SILICONE-BASED PRESSURE-SENSITIVE ADHESIVE (PSA) ON TRANSDERMAL PATCH DELIVERY SYSTEM

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Article History: **Received:** 27.09.2022 **Revised:** 27.10.2022 **Accepted:** 06.11.2022

Abstract: Pressure Sensitive Adhesive (PSA) is a type of adhesive generally made from viscoelastic, sticky polymer chains, making it widely used as pads and ultra-thin coatings in medical applications. Some types of PSA materials are popular, one of which is silicon-based materials. Silicone is the commercial name for many silicon-based products. Technically, silicone (polysiloxane) is a polymer with the chemical formula [R2SiO]n, in which R can be any organic groups including methyl, phenyl, alkenyl, and hydrogen. Silicone PSA is increasingly used in medical applications such as in drug delivery systems in the form of transdermal patches. Silicone PSA offers excellent solubility and permeability for lipophilic drugs, but in some cases, it can be used in hydrophilic drugs. The use of PSA has proved to have some effects on transdermal patch preparations in accordance with the shape, design, and base used. Several studies indicate that PSA transdermal patches have such benefits as being able to control drug release both in vitro and in vivo, maintain the stability of a preparation and active substance, and provide the same effectiveness as that of a patch with other mechanisms.

Keywords: PSA (Pressure Sensitive Adhesive), Silicone, Polydimethylsiloxane (PDMS), Transdermal Patch

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DOI: 10.31838/ecb/2022.11.10.014

INTRODUCTION

Silicone is the commercial name for a large number of silicon-based products. Silicone (more precisely named polysiloxane) is technically a polymer with [R2SiO]n as the chemical formula, where R is an organic group that can greatly vary from methyl, phenyl, and alkenyl, to hydrogen. Silicone structurally consists of an inorganic silicon-oxygen backbone (…–Si–O–Si–O–Si–O–…) with organic side groups attached to four-coordinate silicon atoms. The most common organic side groups include hydrocarbons, such as methyl and phenyl. The inorganic-organic polarity property provides silicon with unique low surface tension. In some cases, organic side groups, such as vinyl and hydride, can be used to connect two or more – Si–O– backbones. By varying the length of the –Si–O– chains, side groups, and crosslinks, silicone can be synthesized with various properties and compositions. The consistency of silicone can vary from liquids with low viscosity, high-viscosity polymers (gums), solid resins or soft gels, tough elastomers, to rigid hard coatings. The most common siloxane is the linear polydimethylsiloxane (PDMS), which is a silicone oil or polymer, while the second largest group of silicone materials is based on branched silicon resins and cage-shaped oligomeric siloxane (Benedek & Feldstein, 2009).

Silicone has a quite unique chemical structure which leads to an unusual intramolecular property. The Si–O bond in the silicone backbone has a bond energy of 108 kcal/mol, which is significantly higher than the C–C bond with 335.9 KJ/mol and the C–O bond with 339.1 KJ/mol. The popular bond angle of Si–O–Si is 143°, and that of O–Si–O is 110° while the length of Si–C bond is 0.188 nm and Si–O has a bond length of 0.163 nm. The siloxane chain flexes and rotates relatively freely around the Si-O axis. Such siloxane backbone properties usually provide high chain mobility and high chemical stability against degradation. This also possibly explains why silicone has an extremely low glass transition temperature (Tg) of approximately 125°C. The polarity between the inorganic Si–O backbone and the dimethyl groups in PDMS as well as the low intermolecular interactions among the methyl groups are responsible for the low surface tension property of PDMS, which is approximately 24 mN/m or even slightly lower in PDMS with a low molecular weight. Silicone is also known to have excellent stability at a high temperature (above 250°C), exhibit chemical inertness (lack of chemical reactivity) to a number of chemicals, and be stable despite environmental influence (oxygen, ultraviolet (UV) light, and humidity) (Benedek & Feldstein, 2009). Due to its duality (amphiphilic property), siloxane also has a fast diffusion property at the interface, in which it achieves a conformation that corresponds to the minimum free energy of the surface, thereby enabling

siloxane to form a highly adherent thin layer on it (De Buyl, 2001).

To describe the chemical structure of various silicone types in a simple and technically accurate manner, a system of abbreviated symbols has been adopted. The definitions and characteristics of the common building blocks for silicone are presented in Figure 1.

