NANOTECHNOLOGY IN ANAESTHESIA: PAST, PRESENT AND THE FUTURE

Abstract

Anesthesia is an ancient science which has undergone progressive evolution over time. Over the last few decades with the advent of nanotechnology the administering anesthesia has become easier, safer and is associated with much favorable outcomes; mainly due to the precision with which nanotechnologically derived anesthesia drugs act. The anesthesia world was introduced to nanotechnology by Sir Richard Feynman. Nanotechnology based drug delivery platforms have evolved and increased in sizable numbers so as to facilitate the administration of commonly used anesthesia drugs, even though only a few drugs have till now received US-FDA approval for use, the number is likely to increase in the coming future with the growing research. Nanocrystals, organic nanoplatforms (Liposomes, polymeric nanoparticles, polymeric micelles, hydrogels, protein-based nanoparticles, dendrimers and inorganic platforms are the commonly used nanoparticle-based drug delivery systems). Drugs which have been experimented upon and have brought encouraging results include propofol, ketamine, benzodiazepines, opioids, inhalational agents, reversal agents like atropine and neostigmine etc. A major drug category which has taken the world of anesthesia by storm is the local anaesthetic especially bupivacaine. Additionally, we can expect nanobots to stand beside us and work shoulder to shoulder in patient welfare. However, the fact that nanotechnologically derived drug delivery systems are free of side effects is not true and a number of issues in terms of adverse drug reactions and ethical issues still exist. But they are likely to be overcome in the coming future.

Keywords: Anesthesia, Nanomedicine, Nanotechnologically, Bupivacaine, Drug Delivery Platforms.

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"*There is plenty of room at the bottom*"[1] …. Sir Richard Feynman

Anaesthesia has witnessed unparalleled advancements in terms of technology and patient safety since its inception. From the initial days of pain relief during surgery employing distractions and magical charms, the future focus has shifted onto drugs and technologies acting on cellular, subcellular and molecular levels, to enhance accuracy with minimal or no adverse effects. This has become possible due to better understanding of physiology and newer, better and safe drug delivery mechanisms. Present day mortality in Anaesthesia is as low as 1/250000, which can be attributed to the newer generation safer medicines and technologies coming into the picture.[2] Gradually, but firmly Anaesthesia is moving into a phase where nanotechnology and artificial intelligence shall be the torchbearers in Anesthesia practice, making Anesthesia safer and even more different from what it has ever been and probably making complications a thing of past.

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale.

I. HISTORY OF NANOTECHNOLOGY

Being a relatively new field of study, nanomedicine is already making its mark in the huge field of anaesthesia and medicine. It all began with the renowned speech given by Sir Richard Feynman, a pioneer in nanotechnology, in 1959 entitled "There is plenty of room at the bottom: An invitation to enter a new field of physics."[1] This speech served as an inspiration and the first step towards the introduction of nanotechnology in the fields of medicine. Sir Feynman mentioned the application of barely discernible machines in medicine, which K. Eric Drexler, Chris Peterson, and Gayle Pergamit later referred to as nanorobots in their book "Unbounding the Future."

In the 1990s, studies on the application of nanotechnology to pharmacology, surgical specialty, and medical technology began. The 1991 book "The Nanotechnology Revolution" introduced the phrase "nanomedicine". The term "nanomedicine" refers to the potential uses of nanotechnology in the field of medicine and its subspecialties, the use of nanomaterials in clinical settings, the development of nanoscale biosensors, platforms for delivering drugs at nanoscales (using polymer-based nanoparticles), and the use of molecular nanotechnology for disease diagnosis and treatment.[3] Nearly all of the world's major nations now have specialized units for nanotechnology and nanomedicine, thanks to a huge push for the field since the year 2000.

In terms of innovative formulations of both traditional and contemporary medications and technologies, Nano-Anesthesia has not been left unaffected by developments and ongoing research in the fields of pain, regional and general anesthesia, and critical care. In this chapter we intend to touch upon the basics of nanotechnology platforms and the applications and future of nanotechnology in the field of anaesthesiology. Applications of nanotechnology in the world of critical care is even more extensive and humongous and are beyond the purview of this chapter.

II. NANOPARTICLES AND NANOTECHNOLOGY-BASED DRUG DELIVERY PLATFORMS

Nanoparticles (NPs) are designed to contain encapsulated, disseminated, absorbed, or conjugated pharmaceuticals and have distinct properties that improve their effectiveness at varying dosages, hence lowering the cost and/or reducing the adverse effects associated with specific drugs. Drug targeting can be accomplished by modifying NP size and surface properties.

Biological compounds such as albumin, gelatin, and phospholipids for liposomes have been tried as drug delivery agents, as have chemical substances such as polymers and solid metal-containing NPs. Nanocarriers can be selectively accumulated at target sites owing to the enhanced permeability and retention (EPR) effect, thereby reducing side-effects with increased potency by improving the stability, efficacy and shelf life.[4,5]

The benefits of using nanoparticle-based drug delivery systems include:

- Enhancing the stability of drugs that are hydrophobic, allowing them to be administered via desired route
- Improving biological dispersion and pharmacokinetics, leading to improved efficacy;
- Reducing adverse effects owing to preferred accumulation at target sites; and
- Reducing toxicity by using biologically compatible nanomaterials.[4,5]

With newer nanoparticles being added by the day in the world of nanotechnology, detailed description of nanoparticles is impossible in a single chapter. Hence, a brief description is being provided

Major Nanocarriers include:

1. ***Nanocrystals*:** By manufacturing the drug on the nano-scopic level it may serve as its own carrier. The drug's surface area is substantially enhanced through a reduction in particle dimension, thereby boosting solubility and dissolution and, as a result, increases both the maximum plasma concentration and the maximum plasma concentration. Nanosized drugs can be administered orally, nasally, or intravenously.[6-8]

2. ***Organic Nanoplatforms:***

- ***Liposomes:*** Liposomes are the most popular and probably one of the most widely utilised drug delivery systems. Liposomes are artificial vesicles that originate from amphiphilic phospholipids in a spherical bilayer structure surrounding an aqueous core. The pharmacokinetic characteristics of liposomes enables them to act as a carrier for the delivery of nucleic acids, proteins and drugs.

  Despite being used extensively, liposomes have several drawbacks, including: poor encapsulation efficiency; quick burst drug release; inadequate shelf stability; and a lack of customizable triggers for drug release.

