LOCTITE®

SKIN SENSITIZATION IN **WEARABLE MEDICAL DEVICES**

ENSURING SAFETY IN ADHESIVE SELECTION

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Abstract

This technical white paper highlights increasing concerns regarding the skin sensitization potential of adhesion promoters, particularly isobornyl acrylate (IBOA), commonly used in light-cure adhesives for assembling wearable medical devices. Skin reactions experienced by those using continuous glucose monitors (CGMs) and insulin pumps have caused diabetic patients and medical professionals to demand alternative adhesive options and strict quality controls to eliminate skin-sensitizing ingredients from these devices. As the number of reported skin reactions increases, regulatory scrutiny by agencies that oversee public health and safety has intensified. The authorities like FDA and EMA are now subjecting stronger concerns on skin sensitizing properties to ensure patient safety.

Introduction

According to the World Health Organization (WHO), the number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Today, more than half a billion people globally are living with diabetes, and this number is expected to continue to rise.

Wearable technologies for diabetes management are essential for improving blood glucose monitoring, patient health outcomes and quality of life. The rising demand for wearable medical technologies has resulted in the need for close attention to product safety, particularly in terms of skin reactions caused by materials used in the manufacture of these devices.

Continuous Glucose Monitors (CGMs) are innovative medical electronic devices used to measure blood glucose levels 24 hours a day. They attach to the skin with an adhesive film and are typically worn on the upper arm. The device includes a biochemical sensor filament that inserts into the subcutaneous tissue to measure interstitial glucose levels. The electrical signal produced by the filament is filtered by the electronics within the small housing and sent to a user interface by Bluetooth or NFC. The user interface displays real-time data on glucose levels and does further data processing.

Insulin pumps, often integrated into a wearable glucose management system, deliver measured doses of insulin at specific times throughout the day and night. These small programmable computerized devices attach to the skin by an adhesive patch, generally on the belly or thigh. Insulin is pushed through a tube into the infusion site in the subcutaneous layer, delivering insulin beneath the skin. In addition to automatically delivering insulin 24 hours a day, insulin can be dosed to cover meals or correct high blood sugar levels.

WOMEN WEARING CGM DEVICE

WOMEN WEARING AN INSULIN PUMP

CGMs and insulin pumps are sophisticated medical wearable devices that improve the ability of diabetic patients to accurately manage blood sugar levels. However, cases of severe adverse skin reactions have been reported by significant numbers of patients using these devices, making it crucial to identify and resolve skin sensitization issues and reduce risks to patients.

The medical industry has been working painstakingly to determine the cause of skin sensitization in patients using medical wearable devices. Isobornyl acrylate (IBOA), a common ingredient in adhesives used in the manufacture of these devices, has been identified as the culprit in many cases.

IBOA – The Allergen of the Year in 2020

IBOA is a monomer used in acrylic polymers to increase adhesion, flexibility, and impact resistance to plastic materials, and is commonly used in the formulation of light-curable adhesives. When exposed to proper light, a light-curable adhesive changes from a liquid monomer to a hardened polymer with high bond strength and durability. Commonly used in the manufacture of medical wearable devices, light-curable adhesives enable high speed automated bonding of sensor assemblies, securely bonding and sealing key components into position with a quick exposure to curing lights.

In 1995, two adult diabetic patients were the first to report skin eruptions around the injection site of their wearable insulin pump. Since then, there has been a rapid growth in the number of reported skin reactions to both CGM devices and insulin pumps, prompting the medical community to petition device manufacturers to investigate.

Medical wearable devices are complex assemblies comprised of multiple materials and components. It took years of careful study, sophisticated chemical analyses of gas chromatography and mass spectrometry, and skin patch testing to confirm that IBOA was the cause of the adverse skin reaction in most cases.

In 2020, IBOA was named Allergen of the Year by the American Contact Dermatitis Society due to large numbers of patients using medical wearable devices suffering from skin reactions. It is hypothesized that sweat and bathing fluids can dissolve IBOA as it leaches from the adhesive within the device housing and transfer it to the skin. In susceptible individuals, IBOA, even in small amounts, triggers an inflammatory immune response called skin sensitization.

