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DEVELOPMENT AND CHARACTERIZATION OF POLYMERIC MICRONEEDLES FOR TRANSDERMAL DELIVERY OF MEGLITINIDE DRUGS

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and associated with severe complications such as cardiovascular diseases, nephropathy, neuropathy, and retinopathy. Among available therapeutic agents, meglitinide drugs including repaglinide and nateglinide, are widely used for the management of type 2 diabetes mellitus because of their rapid insulin secretagogue activity. However, conventional oral administration of these drugs is limited by extensive hepatic first-pass metabolism, low bioavailability, short half-life, gastrointestinal side effects, and frequent dosing requirements. To overcome these limitations, polymeric microneedle-based transdermal drug delivery systems have emerged as a promising and minimally invasive alternative.

Polymeric microneedles create transient microchannels in the stratum corneum, thereby enhancing drug permeation and improving systemic absorption without causing significant pain or tissue damage. This review discusses the development and characterization of polymeric microneedles for transdermal delivery of meglitinide drugs. Various types of microneedles, including solid, dissolving, and hydrogel-forming systems, along with commonly used natural and synthetic polymers, fabrication techniques, and evaluation parameters are comprehensively described. In addition, the review highlights physicochemical characterization, mechanical strength, insertion studies, drug loading efficiency, and controlled release behavior of microneedle systems. Furthermore, recent

applications, therapeutic effectiveness, in vitro and in vivo evaluation studies, and future prospects of microneedle-mediated antidiabetic therapy are critically discussed. Overall, polymeric microneedles represent an innovative, patient-friendly, and efficient transdermal platform with significant potential to improve bioavailability, therapeutic efficacy, and patient compliance in diabetes management.

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The disease has emerged as a major global health concern due to its rapidly increasing prevalence and associated complications, including cardiovascular diseases, nephropathy, neuropathy, and retinopathy.[1] Among the different forms of diabetes, Type 2 Diabetes Mellitus (T2DM) accounts for the majority of cases and is commonly associated with insulin resistance and impaired pancreatic β-cell function. Effective glycemic control is therefore essential to minimize long-term complications and improve patient quality of life.[2] Meglitinides are a class of oral antidiabetic agents widely used for the management of T2DM. Drugs such as repaglinide and Nate glinide act by stimulating rapid insulin secretion from pancreatic β-cells through closure of ATP-sensitive potassium channels. These agents are particularly useful in controlling postprandial hyperglycemia because of their rapid onset and short duration of action.[3] Compared with sulfonylureas, meglitinides exhibit a lower risk of prolonged hypoglycemia and offer greater flexibility in dosing schedules. However, despite their therapeutic benefits, conventional oral delivery of meglitinide drugs is associated with several limitations, including extensive hepatic first-pass metabolism, low and variable bioavailability, short plasma half-life, frequent dosing requirements, and gastrointestinal side effects. Such limitations may reduce therapeutic efficacy and patient compliance during long-term treatment.[4] To overcome the drawbacks associated with oral therapy, transdermal drug delivery systems (TDDS) have gained considerable attention as an alternative and non-invasive route of administration. Transdermal delivery offers several advantages, including avoidance of first-pass metabolism, sustained drug release, improved bioavailability, reduced gastrointestinal irritation, enhanced patient compliance, and maintenance of steady plasma drug concentrations. However, the outermost layer of the skin, the stratum corneum, acts as a major barrier limiting the permeation of many therapeutic agents, especially hydrophilic and high molecular weight drugs.[5] In recent years, microneedle-based transdermal systems have emerged as a promising strategy for enhancing drug permeation across the skin. Polymeric

microneedles are minimally invasive micro-scale structures capable of creating transient micropores in the skin without reaching deeper pain receptors or blood vessels. These systems facilitate efficient drug delivery while minimizing pain, tissue damage, and risk of infection. Polymeric microneedles can be fabricated using biodegradable and biocompatible polymers, enabling controlled and targeted drug release. Their ability to improve transdermal permeation of antidiabetic agents has attracted significant interest in pharmaceutical research.[6] The present review focuses on the development and characterization of polymeric microneedles for transdermal delivery of meglitinide drugs. The review discusses the physicochemical and pharmacological properties of meglitinides, various types of polymeric microneedles, fabrication techniques, selection of polymers, evaluation parameters, drug release behavior, skin permeation studies, and therapeutic applications. Furthermore, recent advancements, challenges, and future perspectives associated with microneedle-mediated transdermal delivery systems for diabetes management are critically highlighted. The objective of this review is to provide a comprehensive understanding of polymeric microneedle technology as an innovative platform for improving the efficacy and patient compliance of meglitinide therapy.[7]