Surface modification, such as attaching polyethylene glycol (PEG), poly (methacrylic acid-co-cholesteryl methacrylate), and poly(actylic acid) to form a protective layer over the liposome surface, can improve liposome stability and structural integrity.[9]

- ***Polymeric NP:*** Colloidal spherical, branching, or core-shell structures made of biodegradable synthetic polymers such as polylactide-polyglycolide copolymers, polyacrylates, and polycaprolactones or natural polymers such as albumin, gelatin, alginate, collagen, and chitosan. These are Stimuli-sensitive polymers can modify their physicochemical attributes in response to environmental signals and external stimuli. Polymeric nanocarriers are classified according to three drug-incorporation processes.

  - Polymeric carriers capable of direct drug conjugation
  - Hydrophobic interactions between pharmaceuticals and nanocarriers.
  - Hydrogels: A water-filled depot for the encapsulation of hydrophilic drugs.

  - ***Polymeric Miscelles*****:** Polymeric Micelles are generated when amphiphilic surfactants or polymeric molecules spontaneously bind together in an aqueous solution. A micelle's inner core is hydrophobic and is surrounded by a shell of hydrophilic polymers. The hydrophobic core acts as a reservoir for medications that are weakly water-soluble or amphiphilic, while the hydrophilic shell stabilises the core, improves blood circulation time, and promotes tissue accumulation. Drug-loaded stimuli-responsive micelles and multifunctional polymeric micelles are being studied.[11,12]

  - ***Hydrogel np*****:** Hydrogels are polymers with hydrophilic properties. They are capable of taking in and retaining more than 20% of their weight in water while preserving the polymer characteristic structure. Swelling properties, network structure, permeability or mechanical stability of these are manageable by external stimuli (magnetic field) or physiological parameters[13-18]

  - ***Protein based NPs:*** Hydrophobic medicines, such as Cremophore EL, which has its use in propofol formulations, have been made as solutions with protein-based NPs. These surfactants have been reported to exhibit hypersensitivity reactions as well as adverse effects in tissues. Albumin conjugation aids in the resolution of both of these issues.[19,20]

- ***Dendrimers:*** Dendrimers are globular molecules having internal cavities that allow medications to be contained within the macromolecule interior and are utilized to offer controlled release from the inner core. The dendritic architecture and branching allow drug loading onto the structure's outer surface via covalent binding or electrostatic interactions.[21-23]

3. ***Inorganic Platforms:*** NPs of gold (Au) Noble metal NPs, such as Au NPs, have emerged as a viable scaffold for drug and gene delivery, serving as a beneficial supplement to more established delivery vehicles. The combination of inertness and low toxicity, ease of production, very large surface area, well-established surface functionalization, and

tunable stability gives Au NPs unique properties that allow for new delivery tactics. They can also serve as drug storage.[24,25]

Internal (e.g., pH) or external (e.g., light, magnetic field) triggers could stimulate the efficient release of these therapeutic substances. Au NPs can be imaged utilising contrast imaging techniques in addition to functioning as a medication delivery vehicle.[26-28]

Other commonly uses inorganic platforms include supramagnetic NPs (superparamagnetic properties of iron (II) oxide particles can be used to guide microcapsules in place for delivery by external magnetic fields)[29], ceramic NPs (Synthesized from porous inorganic substances, such as silica, alumina. Silica NPs have generated interest owing to their biocompatible nature, and ease of modification which facilitates cross linking with drugs)[30-32], Carbon based NPs (surface functionalized for the grafting of nucleic acids, peptides and proteins. They suffer from a high incidence of toxic reactions) and integrated NPs.[33-35]

III. NANOTECHNOLOGY AND ANAESTHESIA

Nanotechnology and its advantages are bound to spill over to the world of anaesthesia either through independent research in the field of anaesthesia pharmacology or through the field of medicine and imaging which would lead to better understanding in the aspects dealing with sleep and controlling consciousness.

There has been a lot of ongoing research in the field of various anaesthesia components namely hypnotic agents (intravenous and inhalational), pain medicine (narcotics and non-narcotic medications), local anaesthetics, reversal agents, blood components and in the field of critical care (including diagnostics and treatment of acute and chronic diseases). Covering all the development is a humongous task and hence, in this chapter we shall be enumerating the principal anaesthetic drugs and their current status in nanotechnological advances.

IV. INTRAVENOUS ANAESTHETIC AGENTS

1. **Propofol:** Propofol is one of the primary and most widely used intravenous anaesthetic drugs in the world. However, intravenous propofol is associated with pain on injection and with peripherally mediated hypotension. Along with these common side effects, propofol has small shelf life and is associated with life threatening complications like propofol infusion syndromes. Also, propofol has an important limitation that it can't be administered by non-parenteral routes.

   Nanotechnology based research in the field of propofol has its major focus on two aspects namely; developing propofol nanoparticles and nanoemulsions to which can be administered via non parenteral methods and developing nanocarriers platform. Both achieving the ultimate effects of reducing the side effects of propofol

   - ***Octanol-Grafted Alginate (Alg-C8) Nanoparticles Encapsulating Propofol*:** Najafabadi et al (2015) synthesized and evaluated octanol-grafted alginate nanocarriers encapsulating propofol. They conducted animal sleep recovery studies in

rats and concluded that encapsulated nanoparticles could be a promising clinical intravenous system for delivery of poorly soluble anesthetic propofol. In addition, this study provided an efficient and facile method for preparing a carrier system for similar water insoluble drugs.[36]

- ***Propofol Nanoemulsion with Solutol and Soy Lecithin*:** Oil-in-water emulsions with mean droplet sizes less than 1000 nm are referred to as nanoemulsions. Microemulsions or submicron emulsions are other names for them. The lipid core of nanoparticles contains a solution of the active substance, such as propofol. Propofol nano-emulsions have been successfully created with droplet diameters under 100 nm. In contrast to the existing market-available milky propofol emulsion, its physical appearance is transparent. Rittes et al. (2016) examined the effects of nanotechnologically-modified propofol nano-emulsion, solutol with soy lecithin, and traditional 10% soyabean oil emulsion in humans. The advantages of using nano-emulsions are numerous.