Skin Sensitization Mechanism

Skin sensitization is an inflammatory immune response occurring in susceptible individuals following repeated or lengthy exposure to a skin sensitizing agent. Unlike skin irritations, skin sensitivities become more severe with each subsequent exposure, requiring less of the sensitizing substance to initiate the inflammatory response.

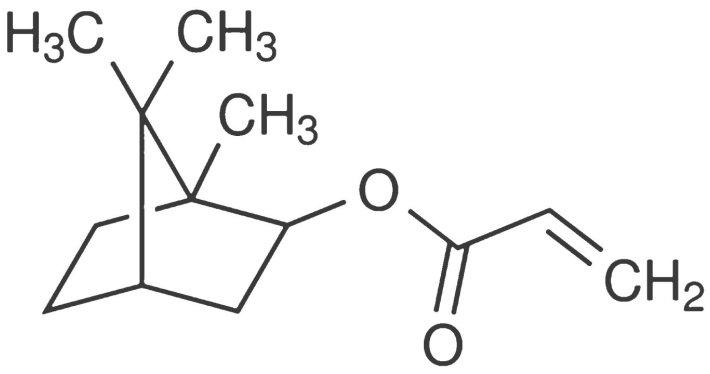
To understand skin sensitization, it is important to recognize that skin plays a major role in immunity. Skin serves as a crucial interface between the body and the external environment, protecting the body from external pathogens with sophisticated dermal immune processes.

The involvement of T cells and cytokines in dermal immune processes is significant in the development of skin sensitization. T cells, a type of lymphocyte, actively patrol skin tissue, detecting and responding to foreign invaders. T cells coordinate and regulate immune responses by triggering the release of signaling proteins, called cytokines. Excessive cytokine production can lead

Skin Sensitization Mechanism – Continued

to chronic inflammation and hypersensitivity. T cells also have the ability to develop memory. T cell memory, acquired during prior encounters with foreign invaders, provides the skin with a heightened ability to respond quickly with subsequent exposures and contributes to the skin's capacity to develop skin sensitization.

IBOA - Risks and Reactions



Chemical Strucutre of Isobornyl Acrylate (IBOA)

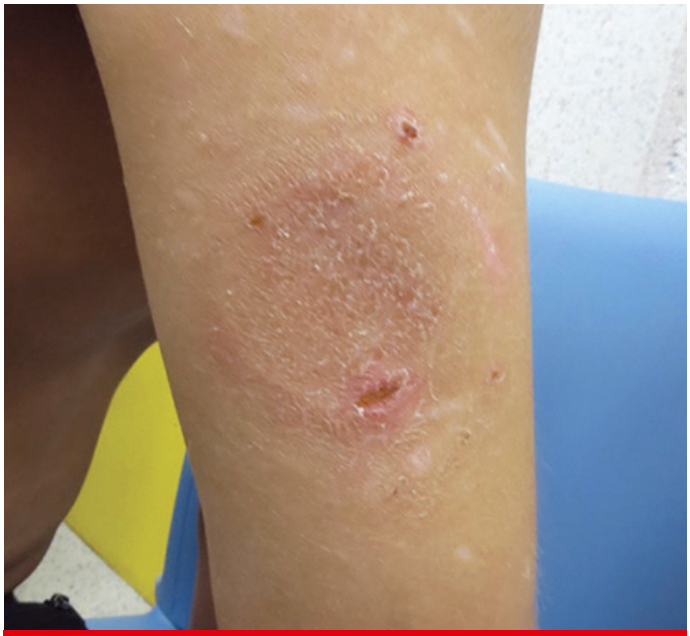
IBOA's ability to induce skin sensitization is attributed to its chemical structure. The acrylate functional group is known for its potential to bind covalently to proteins to form hapten-protein complexes that act as antigens, telling the body that something foreign is present. These chemically modified proteins present themselves to T cells, triggering an immune response that leads to excessive cytokine production in susceptible individuals.

Multiple patient testimonials and case studies involving those who developed adverse skin reactions from using CGM devices or insulin pumps have been published online. Symptoms range from mild to severe, with mild symptoms manifesting as redness, burning, and itching. More serious reactions are described as eruptions, blistering, bleeding, abscesses with severe edema that results in oozing, infection, and scarring.

