48]. Generation of ROS seems to be a very common after NPs degradation, though its severity and toxic potential rely on the particle type [50]. ROS production is caused by lipid peroxidation and electron-transfer processes associated with the Stone–Wales defects in multiwalled carbon nanotubes, cation modified NPs electrostatically interact with largely anionic cellular membranes [51].

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**Table 1. Nanocarriers and their biopharmaceutical characteristics.**

| Formulation system | Route | Observed pharmacokinetics/pharmacodynamics in vivo | References |
|--------------------|-------|---------------------------------------------------|-------------|
| **Dendrimers**     |       |                                                   |             |
| Docorubicin        | Polysine dendrimer | IV | Prolonged systemic exposure Enhanced accumulation in tumor tissues | [77] |
| Nobiletin          | Nanosized amorphous particles | Oral | Improved oral bioavailability and hepatoprotection | [78] |
| **Inhalable dry emulsions** | Pulmonary |       | Enhanced anti-inflammatory effects in lung | [79] |
| Halofantrine       | Self-emulsifying drug delivery system | Oral | Improved oral bioavailability | [80] |
| Simvastatin        | Self-emulsifying drug delivery system | Oral | Improved oral bioavailability | [81] |
| Cytarabine/daunorubicin | Liposome (DSPC/DSPG/Chol) | IV | Decreased clearance | [82] |
| Paclitaxel         | Block copolymeric micelles | IV | Increased systemic exposure, decreased clearance | [83] |
| Tranilast          | Self-micellizing solid dispersion | Oral | Improved oral bioavailability | [34] |
| **Polymeric nanoparticles** |       |                                                   |             |
| Celecoxib          | Ethyl cellulose/casein nanoparticles | Oral | Improved oral bioavailability | [36] |
| Docetaxel          | PLA-PEG nanoparticles | IV | Extended half-life, enhanced antitumor effect | [39] |
| Insulin            | Hydrogel nanoparticles | Oral | Improved oral bioavailability | [38] |
| Paclitaxel         | Albumin nanoparticles | IV | Low inter-/intrapatient variability, tumor targeting | [35] |
| siRNA              | Chitosan analog nanoparticles | Oral | Improved systemic distribution and gene silencing | [37] |
| VIP derivative      | PLGA nanoparticles | Pulmonary | Enhanced anti-inflammatory effects | [84] |

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References

[32] Carbon nanotubes, cation modified NPs electrostatically interact with largely anionic cellular membranes. [47] Small amounts of generated ROS are well tolerated by the body. [49] The generation of reactive oxygen species (ROS) within cells can be the result of oxidative stress, which can be both non-radical (singlet oxygen and hydrogen peroxide) and radical (hydroxide radicals, nitric oxide).
**Genotoxicity**

Genotoxicity can be caused by either coordinate physical (e.g. intercalation into the twofold helix of DNA) or compound connections of NPs with the DNA [52]. However, the complexation of NPs with DNA can incite oxidative pressure which produces ROS and RNS (reactive nitrogen species) which can harm the DNA. The impact can be DNA discontinuity, breakage of DNA double-strand, concealment of DNA capacities. The evaluation of genotoxicity includes the location of DNA fracture, DNA transformation, breakage of DNA double-strand and changes in the direction of DNA replication and quality [49].

**Immunogenicity**

The immunogenic reaction produced by the NPs is due to the adjustment of cell-interceded reactions [49]. It is an effect of the cell treating the NPs as foreign materials prompting cytokines or protein signalling response (e.g. TNF-α and chemokine IL-8). This reaction can be evaluated by ELISA or the microbeads examine technology [53].

**Liposome application in pain management**

Various nanocarriers classes including polymeric and liposomes nanoparticles have been considered as medications for pain delivery and rising numbers of clinical trials so that they possess strong potential toward offering greater safety for the drug, prolonged release, efficacy and patient tolerance [54]. Such nanocarriers that have shown clinically improved performance over existing platforms for pain treatment.

With respect to clinical studies which showed the safety of Exparel; a liposomal formulation compared with oral opioid or traditional IV regimens, a number of studies showed that Exparel had a good safety profile than with other conventional treatments [55]. A retrospective study by Butz et al., carried out on 90 patients with immediate implant-plant breast reconstruction, showed that liposomal bupivacaine reduced patient visual analog pain scores in the immediate postoperative period, when compared with a bupivacaine pain pump and oral/ intravenous narcotic management of pain and decreased inpatient length of stay [56,57].