  First, compared to conventional emulsions, nanoemulsions have proven to be more stable. Enhancing stability shall increase the longevity and shelf life and lessens the likelihood that the oil phase may separate from the water phase. Because there is less leakage or cracking as a result of increased stability, there is also less free propofol outside the nanoparticles. Propofol nano-emulsions may reduce pain on injection. Additionally, nano-emulsions may also exhibit and possess an array of antibacterial properties.[37]

- ***Non Parenteral Propofol Delivery using Chitosan Amphiphle Nanoparticles*:** N-palmitoyl-N-monomethyl-N,N-dimethyl-N,N,N,trimethyl-6-O-glycolchitosan (GCPQ) - propofol nanoparticles were tested in mice by Uchegbu et al. (2014), demonstrating their centrally active nature. GCPQ-propofol nanoparticles may offer a successful technique of administering non-parenteral propofol.[38]

- ***Non Lipid Propofol (NLP) Nanoemulsion*:** Sudo et al. compared NLP (1%), which contains propofol, macrogol hydroxy stearate, and glycerol, to regular propofol. There was no discernible difference in the hemodynamics or hypnotic dosages. However, the NLP group experienced much less pain throughout the injection.[39]

- ***Propofol-Loaded Nanomicelle:***

  - **Formulation of propofol- carboxylic acid-poly [ethylene glycol (COO-PEG)]-b-poly[D,L lactide (PDLA)]-nanomicelle** was developed and drug release assay performed. It was observed, COO-PEG-PLDA nanomicelles improved the induction time of anesthesia, anesthesia period and walking time induced by propofol.[40]
  - **propofol-mixed micelles using DSPE mPEG2k and Solutol HS:** The low lipid micelles have exhibited reduced incidence of hyperlipidemia, pain, pain and displayed better safety profile over conventional propofol[41]
  - **propofol in poly (N-vinyl-2-pyrrolidone)-block-poly(D,L-lactide), PVP-PLA, polymeric micelles (Propofol-PM):** Propofol loaded in PVP-PLA micelles

(Propofol-PM) have also been studied and have exhibited better stability, lesser pain and no support to microbial growth.[42]

2. **Ketamine:** Ketamine has always been important part of an anesthesiologists armamentarium and the nanotechnological advances are attempting to make it even more potent with minimal adverse effects while ensuring a sustained release.

   - **Sustained-release ketamine-loaded Polyethylene glycol- poly-lactic-co-glycolic acid (PEG-PLGA) nanoparticles** – Study conducted by Han et al concluded high drug loading and a sustained release profile can be achieved with ketamine-loaded PEG-PLGA nanoparticles.[43]

   - **Ketamine-loaded poly-lactic-*co*-glycolic acid (PLGA) nanoparticles** can also be coupled to an apolipoprotein E (ApoE). They provided a distinct advantage of better penetration of blood brain barrier and increased drug therapeutic window as an anaesthetic along with the therapeutic advantage that they may be injected intrathecally which would facilitate direct access to the nervous system[44]

3. **Benzodiazepines:**

   - **Midazolam:** Midazolam is water insoluble. By formulation of nanocrystals loaded midazolam the pharmacological properties of midazolam can be changed and this has garnered much attention. Midazolam's pharmacokinetic properties and favourable neuroprotective effects were all dramatically altered by nanocrystals, which ultimately increased its efficacy.[45]

   - ***Diazepam*:**

     - **Diazepam (Dzp)-Loaded Poly (lactic-co-glycolic acid) Nanoparticles** (NP) to achieve delivery in the brain through intranasal administration have been prepared. Similar PLGA NPs of lorazepam and midazolam have also been attempted via nano-precipitation method. Their major advantage has been however for control of status epilaepticus.[46] Attempt is also being made to manufacture diazepam liposomes to increase intravenous bioavailability

     - **Opioids:** Pain management is one branch of clinical anaesthesia that has probably benefitted the most from nanotechnology in terms of current pharmacological therapies being modified nanotechnologically which includes opioids and local anaesthetics to extensive futuristic research. To mention a few, modified endogenous opioids like LENK-squalene bioconjugate nanoformulated in dextrose, nanotechnologically modified neurotoxins like tetradotoxin and saxitoxin, pH-responsive nanoparticles target NK1R in the endosome to target chronic pain, encapsulated GPCR agonists sumatriptan and zolmitriptan in various nanoparticles (chitosan solid lipid, ApoE-bovine serum albumin, and PLGA-poloxamer),development of external stimuli directed naotechnologically derived-pain management delivery systems (Infra-red, near infra red, ultrasound and magnetic waves) and futuristic gene therapy, nucleic acid scavangers.[47-58] In this

text we shall be restricting ourselves to the commonly used pharmacological therapies only

- **Morphine:**

  - **Poly(lactide-co-glicolide) nanoparticles incorporated Morphine Hydrochloride** have been synthesized and found to prolong duration of plasma levels of morphine**.**[59]

  - **Morphine Loaded Hydroxyapatite Nanoparticles (HAPs**): Kolemek et al Synthesized Morphine Loaded Hydroxyapatite Nanoparticles (HAPs). They observed increased duration of action for HAP loaded with morphine primarily due to increased circulation time. They also had negligible toxic effect due to HAP making this preparation holding a promise in future.[60]

    Liposomes and polymeric nanoparticles have been employed to encapsulae opioids for extended-release (ER) and reduced systemic toxicity.

    Depodur and Avinza, two ER morphine derivatives, were approved by the FDA and have been marketed and commercialised subsequently.[61]

  - **Liposomal Extended-Release Morphine:** Depodur employs DepoFoam, a multivesicular liposomal delivery method comprised of multiple non-concentric aqueous chambers carrying a medication.[62]

  - **Morphine based on Ammonium Methacrylate Polymers:** Orally administered Avinza includes ER morphine capsules in proprietary beads made of ammonium-methacrylate copolymers that are solubilized by gastrointestinal fluids .[63] After then, the medication solution diffuses out of the capsule, producing therapeutic plasma levels for up to 24 hours.[64]

4. **Fentanyl:** The use of **oral transmucosal fentanyl citrate (OTFC)** in cancer pain management makes it an attractive application of nanotechnology for cancer patients who are currently on opioids and continue to have such pain outbreaks. OTFC was developed and approved expressly for the treatment of breakthrough pain in cancer patients. It has also encroached in the domains of pediatric anaesthesia.[65]

   - **Fentanyl-Bearing Biocompatible Polylactide and Polyglicolide Nanoparticles** (Fen-PLA/PLGA NPs) with regulated size, surface characteristics, and antinociceptive qualities have been explored, and animal experiments are now underway. In a mouse model, the results show that a single subcutaneous dose of the produced NPs produces therapeutically appropriate doses for up to six days[66.]

