REVIEW OF BIODEGRADABLE POLYMERIC INSULIN MICRONEEDLE

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Abstract

Here's a concise abstract for biodegradable polymeric insulin: "Biodegradable polymeric insulin represents a novel approach in diabetes management by offering a controlled and sustained release of insulin. This system involves encapsulating insulin within biodegradable polymers such as polylactic acid (PLA) or poly(lactic-co-glycolic acid) (PLGA), which protect insulin from degradation while facilitating gradual release. The biodegradable nature of the polymers ensures that the system breaks down into non-toxic byproducts, eliminating the need for surgical removal. Such systems have the potential to improve patient compliance, reduce the frequency of injections, and maintain stable blood glucose levels, thus enhancing therapeutic outcomes for diabetes patients. This approach also opens avenues for future developments in drug delivery systems that aim to optimize therapeutic efficiency and patient convenience."

This abstract provides a high-level summary of the subject, emphasizing key points. Let me know if you'd like to expand or focus on any specific aspect! Here's a detailed abstract for biodegradable polymeric insulin delivered via microneedles:

"Biodegradable Polymeric Insulin Delivery via Microneedles: A Novel Approach for Diabetes Management

The development of biodegradable polymeric microneedles for insulin delivery offers a promising alternative to traditional subcutaneous insulin injections. This innovative system combines the advantages of microneedle technology and biodegradable polymers to achieve painless, controlled, and sustained insulin release. Microneedles, typically fabricated from biocompatible and biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), or chitosan, are designed to penetrate the outer layer of the skin without reaching the pain receptors, thus providing a minimally invasive and user-friendly method for insulin administration.

Insulin is encapsulated within the biodegradable polymer matrix, where the degradation of the polymer facilitates a controlled release of insulin over time. This approach ensures the protection of insulin from premature degradation and provides a sustained release profile, which can significantly reduce the frequency of administration and improve patient compliance. The polymeric microneedles dissolve naturally after delivering the drug, leaving no residual materials in the body, and the polymers break down into non

Keywords:*1.Biodegradable microneedles, 2. Polymeric insulin delivery, 3. Transdermal insulin, elivery, 4. Microneedle drug delivery, 5. Sustained insulin release*

Introduction

Polymeric materials obtained from petroleum resources are non-biodegradable, and their accumulation in landfills poses significant environmental challenges. In contrast, natural and synthesized biodegradable polymeric materials have garnered increasing

interest due to their potential for environmental sustainability. However, these biodegradable options often face challenges in biocompatibility and reproducibility compared to their non-biodegradable counterparts. Through the modification of natural polymeric materials via various techniques, including chemical, microbiological, enzyme-mediated, and chemo-enzymatic synthesis, a diverse range of biodegradable polymeric materials can be developed as viable alternatives.

In recent years, substantial advancements have been made in drug delivery systems utilizing both natural and synthetic polymers. Polymers are a critical class of materials due to their wide availability, diverse properties, and high tunability. These polymeric materials inherently possess flexibility, allowing them to be synthesized and modified to exhibit the desired properties for controlled drug release while maintaining biocompatibility. Pharmaceutical manufacturers commonly employ polymers in the fabrication of various drug delivery systems, including tablets, implants, microspheres, nanoparticles, drug-eluting stents, in situ forming gels, and polymeric scaffolds for tissue engineering.

Furthermore, researchers are increasingly leveraging data science and polymer informatics to design new materials and understand their structural-property relationships. Material performance is closely linked to factors such as strength, porosity, particle size, amorphous nature, biocompatibility, and dissolution performance. Biodegradable biomaterials can be categorized as natural or synthetic based on their sources and whether they are derived from naturally occurring extracellular matrices. Natural polymeric biomaterials include proteins such as collagen, fibrin, and silk, as well as polysaccharides like chitin/chitosan, alginate, hyaluronic acid, and lignin. Additionally, a family of native polyesters known as polyhydroxyalkanoates has emerged as a recognized category of natural biodegradable biomaterials.