2. Polymeric Microneedles: Types and Design Principles

Microneedles are micron-sized needle-like structures designed to penetrate the stratum corneum and create temporary microchannels for enhanced transdermal drug delivery. Typically ranging from 25–2000 µm in length, microneedles enable painless and minimally invasive administration of therapeutic agents without causing significant damage to deeper tissues. Among various microneedle systems, polymeric microneedles have attracted substantial attention because of their biocompatibility, biodegradability, ease of fabrication, and capability for controlled drug release. These systems have shown promising applications in the delivery of antidiabetic drugs, vaccines, peptides, and other bioactive molecules.[8]

2.1 Classification of Microneedles

Microneedles can be classified based on their structure, mechanism of drug delivery, and material composition. Polymeric microneedles are mainly categorized into solid, dissolving, and hydrogel-forming microneedles.[9]

2.1.1 Solid Microneedles

Solid microneedles are primarily used to create micropores in the skin through a “poke-and-patch” approach. In this technique, microneedles puncture the stratum corneum, after which a

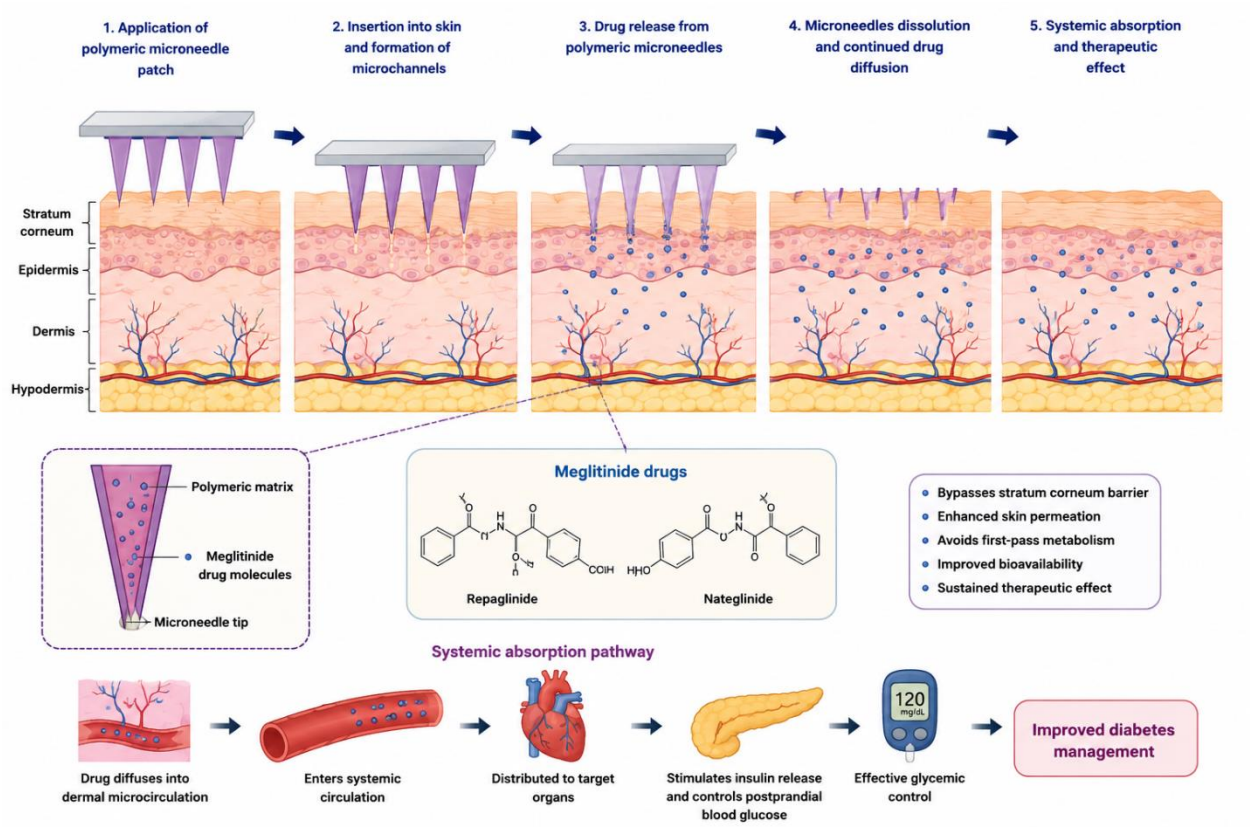
drug-loaded formulation such as a patch, gel, or cream is applied over the treated area to facilitate drug diffusion through the created microchannels.[10] Solid microneedles are generally fabricated from strong polymers or metals to provide sufficient mechanical strength for skin penetration. Although they effectively enhance permeation, they usually require a two-step administration process and may offer limited control over drug release.[11]