5. **Tramadol:**

   - **Tramadol Gel:** Ethosomes are elastic nanovesicles comprised of phospholipids (20-45% ethanol) containing desired medication. The ethosomes overcome the problems of Liposomes and Proliposomes, such as lower stability, scalability concerns, drug

leakage, vesicle fusion, and vesicle breaking. Topically applied ethosomes increase the drug molecule's residence duration in distinct layers of skin, such as the stratum corneum and epidermis, and inhibit systemic absorption.
To counteract the drawbacks of oral medication, topical ethosomes allow for improved permeation and lower dose.[67]

- **PLGA Loaded Tramadol:** Poly (lactic-co-glycolic acid) (PLGA) nanoparticles loaded with Tramadol hydrochloride laced with transferrin and lactoferrin were prepared by Lalani et al. They could be administered intranasally and thereby bypassing blood brain barrier and also increasing duration of action.[68]

V. NANOTECHNOLOGY AND INHALATIONAL AGENTS

Intravenous distribution of halogenated volatile anaesthetics has piqued the interest of researchers and anaesthesiologists alike ever since they have come into anaesthesia practice and a constant effort is on with the aim of improving on existing routes of administration. Direct injection into the bloodstream removes the need for the anaesthetic to equilibrate with the lungs, resulting in a faster onset of anaesthesia. Direct IV infusion of plain halothane, whether purposeful or unintentional, resulted in substantial lung damage and mortality in both animals and people. Fat emulsions have been employed for intravenous administration of halothane, sevoflurane and isoflurane

Despite the numerous advantages inhaled anaesthesthetics render to the current anaesthesiology practice, which include favourable cardiovascular effects, significant bronchodilator effects, and obstetric indications. These medications have a number of side effects, including effects on the liver (halothane hepatitis) and the kidney (compound A formation from sevoflurane etc.

If the inhalational agent could be modified so that it could pass through the lung and reach the brain and other organs except the liver without producing nephrotoxic metabolites, the new molecule could have all of the useful effects of an inhalational anaesthetic agent without causing significant hepatic or renal side effects.

Owing to the enhanced interest in the intravenous (IV) administration of halogenated anaesthetics, the IV route has been investigated in animals. Emulsification of inhalation anaesthetics may shorten the time necessary to attain equilibrium in the brain and tissues, allowing the anaesthetic state to be established more reliably and quickly than given through the lungs**.**[69] Furthermore, it has been proposed that the amount of anaesthetic drug required to achieve anaesthesia could possibly be greatly lowered, thus lowering both the incidence of side effects and expenses. The minimum alveolar concentration (MAC) of emulsified halothane in swine was substantially lower than that of inhaled halothane. Emulsified halogenated anaesthetics can be delivered intravenously, intrathecally, epidurally, subcutaneously, or intraperitoneally.[70-72]

Various nanoemulsification formulations of various halogenated inhalation agents including 15 pc isoflurane, 20 and 30 pc sevoflurane, have been synthesised. However, it was demonstrated shown that the amount of injectable isoflurane required to maintain general anaesthesia was not less than that of inhalable isoflurane. Laboratory tests revealed no

evidence of acute hepatic or renal damage following infusion. The instability of concentrated emulsions of sevoflurane in Intralipid limits the clinical value of Intralipid for intravenous delivery in human patients. On the contrary, the use of fluoro-surfactants enables for the far more convenient usage of stable and concentrated sevoflurane emulsions.

VI. REVERSAL AGENTS

1. Atropine

- Nano-atropine sulfate dry powder: Nanotechnology precipitation method has enabled formulation of inhaled atropine in form of dry powder which can be used in organophosphorus poisoning. It can be supplied with pesticide as dry powder inhaler rotacaps and can be used in case of accidental poisoning. The formulation appears to have the benefit of early therapeutic drug concentration in blood due to lungs absorption as well as sustained action due to gut absorption and hence bypassing of first pass metabolism[73]
- Atropine-functionalized gold nanoparticles (Au-MUDA-AT NPs): Even though currently synthesized on experimental basis, Au-MUDA-AT NPs are a potential therapeutic tool for the modulation of intestinal secretion and motility owing to easy passage across the cell lining.[74]

2. Neostigmine

- Primarily used to reverse effects of muscle relaxants, neostigmine also possesses analgesic properties, neostigmine poly vinyl alcohol (PVA) nanofibers embedded with neostigmine have been synthesized and tested in rats. These neostigmine embedded nanofibers can be used epidurally as well as intrathecally to provide central analgesic action[75]
- Sustained release polymeric nanoparticles of neostigmine bromide: Polymeric (chitosan) nanoparticles of neostigmine bromide exhibit sustained release pattern of upto 24 hrs[76]

VII. LOCAL ANAESTHETICS

The first report on the use of LAs compressed in liposomes was published two decades ago, topical liposomal 5% tetracaine formulation provided better pain relief than 20% benzocaine gel in an infiltrative injection of 4% prilocaine.[77]

Lidocaine, bupivacaine, ropivacaine, and tetracaine gels (topical or transoral) and parenteral formulations have all been developed.

Nanoformulated Liposomes and Local Anaesthetics: Liposomal bupivacaine: De Oliveira and colleagues were among the first to describe the use of liposomal bupivacaine, Exparela, on healthy volunteers to achieve lasting alleviation of pain in a single dose and were found to be more potent.[78] Lonner et colleagues concluded that liposomal bupivacaine had fewer cardiotoxic adverse effects . [77]Administering liposomal bupivacaine to postoperative patients effectively reduces the demand for narcotics

Uses of Liposomal Bupivacaine

- Liposomal bupivacaine was approved by the FDA for surgical site infiltration in October 2011. It is currently approved for postoperative pain management via local infiltration.
- Research suggests that utilising liposomal bupivacaine for TAP blocks and local surgical site infiltration following abdominal surgery could be beneficial.
- Liposomal Bupivacaine has been explored for use in epidural injections, intra-articular injections, and peripheral nerve blocks.
- Liposomal bupivacaine may be beneficial in chronic pain patients.

Liposomal ropivacaine was analysed by Franz-Montan and co-workers in a carbopol gel formulation administered to oral mucosa before LA injection enhanced the pain relief of inserting needles[78]

VIII. NANOPARTICLES AND LOCAL ANAESTHETICS

The lipid–polymer hybrid nanoparticles have demonstrated increased encapsulation efficiency than liposomes and a better-sustained release rate of liposomal encapsulated lidocaine. Liposomal encapsulated lidocaine was also combined with poly (ε-Caprolactone) to report a prolonged duration of action in mice.[79]

Alginate nanoparticles encapsulated with bupivacaine have found to be reducing the bupivacaine induced cardiotoxicity while prolonging the action in experimental animals. Racemic bupivacaine containing 25% dextrobupivacaine and 75% levobupivacaine were evaluated after compounding with chitosan/alginate nanoparticles as a preclinical trial as NovaBupi was found to prolong the local anaesthetic action[80]

1. **Hydrogels and Local Anaesthesia:** Hydrogels have been employed to deliver LA drugs. Mebeverine as a local anaesthetic drug encapsulated in hydrogels was tested for management of painful oral conditions and found to be more effective.[81]
   Genipin-crosslinked catechol-chitosan based hydrogel for lidocaine buccal mucosa delivery displayed sustained release LA in rabbits.[82]

2. **Nanoformulated Cyclodextrins:** nnaoformulated cyclodextrins have been compounded/ complexed with lignocaine and it was concluded cyclodextrins play an efficient role in safe administration and controlled release of the drug.[83]

3. **Nanospheres, Nanorods Coupled Local Anaesthetics:** Lidocaine coupled poly(D,L-lactic acid) nanospheres/ nanorods were administered and were demonstrated to be much less toxic than the free medication, and to have better anaesthetic efficacy as well as prolonged duration and intensity of analgesia.[84,85]

4. **The Age of Nanobots and Anaesthesiology:** Nano robots or nanobots in itself is a vast but interesting area and need a separate chapter altogether. However, a brief introduction to the concept of nanobots or nano-robots has been included herewith.

