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Microneedle Technology: An Overview Focusing on its Types, Drug and Hormonal Delivery System in Animals

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ABSTRACT

Microneedle technology has garnered significant attention in the biomedical field as a minimally invasive drug delivery system emphasized by exponential increase in the rate of academic publications in this era. Its application in veterinary medicine is emerging as a promising tool, particularly in the delivery of drugs and hormones such as progesterone, insulin, Human growth hormone etc. This review explores different types of microneedles and their use in drug and hormonal delivery systems for animals. Also, the mechanisms, benefits, challenges, and future prospects of using microneedles for drug and hormonal administration in veterinary applications has been discussed briefly. A bird eye view on all these aspects strongly aided our scientists and technocrats to tackle the obstacles in drug and hormonal delivery system more wisely, precisely and efficiently.

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Introduction

Drug and hormonal delivery in animals is often a complex challenge due to the difficulty of ensuring consistent and controlled administration. Traditional delivery methods such as injections or oral medications have limitations, including stress to the animals, potential for infection, inconsistent absorption rates, and variability in drug bioavailability. These challenges are especially relevant in the context of delivering hormones like insulin, growth hormone progesterone, which is crucial for managing blood sugar levels, appropriate growth rate and reproductive cycles in humans and animals, including livestock.

Microneedle (MN) technology presents an innovative approach for drug and hormonal delivery in continuous manner in both human and veterinary medicine. First recorded use of microneedle recorded in 1905 by German dermatologist Ernst Kromayer and their suitable usage in transdermal delivery of therapeutics were first mentioned in 1998 by a research paper headed by Mark Prausnitz. MNs are designed to pierce the skin in a minimally invasive manner, facilitating the delivery of drugs directly into the skin or systemic circulation. They are also used for non transdermal drug delivery in vascular tissue, GIT tract, eyeballs and mucosa of buccal cavity [1-4]. This review focuses on the application of microneedles for the administration of drugs and hormones in animals and discusses its potential to overcome the limitations of traditional methods. Microneedles (MNs) are transforming various fields of biomedical research, offering a platform for innovative and minimally invasive drug and hormonal delivery systems. Their unique design allows for the precise delivery of drugs, hormones, vaccines, and other therapeutics through the skin, which has positioned MNs as a valuable tool in the both clinical and preclinical research. Their potential applications extend beyond drug and hormonal delivery, covering areas such as diagnostics, biosensing, sampling, nanodelivery and gene therapy, making them an integral part of future biomedical innovation.

Microneedle and Types

Microneedles are a class of drug and hormonal delivery devices that consist of micron-scale needles, typically ranging from 25 to 2000 µm in length [5]. The application of MNs in veterinary medicine is particularly attractive due to the minimal discomfort they cause, making drug and hormonal delivery more feasible in species that are difficult to handle or stress-prone, such as livestock or wildlife. These devices with their unique three dimensional microstructure can penetrate the outermost layer of the skin, the stratum corneum, without causing significant pain aiding patient compliance and self administration [6]or lesser damage to the underlying tissue with increase drug permeability and absorption[7,8] which is a crucial advantage over conventional hypodermic needles and also provides edge over traditional transdermal drug delivery limitations like allergicity and superficial delivery sites [9-11].

Solid Microneedles (SMN)

Microneedles are fabricated from a range of materials, including polymers, metals, and ceramics, depending on the property of drug and the required pharmacokinetics. Initially silicon, metal and ceramic made solid microneedles that are primarily used to create micropores in the skin, before the application of drug patches are used for transdermal drug delivery but these MNs having cumbersome and expensive manufacturing process, low drug loading rate and demounted needle tip, making them unsuitable for effective drug delivery [12,13].

Dissolving Microneedles (DMN)

Dissolving/soluble MNs dissolve after insertion into the skin, releasing the drug in a controlled manner and opened up new era of drug delivery with an advantage of being innocuous, ecofriendly, secure, efficient, less painful and biocompatible drug delivery approach [14]. They are showing promising result in the field of fast drug delivery especially vaccine delivery but they also posses limitation in the effective amount of drug deliver in comparison to its loaded rate in the needle [26-28]. Not only this the manufacturing of these needles require detailed pharmacokinetic, cytotoxity and clinical trials regarding the nature of polymer used in their construction that also show compatibility with the site of drug delivery as it dissolves after insertion into the skin [23].