2.1.2 Dissolving Microneedles

Dissolving microneedles are fabricated using water-soluble and biodegradable polymers containing the incorporated drug within the needle matrix. Upon insertion into the skin, the microneedles dissolve in interstitial fluid and release the encapsulated drug directly into the epidermal or dermal layers.[9] This system eliminates the issue of sharp biohazardous waste and improves patient safety. Dissolving microneedles are highly suitable for controlled and sustained delivery of antidiabetic drugs such as repaglinide and Nate glinide. Additionally, they provide enhanced patient compliance due to painless administration and ease of self-application.[6]

2.1.3 Hydrogel-Forming Microneedles

Hydrogel-forming microneedles consist of crosslinked polymeric networks capable of absorbing interstitial fluid after insertion into the skin. These microneedles swell to form continuous pathways between the drug reservoir and dermal microcirculation, allowing controlled diffusion of therapeutic agents. Unlike dissolving microneedles, hydrogel-forming systems remain structurally intact and are removed after drug delivery. They offer advantages such as sustained drug release, improved mechanical stability, and reduced risk of polymer deposition in the skin. These characteristics make them promising candidates for long-term management of chronic diseases such as diabetes mellitus.[12]



2.2 Polymers Used in Microneedle Fabrication

Selection of suitable polymers is a critical factor influencing the mechanical strength, biocompatibility, drug loading capacity, dissolution behavior, and release characteristics of microneedles. Various natural and synthetic polymers have been investigated for microneedle fabrication.[13] Natural polymers commonly employed include hyaluronic acid, chitosan, gelatin, alginate, dextran, and starch. These polymers possess excellent biocompatibility, biodegradability, and low toxicity. Hyaluronic acid is particularly preferred due to its skin compatibility and rapid dissolution properties.[14] Synthetic polymers such as polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), and polymethyl methacrylate (PMMA) are also widely utilized. These polymers provide superior mechanical strength, controlled degradation, and improved formulation stability. Blending of polymers is often performed to optimize flexibility, drug release, and insertion capability of the microneedles.[15] The choice of polymer depends on several factors including drug physicochemical properties, desired release profile, fabrication method, and intended therapeutic application.[16]

2.3 Mechanism of Transdermal Drug Delivery Using Microneedles

The primary barrier to transdermal drug delivery is the stratum corneum, which restricts permeation of most drugs. Microneedles overcome this limitation by creating microscopic channels in the skin without stimulating deeper nerve endings, thereby enabling painless delivery.[9]

The mechanism of drug delivery through polymeric microneedles generally involves the following steps:

1. **Insertion into the Skin:** Microneedles penetrate the stratum corneum and form transient microchannels.
2. **Drug Release:** Depending on the microneedle type, the drug is released by dissolution of the polymer matrix, diffusion through swollen hydrogel networks, or application of a secondary formulation.[9]
3. **Drug Diffusion:** The released drug diffuses into epidermal and dermal tissues and enters systemic circulation through dermal microvasculature.[17]
4. **Skin Recovery:** After removal of the microneedles, the microchannels gradually close, restoring the skin barrier function with minimal irritation or infection risk.[9]

This mechanism significantly enhances the bioavailability of poorly absorbed drugs and facilitates controlled drug administration.