One scientific article, published by WILEY Online Library, describes 15 subjects suffering from adverse skin reactions to wearable diabetic management devices. Data collected from this study (and similar studies) provides evidence that IBOA is not suitable for use in medical wearable devices that have prolonged contact with the skin.

Evidence includes:

- The onset of adverse reactions varies from a few days to several months of use, conforming to skin sensitization mechanisms with previous exposures causing a quicker reaction.
- Skin patch testing with IBOA at various concentrations demonstrates that comparatively low levels of IBOA are enough to cause skin sensitization.
- Severe inflammation is associated with unreliable glucose level measurements, likely due to interstitial fluid dilution caused by edema.
- Utilizing some type of barrier between the device and the skin can help reduce the severity of symptoms but does not completely resolve the dermatitis.



Acute skin reaction to CGM device[1]

[1] Allergic contact dermatitis caused by isobornyl acrylate in ... (n.d.). https://onlinelibrary.wiley.com/doi/10.1111/cod.12866

Regulatory and Standards

Authorities such as the FDA and EMA have recognized the urgent need to address skin sensitization issues in medical wearable devices. The rapidly growing problem of skin sensitization requires actions by the device manufacturer to fulfill the FDA and the EU MDR regulatory guidelines for biocompatibility evaluation of medical devices that come into direct contact or indirect contact with the human body in accordance with International Standard ISO 10993.

Regulations for biocompatibility are based on the ISO 10993 standard for the biological evaluation of medical devices and mandates testing of all materials and components regarding their leachables, to run the required toxicological assessment on potential hazardous ingredients, like sensitizing substances. In this context, it is relevant to comprehend that skin sensitizing substances, like IBOA, can leach from inside a wearable medical device and come in contact with the skin under the influence of sweat and humidity.

Biocompatibility testing protocols are especially rigorous for CGMs and insulin pumps due to their high potential for skin sensitization. Ultimately, it is the responsibility of the OEM to demonstrate to regulatory agencies that their device has an appropriate level of biocompatibility. OEMs of wearable diabetic management devices will need to submit ISO 10993 test results to the appropriate governing regulatory agency in order to gain approval to market their CGM devices and insulin pumps. It is important to note that suppliers of adhesive materials can support communication with regulatory agencies by providing biocompatibility test data that supports their adhesive materials, simplifying OEM testing requirements.

Adhesive Alternatives

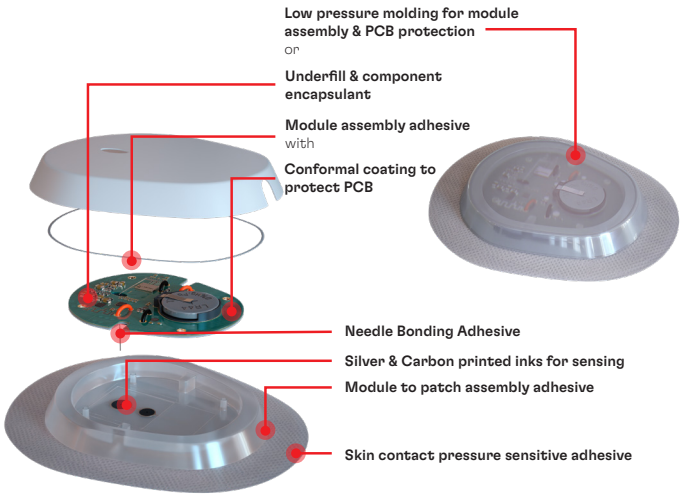
There is a great need for instant bonding adhesives that are safe and effective for use in medical wearable devices, and that do not sacrifice bond quality and performance. Ensuring skin-friendly wearable devices necessitates the careful formulation of alternative biocompatible adhesives, without IBOA. Proper biocompatibility testing on cured adhesives according to ISO 10993-10 is documenting no skin-sensitizing performance of the cured adhesive.

