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Review

Nanoliposome encapsulated anesthetics for local anesthesia application

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ABSTRACT

The systemic administration of opioids leads to potentially severe and undesirable and side effects like sedation and drowsiness, vomiting and nausea, allergies, respiratory depression, and neutrophil dysfunction. The application of nanotechnology in medical field has drawn a great attention in recent times. Several treatments available are tedious and expensive. Application of nanotechnology brings about faster cure and cost effectiveness. Nanoliposomes are one of the widely used names for nanoparticles used in medicine. Recently, nanoliposomes are used as a crucial novel drug delivery systems. The use of nanoliposomal formulation brings about a good results to pain control, rapid patient recovery, increased patient comfort, treatment costs reduction, and shortens length of hospitalization. This review presents a brief description about the achievements in the field of nanoscience and nanotechnology related to the application of nanoliposomes in anesthesia.

Contents

1. Introduction

Nanotechnology can be defined as the science and technology involved in the synthesis, characterization and application of

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materials and devices, by controlling their shapes and size at nano scale level. Nanotechnology applications to medicine and physiology involves devices and materials designed to interact with the body at subcellular scales with a higher degree of specificity. A maximum therapeutic efficacy with a minimal side effects results from targeted cellular and tissue-specific clinical applications [1–6].

Pain management represents one of the aims of anesthesia and perioperative care [7–12]. Opioids are the 'gold standard' of pain control in advanced disease patients. However, their systemic administration poses some undesirable side effects. For instance, light sedation coupled with local or regional anesthesia [13,14], may not be appropriate for involved procedures. Drug-loaded nanoparticles provide an excellent solution for higher therapeutic efficacy, reducing drug toxicity and the increasing tropism [15–23]. Several nanocarriers are available, including nanoparticles, nanoliposomes, liposomes, micelles, solid lipid particles, quantum dots, surfactant vesicles, and different nanodevices [14,24–29]. Liposome is a popular phrase covering various classes of lipid vesicles, but, the term nanoliposome is lately been introduced to completely refer to nanoscale lipid vesicles [30]. Large surface area to volume ratio of nanocarriers resulted in enhanced pharmacokinetics and biodistribution of therapeutic agents; thus, they reduce drug toxicity by their targeted accumulation at the major site [31–34].

Nanoliposomes are capable of elevating the performance of bioactive agents by enhancing their bioavailability, *in vitro* and *in vivo* stability, in addition to inhibiting unwanted interactions with other molecules. Nanoliposome has been widely used in medical and pharmaceutical field due to its strong biological characteristics such as biocompatibility, biodegradability, and low toxicity. For this reasons, here, we present a description about the recent development in the field of nanoscience and nanotechnology related to the application of nanoliposomes in anesthesia [35–38].

2. Anesthesia

Anesthesia categorized into three main parts: general, regional, and local anesthesia, all of which have an influence on the nervous system in some way, and can be administered applying different techniques and various medications [39].

2.1. Local anesthetic (LA)

A local anesthetic drug numbs just a small specific part of the body. With local anesthesia, a person is sedated or awake, depending on the requirement. Local anesthesia lasts for a short period of time and is often used for small outpatient procedures. The medicine used can numb the area during the procedure and for a short period time, to help control post-surgery discomfort [40,41].

Surgery is naturally extremely painful. Local anesthetic agents application is capable of blocking nerve conduction from the operation site. A perfect LA agent would block pain and cover the duration of the pain with no local irritant effects, non-allergenic potential, high therapeutic index, and provide sensory block rather than motor blockade. All of the local anesthetics have the suffix "-caine" in their names [42].

Clinical local anesthetics belong to one of the two classes: aminoester and aminoamide local anesthetics. Synthetic local anesthetics are structurally related to cocaine. They differ from cocaine mainly in that they have a very low abuse potential (lower dose) and do not produce hypertension (with few exceptions) vasoconstriction. There are different techniques used in local anesthetics, these include spinal anesthesia (subarachnoid block), epidural block, topical anesthesia, plexus block, and infiltration [43].

Suitable administration of local anesthetics depends on individual features of the patient, presence or absence of epinephrine, dose of local anesthetic to be administered, speed of administration, method of administration and local tissue vascularity [44].