2.4 Advantages Over Conventional Delivery Systems

Polymeric microneedle systems offer several advantages compared to conventional oral and hypodermic drug delivery methods, Avoidance of hepatic first-pass metabolism, Improved bioavailability of poorly absorbed drugs, Painless and minimally invasive administration, Enhanced patient compliance and self-administration, Sustained and controlled drug release, Reduced gastrointestinal side effects, Lower risk of needle-stick injuries and infections, Elimination of sharp biomedical waste in dissolving systems, Rapid onset of therapeutic action, Improved stability of sensitive therapeutic agents, For antidiabetic therapy, polymeric microneedles provide an attractive alternative to oral administration by maintaining consistent plasma drug levels and reducing dosing frequency. Consequently, these systems have emerged as a promising platform for the effective transdermal delivery of meglitinide drugs and other therapeutic agents.[18]

Drug	Polymer	Microneedle Type	Fabrication Method	Drug Release Profile	Key Findings
Repaglinide	Polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP)	Dissolving microneedles	Micro molding	Rapid initial release followed by sustained release	Enhanced transdermal permeation and improved bioavailability compared to oral delivery
Nateglinide	Hyaluronic acid	Dissolving microneedles	Solvent casting and molding	Fast dissolution within skin layers	Improved skin penetration and reduced dosing frequency
Insulin	Chitosan, PVA	Hydrogel-forming microneedles	Crosslinking and micro molding	Controlled and prolonged release	Effective glycemic control with sustained plasma insulin levels
Metformin hydrochloride	Gelatin, PVP	Dissolving microneedles	Micro molding	Biphasic release profile	Enhanced patient compliance and reduced gastrointestinal side effects
Glibenclamide	Poly (lactic-co-glycolic acid) (PLGA)	Solid microneedles	Hot-melt molding	Diffusion-controlled release	Increased transdermal flux and improved therapeutic efficacy
Exenatide	Hyaluronic acid, Dextran	Dissolving microneedles	Centrifugal lithography	Sustained release over several hours	Improved peptide stability and painless administration
Insulin	Alginate, Chitosan	Hydrogel-forming microneedles	Ionic gelation and molding	Extended controlled release	Maintained prolonged hypoglycemic effect in diabetic models
Repaglinide nanoparticles-loaded system	PVA, PVP, PLA	Dissolving microneedles	Nano-micro molding	Sustained and enhanced release	Improved drug stability and higher permeation efficiency
Pioglitazone	Carboxymethyl	Dissolving	Micro	Rapid	Enhanced

	cellulose (CMC)	microneedles	molding	dissolution and release	bioavailability with minimal skin irritation
Insulin-loaded nanoformulation	Hyaluronic acid hydrogel	Hydrogel-forming microneedles	3D printing and crosslinking	Glucose-responsive release	Smart insulin delivery with controlled therapeutic response

Abbreviations: PVA = Polyvinyl alcohol; PVP = Polyvinylpyrrolidone; PLA = Polylactic acid; PLGA = Poly (lactic-co-glycolic acid); CMC = Carboxymethyl cellulose.

3. Fabrication and Characterization of Polymeric Microneedles

The successful development of polymeric microneedles for transdermal delivery of meglitinide drugs depends largely on appropriate fabrication techniques and comprehensive characterization of the prepared systems. Fabrication methods influence microneedle geometry, mechanical strength, drug loading efficiency, and release behavior, while characterization studies ensure quality, performance, safety, and therapeutic effectiveness. Various analytical and evaluation techniques are therefore employed during the development process of polymeric microneedle systems.[19]

3.1 Fabrication Techniques and Molding Methods

Several fabrication techniques have been developed for the preparation of polymeric microneedles, depending on the type of polymer, drug properties, and desired release profile. Among these methods, micro molding is the most commonly used technique because of its simplicity, reproducibility, and cost-effectiveness.[20]

3.1.1 Micro molding Technique

In the micro molding method, a polymeric drug solution is poured into microstructure molds fabricated from materials such as polydimethylsiloxane (PDMS). The solution is then subjected to centrifugation, vacuum, or pressure to ensure complete filling of the mold cavities. After drying or crosslinking, the formed microneedles are carefully removed from the molds. This method is widely employed for preparing dissolving and hydrogel-forming microneedles containing antidiabetic drugs.[21]

3.1.2 Solvent Casting Method

In solvent casting, polymers and drugs are dissolved in suitable solvents and cast into microneedle molds followed by solvent evaporation. The method is relatively simple and

suitable for heat-sensitive drugs. However, residual solvent toxicity and prolonged drying time may limit its application.[21]