Coated Microneedles (CMN)

Coated MNs have a thin layer of drug coated on their surface that is absorbed once the microneedles are inserted into the skin due to this it has ability to deliver genetic material and protein in a minimally presumptuous manner but the residue of drug left at the tip of the needle might infect other patient [23,24].

Hydrogel-Forming Microneedles (HFMN)

Hydrogel-forming microneedles were first reported in 2012 made up of cross-linked hydrogels and having unique functional mechanism of working [22]. They can swell upon insertion into the skin due to hydrophilic nature of polymer in it, creating pathways for drug diffusion making them favorable for various biomedical applications like uptake of interstitial fluid [29]. It can also absorb water without dissolving and are unique in that they don't leave viscous residue on the skin after insertion along with minimum damage to both needle and skin [30]. They have high drug loading capacity and modular rate of drug release.

Hollow Microneedles (HMN)

Hollow microneedles are needle like structure with a hollow channel running through their centre, made up of variety of materials like glass, metal, silicon, ceramic and fabricated using Micro-Electro-Mechanical System, lithography, etching and very recently 3-D printing and deliver drug using pressure driven, electric driven or diffusion approaches. They have high drug delivery capacity and high stiffness due to the nature of material used in their manufacturing. They have numerous biomedical applications like monitoring purpose, drug/vaccine delivery in skin, eyes , chemical substance, oligonucleotide and protein delivery that's why often called as 'all in one drug' delivery approach. They can only be used to deliver liquid formulations that are generally unstable as the temperature increases, hinders their applicative role in drug delivery [25, 31]. Also their working efficiency is limited by insertion of tissue in the bore of their needle that can be overcome by either retracting the microneedle array or by placing the bore on the side of microneedle.

The use of MNs in veterinary medicine, although still in early stages, has shown promising potential. Animals present unique challenges for drug delivery, including issues of compliance, handling, and stress minimization. Microneedles provide a less invasive alternative, which may reduce the stress associated with injection-based drug and hormonal delivery. Furthermore, Microneedle delivery systems may also improve drug bioavailability. The transdermal route bypasses the gastrointestinal tract, avoiding first-pass metabolism and reducing the variability often seen with oral medications. Additionally, microneedles provide the possibility of sustained release, which is particularly beneficial for hormones such as progesterone that require a stable plasma concentration over time. Different types of Microneedles along with their advantages and disadvantages has been briefed in table1.

Table 1: Various Types of Microneedles

S.No.	Type	Advantages	Disadvantages	References
1.	Solid microneedle	Less painful, precise	low drug loading rate, demounted needle tip	12,13
2.	Dissolving microneedle	Efficient drug delivery, less painful, precise, biocompatible	Require detailed study of dermatology of targeted animal and nature of bymaterial use in its construction	14,23,26,27,28
3.	Coated microneedle	Low drug delivery capacity	Leftover of drug at tip act as source of infection	23,24
4.	Hydrogel forming microneedle	Modular drug release rate and high drug loading capacity	Require detailed study of dermatology of targeted animal and nature of bymaterial use in its construction	22,29,30
5.	Hollow microneedle	High drug delivery capacity, fast and precise	Require external force for delivery system to operate	25,31

Current Role of Microneedles in Research

Drug and Hormone Delivery Optimization

Microneedles enable controlled, localized delivery of drugs and hormones directly into the skin or systemic circulation as reported by various past researches for example transdermal delivery of metformin, lidocaine etc [60,61]. This precise control over drug release is particularly useful in pharmacokinetic and pharmacodynamics studies where accurate dosing is critical. By allowing drugs to bypass first-pass metabolism, MNs ensure higher bioavailability and more consistent plasma levels. This is especially useful for hormonal therapies, including insulin, human growth hormone where stable dosing is essential for effective treatment [62,63].

In animal studies, MNs can deliver both large and small molecules, enabling researchers to investigate the pharmacological effects of various compounds with reduced animal handling stress. This is critical when working with stress-sensitive species, as stress can skew research outcomes, especially in behavioral or physiological studies.

Vaccination Research

MNs are gaining attention in vaccine research, providing a platform for developing new vaccination strategies that are more efficient and less painful [71]. This is especially important in the veterinary sector, where frequent vaccination is needed, but the stress and pain associated with traditional needle injections can be significant. MNs also show promise for human-animal interface diseases, such as zoonotic infections, where rapid and effective vaccine delivery in animals can prevent outbreaks that might affect human populations for example in the treatment of AIDS [70, 73].