2.2. Local anesthetic drugs

2.2.1. Levobupivacaine

Levobupivacaine is a local anesthetic agent that induce nerve block, infiltration, ophthalmic, epidural and intrathecal anaesthesia in adults; and infiltration analgesia in children. Levobupivacaine shoudn't be used for intravenous regional anesthesia [45]. Dosages, onset time, and duration of action of levobupivacaine are listed in Table 1.

2.2.2. Ropivacaine

Ropivacaine is a long acting amide local anesthetic agent that was first synthesized as a pure enantiomer. It produces an effects similar to other local anesthetics, by reversible sodium ion influx in nerve fibres inhibition. It doesn't possess the ability to penetrate large myelinated motor fibres, and is less lipophilic than bupivacaine, resulting in a relatively decreased motor block. Hence, Ropivacaine has a greater degree of motor-sensory differentiation, which could be an advantage when the motor blockade is undesirable [46]. Dosages, onset time and duration of action of Ropivacaine are listed in Table 1.

2.2.3. Bupivacaine

Bupivacaine hydrochloride is 2-Piperidinecarboxamide, 1-butyl-*N*-(2, 6-dimethylphenyl)-, monohydrochloride, monohydrate. It is a white crystalline powder that is readily soluble in 95% ethanol, soluble in water, and slightly soluble in chloroform or acetone. Bupivacaine is potent for sympathetic nerve block, peripheral nerve block, local infiltration, epidural and caudal blocks. It is sometimes administered in combination with epinephrine to prevent systemic absorption, and to extend the duration of its action. It is the most frequently used local anesthetic in epidural anesthesia during labor, and also in postoperative management of pain. Dosages, onset time and duration of action of Bupivacaine are listed in Table 1.

Other anesthetic agents such as Lidocaine [47,48], Procaine, Mepivacaine, Etidocaine, Chloroprocaine, Tetracaine etc are also included (Table 2).

3. Pharmacodynamics

Local anesthetics are weak bases and are categorized as either amides or esters. Effectiveness is associates with octanol solubility and is a function of lipid solubility of the molecule. The onset of a local anesthetic is influenced by many factors, including pKa and lipid solubility. The period of action relates with effectiveness and lipid solubility. Highly lipid soluble local anesthetics have a longer period of action [49].

According to the modulated receptor model, sodium ion channels varies between a number of conformation states, and local anesthetics attach to these alternative conformational states

Table 1
Dosages, onset time and duration of action of Levobupivacaine, Ropivacaine, and Bupivacaine.

	Levobupivacaine	Ropivacaine	Bupivacaine
Volume and dose	20 ml 0.5%	20 ml 0.55%	30 ml 0.5%
Onset	Medium	Medium	Slow
Duration (with Epinephrine)	4–6 h (8–12 h)	3 h (6 h)	4 h (8 h)

Table 2
Methods of nanoliposomes preparation.

Mechanical	Non-mechanical
Sonication	Reverse Phase Separation
Homogenation	Lipid-detergent micelles outing
Extrusion	Drying with frizzing
Tiny fluidization	Solution injection
	Thin layer hydration
	Heating or Mozafari method

with different affinities. Local anesthetics bind to the inactivated and activated states more freely than the resting state, thus, attenuating the conformation change. In summary, local anesthetics mechanism of action is via inactivating voltage-gated sodium channels [50,51].

Differential local anesthetic blockade is frequently observed. Nerve fibers are categorized based on fiber diameter. Large, myelinated nerve fibers are more sensitive to local anesthetic blockades as compared to smaller, unmyelinated fibers. In clinical application, an advanced increase in local anesthetic concentrations led to an advanced interruption of transmission of sensory, autonomic, and motor neural impulses [52,53].

4. Pharmacokinetics

Systemic absorption of administered local anesthetics rely on the flow of blood. The spot of injection and nearby vascularity of the site take a part in the absorption rate. The existence of vasoconstrictors, like epinephrine administration, leads to vasoconstriction at the spot of injection and reduces systemic absorption. The resulting decreased absorption lowers the peak local anesthetic concentration in the blood and eventually extends the duration of action [54]. Epinephrine has also been presented to improve the quality of the analgesic, and reduces toxic side effects. Its addition has a noticeable effect on shorter acting agents than longer acting ones. For instance, the epinephrine addition to lidocaine will prolong the anesthetic duration by at least 50%, while epinephrine has slight effect on the duration of bupivacaine peripheral nerve blocks [55,56].