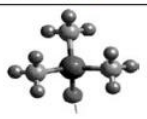
Formula Type	Stereo Model	Symbol	No. Linkage to Oxygen	Wt % [SiO] (Inorganic) (%)
$(CH_3)_3SiO_{1/2}$		*M*	Mono	44.5
$(CH_3)_2SiO$		*D*	Di	59.5
$(CH_3)SiO_{3/2}$		*T*	Tri	77.6
$SiO_{4/2}$		*Q*	Quadri	100.0
$(C_6H_5)_2SiO$		*D'*	Di	22.3
$(CH_3)(H)SiO$		*D'*	Di	73.4

Figure 1. Definitions and characteristics of common building blocks for silicone

SILICONE IN PHARMACEUTICAL APPLICATIONS

The diversity of the physical forms and physicochemical properties of silicone has led to its massive use in various healthcare applications, including in medical devices and as an active pharmaceutical ingredient (API) as well as excipient in pharmaceuticals for more than 60 years. Silicone or Polydimethylsiloxane (PDMS) with a high molecular weight is widely applied in pharmaceuticals but only limitedly used in industries. Silicone polymers in anti-flatulence and silicone elastomers can be used in silica tubes to transport various liquids, and this is probably the largest pharmaceutical application of polydimethylsiloxane (Colas & Corning, 2004).

Silicone can be used as an active ingredient, such as Dimethicone or more commonly referred to as Simethicone (a mixture of Dimethicone and silicon dioxide). Although there are limited data about the use of silicone as an excipient, there is some information which indicates that silicone can also function as an excipient in siliconization formulations (syringe, piston, and needle lubricant or stopper lubricant), skin adhesives (drug-permeable), elastomers (control membrane of drug release), release liner coating for transdermal patches (release coating) and skin topicals, as a polymer, volatile, or as a copolymer to carry active substances or to improve the dispersion and aesthetic quality (Colas & Corning, 2004).

In recent cases, the use of a silicone-based hybrid Pressure Sensitive Adhesive (PSA) technology provides potential performance benefits and can increase the effectiveness of drug delivery in transdermal systems. Pressure Sensitive Adhesive (PSA) is a self-adhesive material which requires no activation immediately before use or is commonly referred to as silicone Pressure Sensitive Adhesive (PSA) (Schalau II et al., 2018).

Silicone as Pressure Sensitive Adhesives (PSA)

Silicone PSA has a long history of use in transdermal drug delivery systems. It offers excellent solubility and permeability to lipophilic drugs but in some cases is desirable for hydrophilic drug delivery. PSA can be further modified in formulations by changing the hydrophilic fillers, copolymers, and plasticizers or by modifying the network using organic-silicon copolymers (Schalau II et al., 2018).

Another application where silicone PSA has become widely accepted is as an active pharmaceutical ingredient (API) or drug, and it is also used in the preparations of transdermal drug delivery. The pressure sensitive adhesives involved in transdermal drug delivery systems can be considered as one of the critical components. Without proper and sustained adhesion to the skin, the drug delivery of such dosage form cannot exist (Schalau II et al., 2018).

The importance of silicon PSA technology is evidenced by its endless, growing applications in commercial and industrial fields. Adhesives containing a small amount of silicon or silane which functions as a modifier are beyond the scope of this context, and so are adhesives associated with silica as a filler or additive.

Pressure Sensitive Adhesive (PSA) is a class of pre-shaped or preformed adhesives that adheres to a substrate under mild pressure. In general, PSA has a significantly higher cohesive strength than its adhesion strength to the substrate. Silicone PSA essentially consists of a high-molecular-weight silicone polymer and a siloxane MQ resin (M is trimethylsiloxy or CH3SiO1/2 unit, and Q is silsesquioxane or SiO4/2 unit) at a selected ratio, and it offers many of the unique properties of silicone. Many of these superior properties of silicone PSA are closely related to the inherent properties of silicon, including its flexibility over a wide temperature range, low intermolecular interactions, low surface tension, thermal stability, UV transparency, high-temperature stability, excellent electrical

insulation property, chemical resistance, and excellent weathering resistance (Benedek & Feldstein, 2009).

Other types of silicone adhesives are known for their ability to relieve traumatic effects on the skin by clean removal from damaged skin without a negative impact on the wound healing process. One example of the most recent innovation in the use of silicone PSA in medical devices is the Embrace® MINIMIZE Silicone Scar Aid which consists of silicone PSA glued to a layer of silicone elastomer (rubber). The unique applicator of this medical device allows the creation of a layer to reduce tension on the healing skin and minimize scar formation (Schalau II et al., 2018). The following are some advantages of PSA.

