DURO-TAK and GELVA

Transdermal Pressure Sensitive Adhesives

June 2017

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Drug Delivery Polymers
Henkel Corporation

Henkel Excellence is our Passion

Presentation Outline

- PSA Chemistries used in TDDS
- Product line overview
- Henkel's capabilities
- USFDA requirements

Henkel's position and history in transdermal market

Henkel (formerly National Starch) has been involved for over 30 years:

- **1982-1984** - Market identified; first adhesives developed
- **1989** - First DURO-TAK adhesive sales for patches in Europe
- **1993** - First DURO-TAK sales for patches in US
- **1990s** – National Starch's adhesives were used in nitroglycerine, estradiol, nicotine, analgesic and cosmetic patches - US, Europe, Asia
- **2000s** – Introduction of "regulation-friendlier" adhesives developed specifically for the transdermal market
- **2012** – Acquisition of Cytec PSA Product Range and GELVA GMS and GME adhesives

Henkel's DURO-TAK and GELVA adhesives are safe, compatible with a wide range of active ingredients, and secure on skin for prescribed length of therapy

DURO-TAK and GELVA Transdermal-Grade Adhesives
In Over 40 Unique Commercial Patch Therapies

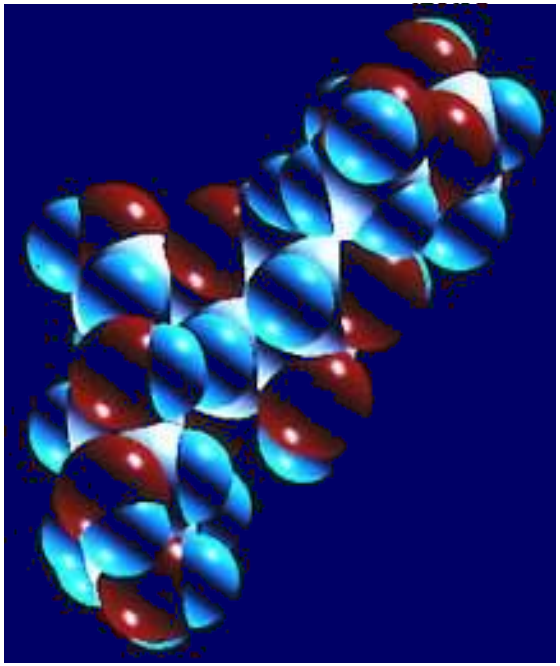
Including:

- Addiction treatment
- Alzheimer's disease
- Anti-fungal treatment
- Anti-inflammatory
- Combination hormones, including hormone replacement (male and female) and birth control
- Hypertension / cardiovascular
- Incontinence
- Other central nervous system conditions
- Pain management for cancer and other conditions
- Parkinson’s disease
- Rheumatoid arthritis

Commercially available patches in US			
Active	**Treatment**	**Brand**	**Adhesive Chemistries used**
Fentanyl	Chronic pain	Duragesic	Acrylate, silicone, PIB
Lidocaine	Chronic pain	Lidoderm	Hydrogel, PIB
Rivastigmine	Alzheimer	Exelon	Acrylate/silicone
Methylphenidate	ADHD	Daytrana	Acrylate/silicone, acrylate
Nitroglycerine	Angina	Minitran, Nitro-Dur	Acrylate
Scopolamine	Motion sickness	Transderm Scop	PIB, acrylate
Norelgestronin/ethinyl estradiol	Contraceptive	Ortho Evra	Acrylate, PIB
Clonidine	High blood pressure	Catapres TTS	PIB, Acrylate
Buprenorphine	Chronic pain	Butrans	Acrylate
Granisetron	Nausea, Vomitting	Sancuso	Acrylate
Selegiline	Depression	Emsam	Acrylate
Rotigotine	Parkinson Disease	Neupro	Acrylate, PIB
Estradiol	Hormone	Alora, Vivelle, Vivelle-Dot	Acrylate (primarily)
Testosterone	Hormone	Androderm, Testoderm TTS	Acrylate
Oxybutynin	Overactive bladder	Oxytrol	Acrylate
Nicotine (OTC)	Smoking cessation	Nicoderm, Habitrol, Nicotrol	Acrylate, PIB

Henkel’s Transdermal Adhesives

DURO-TAK and GELVA Transdermal Grade PSAs Product Chemistries

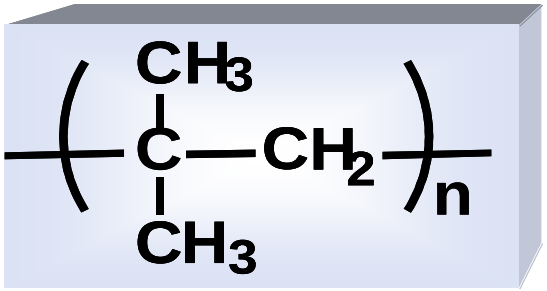


- Acrylic copolymers
- Acrylic/VA copolymers
- Polyisobutylene rubbers
- Tackified styrenic rubbers

Adhesive Chemistry Comparison

Adhesive Chemistry	Advantage	Disadvantage
Acrylic copolymer	• Good solubility and release characteristics for a broad range of drugs • Highly versatile chemistry • Good balance of adhesive properties • Good long term wear properties	• Residual monomers • Impurities, by-products • Possible chemical interactions with drug
Polyisobutylene	• Non reactive • Removes gently • No residual monomer (gas)	• Limited wear properties • Cold flow • Low drug solubility • Poor enhancer tolerance
Silicone	• Gentle removal • Biocompatible • Excellent permeability	• Very expensive • Cold flow, not cross-linkable • Low drug solubility • Requires special release liner
Styrenic rubber	• High tack & skin adhesion • High cohesion • Llow residual monomer	• Hydrophobic • Limited enhancer resistance • Little history of use

