Healthcare Solutions

DUPONT™

Silicone adhesives for transdermal drug delivery systems

Product Applications and Benefits

LIVEO™

The right adhesive for the right application

Transdermal drug delivery patches are designed to deliver a therapeutically effective amount of drug across a patient's skin to efficiently treat targeted diseases. Transdermal patches typically involve a pressure sensitive adhesive used as a patch fixation system and/or drug matrix.

Every specific transdermal patch typically requires a number of properties that can be drug dependent like:

- Good adhesion profile for the application period
- Adequate drug loading
- Manageable patch size
- Sufficient skin flux of the drug
- Sufficient control of the delivery rate to avoid overdosing
- Depletion rate over the designed dosage period

This brochure will help you choose the right adhesive to meet your specific needs. Silicone adhesives are currently used in a wide range of pharmaceutical applications from hormone therapy to central nervous system related pathologies.

Liveo™ BIO-PSA Silicone Adhesives are chemically very stable, non-sensitizing, non-irritating and non-cytotoxic.

U.S. Food and Drug Administration Drug Master Files and Technical Files are available for products used in pharmaceutical applications.

We work with our customers to ensure that our silicone adhesives meet their regulatory and toxicology requirements. DuPont is ISO 9001 Certified and compliant with regulatory guidelines appropriate to your needs.

We also work with our customers to customize our solutions to their specific needs.

BIO-PSA silicone adhesives

Silicone adhesive technology for transdermal and topical drug delivery

Transdermal and topical drug delivery systems need suitable adhesives to secure the patch to the skin and insure proper drug loading, stability and release. DuPont has specifically designed a line of pressure sensitive adhesives, the Liveo™ BIO-PSAs, to prepare transdermal and topical drug delivery systems.

Liveo™ BIO-PSAs are compatible with a wide range of drugs, skin permeation enhancers and other suitable excipients, in liquid or powder forms.

Liveo™ BIO-PSAs can be formulated to provide various rates of drug permeability through the skin allowing a controlled drug release to a patient over time.

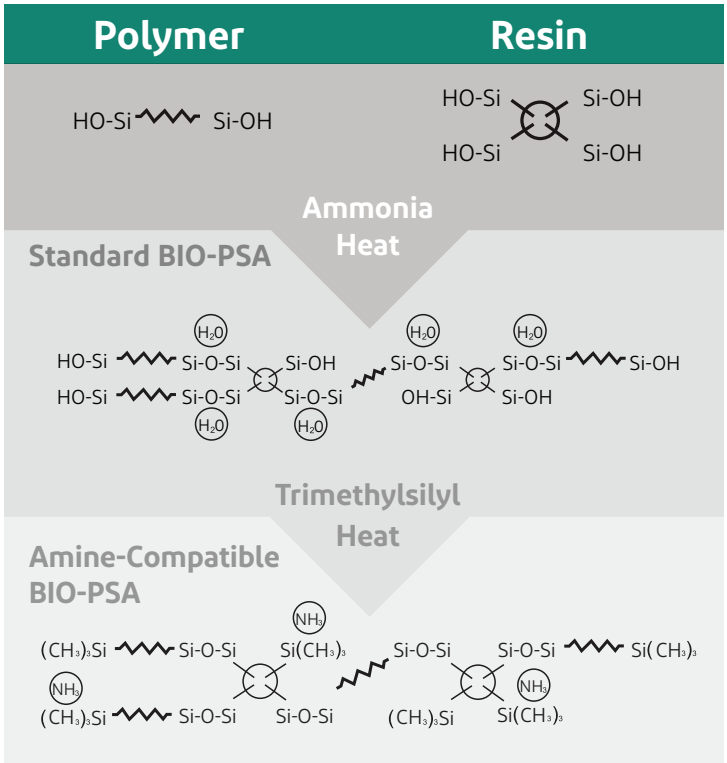
Liveo™ BIO-PSAs offer excellent skin adhesion for extended periods of time, moisture resistance, and are non-skin-irritating and non-skin-sensitizing.

DuPont offers a variety of BIO-PSA silicone adhesives according to their:

- Compatibility with amine functional molecules
- Polarity level (silanol content)
- Tack level
- Processing technology, solvent-based or hot melt system

Chemistry overview

Liveo™ Standard BIO-PSAs are obtained following a condensation reaction between a silanol endblocked polydimethylsiloxane (PDMS) and a silicate resin. To produce Liveo™ Amine-Compatible BIO-PSAs, the adhesive is further reacted with trimethylsilyl in order to reduce the silanol content of the adhesive polymer. Both standard and amine-compatible Liveo™ BIO-PSAs are then diluted in the appropriate solvent, mainly ethyl acetate or n-heptane, to obtain solvent-based materials. To produce a solvent-free version of the standard BIO-PSA, having melt characteristics applicable for hot melt coating, a PDMS plasticizer is added to the adhesive obtained from the reaction between silanol endblocked PDMS and silicate resin.