Temperature Stability: The key property of silicone PSA (and silicone in general) is its superior temperature stability. This is extremely important when the silicone is not only at high temperatures but also at very low temperatures. The temperature range over which silicone PSA can remain stable is between 100ºC and 260°C even though in some applications PSA can become stable outside this temperature range.

Chemical Resistance: Silicone PSA exhibits outstanding chemical stability under acidic or alkaline conditions. Therefore, silicone PSA can be used in "etching" or "chemical" cleaning operations. In addition, silicone also shows moderate stability against different solvents.

Environmental Stability: Silicone PSA exhibits excellent stability against humidity, weathering, and UV, which makes it suitable for outdoor use where long term stability is required.

Flexibility: Silicone PSA is highly flexible, exhibits good suitability, and can be removed cleanly. This makes silicone PSA suitable for use as a "coat" in applications where certain surfaces need protection. The rheology of silicone PSA is also responsible for its vibration damper property.

Chemical Reactivity in Low Drugs: The “medical grade” silicone PSA is further used to substitute the silanol group in a matrix to ensure the compatibility of silicone PSA (the lack of reaction potential) with the active drug.

High Gas Permeability: Silicone and silicone PSA have excellent oxygen permeability and high moisture vapor transmission rate (MVTR). For example, at 25°C the oxygen permeability of silicone rubber is approximately 400 times that of butyl rubber, making silicone PSA beneficial for medical applications (although preventing it from applications where a gas-tight seal is required).

Low Toxicity: Silicone and silicone PSA have been used in a large number of medical devices and applications (Benedek & Feldstein, 2009). Silicone is generally known to have no effects on the human immune system, no carcinogenic potential, and no skin irritation induced. In addition, the risk of toxicity to living organisms and the environment is very low, making it suitable to be developed in the manufacture of various types of patches and dressings (Pieńkowska et al., 2011). In general, siloxane (silicone) is also well tolerated by living organisms, making it important in the development of medicine, healthcare, and treatment innovative methods. Silicone is generally considered non-toxic to humans and the environment (Mojsiewicz-Pieńkowska et al., 2016).

CRITERIA OF TRANSDERMAL PATCHES

To successfully develop drugs using the transdermal drug delivery systems, the drugs must be carefully selected. Some of the drug properties desirable for the transdermal drug delivery systems are listed as follows.

Adhesive system

a) It should adhere aggressively to the skin during the administration intervals without being affected by such activities as shower, exercise, etc.

b) It should be easy to clean and leave no stains on the skin.

c) It should have good contact with the skin at both macroscopic and microscopic levels (Prabhakar et al., 2013).

Criteria of drugs in TDDS

Physicochemical Properties

d) The solubility of active drug substance in a transdermal patch preparation is less than 1 mg/ml.

e) The lipophilicity of active substance content is $10 < K_{o/w} < 1000$

f) The drug molecular weight is ≤ 500 Dalton

g) The drug melting point in a transdermal patch preparation is less than 200ºC

h) The pH of the preparation ranges from 5 to 9

Biological Properties

a) The delivery dose is less than 10 mg/day.

b) It does not irritate or induce allergic reactions.

c) It has a short half-life (t1/2).

d) The drug tolerance should not be lower than the release profile of nearly zero order in the transdermal delivery.

e) Drugs with a long-term administration or effects on non-target tissues can also be formulated in the transdermal delivery.

Silicone and Transdermal Patch Preparation

Silicone Pressure Sensitive Adhesive or PSA, which is a PDMS tissue or silicone resin, functions in various Transdermal Drug Delivery Systems (TDDS) to improve drug absorption into the skin. Silicone PSA is a viscoelastic compound in which the PDMS fluid contributes to the wetting and spreadability of adhesives and resins, acting thereby as a reinforcing agent to the elastic rheological components. The permeability in PDMS allows slow-speed, controlled diffusion of various active substances for some specific purposes, such as the use of nitroglycerin (angina pectoris), estradiol (hormone replacement), and fentanyl (pain management). The reservoir and matrix systems often become the last thing to consider due to the greater simplicity of construction (Thomas, 2018).

A transdermal patch or Transdermal Drug Delivery System (TDDS) is defined as a single-dose, flexible, multi-layered pharmaceutical dosage form of diverse sizes containing one or more active substances to be applied onto intact skin for systemic treatment. This preparation is usually formulated with Pressure Sensitive Adhesive (PSA), such as PDMS, which guarantees adhesion to the skin. A transdermal patch includes a backing sheet which is impermeable to the active substance and usually to water. The patch releasing surface is covered by a protective liner which can be removed before the patch is applied to the skin layer (Thomas, 2018).