The next major development will be the introduction of robots into human bodies, where they will carry out their incredibly specific tasks. This will be made feasible by a combination of complex medical procedures and fine technology. The future of medical nanorobotics holds the promise of potent new tools for the detection and treatment of a wide range of human ailments as well as the advancement in fields of anaesthesia and surgery. Respirocyte, Clottocyte, Pharmacytes (for nanorobotic medication administration), Dentifrobots (dental nanorobots), and Vasculoids (as an artificial nanomechanical vascular system) are some of the several types of possible nanorobots which can change the way medicine is practiced.[86] The perfect nanorobots would possibly form a polymeric structure. They might self-replicate/duplicate, communicate amongst themselves and later be retrieved either via exhalation, scavanging or excretory mechanisms.[87] The potential applications of nanorobots include:

- ***Precision Drug Delivery Systems*:** Pharmacytes are nanorobots created specifically to deliver drugs with high Precision at specific target areas by nanoinjection or by gradual cytopenetration at any target cell. This would allow for a reduction in anaesthetic drug dosage, translating into fewer complications, adverse reactions, side effects and a better safety profile.

- ***Body Surveillance and Peri-Operative Diagnostics*:** Monitoring continuously of vitals and wireless transmission could be possible using nanorobots, leading to a quantum leap in diagnostics. This would also help in quick response in case of sudden change in vitals, or could warn against a possible risk, such as high blood glucose in case of diabetics and could possibly change the entire meaning and reach of point of care testing along with intra-operative monitoring and diagnostics.

- ***Dental Anesthesia and Dental Surgery*:** Dentifrobots can help realign/repair teeth oral while providing analgesia, desensitizing teeth, and manipulating tissues.

- ***Use in Active Bleeding as Platelet Substitutes*:** Clottocytes would unfold a fibre mesh that would trap blood cells when the nanobot reached the site of the damage, simulating the natural platelet ability to accumulate at the bleed in order to establish a barrier. One injection of clottocytes would have 10,000 times the clotting power of an equivalent volume of normal platelets

- ***Respirocytes*:** Respirocytes are fictitious nanobots which can act as RBC substitutes. They may assist in transfer of gases to and from the lungs. They may be 200 times potent as compared to normal RBCs.

- ***Cancer Detection and Treatment*:** The nanorobot could deliver precision chemotherapeutic agents at cancer site. This possibly can be utilized alone or in conjunction with techniques such as Radiofrequency or microwave ablations which are extremely painful and require high dosage of analgesics

IX. ARE THE NANOPARTICLES SAFE FOR US?

Human safety is of utmost importance and the most essential aspect regarding the safe usage of nanomaterial products in healthcare settings. The vast majority of clinical trial data

for nanomedicine products focus primarily on therapeutic potency rather than biosafety or adverse effects of NPs on people. As a result, human clinical trials comprise the most crucial stage in the clinical deployment of nanomaterial technologies. Because of their incredibly small size and large surface area, NPs may be highly reactive due to their physical and chemical properties. NPs may interact with biological components in the human body or accumulate there.

As per some of the animal studies, some NPs have demonstrated a negative impact on health. Carbon NPs, for example, are classified as possibly dangerous to humans by WHO/International Agency for Research on Cancer based on animal studies. [88]In animal investigations, multiwalled carbon nanotubes have a limited record of carcinogenicity.[89,90] Sargent et al. (2014), on the other hand, demonstrated that inhaling multiwalled carbon nanotubes causes cancer in mice. It is also unknown if human exposure to NPs designed for medical use promotes cancer.[91]

More than two-thirds of the nanoparticulate systems now licensed for therapeutic clinical use in humans are soft particles, with liposomes NPs being the majority. These medicinal or carrier NPs are generally thought to be less harmful than hard solid NPs. Despite soft NPs having a safer low toxicity profile, larger equivalents can accumulate in key organs and produce hazardous consequences, which should not be overlooked.[92,93]

The main disadvantages of animal investigations are the use of dosages and exposure times which differ significantly from human administration routes in clinical use. Furthermore, because people and animals differ immensely structurally, genetically and physiologically that animal experimental results can’t be applied to humans in toto. Human biosafety evaluation for nanomedicine products is still in its early stages, with only a handful nanotechnologically derived/based medicinal preparations approved by the FDA. While researching nanomedicine products for human use, one should be prepared for accidental overdose, abuse, or accumulation of NPs in human tissue and organs, i.e., how to treat overdose toxicities and stimulate superfluous NP excretion from the body.

In a nutshell!!

There are enormous expectations regarding the potential of nanomedicine in anesthesiology, pain management and critical care in terms of diagnostic and therapeutic domains. The future of nanomedicine envisions early and significant alterations at the molecular and cellular level with unambiguous imaging techniques and minimally invasive patient therapy with specially formulated medications.

REFERENCES

[1] Feynman, R.P. (1992). There’s plenty of room at the bottom. Resonance, 16, 890-905.
[2] Gottschalk A, Van Aken H, Zenz M et al. Dtsch Arztebl Int 2011; 108: 469
[3] Viseu, A.. "nanomedicine." Encyclopedia Britannica, September 7, 2023. https://www.britannica.com/science/nanomedicine.
[4] Moghimi SM, Hunter AC, Murray JC. Long-circulating and target specific nanoparticles: theory to practice. Pharmacol. Rev.53(2),283–318 (2001).
[5] Emerich DF, Thanos CG. The pinpoint promise of nanoparticle-based drug delivery and molecular diagnosis. Biomol. Eng.23(4),171–184 (2006).