Polyisobutylene Rubber PSAs



- Made by cationic polymerization
  - BF_3 or $AlCl_3$ catalyst
  - BHT stabilizer
- Mixture which may include low, medium & high molecular weight PIBs, plasticizers and tackifiers
- Linear and clean
- Hydrophobic
- Inert, odorless, non-toxic
- Good O_2 stability
- Limited selection of raw materials and raw material sources (BASF)

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Styrenic rubber based PSAs

- Styrenic block copolymers – SBS or SIS
- Requires formulation – Tackifier, plascitizer (oil)
- Greater cohesive strength than PIBs with minimal viscosity increase

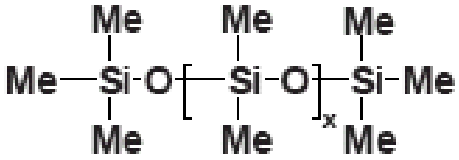
Ingredient	Parts*, %	Function
Block copolymer	20 - 50	Backbone of adhesive Provides strength and flexibility
Tackifier	40 - 60	Provides tack Lowers viscosity Raises Tg and softens
Plasticizer (Oil)	10 - 30	Reduces viscosity Processing aid
Antioxidant	< 1	Heat resistance

*Based on 100 parts solids

Styrenic rubber based PSAs

- SBS or SIS triblock copolymers
  - Diblock copolymer commonly added together
- Tackifiers
  - Rosin esters, Terpene & Hydrocarbon
  - Choice depends on compatibility
  - Increase tack and peel
- Diluents
  - Oils or plasticizer
  - Choice depends on polymer system used
- Antioxident
  - Not required in solvent based formulation
  - Block copolymers and tackifiers usually contain AOs

Silicone PSAs



- Produced thru a condensation reaction between PDMS and a silicate resin
- Residual silanol groups end-capped
- Low Tg (- 80^{o}C)
- High free volume (large spacing between atoms)
  - High permeability for gases, moisture and active drugs
  - Poorly soluble drugs can be loaded
- Low surface energy (22 dyne/cm)
- Biocompatible – used in implant and medical devices since 1950s
- Pure – no additives

	Bond	Length (nm)	Bond	Angle (°)
Hexamethyldisiloxane	Si-O	0.163	Si-O-Si	130
Dimethylether	C-O	0.142	C-O-C	111
Propane	C-C	0.154	C-C-C	112

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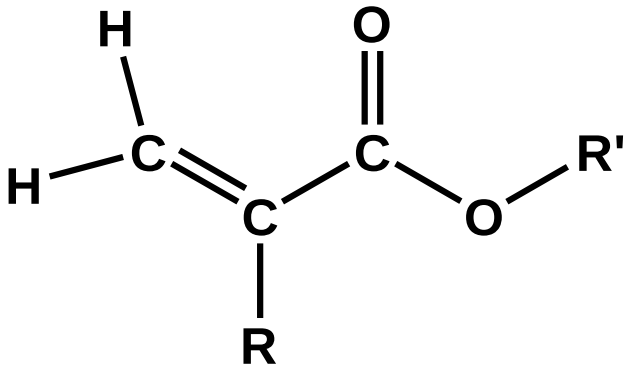
Acrylic PSAs



What is an acrylate?

R’ = H, acrylic acid
R’ = CH_3, methyl acrylate
R’ = CH_2CH_3, ethyl acrylate

R = H, acrylate
R = CH_3, methacrylate

Whether in solution, emulsion or 100% solids forms, acrylic PSAs are typically composed of:

70 - 90 %	Soft monomers
10 - 30 %	Hard monomers
0 - 6 %	Functional monomers

Acrylic Monomers

- **Soft Monomers**
  - Low Tg
  - Build tack
- **Hard Monomers**
  - High Tg
  - Provide internal strength
- **Functional Monomers**
  - Specific adhesion (H-bonding)
  - Provide x-linking sites
  - Build up adhesion with time

- 2-Ethylhexyl acrylate Tg = -65°C
- Butyl acrylate Tg = -54°C

- Vinyl acetate Tg = +32°C
- Methyl acrylate Tg = +9°C
- Methyl methacrylate Tg = +105°C

