Japanese topical patch formulations: What can we learn?

Dr. Armin Breitenbach | 09.2014

What makes a good adhesive?

A balance is required:

- Wetting
  (surface tension/energy)
- Flowability
  (to cover all the mountains
  and valleys of the skin)
- Cohesion (inner holding force)

A good balance…

The basic TDS challenge: balance
(too) strong adhesion is not preferred

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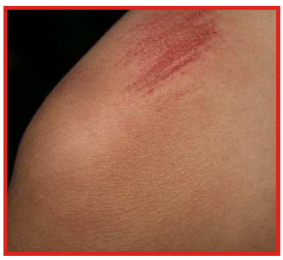
(too) strong adhesion is not preferred



- Skin stripping upon patch removal = removal of corneocytes
  = a reduced barrier function of the skin = increased permeability
- No continuous patch application at the same skin site = application site rotation
- But in case of local delivery (e.g. neuropathic pain), a change of the application site is not possible

The basic TDS challenge: balance
but (too) low adhesion is no option either

Adhesion: even a regulatory issue!

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368 ***4.2.6.3. Adhesive proper***
369 ***4.2.6.3.1. In vitro adhesi***

370 *In vitro* adhesive tests shou
371 transdermal patch. Althougl
372 attributes to be specified in
373 Tests should address the re
374 surface e.g. tack, and the r

871 **Annex 2**
872 **In vivo skin adhesion**

873 The investigation of *in vivo* adhesive performance may be included as a component part of human
874 clinical pharmacokinetic and efficacy studies (both single dose and multi dose), or may be an
875 independent study with either patients or volunteers.

876 For transdermal patches covering a range of different dosage strengths, as a minimum, the smallest
877 and the largest patch sizes should be tested *in vivo*. For transdermal patches covering a range of
878 different dosage strengths the smallest and the biggest patch sizes should be tested *in vivo*.

879 The elements of assessment should include:

880 • The sites of application;
881 • Transdermal patch application;
882 • Residue formation on release l liner removal and on transdermal patch removal;
883 • The percentage transdermal patch area adherence to the skin;
884 • Cold flow, such as the formation of a dark ring about the transdermal patch during use, patch
885 movement or displacement, wrinkling;
886 • The robustness of the product to normal human behaviours e.g. moisture resistance to washing,
887 showering, saunas, use of moisturisers, risk of removal during exercise and or sleeping, possible
888 transfer to partners or family.

889 The results of the study should inform the SmPC and PI. See also section 4.2.9.

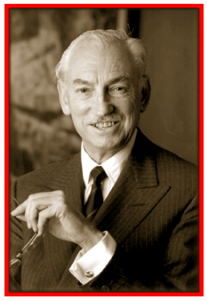
Typical PSAs

Indication	Product name	Distributor	Adhesive(s)
Severe pain	Durogesic Fentanyl ratiopharm Fentanyl Hexal Fentanyl Mylan Transtec	Johnson&Johnson Ratiopharm/Teva Hexal Mylan Grünenthal	Acrylate Acrylate Acrylate, Silicone Silicone Acrylate
Hormone replacement therapy	Estraderm Dermestril Evorel Fem7	Novartis Rottapharma Schwarzpharma Merck KgaA	Polyisobutylene Acrylate Acrylate Styrenic rubber
Contraception	Evra	Ortho-McNeil (J&J)	Polyisobutylene
Angina Pectoris	Deponit Minitran	Schwarzpharma 3M	Acrylate Acrylate
Smoking cessation	Nicorette Nicoderm	Pfizer GSK	Polyisobutylene EVA/Polyisobutylene
Parkinson disease	Neupro	UCB	Silicone
Alzheimer's disease	Exelon	Novartis	Acrylate/Silicone

- Synthetic rubbers, such as acrylics, silicones, PIB and styrenes

Isn't there something more?