[6] Kharb V, Bhatia M, Dureja H, Kaushik D. Nanoparticle technology for the delivery of poorly water-soluble drugs. Pharm. Technol.30(2),82–92 (2006).
[7] Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: a formulation approach for poorly-water-soluble compounds. Eur. J. Pharm. Sci.18,113–120 (2003).
[8] Kipp JE. The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. Int. J. Pharm.284,109–122 (2004).
[9] Nanotechnology in Therapeutics.A Focus on Nanoparticles as a Drug Delivery System. Suwussa Bamrungsap; Zilong Zhao; Tao Chen; Lin Wang; Chunmei Li; Ting Fu; Weihong Tan; Nanomedicine. 2012;7(8):1253-1271.
[10] Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv. Drug Deliv. Rev.55,329–347 (2003)
[11] Gabizon A, Horowitz AT, Goren D, Tzemach D, Shmeeda H, Zalipsky S. In vivo fate of folate-targeted polyethylene-glycol liposomes in tumor-bearing mice. Clin. Cancer Res.9(17),6551– 6559 (2003).
[12] Nishiyama N, Kataoka K. Current state achievements and future prospects of polymeric micelles as nanocarriers for drug and gene delivery. Pharmacol. Ther.112(3),630–648 (2006).
[13] Lowman AM, Peppas NA. Hydrogels. In: Encyclopaedia of Controlled Drug Delivery. Mathiowitz E (Ed.). John Wiley & Sons, NY, USA, 397–418 (1999).
[14] Gupta P, Vermani K, Garg S. Hydrogels: from controlled release to pH-responsive drug delivery. Drug Discov. Today7,569–579 (2002).
[15] Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Adv. Drug Deliv. Rev.60,1638–1649 (2008).
[16] Zubris KAV, Colson YL, Grinstaff MW. Hydrogels as intracellular depots for drug delivery. Mol. Pharmaceut.9(1),196–200 (2011).
[17] Liang Y, Deng L, Chen C et al. Preparation and properties of thermoreversible hydrogels based on methoxy poly(ethylene glycol)-grafted chitosan nanoparticles for drug delivery systems. Carbohyd. Polym.83(4),1828–1833 (2011).
[18] Barbucci R, Pasqui D, Giani G et al. A novel strategy for engineering hydrogels with ferromagnetic nanoparticles as crosslinkers of the polymer chains. Potential applications as a targeted drug delivery system. Soft Matter7(12),5558–5565 (2011).
[19] Wang G, Uludag H. Recent developments in nanoparticle-based drug delivery and targeting systems with emphasis on protein-based nanoparticles. Expert Opin. Drug Deliv.5(5),499–515 (2008).
[20] Green MR, Manikhas GM, Orlov S et al. Abraxane®, a novel Cremophor®-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann. Oncol.17(8),1263–1268 (2006).
[21] Lee CC, MacKay JA, Fréchet JMJ, Szoka FC. Designing dendrimers for biological applications. Nat. Biotechnol.23,1517–1526 (2005).
[22] Gupta U, Agashe HB, Asthana A, Jain NK. A review of in vitro-in vivo investigations on dendrimers: the novel nanoscopic drug carriers. Nanomedicine2(2),66–73 (2006).
[23] Svenson S, Tomalia DA. Dendrimers in biomedical applications – reflections on the field. Adv. Drug Deliv. Rev.57(15),2106–2129 (2005).
[24] Connor EE, Mwamuka J, Gole A, Murphy CJ, Wyatt MD. Gold nanoparticles are taken up by human cells but do not cause cytotoxicity. Small1,325–327 (2005).
[25] Hostetler MJ, Wingate JE, Zhong CJ et al. Alkanethiolate gold cluster molecules with core diameters from 1.5 to 5.2 nm: core and monolayer properties as a function of core size. Langmuir4,17–30 (1998).
[26] Polizzi MA, Stasko NA, Schoenfisch MH. Water-soluble nitric oxide-releasing gold nanoparticles. Langmuir23(9),4938–4943 (2007).
[27] Han G, You CC, Kim BJ et al. Light-regulated release of DNA and its delivery to nuclei by means of photolabile gold nanoparticles. Angew. Chem. Int. Ed. Engl.45(19),3165–3169 (2006).
[28] Skirtach AG, Javier AM, Kreft O et al. Laser-induced release of encapsulated materials inside living cells. Angew. Chem. Int. Ed. Engl.45(28),4612–4617 (2006).
[29] Brazel CS, Ankareddi I, Hampel ML, Bagaria H, Johnson DT, Nikles DE. Development of magnetothermal-responsive delivery systems using FePt nanoparticles imbedded in poly(N-isopropylacrylamide)-based hydrogels. Control Rel. Soc. Trans.33,762 (2006).
[30] Orive G, Hernández RM, Gascón AR, Pedraz JL. Micro and nano drug delivery systems in cancer therapy. Cancer Ther.3,131–138 (2005).
[31] Medina C, Santos-Martinez MJ, Radomski A, Corrigan OI, Radomski MW. Nanoparticles: pharmacological and toxicological significance. Br. J. Pharmacol.150,552–558 (2007).