Chitin and chitosan are types of polysaccharides found in abundance in various marine sources. Chitin is a polymer composed of β,1-4-linked N-acetyl glucosamine units and is a complex biopolymer. It is present in the exoskeletons of arthropods as well as crustaceans such as crabs, lobsters, and shrimps. Chitin is water-insoluble and is often transformed into carboxymethyl chitosan and other chitosan derivatives. Chitin extracted from lobster processing waste is used in a variety of ways in food, healthcare, agriculture, pharmaceuticals, and biomedical fields. On the other hand, chitosan is a linear polymer derived from chitin via the deacetylation process, consisting of both N-acetyl glucosamine and D-glucosamine residues.

Upsurge prevailing in developing countries regarding the ecological detriment due to pollution has stretched to perilous heights as a result of the use of polymeric materials. Similar durability characteristics of this type of polymeric material for varied execution in

packaging supplies, structural materials, and basic commodities can remedy disposal snags for traditional petroleum-derived polymers, which are not readily biodegradable. Being resistant to biodegradation, they accumulate in the environment. This is the primary reason for the interest in biodegradable polymeric materials. Biodegradable polymeric materials (BPMs) represent a growing field. Owing to their wide-ranging properties, both synthetic and natural polymeric materials perform a vital and ubiquitous role in everyday life. Having a period of effectiveness, BPMs divulge the phenomenon of biodegradation. It is valuable to distinguish between BPMs on the basis of their origin: native or synthetic. Native BPMs represent the synthesis developed during a long course of evolution in nature, while synthetic BPMs are the result of a mere century of research and development, both resulting in materials possessing tailored characteristics for diverse applications. They include proteins (collagen, gelatin, and albumin), polysaccharides (cellulose, chitin, and alginate), nucleic acids, and lipids, which illustrate totally diverse characteristics reliant on the conditions under which they are used. Synthesized BPMs have received increasing interest owing to the difficulty in obtaining reproducibility when using natural polymeric materials. Although first introduced in the 1980s, synthetic BPMs have been attracting attention in the last two decades, primarily due to ecological fouling and the realization that our natural resources are finite.

To be effective, an orally administered protein drug must transit along the gastrointestinal (GI) tract, pass through the mucus layer, traverse across the intestinal epithelium, enter into the portal vein, and finally reach the systemic circulation (Chen et al., 2011). However, oral administration of pure insulin showed less effect due to the following factors. Firstly, insulin can be easily degraded by the acidic conditions in the stomach and the proteases existing in the GI tract. Secondly, insulin is a hydrophilic protein with a molecular weight of about 6000 Da, making it difficult for insulin to be encapsulated in hydrophobic carriers, and the permeation of insulin through the intestinal epithelium is limited. Thirdly, because of the liver first-pass effect, the bioavailability of untreated insulin is extremely low.

History

The history of biodegradable polymeric insulin microneedles is tied to advancements in both microneedle technology and the development of biodegradable polymers for drug delivery. Microneedles, first proposed in the 1970s, gained significant research interest in the 1990s as a minimally invasive method for transdermal drug delivery. The concept of microneedles involves using tiny, needle-like structures to painlessly penetrate the outer layer of the skin, enabling drug delivery without reaching the deeper pain receptors.

Early Development: Microneedles and Insulin Delivery

In the early 2000s, researchers began to explore microneedles as a delivery system for

various drugs, including insulin. The key challenge was delivering insulin, a large and hydrophilic molecule, through the skin, a barrier designed to keep such molecules out. Initial microneedle designs were made from silicon or metals, but these materials were non-biodegradable and posed risks related to residual material left in the skin after drug delivery.

Absorption of insulin by microneedle

Microneedle-based insulin delivery is an innovative technique that overcomes several limitations of traditional insulin injections. This system involves the use of tiny needles, often less than a millimeter in length, to penetrate the skin's outer layer, the stratum corneum, and deliver insulin into the dermis or epidermis, where there are fewer nerve endings and abundant blood vessels. The following is a detailed explanation of how insulin is absorbed using microneedles:

1. Microneedle Structure and Design:

Solid Microneedles: These are used to create microchannels in the skin. Insulin is applied to the skin afterward, and it diffuses through these channels into the bloodstream.

Coated Microneedles: These microneedles have insulin coated on their surface. When inserted into the skin, the coating dissolves, and insulin is delivered directly into the skin.

Dissolvable Microneedles: Made of biodegradable materials, these microneedles dissolve within the skin, releasing insulin as they degrade.