The Western approach
Renaissance of modern TDS in the 70ies



Duragesic:

- Fentanyl in an ethanolic **hydroxyethyl cellulose gel**
- Reservoir damage caused fatal overdoses
- Yet, a 10 cm² patch only contained 2.5 mg API

Durogesic:

- "Modern" drug in adhesive (DIA) patch
- Fentanyl in an acrylic rubber
- > 4.2 mg API required
  to achieve the same performance

By Alejandro Zaffaroni, ALZA, 1968

The Western approach
Drug in Adhesive, based on synthetic rubbers

Neupro by UCB

A silicone rubber,
yet the unique performance is achieved
by the addition of a **hydrophilic polymer: PVP**

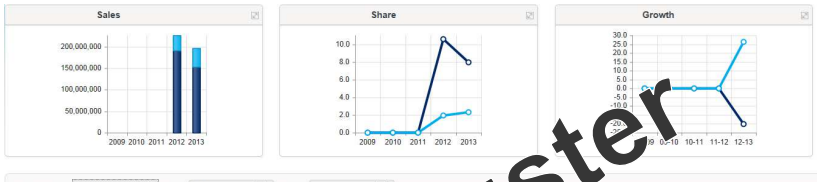
Exelon by Novartis

An acrylic rubber,
yet the unique performance is achieved
by the addition of a **hydrophilic polymer: Plastoid B**

There are these “modern“ TDS champions

© AMC

But there are some hidden champions as well, e.g. Lidoderm



Blockbuster

Data Source: IMS Standard | Units: Units | Period: Calendar Year

		International Product Name	Corporation	2009	2010	2011	2012	2013	Change
		Total				0	226,502,423	197,194,976	197,194,976
☑	■	LIDODERM	ENDO				191,331,916	152,779,918	152,779,918
☐	■	LIDOCAINE ACVI	ACTAVIS				2,058,873	44,615,423	44,615,423
☑	■	VERSATIS	GRUENENTHAL +7				35,170,507	44,415,058	44,415,058

Data Source: IMS Audited | Units: Units | Period: Calendar Year

		International Product Name	Corporation	2009	2010	2011	2012	2013	Change
		Total		0	0	0	1,079,441,064	985,546,302	985,546,302
☑	■	LIDODERM	ENDO				981,091,201	868,126,248	868,126,248
☐	■	LIDOCAINE ACVI	ACTAVIS				56,161	209,499,630	209,499,630
☑	■	VERSATIS	GRUENENTHAL +7				98,349,862	117,420,055	117,420,055

© IMS

The technology behind this success: mainly water

We‘re consisting of it (~ 75%)

And the technology comes from a place, where water is regarded something special

Japan

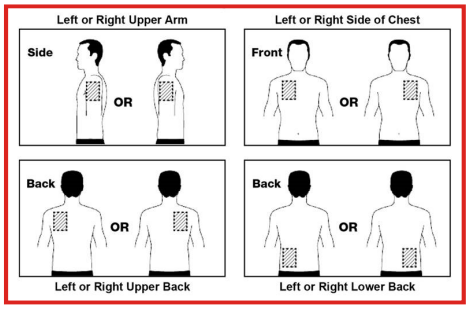
Some facts:

- 11th by population (~ 127 million)
- 2nd by pharma market size
- 1st by longest life expectation (~ 80 y)

- Climate varies from tropical in south to cool temperate in north = at least partially extreme humidity

Why hydrogels?

- Current chronic (trans)dermals require an application site rotation due to skin stripping
- But what about continuous local treatment required in pain, such as e.g. sports injuries, neuropathic pain, …?



- And what about a culture, that takes a bath every day? How useful is a common multiple-day patch here?

Just an example…

- **The bockbuster „fentanyl TDS“ is a 3-4 day patch in the whole world…**
- **…except for the 2nd largest pharmaceutical market: Japan**
- **Fentos tape (Hisamitsu & Kyowa Hakko Kirin) is a one-day patch only!**

Hydrogels?