[32] Rawat M, Singh D, Saraf S, Saraf S. Nanocarriers: promising vehicle for bioactive drugs. Biol. Pharm. Bull.29(9),1790–1798 (2006).
[33] Krueger A. New carbon materials: biological applications of functionalized nanodiamond materials. Chem. Eur. J.14(5),1382–1390 (2008).
[34] Lacerda L, Bianco A, Prato M, Kostarelos K. Carbon nanotubes as nanomedicines: from toxicology to pharmacology. Adv. Drug Deliv. Rev.58(14),1460–1470 (2006).
[35] Magres A, Kasas S, Salicio V et al. Cellular toxicity of carbon-based nanomaterials. Nano Lett.6,1121–1125 (2006).
[36] Hassani Najafabadi A, Azodi-Deilami S, Abdouss M, Payravand H, Farzaneh S. Synthesis and evaluation of hydroponically alginate nanoparticles as novel carrier for intravenous delivery of propofol. J Mater Sci Mater Med. 2015 Mar;26(3):145.
[37] Rittes JC, Cagno G, Perez MV, Mathias LA. Comparative evaluation of propofol in nanoemulsion with solutol and soy lecithin for general anesthesia. Braz J Anesthesiol. 2016 May-Jun;66(3):225-30, Wang H, Cork R, Rao A. Development of a new generation of propofol. Curr Opin Anaesthesiol. 2007 Aug;20(4):311-5.
[38] Uchegbu I, Jones M-C, Corrente F, Godfrey L, Laghezza D, Carafa M et al. The Oral and Intranasal Delivery of Propofol Using Chitosan Amphiphile Nanoparticles. Pharmaceutical Nanotechnology. 2014;2(2):65-74
[39] R.T. Sudo, L. Bonfá, M.M. Trachez, R. Debom, M.D. Rizzi, G. Zapata-Sudo. Anesthetic profile of a non-lipid propofol nanoemulsion. Rev. Bras. Anestesiol., 60 (5) (2010 Sep-Oct), pp. 475-483
[40] Propofol-loaded nanomicelle with improved anesthetic, pharmacokinetic, hemocompatibility, safety, and permeation profiles. Hongfei Chen, Long He, Da Li, Feng Jin, Yanqiu Ai. Arabian Journal of Chemistry.2021; 14(5): 103093.
[41] Chu Y, Sun T, Xie Z, Sun K, Jiang C. Physicochemical Characterization and Pharmacological Evaluation of Novel Propofol Micelles with Low-Lipid and Low-Free Propofol. Pharmaceutics. 2022 Feb 14;14(2):414
[42] Ravenelle F, Gori S, Le Garrec D, Lessard D, Luo L, Palusova D, Sneyd JR, Smith D. Novel lipid and preservative-free propofol formulation: properties and pharmacodynamics. Pharm Res. 2008 Feb;25(2):313-9.)
[43] Han FY, Liu Y, Kumar V, Xu W, Yang G, Zhao CX, Woodruff TM, Whittaker AK, Smith MT. Sustained-release ketamine-loaded nanoparticles fabricated by sequential nanoprecipitation. Int J Pharm. 2020 May 15;581:119291
[44] Hirano S, Bovi M, Romeo A, Guzzo F, Chiamulera C, Perduca M. Ketamine nano-delivery based on poly-lactic-co-glycolic acid (PLGA) nanoparticles. Applied Nanoscience. 2018 Apr;8(4):655-63.
[45] Zhang X, Li Z, Gao J, Wang Z, Gao X, Liu N, Li M, Zhang H, Zheng A. Preparation of Nanocrystals for Insoluble Drugs by Top-Down Nanotechnology with Improved Solubility and Bioavailability. Molecules. 2020 Feb 28;25(5):1080.
[46] Sharma D, Sharma RK, Sharma N, Gabrani R, Sharma SK, Ali J, Dang S. Nose-To-Brain Delivery of PLGA-Diazepam Nanoparticles. AAPS PharmSciTech. 2015 Oct;16(5):1108-21. doi: 10.1208/s12249-015-0294-0.
[47] Cárdeno A, Aparicio-Soto M, Montserrat-de la Paz S, Bermudez B, Muriana FJG, Alarcónde-la-Lastra C, Journal of Functional Foods, 14 (2015) 779–790
[48] Zhao C, Liu A, Santamaria CM, Shomorony A, Ji T, Wei T, Gordon A, Elofsson H, Mehta M, Yang R, Kohane DS, Nat Commun, 10 (2019) 2566.
[49] Curley J, Castillo J, Hotz J, Uezono M, Hernandez S, Lim JO, Tigner J, Chasin M, Langer R, Berde C, Anesthesiology, 84 (1996) 1401–1410
[50] Ramirez-Garcia PD, Retamal JS, Shenoy P, Imlach W, Sykes M, Truong N, Constandil L, Pelissier T, Nowell CJ, Khor SY, Layani LM, Lumb C, Poole DP, Lieu T, Stewart GD, Mai QN, Jensen DD, Latorre R, Scheff NN, Schmidt BL, Quinn JF, Whittaker MR, Veldhuis NA, Davis TP, Bunnett NW, Nat Nanotechnol, 14 (2019) 1150–1159
[51] Girotra P, Singh SK, Pharm Res, 33 (2016) 1682–1695.
[52] Girotra P, Thakur A, Kumar A, Singh SK, Int J Biol Macromol, 96 (2017) 687–696.
[53] Mendoza G, Arruebo M, Expert Opin Drug Deliv, 17 (2020) 627–633.
[54] Linsley CS, Wu BM, Ther Deliv, 8 (2017) 89–107
[55] Mantha VR, Nair HK, Venkataramanan R, Gao YY, Matyjaszewski K, Dong H, Li W, Landsittel D, Cohen E, Lariviere WR, Anesth Analg, 118 (2014) 1355–1362
[56] Rwei AY, Paris JL, Wang B, Wang W, Axon CD, Vallet-Regi M, Langer R, Kohane DS, Nat Biomed Eng, 1 (2017) 644–653