Customized pressure sensitive adhesives (PSAs)

Liveo™ BIO-PSA Silicone Adhesives are designed for flexibility through custom formulation to meet your needs. DuPont's current product line of BIO-PSAs allows you to adjust various critical parameters which are considered during the development of a patch drug delivery system including: adhesive performance, drug compatibility and diffusion, and coating condition (solvent based or hot melt). The safety, efficacy and stability of Liveo™ BIO-PSAs have been demonstrated by more than 30 years of use in the healthcare industry.

Benefits of Liveo™ BIO-PSA Silicone Adhesives in drug delivery

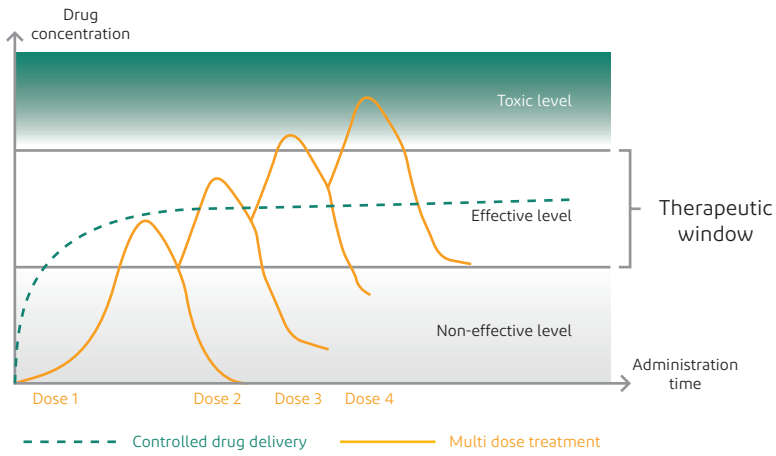
- Strong adhesion with long wear characteristics
- Customized adhesion for adapting the application, skin type, level of activity and environment
- Compatibility with amine functional drug—various silicone options are available for ease of formulation with drugs
- Controlled drug diffusion rate
- Easy removal from skin
- Non-irritating and non-sensitizing over extended wear

Processing options

Liveo™ BIO-PSAs can be coated as a diluted form or as a hot melt material. The solvent-based adhesives are mainly available in heptane or ethyl acetate; the solvent selection is chosen based on the drug solubility and coating criteria. The hot melt adhesive is solvent-free and can be softened with heat, then cooled to a nearly flow-less state.

Both adhesive forms are generally coated onto a suitable release liner (e.g., fluoro coated liner) and then transferred to the final substrate (e.g., backing) by laminating.

Why controlled drug delivery?



BIO-PSA Silicone Adhesives overview

Summary table of Liveo™ BIO-PSAs

Liveo™ BIO-PSA Silicone Adhesives	Resin/Polymer Ratio	Silanol Content	Typical Solids Content %	Solvent
Standard BIO-PSA				
7-4401*	65/35	High	70	Heptane
7-4402*	65/35	High	60	Ethyl Acetate
7-4501	60/40	High	70	Heptane
7-4502	60/40	High	60	Ethyl Acetate
7-4601	55/45	High	70	Heptane
7-4602	55/45	High	60	Ethyl Acetate
SRS7-4501	60/40	Medium	70	Heptane
SRS7-4502	60/40	Medium	60	Ethyl Acetate
SRS7-4601	55/45	Medium	70	Heptane
SRS7-4602	55/45	Medium	60	Ethyl Acetate
Hot Melt 7-4560	60/40	High	100	None
Amine-Compatible BIO-PSA				
7-4101*	65/35	Low	60	Heptane
7-4102*	65/35	Low	60	Ethyl Acetate
7-4201	60/40	Low	70	Heptane
7-4202	60/40	Low	60	Ethyl Acetate
7-4301	55/45	Low	70	Heptane
7-4302	55/45	Low	60	Ethyl Acetate