3.1.3 Hot-Melt Molding

Hot-melt molding involves heating thermoplastic polymers until molten and subsequently filling them into microneedle molds under pressure. Upon cooling, solidified microneedles are obtained. This technique eliminates the use of organic solvents but may not be suitable for thermolabile drugs.[9]

3.1.4 Drawing Lithography and 3D Printing

Advanced fabrication technologies such as drawing lithography, laser engineering, and 3D printing have recently gained significant interest. These methods allow precise control over microneedle geometry, dimensions, and drug distribution. Three-dimensional printing, in particular, offers customization, rapid prototyping, and reproducibility in microneedle fabrication.[22]

The selection of fabrication technique is mainly influenced by polymer characteristics, mechanical requirements, scalability, and desired therapeutic performance.[23]

3.2 Mechanical Strength and Insertion Studies

Mechanical strength is a critical parameter in polymeric microneedle design because insufficient strength may lead to needle bending or breakage during skin insertion. Microneedles must possess adequate rigidity to penetrate the stratum corneum effectively without structural failure.[9]

Mechanical properties are commonly evaluated using compression testing, texture analyzers, and force-displacement studies. These tests determine the fracture force, deformation behavior, and insertion capability of microneedles under applied pressure.[24]

Insertion studies are performed to assess the ability of microneedles to penetrate skin layers successfully. Different experimental models such as excised animal skin, porcine skin, Parafilm® membranes, and artificial skin models are widely used for insertion analysis. Techniques including methylene blue staining, histological examination, optical microscopy, and confocal laser scanning microscopy help visualize the depth and uniformity of skin penetration.[25] Adequate mechanical strength and insertion efficiency are essential for ensuring reproducible drug delivery and therapeutic effectiveness.

3.3 Drug Loading and Release Characteristics

Drug loading capacity significantly influences the therapeutic performance of microneedle systems. Meglitinide drugs are generally incorporated either within the polymeric matrix or coated onto the microneedle surface depending on the formulation strategy.[26] Drug loading efficiency is determined using analytical methods such as ultraviolet-visible spectroscopy (UV-Vis), high-performance liquid chromatography (HPLC), and spectrophotometric techniques. Uniform distribution of the drug throughout the microneedle matrix is important to achieve accurate dosing and consistent therapeutic outcomes.[27] In vitro drug release studies are commonly performed using dissolution apparatus, Franz diffusion cells, or dialysis membrane methods. Release profiles depend on factors such as polymer composition, crosslinking density, drug-polymer interactions, microneedle geometry, and dissolution behavior.[28] Dissolving microneedles generally exhibit rapid drug release upon skin insertion, whereas hydrogel-forming microneedles provide sustained and controlled release over prolonged periods. Controlled release behavior is particularly advantageous for antidiabetic therapy because it helps maintain stable blood glucose levels and reduces dosing frequency.[29]

3.4 Physicochemical and Morphological Characterization

Physicochemical characterization is essential to evaluate the structural integrity, compatibility, and performance of polymeric microneedles.[28]

Morphological Characterization

Morphological analysis is performed to examine microneedle shape, dimensions, surface smoothness, tip sharpness, and structural uniformity. Commonly used techniques include, Scanning Electron Microscopy (SEM), Optical Microscopy, Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM), These methods provide detailed information regarding microneedle architecture and surface characteristics that influence insertion efficiency and drug delivery performance.[30]

Physicochemical Characterization

Various analytical techniques are employed to investigate physicochemical properties and drug-polymer interactions, Fourier Transform Infrared Spectroscopy (FTIR) for compatibility studies, Differential Scanning Calorimetry (DSC) for thermal behavior analysis, X-ray Diffraction (XRD) for crystallinity assessment, Thermogravimetric Analysis (TGA) for thermal stability, Zeta potential and particle size analysis for nano-enabled systems These

studies help confirm drug encapsulation, polymer stability, and absence of undesirable chemical interactions[31]