[57] Moreno AM, Alemán F, Catroli GF, Hunt M, Hu M, Dailamy A, Pla A, Woller SA, Palmer N, Parekh U, McDonald D, Roberts AJ, Goodwill V, Dryden I, Hevner RF, Delay L, Gonçalves dos Santos G, Yaksh TL, Mali P, Science Translational Medicine, 13 (2021) eaay9056.
[58] Liang H, Peng B, Dong C, Liu L, Mao J, Wei S, Wang X, Xu H, Shen J, Mao H-Q, Gao X, Leong KW, Chen Y, Nature Communications, 9 (2018) 4291
[59] Gomez-Murcia V, Montalban MG, Gomez-Fernandez JC, Almela P. Development of Poly(lactide-co-glicolide) Nanoparticles Incorporating Morphine Hydrochloride to Prolong its Circulation in Blood. Curr Pharm Des. 2017;23(13):2015-2025.
[60] Kölemek, H., Bulduk, İbrahim, Ergün, Y., Konuk, M., Korcan, S. E., Liman, R. and Çoban, F. K. (2019) "Synthesis of Morphine Loaded Hydroxyapatite Nanoparticles (HAPs) and Determination of Genotoxic Effect for Using Pain Management", Journal of Pharmaceutical Research International, 25(6), pp. 1–13.
[61] Bhansali D, Teng SL, Lee CS, Schmidt BL, Bunnett NW, Leong KW. Nanotechnology for Pain Management: Current and Future Therapeutic Interventions. Nano Today. 2021 Aug;39:101223
[62] Sao Pedro A, Fernandes R, Villarreal CF, Fialho R, Albuquerque EC, J Microencapsul, 33 (2016) 18–29]. A single epidural injection of Depodur provides analgesia for 48 hours [Alam M, Hartrick CT, Pain Pract, 5 (2005) 349–353
[63] Balch RJ, Trescot A, J Pain Res, 3 (2010) 191–200
[64] Sao Pedro A, Fernandes R, Villarreal CF, Fialho R, Albuquerque EC, J Microencapsul, 33 (2016) 18–29
[65] Mystakidou K, Tsilika E, Tsiatas M, Vlahos L. Oral transmucosal fentanyl citrate in cancer pain management: a practical application of nanotechnology. Int J Nanomedicine. 2007;2(1):49-54
[66] M. Kovaliov , S. Li , E. Korkmaz , D. Cohen-Karni , N. Tomycz , O. B. Ozdoganlar and S. Averick , RSC Adv., 2017, 7 , 47904 —47912
[67] Sundar VD, Divya P, Dhanaraju MD. Design Development and Characterisation of Tramadol Hydrochloride Loaded Transethosomal Gel Formulation for Effective Pain Management. Indian J of Pharmaceutical Education and Research. 2020;54(2s):s88-s97).
[68] (Lalani J, Rathi M, Lalan M, Misra A. Protein functionalized tramadol-loaded PLGA nanoparticles: preparation, optimization, stability and pharmacodynamic studies. Drug Dev Ind Pharm. 2013 Jun;39(6):854-64.)
[69] (Eger RP, MacLeod BA. Anaesthesia by intravenous emulsified isoflurane in mice. Can J Anaesth. 1995 Feb;42(2):173-6.
[70] Musser JB, Fontana JL, Mongan PD. The anesthetic and physiologic effects of an intravenous administration of a halothane lipid emulsion (5% vol/vol). Anesth Analg. 1999 Mar;88(3):671-5,
[71] Zhou C, Liu J, Chen XD. General anesthesia mediated by effects on ion channels. World J Crit Care Med. 2012 Jun 4;1(3):80-93.,
[72] Lucchinetti, Eliana PhD*†; Schaub, Marcus C. MD, PhD‡; Zaugg, Michael MD, DEAA*†. Emulsified Intravenous Versus Evaporated Inhaled Isoflurane for Heart Protection: Old Wine in a New Bottle or True Innovation?. Anesthesia & Analgesia 106(5):p 1346-1349, May 2008. | DOI: 10.1213/ane.0b013e31816d1661)
[73] Ali R, Jain GK, Iqbal Z, Talegaonkar S, Pandit P, Sule S, Malhotra G, Khar RK, Bhatnagar A, Ahmad FJ. Development and clinical trial of nano-atropine sulfate dry powder inhaler as a novel organophosphorous poisoning antidote. Nanomedicine. 2009 Mar;5(1):55-63.)
[74] Claßen Rebecca, Pouokam Ervice, Wickleder Matthias, Diener Martin and Mattern Annabelle. 2022Atropine-functionalized gold nanoparticles binding to muscarinic receptors after passage across the intestinal epitheliumR. Soc. open sci.9:220244. 22024
[75] Yosefifard M, Hassanpour-Ezatti M. Epidural administration of neostigmine-loaded nanofibers provides extended analgesia in rats. Daru. 2014 Nov 18;22(1):73.
[76] Kaushal Kumar et al. Int J Sci Res Sci Technol. March-April-2019; 6(2) : 964-977
[77] Lonner J. Role of liposomal bupivacaine in pain management after total joint arthroplasty. J Surg Orthop Adv. 2014;23:37–41.
[78] Franz-Montan M, De Paula E, Groppo FC, et al. Liposome-encapsulated ropivacaine for intraoral topical anesthesia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;110:800–804.
[79] Yin QQ, Wu L, Gou ML, et al. Long-lasting infiltration anaesthesia by lidocaine-loaded biodegradable nanoparticles in hydrogel in rats. Acta Anaesthesiol Scand. 2009;53:1207–1213.
[80] Cereda CMS, Mecatti DS, Papini JZB, Bueno DV, Franz-Montan M, Rocha T, Pedrazzoli Júnior J, de Paula E, de Araújo DR, Grillo R, Fraceto LF, Calafatti SA, Tofoli GR. Bupivacaine in alginate and chitosan nanoparticles: an in vivo evaluation of efficacy, pharmacokinetics, and local toxicity. J Pain Res. 2018 Apr 6;11:683-691.

[81] Abdel-Hamid SM, Abdel-Hady SE, El-Shamy AA, et al. Formulation of an antispasmodic drug as a topical local anesthetic. Int J Pharm. 2006;326:107–118.
[82] Xu J, Strandman S, Zhu JXX, et al. Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery. Biomaterials. 2015;37:395–404.
[83] (Arakawa Y, Kawakami S, Yamashita F, et al. Effect of low-molecular-weight beta-cyclodextrin polymer on release of drugs from mucoadhesive buccal film dosage forms. Biol Pharm Bull. 2005;28:1679–1683.
[84] Görner T, Gref R, Michenot D, et al. Lidocaine-loaded biodegradable nanospheres. I. Optimization of the drug incorporation into the polymer matrix. J Control Release. 1999;57:259–268.
[85] amos Campos EV, Silva de Melo NF, Guilherme VA, et al. Preparation and characterization of poly(ε-caprolactone) nanospheres containing the local anesthetic lidocaine. J Pharm Sci. 2013;102:215–226.
[86] Apoorva Manjunath, and Vijay Kishore, "The Promising Future in Medicine: Nanorobots." Biomedical Science and Engineering, vol. 2, no. 2 (2014): 42-47. doi: 10.12691/bse-2-2-3.
[87] Mithilesh K, Misha G, Ashish G, Summit K, Jayashree S. Nanotechnology in Anesthesia and Pain – A Review. Theranostics 004 Brain,Spine & Neural Disord. 2018; 4(1): 555627.)
[88] Baan RA. Carcinogenic hazards from inhaled carbon black, titanium dioxide, and talc not containing asbestos or asbestiform fibers: recent evaluations by an IARC Monographs Working Group. Inhalation toxicology. 2007 Jan 1;19(sup1):213-28.
[89] Sakamoto Y, Nakae D, Fukumori N, Tayama K, Maekawa A, Imai K, Hirose A, Nishimura T, Ohashi N, Ogata A. Induction of mesothelioma by a single intrascrotal administration of multi-wall carbon nanotube in intact male Fischer 344 rats. The Journal of toxicological sciences. 2009 Feb 1;34(1):65-76.
[90] Zhao J, Castranova V. Toxicology of nanomaterials used in nanomedicine. Journal of Toxicology and Environmental Health, Part B. 2011 Nov 1;14(8):593-632.
[91] Sargent LM, Porter DW, Staska LM, Hubbs AF, Lowry DT, Battelli L, Siegrist KJ, Kashon ML, Mercer RR, Bauer AK, Chen BT. Promotion of lung adenocarcinoma following inhalation exposure to multi-walled carbon nanotubes. Particle and fibre toxicology. 2014 Dec;11(1):1-8.
[92] Su H, Wang Y, Gu Y, Bowman L, Zhao J, Ding M. Potential applications and human biosafety of nanomaterials used in nanomedicine. J Appl Toxicol. 2018 Jan;38(1):3-24. doi: 10.1002/jat.3476.
[93] Patra, J.K., Das, G., Fraceto, L.F. et al. Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnol 16, 71 (2018).)