- Acrylic acid Tg = +106°C
- 2-Hydroxyethyl acrylate Tg = -15°C

Acrylics/VA vs All acrylics

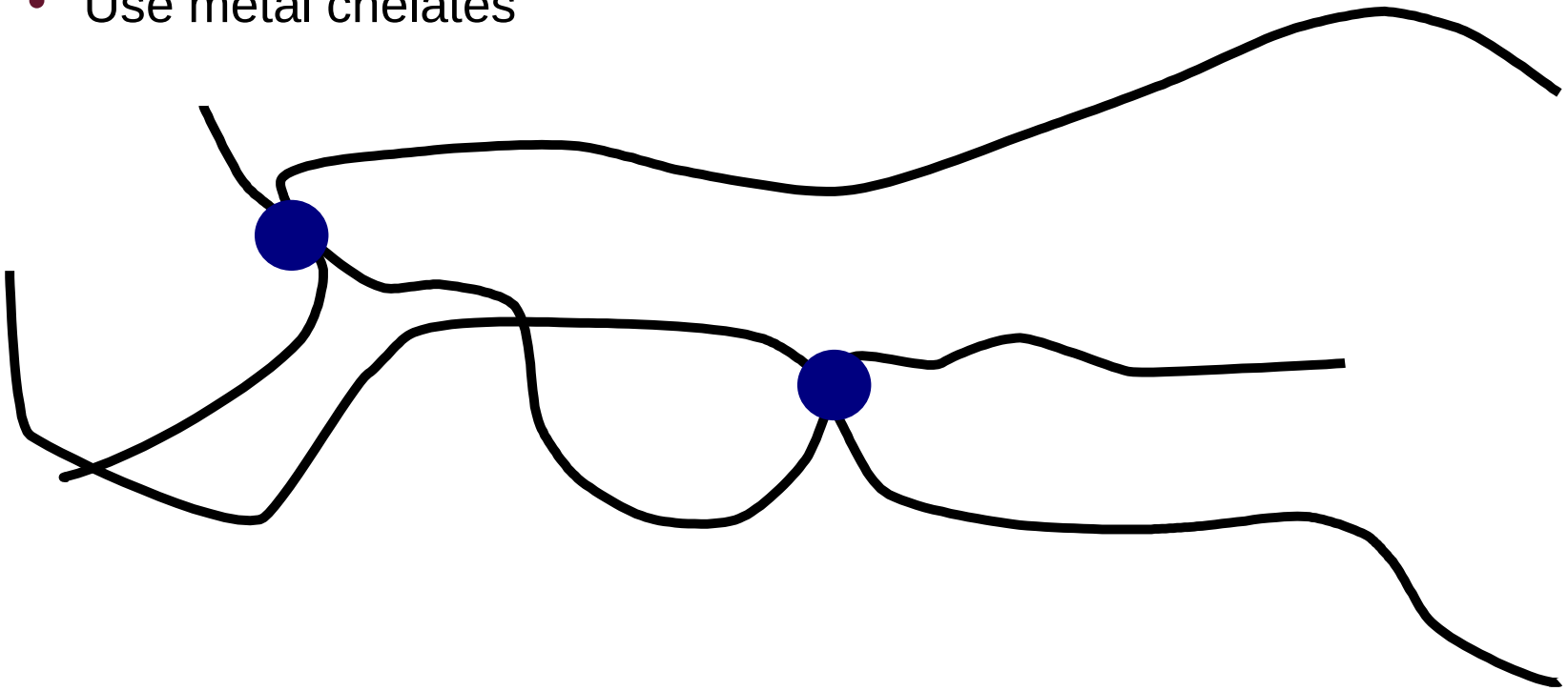
- VA sometimes imparts additional resistance to plasticizing components (e.g. drug or enhancer)
- VA-acrylics usually has lower MW than all acrylics (when MA or MMA is substituted for VA) – less cohesion, but higher tack/peel (thus better skin adhesion)
- VA less reactive than acrylates - higher residual, but has a low BP.
- Residual VA can react with drug before coating (Clonidine undergoes rapid acylation in the presence of VA)
- VA-acrylics are more skin friendly than all acrylics

Vinyl acetate

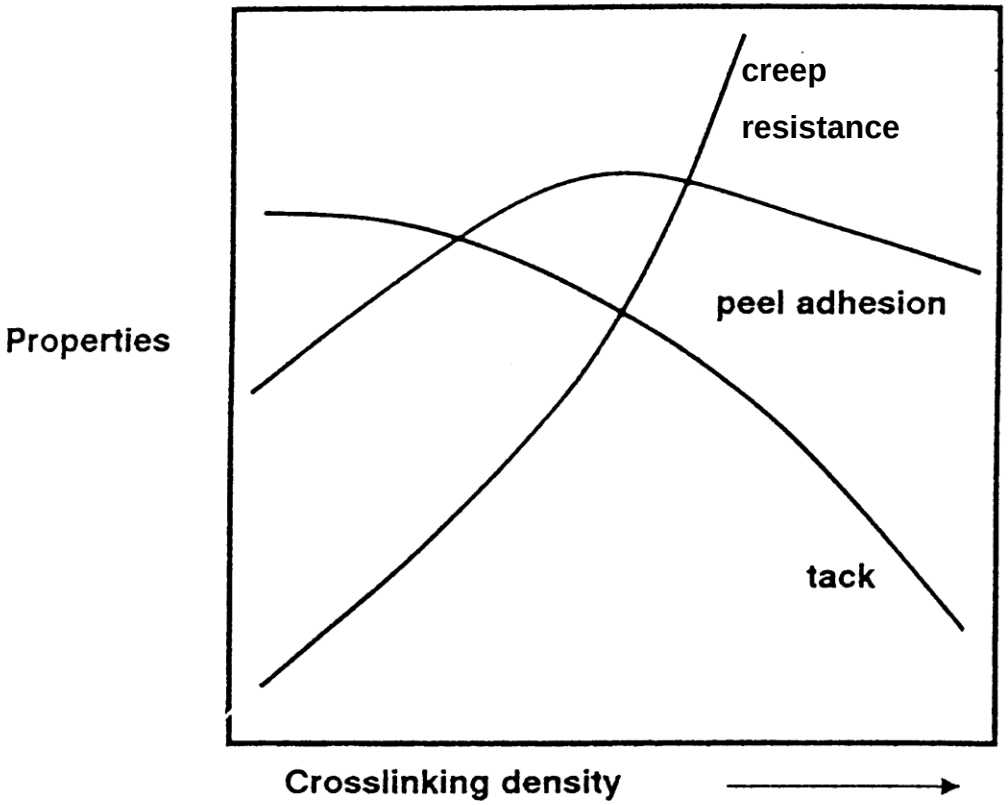
Acrylic PSAs: Crosslinkers

Function:

- Provide chemical bonds between polymer chains
- Increase internal strength (reduce cold flow), but *usually* at the expense of tack and peel
- Use metal chelates



Effect of Crosslinking on PSA Performance



from Advances in Pressure Sensitive Adhesive Technology, Don Satas, p. 3, © 1989, Satas & Associates, RI.