Transdermal Sampling

MNs can also serve as minimally invasive tools for sampling interstitial fluid, blood, or other biofluids in both animals and humans [66]. This capability opens up new avenues for diagnostic research. For example, MNs could be used to monitor blood glucose levels, electrolyte concentrations, or hormone levels in real-time without the need for more invasive procedures like venipuncture. In research involving progesterone, this could allow continuous monitoring of hormone levels in animals, enhancing studies on reproduction and endocrine function.

Gene and Protein Delivery

The application of microneedles in gene therapy and protein delivery is a rapidly expanding research area. MNs can deliver DNA, RNA, or proteins such as monoclonal antibodies into the skin, where they can trigger immune responses or modify genetic expressions. This has profound implications for veterinary research, particularly in areas such as immunology and genetic engineering of livestock [65,67].

Localized Therapeutic Research

In cancer research or studies involving localized skin diseases, microneedles can be used to deliver drugs directly to the site of interest. This localized delivery can increase the therapeutic concentration at the target area while minimizing systemic side effects, which is crucial for developing novel cancer therapies, also shows promising results in this field of research [68, 69] especially in screening of skin melanoma, wound healing treatments, and dermatological applications.

Microneedle in Hormone Delivery

Progesterone

Progesterone plays a critical role in regulating the reproductive cycle of female animals as well as mammals and endogenously produced by corpus luteum, ovaries and placenta [15]. It is commonly used in livestock management to synchronize estrus, enhance fertility, and manage reproductive disorders. In particular, controlled delivery of progesterone is essential in animal breeding programs, both to synchronize ovulation and to maintain pregnancies. Current progesterone delivery methods in animals include oral administration, injections, and implants [16-19]. Each of these methods presents challenges. Oral administration has issues related to inconsistent absorption and first-pass metabolism, while injections can cause stress, discomfort and is prone to local nodules from pain, irritation at the injection site to the animal as well as local aseptic abscesses and sciatic nerve injury [20, 21]. Implants, while providing sustained release, require surgical procedures for implantation and removal, increasing the risk of infection, stress luteal phase vaginal bleeding, low bioavailability and various other issues that limit its clinical applications. The key advantages of microneedles in delivering progesterone include: Minimized Invasiveness: Microneedles provide a less invasive option compared to injections and implants, reducing the stress and pain experienced by animals, Improved Drug Delivery: Microneedles can offer more consistent and controlled delivery, enhancing bioavailability and maintaining stable plasma levels of progesterone, which is critical for reproductive management, Sustained Release: Some microneedle systems are designed to provide sustained release of drugs, allowing for long-term progesterone administration without frequent handling of animals, Reduced Risk of Infection: Since microneedles are minimally invasive, the risk of infection and tissue damage is reduced compared to traditional needle injections or surgical implantation of hormone delivery devices.

Oxytocin

Oxytocin is non peptide hormone, also known as 'Love hormone' naturally produce in both male and female by hypothalamus gland and stores it in posterior pituitary gland from where it releases into the blood stream and used to initiate uterine contraction during childbirth and labor, mammary gland contraction during lactation and to treat postpartum haemorrages, a major reason for maternal mortalities. It is also responsible for social bonding and Autism. It is generally administrated via intravenous or intramuscular mode that is limited by the dearth of skilled staff. It is reported that Polyacrylic acid based thermostable MN has showed promising result in the delivery of oxytocin with no significant loss for upto 2 months at 40o C and 75% relative humidity while MNs having coat of trehalose has retained 75% potency of Oxytocin at 40o C for 12 months [32].

Human Growth Hormone (hGH)/Growth Hormone/Somatotropin: Human growth hormone is a single chain polypeptide hormone containing 191 amino acids which is produced by anterior pituitary gland, responsible for regulating growth, operates as an acute phase stress reactant and role in efficient metabolism in the body. Its secretion is regulated by growth hormone releasing factor and stomatostatin. Its administration is through subcutaneous and intramuscular pathway via injection that is limited by immense pain and long path of metabolisation [34]. Transdermal route of its administration shows better results but macromolecular properties of hGH hinders its bioapplication. Therefore Microneedle technology raises curtains to these obstacles and put forward a pathway for the effective administration of hGH. In this regard a study on transdermal release of hGH through MN composed of carboxymethylcellulose and trehalose gives promising results for effective and self administrative release of hGH in the body of animal without generation of sharp bioharzaduos waste. Also these MN can be stored for upto 15 months at room temperature and humidity conditions without decreasing in their activity [33, 35].