Typical properties of Liveo™ BIO-PSAs

Solvent-based BIO-PSAs

Parts resin	Tack level	Peel adhesion (g/cm)		Shear (kg/6.3cm^2)		Complex viscosity at 0.01 rad/s and 30°C (P)	
		Standard and SRS	Amine-compatible	Standard and SRS	Amine-compatible	Standard and SRS	Amine-compatible
55	High	500	700	15	14	5.10^6	5.10^6
60	Medium	700	900	16	17	5.10^7	1.10^8
65*	Low	-	-	-	-	5.10^8	1.10^9

Hot melt BIO-PSAs

Parts resin	Tack level	Peel adhesion (g/cm)	Shear (kg/6.3cm^2)	Complex viscosity at 0.01 rad/s and 30°C (P)
60	Very high	300	11	5.10^5

* These are used in combination to optimize the adhesive performance.

Visco-elastic properties of Liveo™ BIO-PSAs

Liveo™ BIO-PSA Silicone Adhesives are visco-elastic compounds based on the "resin-in-polymer" concept. They are typically evaluated by the dynamic rheology "oscillation test" method. The rheological parameters, viscous modulus (G"), elastic modulus (G') and complex viscosity (Eta*) are scrutinized for performance comparison.

Principle of adhesion/release: When the viscous modulus is low, optimum wetting/optimum bonding occurs. Sufficient elasticity is required to break the adhesive interface and remove the device.

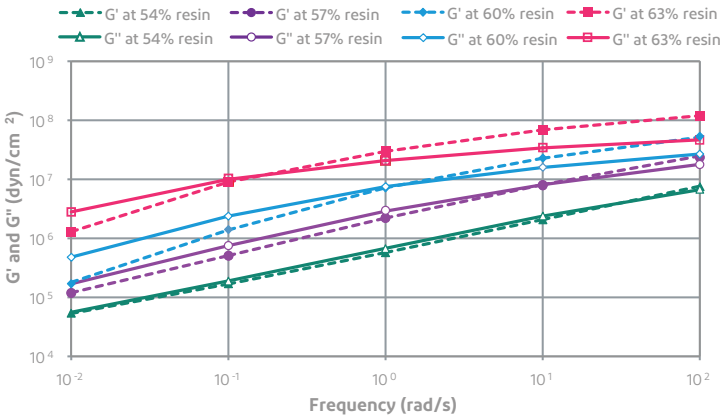
The increase in resin content within the adhesive polymer — from 54% to 63%—results in increased elastic modulus (G') and viscous modulus (G") values over the entire frequency range. These physical characteristics are foremost to achieve lower tack and higher cohesiveness (cold flow resistance).
Good adhesive performance is obtained when G' values are low (possibly lower than G") at low frequency rates (e.g., 0.01 rad/s). Nevertheless, the swift increase in G' values (preferably higher than G") as the frequency is increased exhibits the optimum creep resistance behavior.

Historical data show that the higher the complex viscosity (Eta*) at low frequencies (e.g., 0.01 rad/s), the more difficult it is for an adhesive to creep. Therefore, when the resin content of a Liveo™ BIO-PSA is increased, the adhesive becomes less likely to creep (cold flow).

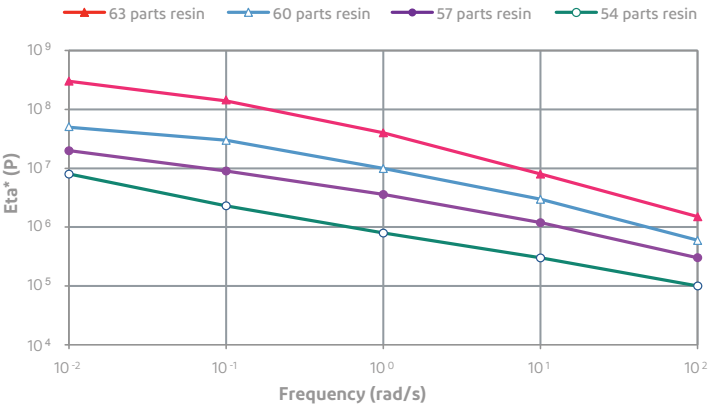
[Class, J.B. and Chu, S.G., *J. Appl. Polym.* Sci., 30 (1985) 815-824 and Chu, S.G., *Handbook of Pressure Sensitive Adhesive Technology,* Edt. Satas D., Warwick, RI, (1989) 158-203].