DURO-TAK and GELVA Transdermal Pressure Sensitive Adhesives

DRUG DELIVERY POLYMERS

Choosing the right adhesive is crucial in achieving the desired efficacy for your patch. Drug flux, drug-in-adhesive loading capacity, enhancer tolerance, system stability, skin compatibility, length of wear and appearance are critical to success.

CONTACT US

To learn more about Henkel drug delivery polymers, please contact us at ai.communications@henkel.com

PRODUCT SELECTION GUIDE

PRODUCT*	TYPICAL PHYSICAL PROPERTIES						PERFORMANCE PROPERTIES			Ethyl acetate	Heptanes	n-Heptane	Hexane	Methanol	Ethanol	Isopropanol	2,4-pentanedione	Toluene	Xylene
	Description	Contains vinyl acetate	Functional groups	Contains crosslinker	Solids (%)	Viscosity (cP or mPa·s)	Peel Adhesion	Shear Resistance	Tack										
DURO-TAK 87-900A	acrylates copolymer	No	none	n/a	43	1800				◆									
DURO-TAK 87-9301					36.5	9500				◆									
DURO-TAK 87-4098	acrylates copolymer	Yes	none	n/a	38.5	6500				◆									
GELVA GMS 3083	acrylates copolymer	No	none	n/a	38	8500				◆									
DURO-TAK 387-2510 / 87-2510	acrylates copolymer	No	-OH	No	40.5	4250				◆			◆						
DURO-TAK 387-2287 / 87-2287	acrylates copolymer	Yes	-OH	No	50.5	18000				◆									
DURO-TAK 87-4287					39	8000				◆									
GELVA GMS 788					41	5250				◆								◆	
DURO-TAK 387-2516 / 87-2516	acrylates copolymer	Yes	-OH	Yes	41.5	4350				◆	◆			◆	◆				
DURO-TAK 87-2074	acrylates copolymer	No	-COOH / -OH	Yes	29.5	1500				◆						◆	◆	◆	
DURO-TAK 87-235A	acrylates copolymer	No	-COOH	No	36.5	8000				◆			◆						
DURO-TAK 387-2353 / 87-2353				No	36.5	8000				◆			◆						
GELVA GMS 9073				Yes	32	5000				◆			◆		◆	◆			
DURO-TAK 87-2852	acrylates copolymer	No	-COOH	Yes	33.5	2500				◆			◆			◆	◆	◆	
DURO-TAK 387-2051 / 87-2051	acrylates copolymer	Yes	-COOH	No	51.5	4000				◆	◆								
DURO-TAK 387-2052 / 87-2052				Yes	47.5	2750				◆	◆				◆	◆			
DURO-TAK 387-2054 / 87-2054				Yes	47.5	2750				◆	◆					◆	◆	◆	
DURO-TAK 87-2194	acrylates copolymer	Yes	-COOH	Yes	45	3000				◆	◆					◆	◆	◆	◆
DURO-TAK 87-2196				Yes	45	2100				◆	◆					◆	◆	◆	
DURO-TAK 87-6908	polyisobutylene	No	none	n/a	38	6000						◆							

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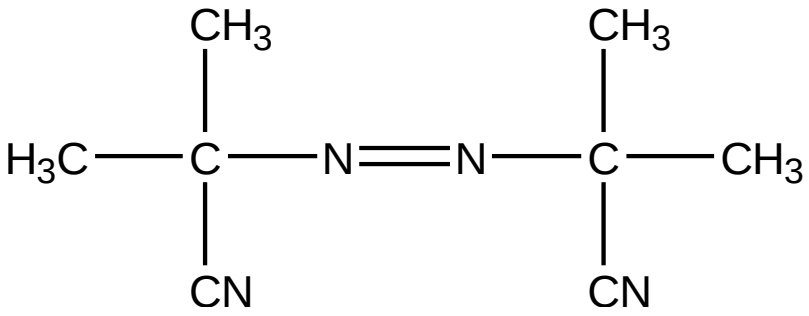
Impurities in Adhesives come from:

- Starting raw materials
  - Solvents, monomers
  - Little tox concerns – low level and volatile
- Reaction by-products or decomposition products
  - Initiator: TMSN, IBN, Benzene
  - API/adhesive interaction
- Residuals
  - Monomers, initiator, stabilizer

Thermal free radical initiators used in acrylate polymerization

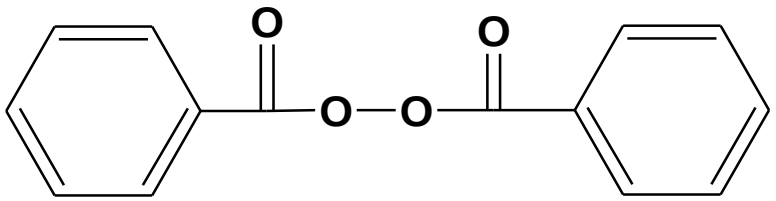
Most commonly used:

azo bis(isobutyronitrile) (AIBN)