Parathyroid Hormone (PTH)

Parathyroid hormone is a polypeptide and systemic hormones composed of 34 amino acids, produced by parathyroid gland located posterior to the thyroid gland present in the neck. It is produced in response to decrease level of calcium in the bloodstream. It carries out varies regulatory, anabolic functions in the body including regulating levels of calcium and phosphate, facilating the synthesis of active Vitamin D and calcitrol in kidneys, treatment of osteoporosis [36-38]. Post menopausal rat model having osteoporosis condition when injected with PTH using dissolved MN has showed prohibition of decrease bone

density with effective bioavailability of the hormone at quick rate [39]. Another study in rat model showed tendon bone healing and repair with PTH in hydrogel MN, having polyvinyl alcohol as manufacturing material by undergoing Growth factor (TGF)-beta/Smad3/mTOR cascade pathway [40]. PTH hydrogel MN also studied to carry out healing of skin wounds using same pathway as discussed in rat model for tendon healing therefore having bioapplication of collagen deposition, tissue regeneration and angiogenesis [41,42]. Past researches also showed early increase in spine bone density, hip bone density using coated MN, signifies their quick response in comparison to conventional approach of hormonal delivery through intramuscular or subcutaneous via needles [43].

Insulin

Insulin is a dipeptide hormone containing two chains linked with disulfide bond. It is produced by beta cells of Pancreas and having role in glucose homeostasis posing it as promising agent for the treatment of diabetes. Diabetes represents hyperglycemic condition that occurs due to insulin resistance. Diabetes type 1 represents an autoimmune disease in which insulin is not formed by pancreas while in Diabetes type 2 lesser amount of insulin is prepared by pancreas. Therefore, the main focus is to cure Diabetes 2 by regulating the level of glucose in bloodstream [47-49]. In conventional approaches Insulin has been derived from animal source but with the advent of chemical and genetic engineering Insulin has been manufactured on commercial scale. Despite of huge research in the treatment of Insulin desired target of controlling this condition has not been yet achieved mainly due to hesitation showed by diabetic patients who have to face daily and multiple intakes of insulin injections transdermally for regulating insulin level in the body [46]. This condition is further deterioted by inadequate methodology of taking the injection resulting in unexplained higher level of glucose and lower rate of insulin absorption due to selective loss of fat at the site of injection [44, 45]. All these lacunae are addressed by MN technology to a greater extent. Various studies are reported that describes the use of different types of MN for delivery of Insulin both in controlled and responsive manner. Intradermal delivery of insulin by microneedles of different heights showed change in pharmacokinetics as compare to conventional insulin delivery by subcutaneous route with better insulin concentration, higher fractional availability, fast onset of insulin injection and efficient uptake and lesser time lapse in the delivery of insulin in the body [50, 51]. Analysis of overall microneedle technology indicates that this approach brings promising results in effective and efficient delivery of insulin to the patients and helps to achieve desired targets.

Challenges and Considerations

Despite of so many potential advantages, several challenges remain in the widespread adoption of microneedle technology for drug and hormone delivery in animals:

Skin Structure Variability and MN Diameter, Density, Sharpness and by Material:

The thickness and properties of animal's skin vary across species, which can affect microneedle penetration and drug absorption. Also the potency of drug and hormonal delivery is hindered by diameter and sharpness of MN. Previous researches showed that sharp tip leads to instability of MN and blunt tip encounters penetration hindrance and ultimately have adverse affect on the efficiency of MN technology in drug and hormonal delivery. Also the density of MN per cm 2 affect the timely delivery of drug into the targeted site [57,58]. Manufacturing composition of MN plays a crucial role in deciding the loading rate of MN and its efficiency in targeted delivery too [59] Therefore, customization of microneedles with respect to nature of cutaneous layer of targeted animal as well as the physical structure and composition of the MN as per specificity of species must be taken into consideration on priority basis for targeted, effective, precise and quick drug and hormonal delivery in the animals.

Dose Precision

Achieving the correct dosage of drug, hormone or any other specific biochemical through microneedles, especially for sustained release, remains a challenge. Further, extensive research is needed to optimize the dose control and pharmacokinetics of the administered biochemical via microneedles technology. It also depends upon targeted animal and type of MN used [59].

Cost and Scalability

Microneedle production at scale, especially for veterinary use, may be expensive. Cost-effectiveness and manufacturing scalability are essential considerations for broad application, particularly in livestock industries. Inspite of the high potency of microneedles their huge cost hinders their inclusivity in the drug and hormonal delivery systems. Research in this area must be carried out at war footing manner to make this technology as a boon in the field of administration of therapeutics [52- 54].