Bupivacaine is an amide local anesthetic are metabolized by the microsomal P450 enzymes in the liver with process including hydroxylation and N-dealkylation. A hepatic function decrease or liver blood flow will decrease the rate of metabolism and can cause a patients to have greater blood concentrations of bupivacaine, resulting in a greater risk of systemic toxicity. Just little unmetabolized local anesthetic is passed out via the renal system [57,58].

Local liposomal bupivacaine administration causes a release of local bupivacaine followed by systemic absorption. The liposomal bupivacaine absorption differs based on the site of injection. In some cases, the drug goes through a short-term, first-order release, then, by a second zero order kinetic release. The first peak arises when the free bupivacaine in the liposomal solution is systemically absorbed and the second peak arises in response to the control release of liposomal bupivacaine. The rate of bupivacaine systemic absorption after its release from the drug delivery system is likely to imitate that of bupivacaine HCl [59].

5. Synthetic agents of local anesthetic

At present, commercial local anesthetic agents are synthesized from erythroxylon coca bush. An usual synthetic local anesthetic molecule is composed of charged amine group and a benzene ring. These two molecules are coupled together by the functional group, which can either an ester [COO-] or an amide [-NH-CO-]. Amides possesses a low potential and longer shelf-life for allergic phenomena, and are more often applied than esters [60–68].

5.1. Nanoliposome

A liposome is a spherical vesicle that have at least one lipid bilayer (a hydrophilic head and hydrophobic tail) (Fig. 2). The liposome can be employed as a vehicle for pharmaceutical drugs and nutrients administration [69,70]. The major kinds of liposomes are the multilamellar vesicle (MLV, with several lamellar phase lipid bilayers), the large unilamellar vesicle (LUV), the small unilamellar liposome vesicle (SUV, with one lipid bilayer), and the cochleate vesicle. A less desirable form are multivesicular liposomes in which one vesicle incorporate one or more smaller vesicles (Fig. 1) [36,71–77].

MLV; Multilamellar vesicle
LUV; Large unilamellar vesicle
SUV; small unilamellar liposome vesicle

Nanoliposomes are nanometric version of liposomes. Nanoliposomes can be up to twenty times smaller than liposomes, depending on the type. Nanoliposome is a new technology for bioactive agents encapsulation and delivery [36,78–80]. The list of bioactive compounds that can be incorporated into nanoliposomes is very large, ranging from pharmaceuticals to cosmetics and nutraceuticals. Due to their biodegradability, biocompatibility, nanosize, nanoliposomes [81–84] have shown potential

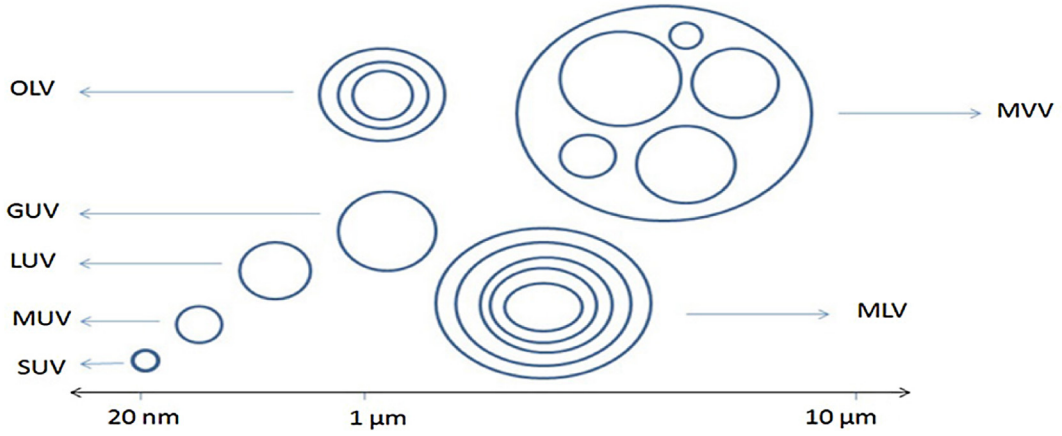

Fig. 1. Classes of Liposomes (Based on size of particles). MLV possessing several lamellar phase lipid bilayers. LUV, SUV and the cochleate vesicle.