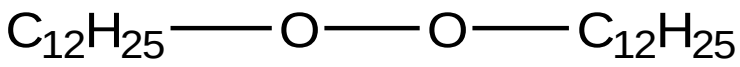


Some other types:

benzoyl peroxide



dilauroyl peroxide



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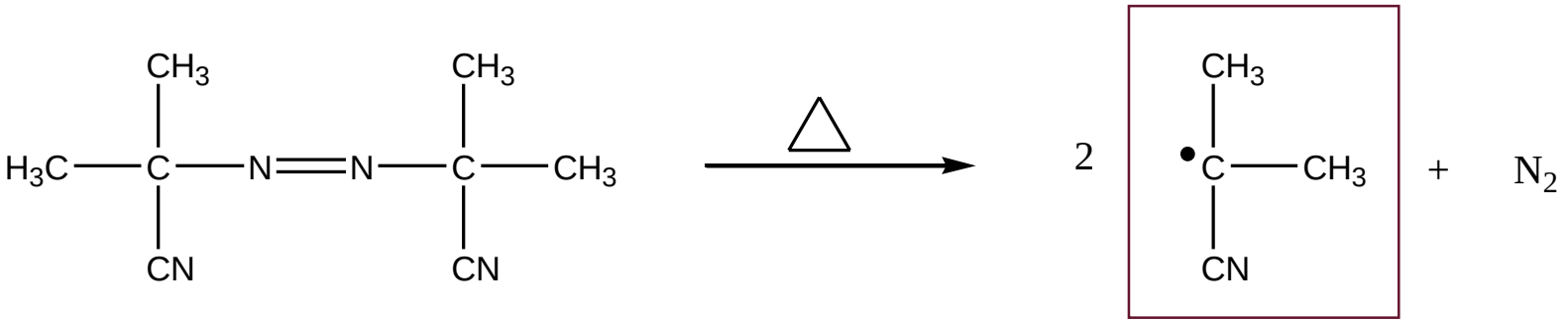
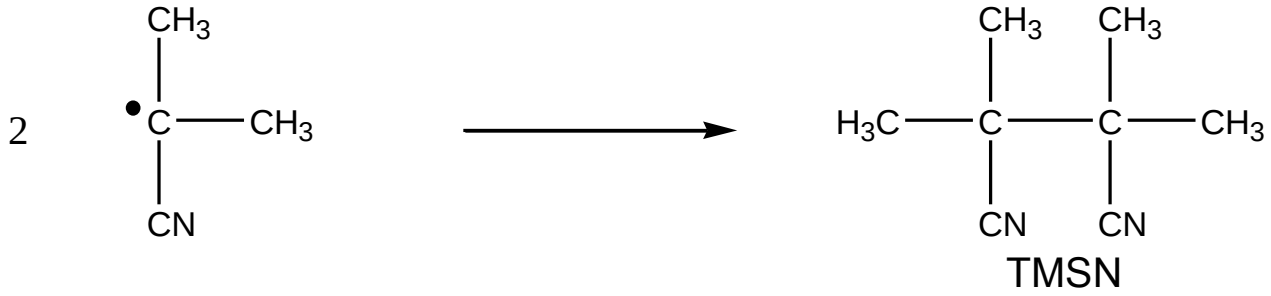
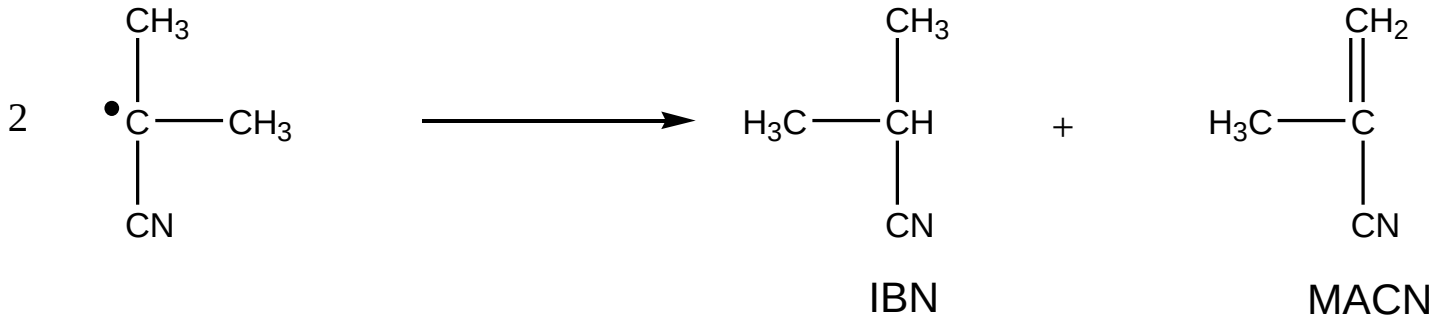
AIBN decomposition



Byproduct reactions:





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Tetramethylsuccinonitrile (TMSN)

- AIBN decomposition by-product
- Colorless solid, MP = 169.1^{o}C
- Neurotoxin
- Sublime
- Typically 200 – 600 ppm present in wet adhesives

Residual monomers

- Without special treatment, residual monomer levels are typically ~ 1-2 wt.% of the solution product.

- For “all-acrylic” products these can be reduced to < 1000 ppm by use of a short half-life initiator and additional holding time at the end of the polymerization. Further reduction in the dried film depends upon drying conditions.

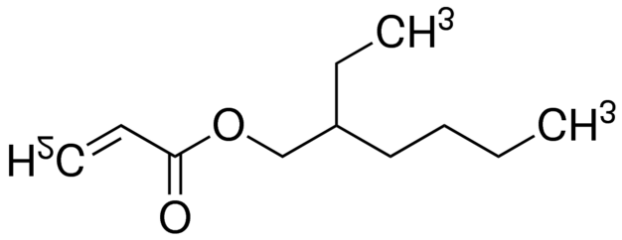
- Vinyl acetate is much less reactive than acrylic monomers and is the major residual component when present.
  - In this case, residual acrylate levels are low.
  - Residual VAc not effectively reduced by a scavenging initiator. However, it is readily removed during drying.

Impurities in 2-Ethylhexyl acrylate

Commercial 2-Ethylhexylacrylate has a purity of > 99%.