Transdermal patches are designed to slowly deliver the active substance through intact skin layers, resulting in a quite long, constant rate of systemic absorption. Limitation of the rate of active substance systemic absorption normally becomes the mechanism of absorption through the skin. Alternatively, the active substance absorption can be limited by introducing or dissolving the active substance into a (semi-solid) reservoir

with a membrane to control the release and diffusion of the active substance from the patch. Transdermal patches can also be formulated by combining the two principles of drug delivery as a means of controlling drug delivery to the skin surface (EMA, 2014).

In addition, transdermal patches usually contain a higher amount of active substance than what should be given to the patient during use. This is necessary to maintain a clinically effective delivery rate from time to time and to allow optimal absorption across the patch's small surface area (EMA, 2014).

Types of Silicone TDDS Formulation

In general, transdermal patches (TDP) can be classified into three groups, namely matrix, reservoir, and drug-in-adhesive. A matrix patch retains the drug in a polymer matrix that controls drug release, in which the formulation of drug-in-adhesive (DIA) contains the drug directly incorporated into the adhesive layer. A reservoir patch contains the drug in a liquid reservoir behind a leak-proof barrier membrane. The DIA patch type is typically used when the drug is capable of smoothly penetrating the skin and matrix while the reservoir formulation is frequently used when the drug is inappropriate or insufficiently soluble in the transdermal device. The complete list of TDP components and representation of different patch types are described in *Table* **1** and Figure 2 as follows (Bird, 2020)**.**

Table 1. TDP Components

Component	Function
Backing	Protects the patch from the external environment, is impermeable to the transdermal patch components, and provides flexibility. Backing is made from elastomers (polyolefin oil, polyester, polyethylene, polyvinylidene chloride, and polyurethane) and preferably no air (by adding aluminum foil).
Membrane	Controls drug release. Membrane is made from natural or synthetic polymers or synthetic elastomers. The thickness ranges from 2 mm to 7 mm.
Adhesive	Binds patch components to the skin. Adhesive consists of silicone, rubber, polyvinyl acetate, or polyisobutylene, depending on the desired skin adhesion properties. Adhesive may contain a permeation enhancer (solvents, surfactants, or other chemicals) to improve skin permeability by changing the structure.
Liner	Protects the patch during storage and must be removed before use.

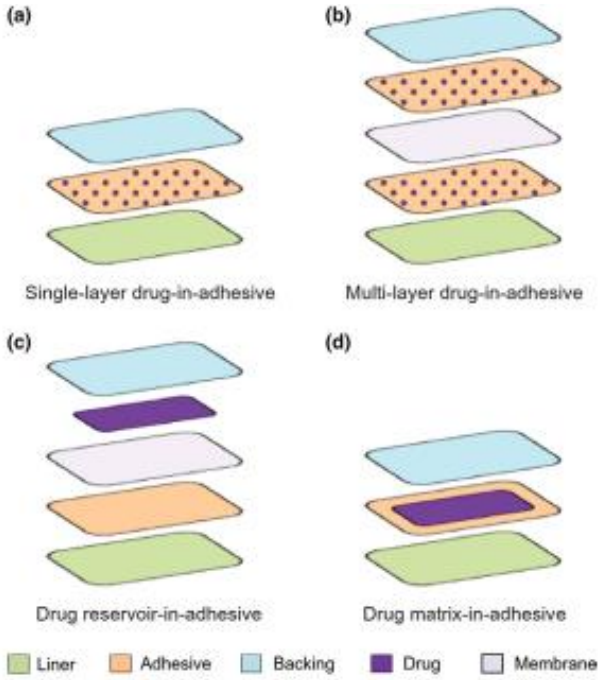


Figure 2. Types of TDP

A number of techniques have been investigated and implemented to overcome the challenges associated with transdermal patches, thereby significantly enhancing the transdermal flux. Some of the techniques used include supersaturated drug solution, lowered melting point, use of microfabricated needle (MN), and addition of adjuvant/permeability enhancer (Bird, 2020)**.**

Polymer is the backbone of transdermal drug delivery systems. The transdermal delivery system is fabricated in a multi-layered polymer lamination, in which the drug reservoir or drug-polymer matrix is sandwiched between the two polymer layers. An outer impermeable backing sheet prevents drug loss on the surface, and a polymer in the inner layer functions as an adhesive and/or rate-controlling membrane. Transdermal drug

delivery systems are broadly classified into three types as follows.