Hollow Microneedles: These function like traditional syringes, where insulin is actively injected into the skin through the needle's hollow core.

2. Skin Penetration and Drug Delivery:

The microneedles puncture the stratum corneum, the outermost layer of the skin, which is a significant barrier for drug absorption.

Microneedles, depending on their length and type, either reach the epidermis or the upper dermis. The epidermis has fewer nerve endings, which makes this process virtually painless.

In the dermis, blood capillaries and lymphatic vessels are abundant. The insulin, once released into these layers, quickly enters the bloodstream due to the proximity of the vasculature.

3. Absorption Mechanism:

Once insulin is deposited into the dermal or epidermal layer, it diffuses into the surrounding tissues.

Insulin is then absorbed into the dense network of capillaries located in the dermis. This allows for faster absorption compared to subcutaneous injections, which deliver insulin into the fatty tissue, where diffusion is slower.

The insulin, once in the bloodstream, binds to insulin receptors and initiates its action, facilitating glucose uptake by cells and reducing blood sugar levels.

4. Advantages of Microneedles for Insulin Delivery:

Painless Delivery: Microneedles are generally painless because they do not reach the deeper layers of the skin where most pain receptors are located.

Improved Patient Compliance: Microneedles are easy to use and cause less discomfort, which can improve adherence to insulin therapy.

Fast Onset of Action: Because insulin is delivered into the dermis, where blood flow is greater, it can be absorbed faster than when injected subcutaneously.

Reduction in Needle Anxiety: Since microneedles are much smaller than traditional needles, they are less intimidating and reduce anxiety, especially in needle-phobic patients.

Potential for Continuous Delivery: Some microneedle patches can be designed for sustained insulin release over time, mimicking the action of an insulin pump.

5. Challenges:

Dose Limitation: Due to the small size of microneedles, there is a limitation on the volume of insulin that can be delivered in a single application.

Skin Reactions: While generally well-tolerated, there may still be localized skin reactions such as redness or irritation.

Cost and Manufacturing: The development and manufacturing of microneedle systems can be more complex and expensive than traditional insulin delivery methods.

6. Applications and Research:

Researchers are working on microneedle patches for insulin delivery that can be applied once or twice daily, replacing multiple daily injections.

Some patches are being designed to work in a "smart" manner, releasing insulin in response to glucose levels in the blood, mimicking the natural function of the pancreas.

Method and material of Biodegradable polymeric insulin

Microneedle

The development of biodegradable polymeric microneedles for insulin delivery involves various methods and materials that ensure both the functionality and biocompatibility of the system. The process is intricate and requires optimization of several parameters, including material selection, microneedle fabrication, insulin encapsulation, and the final performance evaluation of the microneedles for sustained and controlled release of insulin.

1. Materials for Biodegradable Polymeric Microneedles
2. The primary materials used for fabricating biodegradable microneedles are biocompatible and biodegradable polymers that break down safely in the body. Common materials include:

Polylactic acid (PLA): A biodegradable polyester derived from renewable resources. PLA has good mechanical properties, which are essential for piercing the skin. It degrades into lactic acid, a naturally occurring compound in the body, making it safe for medical applications.

Poly(lactic-co-glycolic acid) (PLGA): A copolymer of lactic acid and glycolic acid. PLGA degrades into lactic acid and glycolic acid, both of which are metabolized in the body. The ratio of lactic acid to glycolic acid can be adjusted to control the degradation rate and, consequently, the insulin release rate.

Chitosan: A natural polysaccharide derived from chitin. It is biodegradable, biocompatible, and can form films or hydrogels, making it an attractive material for microneedles. It also has intrinsic properties that enhance wound healing and improve drug delivery.

Hyaluronic acid (HA): A natural biopolymer with excellent biocompatibility. HA-based microneedles are soft, ensuring minimal skin irritation, and can dissolve quickly in skin interstitial fluid, making them suitable for rapid insulin release.

Polyvinyl alcohol (PVA) and Polyvinylpyrrolidone (PVP): These are synthetic, water-soluble polymers often used in dissolvable microneedles for fast drug delivery.