The following impurities are possible:

2-Ethylhexylacetate
2-Ethylhexylpropionate
2-Ethylhexanol
2-Methylstyrol
Styrol
n-Butylmethacrylate
n-Butylacrylate
Methylmethacrylate
Ethylacrylate
Methacrylate
2-Ethyl-4-methylpentylacrylate
2-Ethylhexylbutyrate
2-Ethylhexylcrotonate
2-Ethylhexylether
2-Ethylhexene
n-Hexylacetate
p-Methoxyphenol
2-Ethylhexyl 3-acryloxypropionate
2-Ethylhexyl 3-(2-ethylhexoxy) propionate
Acrylic acid
Water



*Source: EU Risk Assessment Report PL-1 Volume: 61

Solvents in 387-2516

- USP Class 1 solvent
  - Benzene (impurity, < 1 ppm)
- USP Class 2 solvents
  - **methanol (1.2 %),** cyclohexane (impurity, not specified), methyl cyclohexane (impurity, < 1.2 %), n-hexane (impurity, not specified)
- USP Class 3 solvents
  - **ethyl acetate (36.1%), heptanes (4.5%),** n-heptane (> 1.7%), **ethanol (14.6%)**

FDA Recommendations for Adhesives in TDDS

- Adhesives
  - MW, MWD, Intrinsic viscosity
  - Spectroscopic analysis (IR), thermal analysis
  - Residual monomers, dimers, solvents
  - Heavy metals, residual catalysts/initiators
- Placebo patch (Adhesive laminate)
  - Establish limits for residual solvents, monomers, extractables and leachables
  - Peel, tack, shear adhesion
  - Should be tested as drug product

Information requested by FDA on adhesives

- Assess the need to establish or tighten internal controls for the raw material
- Provide a detailed narrative of the manufacturing process, including all the process parameters, process controls, and in-process tests
- Provide details regarding the presence of residual crosslinker (aluminum acetylacetonate) and any by-products from the crosslinking reaction (e.g., 2,4-pentanedione)
- Provide information regarding the levels of azobisisobutyronitrile (AIBN) and isobutyronitrile

Deficiency Letters customer received

- Test the final laminate for residual monomers and other adhesive impurities including catalysts, initiators, crosslinker and by-products and potential impurities from all other drug components including backing layer, release liner, ink and pouch of the final drug product

- Request historical *rheology* values from the adhesive manufacturer to better understand the adhesive manufacturer's process capabilities and the potential influence on finished product

Deficiency Letters customer received

- *The viscosity specification of the adhesive, 4,000 - 15,000 cps, appears to be too wide and not justified by the observed viscosity range of 8650 cps to 9720 cps for the adhesive lots used in manufacturing of the exhibit batches.*

- *Provide additional justification regarding the effect of adhesive with extreme high or low viscosity values on the quality and performance of the finished product or tighten the viscosity specification for the adhesive at the raw material stage.*

- *We are concerned that the rheological and other raw-material properties of the adhesive used in the biobatch may not be consistent with historical or future adhesive lots*

Deficiency Letters on PIBs

- ***Provide information on the impurities, monomers, residual solvents, and viscosity of these adhesives (PIBs)***. *We (FDA) note that adhesive raw-material properties often affect final drug-product quality attributes……We are concerned that the viscosity and other raw material properties of the adhesive used in the biobatch may not be consistent with historical or future adhesive lots*
- *Discuss and provide evidence (such as in-house test methods or supplier COAs) for controls are in place for the following potential impurities: benzene, toluene, isobutylene and butane monomers, and antioxidants added by the raw material suppliers*

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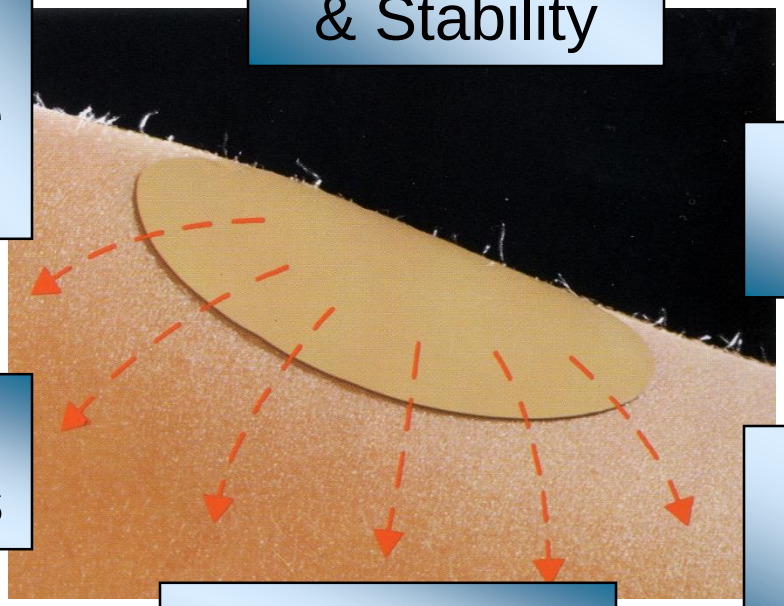
Transdermal Grade PSAs at Henkel

- Manufactured following IPEC GMP guidelines
- Drug Master File filed with FDA
- Biocompatibility Safety Testing done (ISO-10993)
  - Cytotoxicity
  - Irritation
  - Sensitization
- Complete chemical component (impurities) profile determined
- Toxicological assessment completed