Impact of the resin content on the adhesive rheology

Comparison of the loss and storage moduli



Impact of the resin loading on the complex viscosity



Toxicology Testing and Summaries

Our toxicology group has performed descriptive toxicology studies (acute, subchronic, reproductive testing and neurotoxicity screening) as well as more specialized investigations, including medical material testing (Class I–VI), whole-body autoradiography, pharmacokinetics, metabolism, image analysis, biochemical and in vitro/in vivo dermal absorption evaluations. We also offer customized resources for your research and consulting needs.

Our toxicology group can also provide Health Summaries, study reports and/or Health Opinions based on safety and toxicology information that has already been generated.

Regulatory Support

Our regulatory team has expertise in supporting the use of silicone adhesives globally in drug products and medical devices. We will partner with you through clinical phase and marketing authorization review to support the use of BIO-PSA products in your application. Most products are already covered in US Drug Master Files and new products continue to be added in support of specific applications.

Regulatory Information Sheets

To help support the registration of drug products containing these adhesives, summaries of "Product Regulatory Information" can be prepared and provided. These summaries follow the International Pharmaceutical Excipient Council (IPEC) Excipient Information Package (EIP) template and include such sections as:

- General Product Information
- Manufacturing, Packaging and Release Site
- Physicochemical Information
- Regulatory Information (based on composition and manufacturing process)
- Biocompatibility Information
- Miscellaneous Product Information

Good Manufacturing Practices†

Liveo™ BIO-PSAs are produced, tested and packaged under strict quality control guidelines at the Healthcare Industries Materials Site (Hemlock, MI). The site is dedicated to the production of silicone materials for healthcare applications. It is registered with the United States Food and Drug Administration as a drug establishment (CFN 1816403). The site quality system for pharmaceutical excipients utilizes principles from The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients.

Examples of GMP principles included are shown below:

- Manufacturing process controls
- Contamination control (clean plant policies)
- Documentation control system/records (including batch records and labeling systems)
- Complete product/process traceability
- Complaint management and corrective action processes
- Central review, customer notification of changes
- Appropriate building, facilities, equipment practices
- Quality system audits and third-party inspections

† DuPont applies the appropriate level of pharmaceutical Good Manufacturing Practices for the intended healthcare application.

UNII Code Assignments

UNII	Preferred Substance Name	PSA Solids	Identifiers	Eta* at 30°C
HQ8518S2VI	Dimethiconol/ Trimethylsiloxysilicate crosspolymer	**7-4400** $C_4H_{12}OSi_2(C_2H_6OSi)n.$ $(C_3H_{10}O_4Si_2)n$	35/65 W/W	2E8 P
83D19O7250	Dimethiconol/ Trimethylsiloxysilicate crosspolymer	**7-4500** **SRS7-4500** $C_4H_{12}OSi_2(C_2H_6OSi)n.$ $(C_3H_{10}O_4Si_2)n$	40/60 W/W	1E7 P
090BX316RI	Dimethiconol/ Trimethylsiloxysilicate crosspolymer	**7-4600** **SRS7-4600** $C_4H_{12}OSi_2(C_2H_6OSi)n.$ $(C_3H_{10}O_4Si_2)n$	45/55 W/W	1E6 P
0A6MDS9SLT	Trimethylsilyl treated dimethiconol/Trimethyl-siloxysilicate crosspolymer	**7-4100:** $(C_6H_{18}O_4Si_3)n.$ $C_4H_{12}OSi_2(C_2H_6OSi)n$	35/65 W/W	5E8P
9N5G1G3D3H	Trimethylsilyl treated dimethiconol/Trimethyl-siloxysilicate crosspolymer	**7-4200:** $(C_6H_{18}O_4Si_3)n.$ $C_4H_{12}OSi_2(C_2H_6OSi)n$	40/60 W/W	5E7P
5VBE2X0WG0	Trimethylsilyl treated dimethiconol/Trimethyl-siloxysilicate crosspolymer	**7-4300:** $(C_6H_{18}O_4Si_3)n.$ $C_4H_{12}OSi_2(C_2H_6OSi)n$	45/55 W/W	2E6P

REFERENCES:

Noll, W. 1968. *Chemistry and technology of silicones*. Academic Press.

Owen, M.J. 1981. Why silicones behave funny, *Chemtech*, 11, 288. (Revised and reprinted in *Chimie Nouvelle*, 85, 27, (2004).)

Hardman, B. and Torkelson, A. 1982. Silicone compounds (Silicones). 20, 922, *Encyclopedia of Chemical Technology*, Kirk-Othmer, Wiley Interscience publ.

Colas, A. 1990. Silicones: Preparation, properties and performance. *Chimie Nouvelle*, 8 (30), 847.