3. Fabrication Methods

Several techniques are used for fabricating microneedles, depending on the desired properties and applications. The methods need to ensure precise control over needle shape, size, and drug loading capacity.

a. Mold-based Microneedle Fabrication

This is the most commonly used method for fabricating biodegradable microneedles, particularly for polymeric microneedles:

Micromolding: In this method, a master template of the microneedle array is created, usually using silicon or other rigid materials. This template is then used to cast microneedles from polymeric materials. The biodegradable polymer solution (e.g., PLGA, PLA) is poured into the mold and allowed to

solidify, either by solvent evaporation or thermal treatment.

Solvent Casting: The polymer is dissolved in a suitable solvent, and insulin or other therapeutic agents are mixed into this solution. The solution is then poured into the mold and dried to form solid microneedles. This process is typically followed by drying or crosslinking to strengthen the microneedles.

Hot Embossing: In some cases, the polymer is heated until it becomes malleable and then pressed into the microneedle mold, where it takes the desired shape upon cooling.

b. Layer-by-Layer Deposition

In this method, multiple layers of polymers and drugs (e.g., insulin) are alternately deposited on the microneedle structures. This allows for precise control over drug loading and release kinetics. The polymer layers dissolve sequentially upon insertion into the skin, providing a sustained release of insulin.

c. Electrospinning

For some microneedle designs, particularly those involving nanofibers or porous structures, electrospinning is used. In this process, polymer solutions are electrically charged, producing fine fibers that can be deposited onto microneedle molds or directly formed into microneedle structures.

4. Insulin Encapsulation and Loading

To incorporate insulin into the microneedles, the following techniques are typically employed:

a. Encapsulation in Polymer Matrices

Insulin is encapsulated within biodegradable polymer matrices, allowing for protection from environmental degradation (e.g., proteolysis or acidic pH in the stomach if ingested). The polymer matrix degrades slowly after microneedle insertion, providing a controlled release of insulin into the skin.

Single-Step Encapsulation: Insulin is mixed with the polymer solution before microneedle fabrication. This ensures uniform distribution of insulin within the microneedles but requires optimization to avoid insulin degradation during the fabrication process.

Multi-Layer Encapsulation: In some cases, insulin can be encapsulated in distinct layers within the microneedles. The outer layer dissolves first, allowing a burst release of insulin, while the inner layers degrade more slowly, providing sustained release.

b. Physical Adsorption

Insulin is adsorbed onto the surface of microneedles after fabrication. This method is faster than encapsulation but may not offer the same degree of sustained release, as it depends on surface interactions between the insulin and the polymer.

5. Characterization of Microneedles

Once the microneedles are fabricated, they must be evaluated for their mechanical

strength, drug loading efficiency, release kinetics, and biocompatibility.

Mechanical Testing: Microneedles must be strong enough to penetrate the skin without breaking. Tensile strength and fracture resistance are commonly tested to ensure that the microneedles can withstand the forces involved during skin insertion.

Drug Release Studies: The rate at which insulin is released from the microneedles is critical. In vitro release studies in simulated body fluids (such as phosphate-buffered saline) are conducted to determine how quickly the polymer matrix degrades and releases insulin.

Insulin Activity: Insulin must retain its bioactivity after encapsulation and release. Biochemical assays are conducted to ensure that the encapsulation process does not degrade the insulin's therapeutic properties.

6. In Vivo Studies and Biocompatibility

After fabrication and in vitro testing, microneedles undergo preclinical testing in animal models to assess their performance in vivo. These tests evaluate:

Biocompatibility: The polymers used for the microneedles must be non-toxic and should degrade into safe byproducts in the body. Biocompatibility is assessed through histological analysis of the skin post-application to check for any inflammatory or adverse reactions.

Pharmacokinetics: In vivo studies measure how much insulin is delivered into the bloodstream, how long it remains active, and its effect on blood glucose levels. This is essential to determine the effectiveness of the microneedle system.

Degradation: The rate of polymer degradation is monitored to ensure that the microneedles dissolve fully after delivering the insulin, leaving no residual materials in the body.

Insulin Encapsulation and Release Mechanisms for Biodegradable Polymeric Insulin Microneedles

1. Encapsulation of Insulin in Biodegradable Polymers: Encapsulating insulin within biodegradable microneedles ensures stability, protection, and controlled release of the insulin once administered into the skin. The encapsulation process must protect insulin from degradation during manufacturing and storage, as well as deliver a therapeutic dose upon administration. The following techniques are commonly used for encapsulating insulin in microneedles:

Physical Entrapment: Insulin is physically mixed or dissolved with the biodegradable polymer solution and solidified into the microneedle matrix. This method traps insulin within the polymer structure.