As a leading manufacturer of advanced adhesive solutions, Henkel has developed innovative medical grade adhesives, LOCTITE® WT 3001 and LOCTITE® WT 3003, suitable for wearable medical devices. LOCTITE® WT 3001 is a self-leveling formula and LOCTITE® WT 3003 is a higher viscosity thixotropic version. These adhesives were developed with patient safety and comfort in mind and follow FDA and EU MDR recommendations. **These newly developed medical grade adhesives are:**

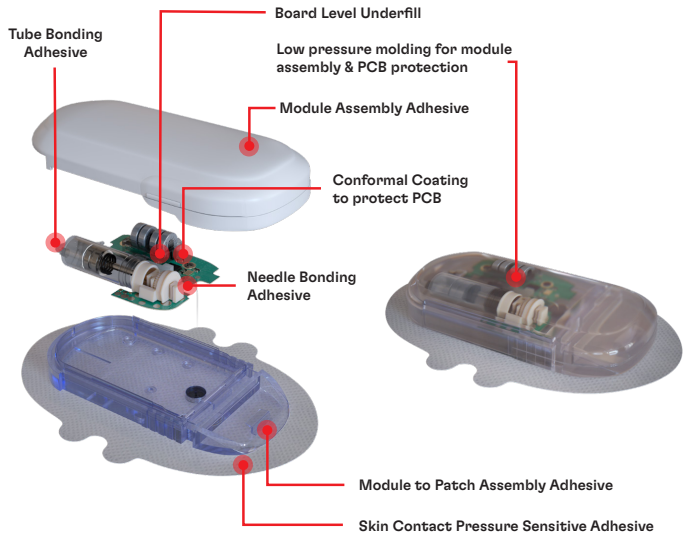
- Free of commonly used CMRs (carcinogen, mutagen, reproductive hazards) such as TPO.
- Free of the commonly used Skin Sensitizer IBOA (Isobornyl Acrylate)
- Widely tested for ISO 10993 biocompatibility including Skin Sensitization
- Instant curing under both UV and Visible light, LED or Bulb based systems
- High contrast red fluorescent for bond detection
- Jet Valve dispensable
- Ideal for bonding to plastics (PC & FR4) and sealing plastic housings,
- Resistant to impacts, thermal cycling, and moisture
- Suitable for a variety of wearable devices with prolonged skin contact
- Formulated reflecting the recent findings on Wearables and their skin sensitizing potential by Leachables.

Medical wearable applications for LOCTITE® WT 3001 and LOCTITE® WT 3003 include:

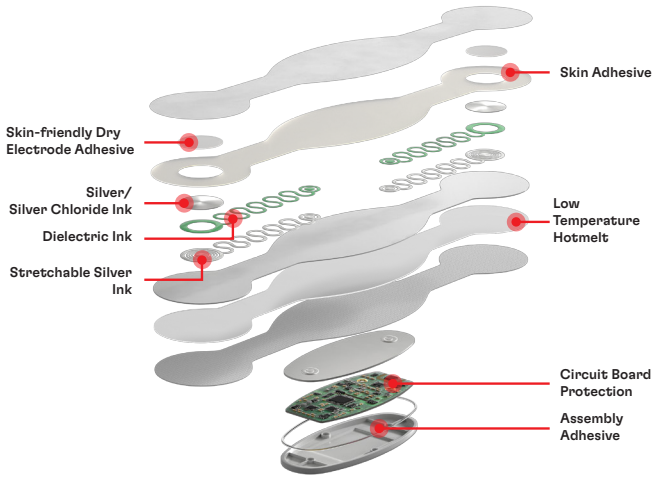
Assembly of CGM devices



Assembly of Insulin patch pump devices



Assembly of Cardiac health patch devices



Conclusion

The growing awareness and regulatory attention surrounding skin sensitization in wearable devices necessitate proactive steps in adhesive selection for device manufacturing and assembly. Manufacturers shall prioritize patient safety to meet consumer demands for devices that are skin friendly. By embracing safer material alternatives and implementing strict quality controls and biocompatibility testing, the industry can evolve to meet the growing market demand for safe medical wearable devices with reduced risk of skin sensitization.

Disclaimer

This white paper provides general information and recommendations only and does not constitute medical or legal advice. Manufacturers are encouraged to consult with regulatory authorities and professionals familiar with specific product segmentation and composition prior to making any decisions or changes related to adhesives in wearable medical devices.

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