Some Considerations in Choosing an Adhesive



Chemical Compatibility & Stability

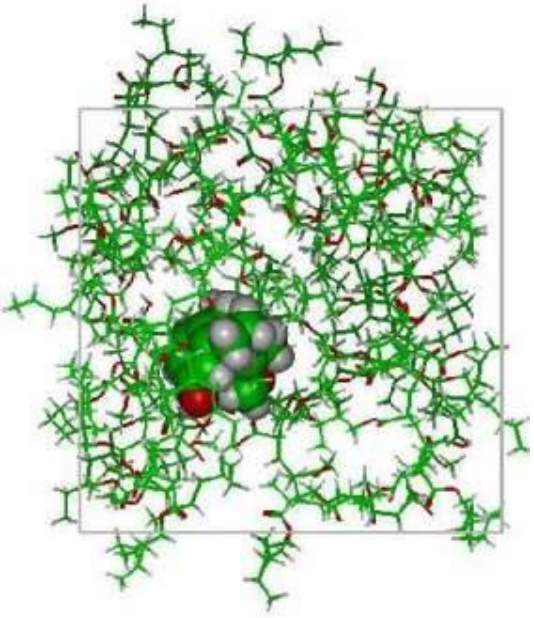
Drug Solubility & Release (flux)

Enhancer Tolerance

Patent Considerations

Adhesion & Removal From Skin

Regulatory Compliance



Drug Solubility & Release
Henkel Support Capabilities

- Proprietary on-line drug-in-polymer solubility calculator available for confidential customer use *(register on www.transdermaladhesives.com)*
- Extensive technical support for transdermal patch developers
- Molecular modeling capability
- Confidential exchange of adhesive, drug & patch formulations expedite formula optimization
- Calculator does not include GELVA products

Solubility Calculator Input Page
Example: Ketoprofen

Drug-in-Polymer Solubility Calculator

Welcome to Henkel's Drug-in-Polymer Solubility Calculator

To begin a calculation enter the Log_{10} of the drug's octanol/water partition coefficient and the drug's solubility in water. The results of solubility generated are in g/100g dry polymer i.e. wt. % of the dried polymer film.

Log_{10} of the drug's octanol/water partition coefficient	3.12
Drug's solubility in water (milligrams / litre)	51

Submit

Solubility Calculator Output Page
Example: Ketoprofen

Results for : Log10of **3.12** Solubility of **51**

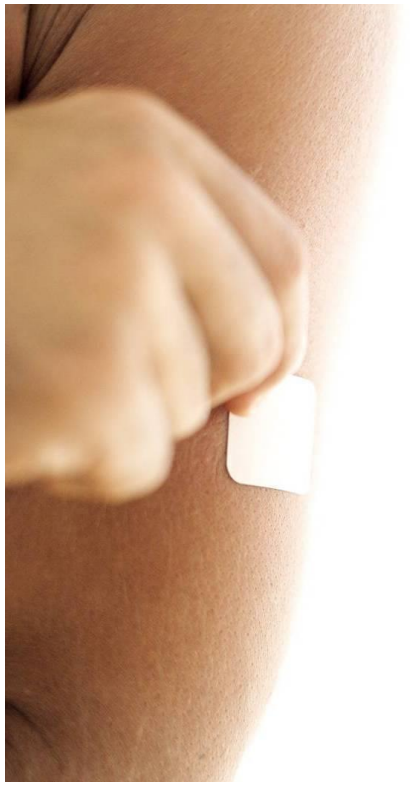
Polymer	Solubility
DURO-TAK 87-2677	6,9029
DURO-TAK 87-9088	6,2729
DURO-TAK 87-901A	4,6794
DURO-TAK 87-9301	4,1984
DURO-TAK 87-900A	4,1343
DURO-TAK 87-2194	3,9415
DURO-TAK 87-2196	3,9415
DURO-TAK (3)87-2051	3,6389
DURO-TAK (3)87-2052	3,6389
DURO-TAK (3)87-2054	3,6389
DURO-TAK 87-2074	3,5362
DURO-TAK 87-235A	3,4797
DURO-TAK (3) 87-2353	3,4678
DURO-TAK 87-2979	3,0744
DURO-TAK 87-4098	3,0173
DURO-TAK (3)87-2825	3,0092
DURO-TAK (3)87-2287	2,7697
DURO-TAK (3)87-2516	2,5982
DURO-TAK (3)87-2525	2,5982
DURO-TAK 87-4287	2,2172
DURO-TAK (3)87-2510	2,0188
DURO-TAK 87-2852	1,7785
DURO-TAK 87-202A	1,6242

Henkel → Company → Brands

Skin Adhesion & Removal
Henkel's Capabilities

- Henkel's DURO-TAK and GELVA PSAs have proven adhesion in a variety of commercial patches
- Henkel conducts internal human wear testing as part of the R&D process for all new adhesives
- Acrylic chemistry enables water uptake required for long term wear
- New adhesives are typically designed with the highest cohesion possible while maintaining good wear properties to aid clean removal
- Polymer composition, molecular weight, and crosslink density may all be varied to accommodate the plasticizing effects of certain drugs, permeation enhancers and other excipients in the formulation.