Chemical Conjugation: Insulin can be chemically linked to polymer chains. This method often allows for more controlled release, as the insulin is only freed once the bonds degrade.

Layer-by-Layer Encapsulation: Insulin is encapsulated in multiple layers within the microneedle. Each layer can consist of different polymers, allowing for staged or sustained release of insulin.

2. Methods of Insulin Encapsulation:

a. Solvent Casting and Molding

In this technique, insulin is mixed with a biodegradable polymer solution (e.g., PLGA or PLA) and cast into microneedle molds. Once the solvent evaporates, solid microneedles with encapsulated insulin are formed. The polymer solution can also be combined with various stabilizing agents to prevent insulin degradation during the process.

b. Microsphere Embedding

Insulin can first be encapsulated into polymeric microspheres or nanoparticles, which are then embedded into the microneedle structure. These microspheres are made from biodegradable polymers such as PLGA. When the microneedles are applied to the skin, the microspheres release insulin over time as the polymer degrades.

c. Spray Drying

Insulin can be encapsulated in nanoparticles or microparticles through spray drying techniques, where insulin and polymer solutions are atomized into a fine mist and quickly dried. These particles can then be integrated into microneedles for gradual release.

d. Electrospinning

For microneedles made from nanofibers, electrospinning can be used to encapsulate insulin. In this process, a polymer solution containing insulin is electrically charged and spun into fine fibers, which are then solidified to form the microneedles. The fibers can release insulin gradually as they degrade.

3. Release Mechanisms for Insulin:

Once the insulin is encapsulated in the microneedles and administered through the skin, the release of insulin is governed by the degradation rate of the biodegradable polymers. Various factors influence the rate and mechanism of insulin release:

a. Diffusion-Controlled Release

In some cases, insulin is released through diffusion as water penetrates the microneedle structure. The hydrophilic nature of insulin allows it to diffuse out of the polymeric matrix gradually, depending on the porosity and composition of the polymer.

b. Degradation-Controlled Release

Biodegradable polymers such as PLA and PLGA degrade in the presence of moisture and enzymes, breaking down into lactic and glycolic acids. As the polymer matrix degrades, insulin is released into the surrounding tissue. The rate of polymer degradation can be controlled by adjusting the molecular weight of the polymer or the ratio of lactic to glycolic acid in PLGA.

Fast Dissolving Microneedles: Some microneedles are designed to dissolve rapidly in the skin's interstitial fluid. These are typically made from polymers like hyaluronic acid or PVP, which release insulin within minutes to hours, offering a burst release suitable for rapid therapeutic effects.

Slow Degrading Microneedles: Polymers such as PLGA can be engineered for slower degradation, allowing for sustained insulin release over several hours or days. This type of controlled release mimics natural insulin secretion patterns and can reduce the frequency of insulin administration.

c. Multi-Stage Release

By layering insulin within different polymeric layers of the microneedle, a multi-stage release profile can be achieved. The outer layers dissolve quickly, providing an initial burst of insulin, while inner layers degrade more slowly for prolonged insulin release.

d. Responsive Release

Some advanced microneedle systems are being developed to release insulin in response to external stimuli, such as glucose levels. These "smart" microneedles can be integrated with glucose-responsive hydrogels or other materials that trigger insulin release when blood glucose levels rise.

4. Factors Influencing Release Rate:

Several factors can affect the rate and efficiency of insulin release from biodegradable polymeric microneedles:

Polymer Composition: The choice of polymer (e.g., PLGA vs. PLA) significantly influences the degradation rate, with PLGA typically offering more tunable release rates based on the lactic-to-glycolic acid ratio.

Molecular Weight of the Polymer: Higher molecular weight polymers degrade more slowly, prolonging insulin release.

Microneedle Geometry: The shape and size of the microneedles affect the surface area exposed to the interstitial fluid and, consequently, the release rate of insulin.

Insulin Loading Density: The amount of insulin encapsulated in the microneedles can impact the release profile. Higher loading densities can increase the duration of insulin release.