- A three-dimensional network of cross-linked hydrophilic polymers and large amounts of water
- It all started as a medical device applied to wounds in order to

  “protect wounds”,
  ”keep them in a moist environment”,
  “promote healing” and
  “ease pain”

- Transparency, the condition of wounds can be observed
- Gentle to the wound, it does not cause skin stripping
- Representing at least a several billion sized market already

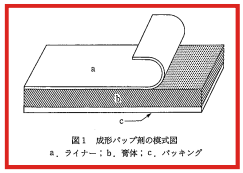


図1　成形パップ剤の模式図
a．ライナー；b．膏体；c．パッキング

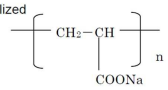
Hydrogels?

- A three-dimensional network of cross-linked hydrophilic polymers and large amounts of water

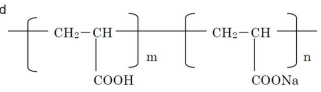
- Already used e.g. for contact lenses and to support tissue growth in tissue engineering

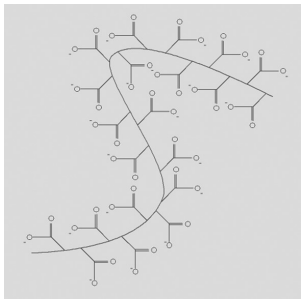
Sodium polyacrylate = poly(sodium propenoate)

Thoroughly neutralized



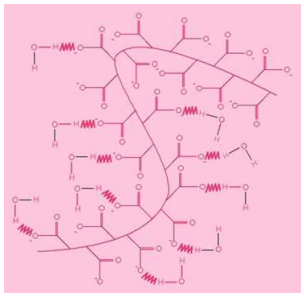
Partially neutralized





In the absence of ions up to 500 times of its own weight of water can be absorbed (compare nappies)

When salts are put into solution polymers shrink and the viscosity of solution decreases



© gcsescience

A gel doesn‘t make a „cataplasm“

- Gelation agent
  Poly acrylic acid, sodium polyacrylate, carboxymethyl cellulose, CMC Na
- Cross-linker (for cohesion)
  Al salts, Mg salts, Ca salts
- Gelation rate modifier
  EDTA, organic acids

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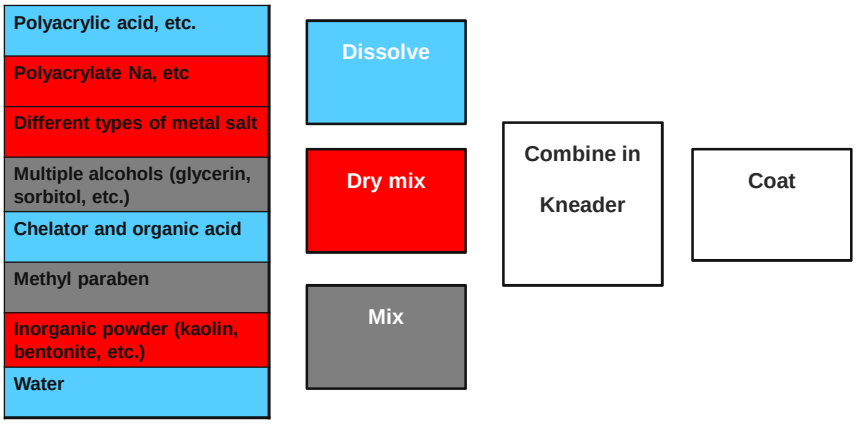
Typical components of a hydrogel patch

Function	Amount	Name of substance
Gel forming agents	5% – 20%	Polyacrylic acid, etc.
		Polyacrylate Na, etc
Cross-linking agent	Moderate amount	Different types of metal salts
Moisturizer	5% – 40%	Multi-functional alcohols (glycerin, sorbitol, etc.)
Gelation rate modifier	Moderate amount	Chelator and/or organic acids
Medicinal dispersant	Moderate amount	Emulsifiers (polysorbate 20, etc.)
Extender	0% – 30%	Inorganic powders (kaolin, bentonite, etc.)
Medicinal ingredient	Moderate amount	Ketoprofen, indomethacin, salicylic acid, etc.
Other	Residual amount	Water, etc.