Lee Smith, A. (Edit.) 1991. *The analytical chemistry of silicones*, John Wiley.

Ulman K. and Thomas X. 1995. Silicone Pressure Sensitive Adhesives for Healthcare applications, in *Advances in pressure sensitive adhesive technology-2*, edited by Satas D. 1995.

Thomas X. 2003. Silicone Adhesives in Healthcare Applications, technical literature form No. 52-1057-01.

Wokovich A., Prodduturi S., Doub W., Hussain A. and Buhse L. 2006. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute, review article in *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 1-8.

The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006.

Ho K.Y. and Dodou K. 2006. Rheological studies on pressure-sensitive silicone adhesives and drug-in-adhesive layers as a means to characterize adhesive performance, *International Journal of Pharmaceutics 333* (2007) 24-33.

Lin S., Durfee L., Ekeland R., McVie J. and Schalau G. 2007. Recent advances in silicone pressure-sensitive adhesives, Journal of Adhesion Science and Technology, Vol. 21, No.7, pp. 605-623 (2007).

Van Buskirk, Arsulowicz D., Basu P., Block L., Cai B., Cleary G., Ghosh T., Gonzalez M., Kanios D., Marques M., Noonan P., Ocheltree T., Scharz P., Shah V., Spencer T., Tavares L., Ulman K., Uppoor R. and Yeoh T. 2012. Passive transdermal systems whitepaper incorporating current chemistry, manufacturing and controls (CMC) development principles, AAPS PharmSciTech, Vol. 13, No. 1 (2012).

DUPONT™

LIVEO™

To learn more about DuPont's healthcare solutions visit:
www.dupont.com/healthcare.html

For country-level information, visit:
www.dupont.com/corporate-functions/our-company/global-locations.html

CAUTION: DO NOT USE DUPONT MATERIALS IN MEDICAL APPLICATIONS INVOLVING PERMANENT IMPLANTATION IN THE HUMAN BODY OR PERMANENT CONTACT WITH INTERNAL BODILY FLUIDS OR TISSUES. DO NOT USE DUPONT MATERIALS IN MEDICAL APPLICATIONS INVOLVING BRIEF OR TEMPORARY IMPLANTATION IN THE HUMAN BODY OR PERMANENT CONTACT WITH INTERNAL BODILY FLUIDS OR TISSUES UNLESS THE MATERIAL HAS BEEN PROVIDED DIRECTLY BY DUPONT UNDER A CONTRACT THAT EXPRESSLY ACKNOWLEDGES THE CONTEMPLATED USE.

The information, suggestions and data contained herein are intended only as an informational guide to assist you in making preliminary selections of materials and are not intended to be all-inclusive or final. Because DuPont cannot anticipate or control the many different conditions under which this information, data, suggestions or materials may be used, DuPont does not guarantee the applicability or the accuracy of this information or the suitability of the information, data, suggestions, or materials in any given situation. The information, data, or suggestions are not intended to substitute for any testing you may need to conduct to determine for yourself the suitability of a particular material for a particular purpose. DuPont makes no guarantee of results and assumes no obligation or liability whatsoever in connection with this information. Such information, data or suggestions are to be used and relied upon at user's own discretion and risk. DuPont makes no warranties, express or implied, and disclaims any and all direct and indirect liability for damages or losses resulting from or relating to the use of any information, suggestion, data, or materials described herein. Statements concerning the use of the products or formulations described herein are not to be construed as recommending the infringement of any patent, copyright, designs or other intellectual property and no liability for infringement arising out of such use is assumed by DuPont. None of this information is to be considered as a license to operate under, or recommendation to infringe, any patents.

DuPont reserves the right not to sell Special Control and Premium Control products for selected applications.

Although these products are tested against certain USP Class VI and ISO 10993 standards, DuPont makes no representation or warranty of suitability of its products for particular healthcare or medical applications or any other representations or warranties based on such testing.

The information set forth herein is furnished free of charge and is based on technical data that DuPont believes to be reliable. It is intended for use by persons having technical skill at their own discretion and risk. DuPont makes no warranties, express or implied, and assumes no liability in connection with any use of this information.

DuPont™, the DuPont Oval Logo, and all products, unless otherwise noted, denoted with ™, ℠ or ® are trademarks, service marks or registered trademarks of affiliates of DuPont de Nemours, Inc.

© 2020 DuPont de Nemours, Inc. All rights reserved.

Form Number: 001-20388-CDP0820