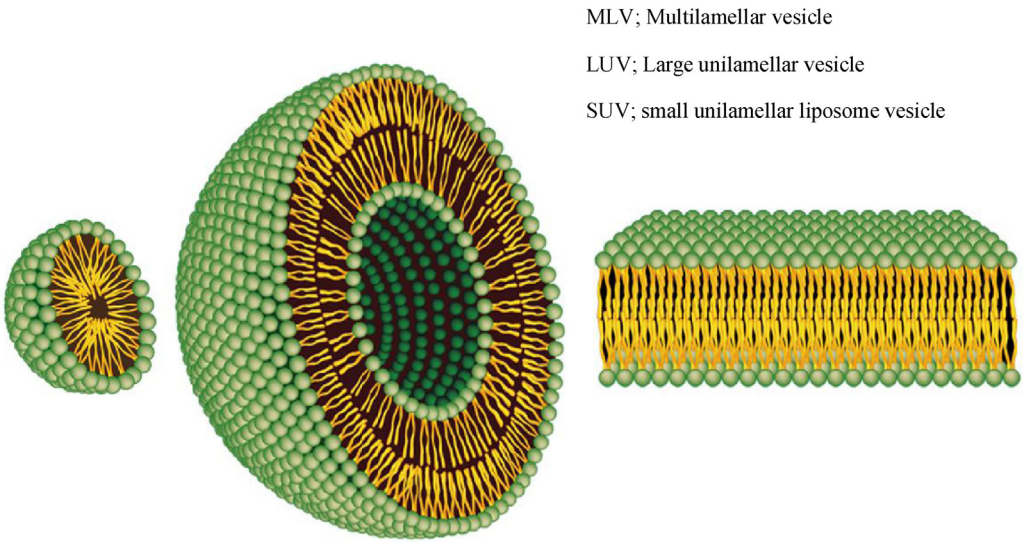

Fig. 2. Representation of the steric organization of a micelle (left), a liposome (center), and a lipid bilayer (right). Whereas liposomes are composed of a lipid bilayer, micelles are constructed of one lipid layer in which the apolar section turns inward and the polar heads interact with the environment. These two different organizations mean that the space enclosed in the micelles is much more limited to that available in liposomes. Adapted from [74].

applications in a wide range of fields, including nanotherapy (such as cancer therapy, gene delivery, and diagnosis), food technology and agriculture [85]. Another benefit of nanoliposomes is its cell-specific targeting (tropism), which is a requirement to achieve specific drug concentrations for ideal therapeutic efficacy in the target site while reducing unpleasant effects on healthy cells and tissues. Flexible nanoliposome has effective permeability characteristics under large stress, making drugs to be available into the systemic circulation via the stratum corneum [75].

Methods of nanoliposomes preparation are listed in Table 4.

5.2. Advantages of nanoliposome

Nanotechnology has demonstrated advantageous applications in medical field delivering drugs to specific cells using nanoparticles. The principle employed is to lower the overall drug consumption and side effects considerably by depositing the active agent only in the morbid region needed. This highly selective method reduces the cost and side effects, at the same time targeting its aim effectively [40,79,86–90].

Another approach which makes use of nanotechnology is the use of block co-polymers, which form micelles for encapsulation of drug. They are able to incorporate small drug molecules into them, and transporting them to the desired location. In addition, improved emulsion delivery systems based on nanotechnology, which would directly transport the molecule to end receptors, have been studied as well. Nanoliposomes are one of the most recognized names used in recent anaesthesia [91]. The benefits of nanoliposomes are listed in Table 5.

5.3. Application of nanoliposome in local anaesthesia

Many efforts have been made to prolong the duration of action of local anesthetic. One area of study has concentrated on incorporating local anesthetics into carrier molecules to enable control release. This formulation will prolong local anesthetic duration by a slow release from the liposome and suspend the peak plasma concentration as compared to ordinary local anaesthetic administration. Several studies have presented bupivacaine to be a potent tool for postoperative pain relief with opioid sparing effects, and it has also been found to possess a suitable adverse effect profile. Its kinetics are satisfactory even in patients with modest hepatic impairment, and it has been found not to interrupt wound healing after orthopedic surgery [92].