Long-Term Wear Properties



Wear performance is influenced by:

- Adhesive choice
- Backing material
- Patch size, shape and site of placement
- Other formulating ingredients
- Individual skin variations
- Environmental conditions

DURO-TAK Transdermal Adhesives Manufacturing

- Both Salisbury and Drogenbos sites are ISO-9001 certified facilities which follow IPEC-GMP guidelines

- Henkel frequently hosts customer plant audits and routinely conducts internal audits based on IPEC-GMP guidelines

Regulatory Support

- Access to US FDA Drug Master Files (DMFs) available on all commercial DURO-TAK and GELVA transdermal grade PSAs
- DMFs contain detailed product information and results of ISO-10993 biocompatibility safety testing (cytotoxicity, irritation, sensitization)
- Comparable information is available in support of filings outside of the US in the form of Applicants' Information Packages (Excipient Master Files)
- Expert Toxicologists

Guidelines in adhesive selection

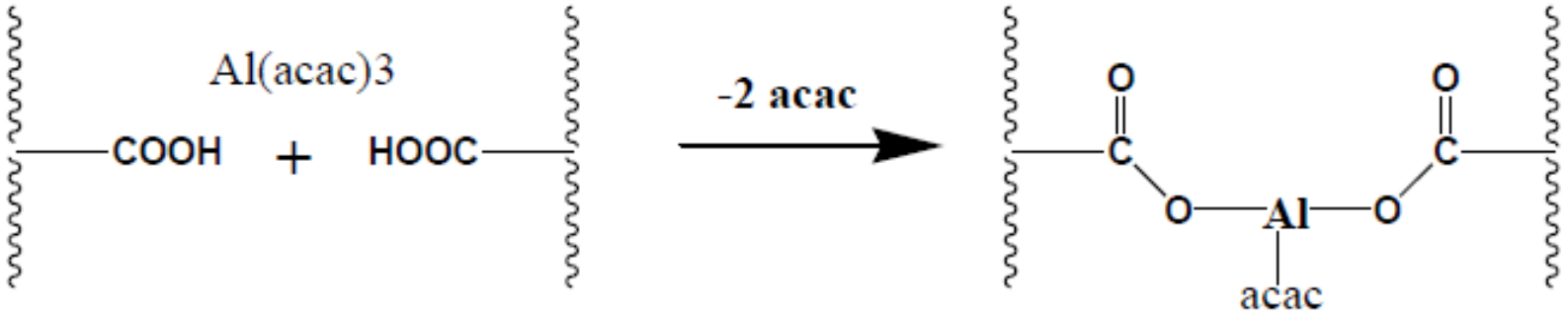
- Solubility of drug in adhesive
  - Henkel's drug-in-polymer solubility calculator
  - Use an adhesive that has a good drug solubility
  - But, if too soluble, drug may not want to come out
- Use the adhesives (chemistry/chemical composition) that others use
- Regulatory friendly adhesive – no cross-linker/stabilizer, pure solvent..
- VA-acrylics tend to give better skin adhesion than all acrylics
  - Higher tack and peel adhesion
- *However,* different chemistries or chemical compositions are often used for the same drug

Transdermal Adhesive Capabilities Summary

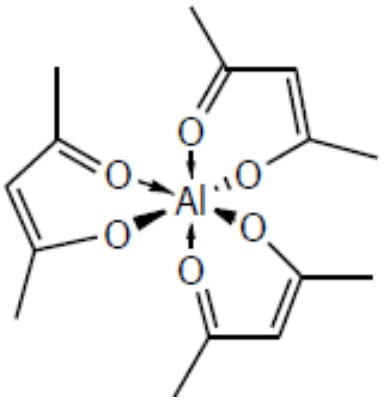
- Global leader in acrylic polymers for transdermal drug delivery
- 25+ products to choose from in a wide range of chemistries and custom formulations; DURO-TAK and GELVA adhesives are used in commercial patches marketed in countries around the world
- Over 50 years experience in acrylic adhesives and 30 years in Transdermal
- Expert technical, manufacturing and regulatory support
- Global infrastructure with local support

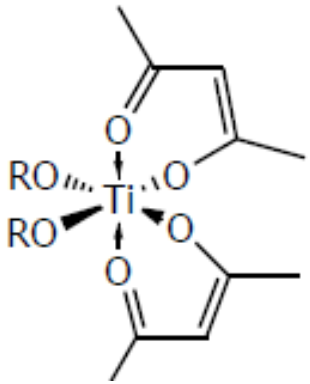
Crosslinking via Chelation

SELF CROSSLINKING REACTION



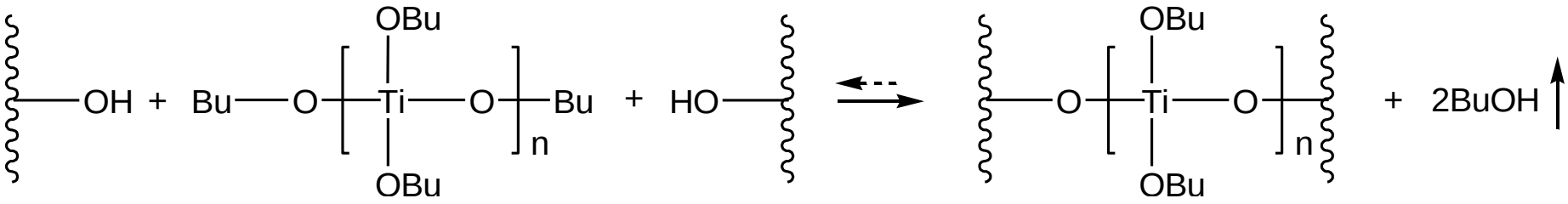
acac = acetylacetonate or 2,4-pentanedione





Henkel

Crosslinking titanium chelate



- Notes:
  - Addition of lower alcohols also inhibits crosslinking
  - Reaction proceeds only upon drying.
  - Water competes strongly and must be avoided.

Crosslinker selection

- Optional components
- Used at a low level to achieve a lightly crosslinked network
- One-part (self-crosslinking) organometallic chemistry employed
  - Poly(butyl titanate) [PBT] or TBT
    - nomally used with hydroxyl functional polymers
  - Aluminum tris(acetyl acetonate)
    - normally used with carboxyl functional polymers
- Note: these are Lewis acids and may not be compatible with some actives