Long-Term Efficacy, Sterilization, Disinfection and Safety

To determine the long-term efficacy of MNs and broad application of this technology, potential side effects of MNs including lack of standardized protocol for sterilization of MNs, their proper disinfection before use, tissue reactions to repeated microneedle use and other safety concerns must be taken into consideration to make them more feasible and effective for long time usage with safety and efficacy [55]. Also it is reported that pretreatment of MN with some sterilization approaches like irradiation and heat neutralize the delivery capacity of MN and thus reduces their efficiency [56]. As microneedles offer less invasiveness, quick, precise approach of drug and hormonal delivery therefore, more research is needed to increase their usage in biomedical industry.

Future Perspectives of Microneedles in Research

Microneedle-Integrated Biosensors

One promising future direction for MN research is the integration of microneedles with biosensors that is used for extraction and analysis of blood samples and interstitial fluid [66]. These "Smart" microneedles could be used to both deliver drugs and monitor physiological parameters such as pH, glucose levels, or specific biomarkers in real-time [74]. Such systems would allow for precise, less invasive, feedback-driven drug delivery; where the microneedle would automatically adjust the dose based on the body's needs and thus improving treatment outcomes, shows lower bioclogging sideffects along with fast recovery of lesion created by insertion of MN sensor [75].

Personalized Medicine

The trend toward personalized medicine, where treatments are tailored to an individual's specific genetic, environmental, and lifestyle factors, could be further accelerated by MN technology. Microneedles can be customized for different animals, species, or individual patients, allowing for species-specific drug formulations and dosages [57-59]. With further development, microneedles could become a critical component of personalized veterinary treatments, especially in complex diseases or hormonal therapies.

Sustained and Pulsatile Drug Delivery Systems

Research is increasingly focusing on developing microneedles that can provide sustained or pulsatile drug release especially for the treatment of diabetes [72]. Sustained release MNs would allow for long-term delivery of drugs like progesterone without the need for frequent administration, reducing handling stress in animals. Pulsatile MN systems, on the other hand, could deliver hormones in a manner that mimics the body's natural rhythm, which could be particularly beneficial for research in endocrinology and reproductive biology.

Microneedles for Large-Scale Veterinary Applications

As MN technology continues to evolve, there is great potential for large-scale use in veterinary medicine, particularly in livestock management. Microneedle patches could be used to administer medications or vaccines to entire herds with minimal handling. For example, progesterone microneedle patches could be designed for mass application in cattle breeding programs, synchronizing estrus across large groups of animals more efficiently and humanely than current methods.

Nanotechnology and Microneedles

The combination of nanotechnology with microneedle technology holds enormous promise. Nanoparticle loaded with drugs can be incorporated into microneedles, allowing for more targeted delivery, enhanced drug stability, and the ability to cross biological barriers. For instance, in cancer research, nanoparticle-loaded MNs could deliver chemotherapeutic agents directly to tumors in animals, improving the precision and efficacy of treatment while minimizing side effects [64].

Microneedles for Regenerative Medicine

Future research may also explore the role of microneedles in regenerative medicine. MNs could be used to deliver stem cells, growth factors, or other regenerative agents directly to damaged tissues in animals. This could have significant implications for treating injuries, degenerative diseases, or tissue regeneration in both companion and farm animals.

Additionally, further investigation into the long-term safety and efficacy of microneedle systems is critical for widespread adoption in veterinary practice.

Conclusion

Microneedles represent an exciting advancement in drug and hormonal delivery technology, with significant potential for use in veterinary medicine. In particular, their application in delivering drugs and hormones could revolutionize treatment therapies and reproductive management in livestock respectively, offering a minimally invasive, controlled, and efficient delivery method. While challenges remain, the continued development of microneedle systems for drug and hormone delivery in animals could provide substantial benefits to animal welfare, productivity, and the agricultural industry. The future of microneedle technology in research is bright, with its potential applications extending far beyond its current use in drug and hormonal delivery. As the field advances, MNs are likely to become an essential tool in both preclinical and clinical research, contributing to more effective therapies, precise drug delivery systems, and enhanced patient outcomes. The continued development of smart microneedles, personalized medicine approaches, and nanotechnology-enhanced microneedle systems will undoubtedly drive innovation in animal and biomedical research, providing new solutions for some of the most pressing challenges in the field.

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