In order to explore two kinds of nano-liposomes in lidocaine hydrochloride nano-liposomes on *in vitro* permeability of drug, and conduct comparison and analysis, this paper Sun et al. investigated collective infiltration condition of ordinary nano-liposomes and lidocaine hydrochloride flexible nano-liposomes by using modified Franz diffusion pool on mice skin. Result shows osmotic quantity of lidocaine hydrochloride flexible nano-liposomes after 9 h was higher than ordinary nano-liposomes. Traces of drugs was found 0.5 and 1 h in flexible nano-liposomes group, whereas drug was not detected in mice plasma of ordinary nano-liposomes group. However, the concentration in flexible nano-liposomes group was lower than the potent concentration. Compared with the typical skin transparent promoter and ordinary liposome, flexible nano-liposomes have more benefits, but its stability is less ascompared to ordinary nano-liposomes due to the addition of surface active substance. Flexible nanoliposomes have great improvement potential as a carrier of transdermal drug delivery [48].

McAlvin et al. [93] used Exparel (DepoFoam bupivacaine); a new liposomal local anesthetic preparation whose biocompatibility near nerve tissue has not been well characterized. The administration of Exparel resulted in sciatic nerve blockade in rats for 4 h as compared to 2 h for 0.5% (w/v) bupivacaine HCl and 3.5 h for 1.31% (w/v) bupivacaine HCl (same bupivacaine content as Exparel). Histology four days after administration shows, median inflammation scores in the Exparel_ group (2.5 of 4) were somewhat higher than those treated with solutions of bupivacaine (score 2). Myotoxicity scores of (2.5 of 6) in the Exparel_group were similar to those in the 0.5% (w/v) bupivacaine HCl group (3), but significantly lower than in the 1.31% (w/v) bupivacaine HCl group (5). Two weeks following administration, inflammation from Exparel(score 2 of 6) was higher than 0.5% (w/v) bupivacaine HCl (1) and same as that from 1.31% (w/v) bupivacaine HCl (1). Myotoxicity in all three groups studied was not statistically significantly different. No neurotoxicity was observed in any group. Tissue reaction to Exparel_ was similar to that of 0.5% (w/v) bupivacaine HCl. Investigation for local tissue injury will be essential in prospective clinical evaluation.

The encapsulation of local anesthetics into nanoliposome to produce a system for prolonged drug release, can extend their

duration of action. This encapsulation will also increase the safety profile of the local anesthetic, as it is released at a slower rate. Studies carried out on naturally occurring local anesthetics have shown promise in the area of reducing systemic pain and neurotoxicity. Extension of the duration local anesthetic formulations in recent development or clinical use include liposomes, hydrophobic based polymer particles such as Poly(lactic-co-glycolic acid) microspheres, pasty injectable and solid polymers like Poly (sebacic-co-ricinoleic acid), and their combination with natural and synthetic local anesthetic [94].

Encapsulation of the local anaesthesia into nanoliposome could provide a system for prolonged release, and hence extended duration of action. For as long as the local anaesthesia drug binds to the sodium channel protein, nerve transmission is blocked and the analgesia is effective. Massive doses of local anaesthesia can be incorporated in the suitcase carrier encapsulating agent and delivered intact to the site of action. Without encapsulation, delivery of such large doses of local anesthetic agents could cause a lethal effect [95].

Nanoliposomes are crucial encapsulation agent, and demonstrate minimum toxicity amongst all the formulations. A nanoliposome product has currently achieved FDA approval, and others are in the clinical trial development.

6. Conclusion

Pharmaceutical nanotechnology is an innovative and highly specialized field, which will revolutionize the healthcare in the nearest future. Thus, nanotechnology is bound to touch each sphere of life [96]. The use of anesthetics-nanoliposome in the quest of achieving greater effectiveness, safety of LA agents, reducing the likelihood of toxicity, and side effects is a breakthrough in medical practice and great advantage for the safety and comfort of the patient. This review may be crucial for future drug delivery applications using nanoliposome loaded with anesthetics. More studies are necessary to confirm its efficacy and safety for use via epidural, intrathecal, or perineural routes [11,97–106].

Competing interests

The authors declare that they have no competing interests.

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