Reservoir System

In this system, the drug reservoir is embedded between an impermeable backing layer and the rate-controlling membrane. The drug is released only through the rate-controlling membrane, which can be microporous or non-porous. In the reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix. On the outer surface of the polymer membrane, a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied (Khandavilli et al., 2002).

Matrix System

Drug-In-Adhesive System: A drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the drug polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesive) onto an impermeable backing layer. On top of the reservoir, a layer of non-drug adhesive polymer is applied.

Matrix Dispersion System: The drug is homogeneously dispersed in a hydrophilic or lipophilic polymer matrix. The drug contains a polymer disc which is then mounted on an occlusive base plate in a compartment made from a drug-impermeable backing layer. Instead of the application of adhesive to the surface of the drug reservoir, the drug is spread around to form a strip of adhesive rim.

Microreservoir System

This drug delivery system is a combination of reservoir and matrix-dispersion systems. A drug reservoir is formed by first suspending the drug in a water-soluble polymer solution and then dispersing the homogeneous solution in a lipophilic polymer to form thousands of microscopic spheres of insoluble drug reservoir. The thermodynamically unstable dispersion is rapidly stabilized by crosslinking the polymer in situ (Khandavilli et al., 2002).

APPLICATIONS OF PSA BENEFITS IN TRANSDERMAL PATCH TECHNOLOGY

A large number of studies have proved that PSA has great potential to be used in transdermal patch preparations. Regardless of the differences in formulations, purposes, methods, and backgrounds of each study, it is highly likely that PSA can provide benefits in the technology of transdermal patches as follows.

Probability in Clinical Use

According to the research by Eunjae Jung et al., the results obtained from the use of PSA in transdermal patch preparations indicate that "patches which have passed a formula optimization process can be further developed for clinical applications, providing a level of FX therapeutic plasma over an extended period (Jung et al., 2015). To the best of our knowledge, our results are "the first to report in vitro and in vivo data on the preparation and optimization of FX-loaded DIA patches, demonstrating their feasibility as an effective transdermal delivery system for FX" (Patel et al., 2012)**.**

Physicochemical Properties

Patel et al. (2012) state that "The result of transdermal preparations using PSA as the delivery mechanism indicate that all of the prepared formulations showed good physical stability. Furthermore, an in vitro skin permeation study of the formulations was performed using the Franz diffusion cells. The formulation containing 5% drug, 85% adhesive solution, and 10% triacetin as the permeation enhancer showed the best in vitro skin permeation through human skin compared to all other formulations. The yield rates were found to follow zero-order kinetics. These results indicate that the Formulation F3 has exhibited optimum release in concentrations independently. The stability study shows that the drug remains stable for six months, and the primary irritation study shows that the transdermal patch is non-irritant" (Jung et al., 2015).

Drug Release Profile

A further study by Ji Eun Lee et al. (2017) shows that "The use of PSA in transdermal patches to identify whether the drug release profile is under control proved to be positive in Formula 1 (using PSA), in which the amount of HNO3 catalyst for the additive, that contained silicone as a catalytic reaction, formed a cross-link between PDMS and the additive. Similarly, the slow reaction can interfere with the effectiveness of cross-linking between the additive and silicone, making it possible to obtain an additive-infused adhesive by controlling the amount of HNO3 (Lee et al., 2017).

The potential of good drug release was also investigated by Behnam Dasht Bozorg and Ajay K. Banga (2020) with regard to TDS-acrylate containing ten times higher amount of drug than silicone TDS but with the permeation flux being only twice as high. The results also show that drug release is not linearly correlated with saturation since silicone TDS consists of the lowest amount of drug content with the highest percentage of release, indicating that the selection of PSA affects the drug release and permeation profile (Bozorg & Banga, 2020).

CONCLUSION

The use of Pressure Sensitive Adhesive (PSA) has proved to have some effects on transdermal patch preparations which are classified according to their forms, types of design, and types of base used. From each of the study and the results obtained from the testing, PSA exhibits several benefits when used in the form of a transdermal patch, including its ability to control drug release both in vitro and in vivo as evidenced by the capability of maintaining the stability of the preparation and the drug content and of providing the same effectiveness of patch usage as that with other mechanisms.

Funding: No funding was received for the preparation of the present article.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors appreciate the support from PT. Catur Dakwah Crane Farmasi, Jl. Olympic Raya Blok A, Kawasan Industri Sentul, Babakan Madang, Bogor, Indonesia and Nanopharmacy Research Center, Universitas Islam Indonesia, Yogyakarta, Indonesia

Conflicts of Interest: The authors declare no conflicts of interest.

Disclosures: The authors declare that the present article was written independently, without any industry role.

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