Additives and Stabilizers: Various excipients, such as polyethylene glycol (PEG) or trehalose, are added to improve insulin stability and control the release profile. These agents prevent insulin aggregation or denaturation during encapsulation and storage.

7. Challenges in Insulin Encapsulation and Release:

Insulin Stability: Maintaining insulin's bioactivity during encapsulation, storage, and release is a significant challenge. Insulin is sensitive to temperature, pH, and solvents, so careful formulation and stabilization strategies are essential.

Controlled Release Precision: Achieving precise control over insulin release to match

physiological needs (e.g., basal vs. bolus insulin release) is difficult. Ongoing research aims to refine these systems for better glucose control.

Manufacturing Scalability: Ensuring that insulin-loaded microneedles can be mass-produced with consistent drug loading and release profiles remains a challenge for commercialization.

Safety

Microneedle insulin delivery systems are a promising alternative to traditional insulin injections, offering a less invasive and potentially painless option for diabetic patients. However, their safety is still being studied as part of ongoing clinical trials and research.

Here are key safety considerations for microneedle insulin:

1. Skin Irritation and Infection: Since microneedles pierce the skin, albeit minimally, there's a potential risk for localized irritation, redness, or infection at the application site. Proper skin care and hygiene practices are essential to mitigate this risk.
2. Accurate Dosing: Microneedles need to deliver precise doses of insulin to ensure blood sugar is controlled effectively. Ensuring consistent insulin absorption through the skin is crucial to avoid hyperglycemia or hypoglycemia.
3. Biocompatibility: The materials used for microneedles, such as polymers, metals, or silicon, must be biocompatible to avoid allergic reactions or other adverse effects when they come into contact with the skin.
4. Breakage and Residue: There's a possibility that microneedles could break during application, leaving fragments in the skin. Modern microneedles are designed to minimize this risk, but this remains a point of safety consideration.
5. Long-Term Use: The long-term effects of microneedle use, including potential impacts on skin health after repeated applications, are still being evaluated.
6. Patient Training: Like any medical device, proper training is essential to ensure users apply the microneedles correctly and safely.

Overall, while early studies suggest microneedle patches are generally safe and well-tolerated, long-term safety data is still being gathered as they move towards wider clinical use.

Conclusion

Biodegradable polymeric insulin microneedles represent a revolutionary advancement in the field of diabetes management, offering an innovative and minimally invasive alternative to traditional insulin delivery methods. This approach addresses several key challenges associated

with insulin administration, including patient compliance, the need for frequent injections, and the discomfort associated with conventional methods like syringes and insulin pumps.

1. Enhanced Patient Compliance: One of the significant advantages of biodegradable polymeric microneedles is their ability to deliver insulin painlessly and with minimal invasion. This feature enhances patient compliance, especially for individuals who are needle-phobic or require frequent insulin doses. The microneedles, applied as a patch or device, dissolve after administration, eliminating the need for needle disposal and reducing the risk of infection associated with reusable devices.

2. Sustained and Controlled Release of Insulin: Biodegradable polymeric microneedles provide the capability for sustained and controlled release of insulin over extended periods. By encapsulating insulin in polymers such as PLGA, PLA, or other biodegradable materials, the insulin release can be precisely modulated based on the polymer's degradation profile. This approach mimics the body's natural insulin secretion patterns, enabling better glycemic control and reducing the need for multiple daily injections.

The polymers used in microneedles can be engineered to degrade at varying rates, allowing for both rapid and sustained insulin delivery. Fast-acting microneedles can provide an initial burst of insulin for postprandial glucose control, while slow-degrading microneedles can maintain basal insulin levels for longer periods, making them highly versatile for different patient needs.

3. Reduced Risk of Hypoglycemia: Controlled release mechanisms help to reduce the risk of insulin overdosing and subsequent hypoglycemia, which is a common complication with conventional insulin injections. By fine-tuning the release profile, insulin microneedles can offer a more predictable pharmacokinetic profile, improving the safety and effectiveness of insulin therapy.

4. Biocompatibility and Safety: The use of biodegradable polymers ensures that the microneedles are biocompatible, reducing the risk of adverse reactions at the application site. Once the microneedles deliver their insulin payload, they naturally degrade into harmless byproducts that are easily metabolized or excreted by the body. This eliminates the need for needle removal and minimizes tissue damage, further enhancing safety.

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