Nevertheless, in a prospective double-blind randomized trial by Nadeau et al. on 34 patients who underwent cosmetic primary subpectoral augmentation of the breast; When compared with traditional bupivacaine, liposomal bupivacaine showed postoperative pain reduction; yet, it did not show a clinical significance in relation to traditional bupivacaine [58,59]. Emerson et al. also revealed that long-acting infiltration of liposome bupivacaine gave a comparable postoperative analgesia as compared to a continuous femoral nerve block, however, with significantly less narcotic medication compared to total knee arthroplasty [60,61].

**Nanoparticles application in pain reduction**

Hassan et al. investigated a one-pot and eco-accommodating technique for the composite of ibuprofen derived silver NPs (IBU-AgNPs) in aqueous media using ibuprofen analgesics sedation. This technique gives a novel, quick and conservative strategy for the treatment of water poisoning and the pain arising from it [62]. Their strategy can as well be employed for the control of other contaminants in water [63]. In a review by Moradkhani et al., the concept of nano-formulated carriers encapsulating analgesic drugs and their Figure 2. A proposed component of MNP-prompt macrophage enrollment into neuronal tissues [1]. Exposure to cytotoxic MNPs empowered the arrangement of ROS in occupant cells [2]. ROS advances articulation and arrival of proinflammatory cytokines, for instance, TNF-α. Through its two receptors (TNFR), TNF-α enacts p38 and ERK mitogen-actuated protein kinases pathways to [3] initiate the outflow of lattice metalloproteinases (MMPs) in its idle, ace-MMP shape. Likewise [4], ROS can straightly forwardly advance MMP enactment from professional shape. MMPs are the main chemicals in the body equipped for corrupting blood-cerebrum and blood-nerve boundaries (BBB/BNB), which [5] advances penetration of coursing macrophages (mΦ) into neuronal tissues. MNP size and surface science decide the instruments and the objectives cells of MNP disguise, and in addition degree of neurotoxicity of MNPs.
effects as a method in pain management have been elucidated [64]. In another clinical and preclinical review that focused on the use of nanotechnology for chronic and acute pain management, and surveying both diagnostic and therapeutic uses [65]. Nanomedicine should be developed further by medical practitioners to improve patients healthcare who are constantly living with pain [66].

Inflammatory pain therapy using nanoparticles for combination therapy with non-steroidal anti-inflammatory medication

The developing of opioid as an alternative treatment have developed recent interest. Amongst them, considerable amount possesses poor bioavailability and shows low viability [67]. Resveratrol and celecoxib were used as a synergistic combination in a tumor micro environment, however, NPs creates a targeted delivery [68].

Anti-inflammatory drug loaded nanoemulsion in a rat CCI model

In neuropathic torment of chronic constriction injury (CCI) using a rodent model, gut suture used to ligate the sciatic nerve causes irritation [69]. Irritation was evaluated by NIR fluorescence in live animal and posthumous histological investigations. However, a decrease in macrophages at the damage site can be corrected using drug loaded nanoemulsion treatment, which changes the delivery of neurotic markers inside macrophages and neighboring tissue [70].

Macrophage directed ED2/CD163 gene therapy using NPs

After surgeries, about 20–50% of chronic postoperative pain (CPSP) occur. Keeping the advancement of tireless postoperative pain-related practices in rats result because of guess of the over-articulation of ED2 in invading macrophages [71]. The speculation of gene therapy has been tried after these points to identify the time course of macrophage invasion and ED2 articulation at the attacked tissue following surgery; overexpressed ED2 in macrophages at the attacked site utilizing nanotechnology approaches; prevents the improvement of mechanical or potentially unconstrained stress related practices following ED2 mobilization in a rodent model of tenacious postoperative [72].

Magneto-cytolytic therapy

The combination of magnetic nanoparticles and external magnetic field serve as two unique advantages from which medicine can immensely benefit [73]. MNPs have been used in vitro and in vivo, their effect can be monitored through an external magnetic field, which determined concentration on delivery [74]. Magnetic nanoparticles accumulated at a diseased site can be activated by this external magnetic field to generate local heating for disease-specific toxicity [75]. They are employed as drug delivery vehicles to block pain, they are also capable of producing a warming effect “magnetically induced hyperthermia” or “magnetocytolysis” [76] (Figure 2).

Future direction and conclusion

Several advances in the management of pain for the surgical patient, surgeons and pain care providers have countless selections of analgesic pharmacotherapy and employed analgesic strategies to select from to give an appropriate postoperative control of pain for 21st-century surgical patient. Nanotechnology is not just a stream of infinite opportunities but a growing field for the nearest future, however, it is convincing to many researchers investigating to achieve great goals every day. A properly synthesized NPs strategies result in the improvement of bioactivity and bioavailability through encapsulation, particle size reduction, surfaces modification and bioactive materials entrapment for pain relieve.

Disclosure statement

No potential conflict of interest was reported by the authors.

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