3.5 Stability and Safety Assessment

Stability studies are conducted to evaluate the physical, chemical, and mechanical stability of polymeric microneedles under different storage conditions. Parameters such as appearance, drug content, moisture uptake, mechanical integrity, and drug release behavior are monitored over time according to regulatory guidelines.[32] Environmental factors including temperature, humidity, and light exposure can significantly affect microneedle stability and therapeutic efficacy. Therefore, appropriate packaging and storage conditions are necessary to maintain product quality.[9] Safety assessment is another important aspect in the development of microneedle systems. Skin irritation, erythema, edema, and cytotoxicity studies are commonly performed using in vitro cell culture models and in vivo animal studies. Histopathological examination is also carried out to evaluate tissue compatibility and skin recovery after microneedle application.[9] Polymeric microneedles are generally considered safe due to their minimally invasive nature and use of biocompatible polymers. Nevertheless, comprehensive safety evaluation is essential before clinical application to ensure patient acceptability and long-term therapeutic safety.[33]

4. Applications of Polymeric Microneedles in Meglitinide Delivery

Polymeric microneedle systems have emerged as an advanced transdermal platform for the effective delivery of antidiabetic drugs, particularly meglitinides such as repaglinide and Nate glinide. The unique ability of microneedles to bypass the stratum corneum barrier and facilitate direct drug transport into the epidermal and dermal layers has significantly improved the therapeutic potential of these agents. Polymeric microneedles not only enhance drug permeation and bioavailability but also provide controlled release characteristics, improved patient compliance, and reduced systemic side effects. Their application in diabetes management has therefore attracted considerable research interest in recent years.

4.1 Enhanced Permeation and Bioavailability

One of the major challenges associated with oral administration of meglitinide drugs is their low and variable bioavailability resulting from extensive hepatic first-pass metabolism and gastrointestinal degradation. Polymeric microneedles effectively overcome these limitations by delivering drugs directly across the skin into systemic circulation.[34] Microneedles create transient microchannels in the stratum corneum, thereby significantly increasing skin

permeability. This enhanced permeation facilitates improved absorption of meglitinide drugs that would otherwise exhibit limited transdermal penetration due to their physicochemical properties. The increased permeation also contributes to rapid onset of pharmacological action and improved therapeutic response.[35] Several studies have demonstrated that microneedle-mediated transdermal delivery results in higher drug bioavailability compared with conventional oral formulations. Improved systemic absorption minimizes dose variability and helps maintain therapeutic plasma concentrations for prolonged periods. Additionally, bypassing gastrointestinal and hepatic metabolism reduces drug degradation and enhances overall drug utilization.[36] The enhanced permeation capability of polymeric microneedles is influenced by factors such as microneedle length, density, geometry, polymer composition, insertion depth, and dissolution behavior. Optimization of these parameters plays a critical role in maximizing transdermal drug transport and therapeutic efficacy.[37]

4.2 Controlled and Sustained Drug Release

Controlled and sustained release is another significant advantage offered by polymeric microneedle systems. Conventional oral meglitinide formulations often require multiple daily dosing because of their short plasma half-life, which may lead to fluctuations in blood glucose levels and reduced patient adherence.[38] Polymeric microneedles enable controlled release of encapsulated drugs through gradual polymer dissolution, diffusion, or swelling mechanisms. Dissolving microneedles provide immediate or moderately sustained drug release depending on polymer composition, whereas hydrogel-forming microneedles allow prolonged and controlled diffusion of the drug from an attached reservoir system.[39] Sustained release characteristics help maintain consistent plasma drug concentrations, thereby improving glycemic control and reducing the frequency of administration. This approach minimizes peak-trough fluctuations associated with oral therapy and decreases the risk of hypoglycemic episodes.[40] Drug release kinetics from polymeric microneedles are affected by several formulation variables, including, Polymer molecular weight, Crosslinking density, Drug loading concentration, Microneedle geometry, swelling behavior of polymers, Skin hydration conditions, by careful optimization of these parameters, microneedle systems can be tailored to achieve desired release profiles suitable for long-term diabetes management.[28]

4.3 In Vitro, Ex Vivo, and In Vivo Evaluation Studies

Extensive evaluation studies are conducted to assess the performance and therapeutic potential of polymeric microneedle systems for meglitinide delivery.[41]

In Vitro Evaluation Studies

In vitro studies are primarily performed to evaluate drug release behavior, mechanical properties, and dissolution characteristics. Franz diffusion cells are commonly used to investigate drug permeation across synthetic membranes or biological tissues. Parameters such as cumulative drug release, release kinetics, and permeation flux are carefully analyzed.[42] Mechanical testing ensures that the microneedles possess sufficient strength to penetrate the skin without fracture. Dissolution studies further help determine the rate of polymer degradation and drug release following insertion.[21]

Ex Vivo Evaluation Studies

Ex vivo permeation studies are generally carried out using excised animal or human skin models, including porcine, rat, or cadaver skin. These studies provide valuable information regarding skin penetration efficiency, drug diffusion, and microchannel formation under realistic biological conditions.[43] Techniques such as histological analysis, confocal laser scanning microscopy, and dye-binding studies are employed to visualize microneedle insertion and assess skin recovery after application.[25]

In Vivo Evaluation Studies

In vivo studies are essential for evaluating pharmacokinetic and pharmacodynamic performance of microneedle formulations. Animal models such as diabetic rats or rabbits are frequently used to assess blood glucose reduction, plasma drug concentration profiles, bioavailability, and therapeutic efficacy.[18] Several studies have demonstrated that polymeric microneedle systems produce prolonged hypoglycemic effects and improved pharmacokinetic profiles compared to conventional oral formulations. In vivo investigations also help evaluate skin irritation, toxicity, and patient acceptability of the developed systems.[34] Collectively, in vitro, ex vivo, and in vivo studies provide comprehensive evidence supporting the effectiveness of polymeric microneedles for transdermal delivery of meglitinide drugs.[41]

4.4 Therapeutic Effectiveness in Diabetes Management

The therapeutic effectiveness of polymeric microneedles in diabetes management is primarily attributed to improved drug delivery efficiency, sustained plasma drug levels, and enhanced patient compliance. By providing minimally invasive and painless administration, microneedles increase patient acceptability and reduce the burden associated with frequent oral dosing or injectable therapies.[44] Microneedle-mediated delivery of meglitinides offers

effective control of postprandial blood glucose levels through rapid and efficient systemic absorption. Sustained drug release further contributes to prolonged glycemic control and reduction in glucose fluctuations.[45] Additionally, transdermal delivery reduces gastrointestinal side effects commonly associated with oral antidiabetic therapy and decreases the risk of hepatic drug interactions. Improved bioavailability may also allow dose reduction, thereby minimizing systemic adverse effects.[46,47] The integration of advanced polymers, smart responsive materials, and controlled-release technologies has further expanded the therapeutic potential of polymeric microneedles in diabetes treatment. These systems may serve as promising alternatives to conventional oral therapy and contribute significantly toward personalized and patient-friendly diabetes management strategies in the future.[48]

5. Challenges, Future Perspectives, and Conclusion

Despite the remarkable advancements in polymeric microneedle technology for transdermal delivery of meglitinide drugs, several scientific, technical, regulatory, and commercial challenges still limit their widespread clinical application. Continuous research efforts are therefore necessary to improve formulation performance, manufacturing feasibility, safety, and patient accessibility. Nevertheless, the growing interest in minimally invasive drug delivery systems and the increasing prevalence of diabetes mellitus indicate strong future potential for microneedle-mediated antidiabetic therapy.[48]

5.1 Manufacturing and Scalability Challenges

One of the major barriers to commercialization of polymeric microneedles is the complexity associated with large-scale manufacturing. Although several fabrication methods such as micro molding, solvent casting, and 3D printing have shown promising laboratory-scale results, maintaining consistency and reproducibility during industrial production remains challenging.[49] Uniformity in microneedle dimensions, drug loading, mechanical strength, and dissolution characteristics is essential to ensure therapeutic reliability and patient safety. Minor variations in fabrication parameters may significantly affect skin penetration efficiency and drug release behavior. Therefore, precise process optimization and stringent quality control measures are required during manufacturing.[50] Another important challenge involves selection of suitable polymers and excipients that provide optimal mechanical properties while maintaining biocompatibility and stability. Some biodegradable polymers may exhibit poor mechanical strength, leading to needle deformation or fracture during insertion. In contrast, highly rigid materials may compromise patient comfort and flexibility.[51] Scaling up

fabrication technologies such as microfabrication and 3D printing can also increase production costs, limiting affordability and accessibility. Additionally, issues related to sterilization, packaging, storage stability, and moisture sensitivity further complicate commercial development of polymeric microneedle systems.[52] To overcome these limitations, future research should focus on Development of cost-effective and scalable manufacturing techniques, Standardization of fabrication protocols, Advanced automation technologies, Optimization of polymer combinations, Improved quality assurance systems, Successful resolution of these challenges is essential for the industrial translation of microneedle-based transdermal drug delivery systems.[53]

5.2 Regulatory and Clinical Considerations

Regulatory approval of polymeric microneedle systems presents another significant challenge due to the complex nature of these combination products, which often involve both medical device and pharmaceutical components. Regulatory agencies require comprehensive evaluation of product quality, efficacy, safety, sterility, and long-term stability before clinical approval.[54] Standardized regulatory guidelines specific to microneedle technologies are still evolving in many countries. This lack of harmonized regulations may delay product approval and commercialization. Critical evaluation parameters include, Mechanical safety and insertion performance, Skin irritation and sensitization potential, Biocompatibility and toxicity, Residual polymer deposition, Sterility assurance, Pharmacokinetic and pharmacodynamic behavior, Clinical studies are necessary to establish therapeutic efficacy, patient acceptability, and long-term safety in diabetic patients. However, conducting large-scale clinical trials can be expensive and time-consuming. Variability in skin properties among different patient populations may also influence microneedle performance and drug absorption.[18] Patient education and acceptance are equally important for successful clinical implementation. Although microneedles are generally painless and minimally invasive, concerns regarding skin application, repeated use, and device handling may affect user compliance.[55] Future regulatory progress will likely depend on collaborative efforts among researchers, pharmaceutical industries, healthcare professionals, and regulatory authorities to establish standardized guidelines and evaluation criteria for microneedle-based products.[53]

5.3 Future Prospects of Microneedle-Mediated Antidiabetic Therapy

The future of polymeric microneedles in diabetes management appears highly promising due to ongoing advancements in biomaterials, nanotechnology, and smart drug delivery systems.

Emerging research is increasingly focused on developing patient-friendly, self-administered, and controlled-release transdermal platforms capable of improving glycemic control and overall therapeutic outcomes.[56] Integration of responsive polymers and smart materials may enable glucose-responsive microneedle systems capable of releasing drugs in response to fluctuating blood glucose levels. Such systems could provide personalized and automated diabetes management while minimizing the risk of hypoglycemia.[57] Combination approaches involving nanoparticles, liposomes, nanoemulsions, and hydrogels within microneedle matrices are also gaining considerable attention for enhancing drug stability, permeation, and sustained release characteristics. Advanced fabrication techniques such as 3D printing and microelectromechanical systems (MEMS) may further improve precision, scalability, and customization of microneedle devices.[58] Future investigations may also explore, Combination delivery of multiple antidiabetic agents, Integration with biosensors for real-time glucose monitoring, Long-acting microneedle patches, Improved wearable transdermal systems, Personalized and precision medicine approaches, As research progresses, polymeric microneedles may become an effective alternative to conventional oral and injectable therapies, thereby significantly improving patient compliance and quality of life in diabetic populations[59]

5.4 CONCLUSION

Polymeric microneedles represent an innovative and promising transdermal drug delivery platform for the administration of meglitinide drugs in the treatment of diabetes mellitus. These systems effectively overcome the limitations associated with conventional oral therapy by enhancing skin permeation, improving bioavailability, bypassing hepatic first-pass metabolism, and providing controlled and sustained drug release. Different types of polymeric microneedles, including solid, dissolving, and hydrogel-forming systems, have demonstrated significant potential in improving therapeutic outcomes and patient compliance. Various fabrication and characterization techniques have been successfully employed to optimize microneedle performance, mechanical strength, drug loading, and safety profiles. Although challenges related to large-scale manufacturing, regulatory approval, and clinical translation still exist, ongoing technological advancements and increasing research interest continue to support the future development of microneedle-mediated antidiabetic therapy. The integration of smart materials, responsive delivery systems, and advanced fabrication technologies is expected to further expand the clinical applicability of polymeric microneedles in diabetes management. Overall, polymeric microneedles offer a minimally

invasive, patient-friendly, and highly efficient approach for transdermal delivery of meglitinide drugs and hold considerable promise as next-generation therapeutic systems for effective and improved diabetes treatment.

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