Typical process



So what's the big deal?

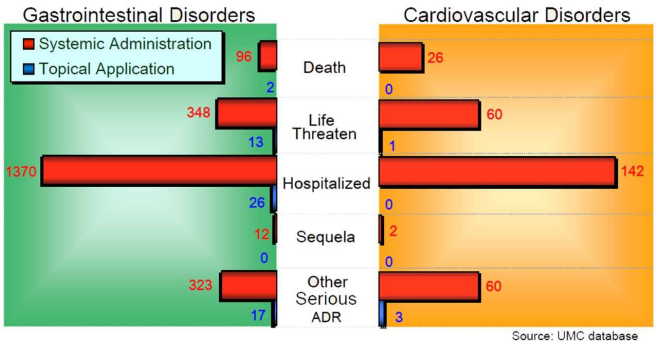
Lidoderm/Versatis patch

- 10 cm x 14 cm ; 700 mg API = 5% (w/w)
- (0.7 g * 100 / 5) / (0.1 x 0.4) m^2 = 1000 g/m^2
  while a typical fentanyl patch = ca. 50 g/m^2
- A hydrogel patch has a thickness of 1 mm and above
- Excluding production losses you have to coat 2,800,000 kg = 2,800 t
  for the annual demand

Why is it worth the effort?

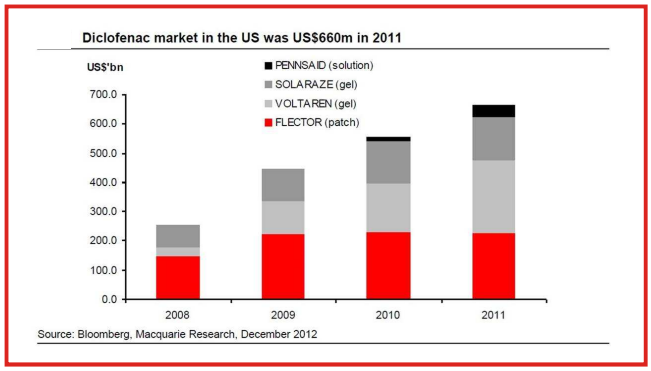
Serious ADRs due to NSAIDS (EU 2006-10)

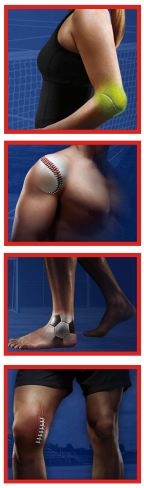
ketoprofen, diclofenac, indomethacin, ibuprofen, niflumic acid, piroxicam



Outside-in (dermal) is much safer than inside-out (oral)

Why is it worth the effort?

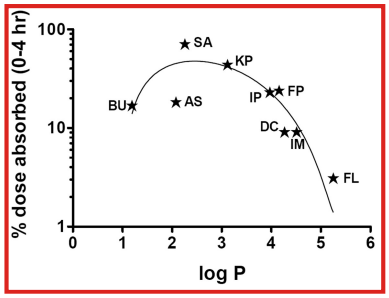




Even besides Lidoderm: it's a huge market!

Skin permeability of NSAIDs in man

NSAID	logP	Dose absorbed (0-4 h) [%]
Salicylic Acid (SA)	2.26	71 ± 2.5
Ketoprofen (KP)	3.12	44 ± 2.7
Flurbiprofen (FP)	4.16	24 ± 2.3
Ibuprofen (IP)	3.97	23 ± 3.2
Bufexamac (BU)	2.08	18 ± 5.2
Aspirin (AS)	1.19	17 ± 2.0
Diclofenac (DC)	4.51	9.1 ± 2.7
Indomethacin (IM)	4.27	9.1 ± 1.2
Flufenamic Acid (FL)	5.25	3.1 ± 1.4



adopted from:
Yano T, Nakagawa A, Tsuji M, Noda K.,
Life Sciences 39 (1986) 1043-1050.

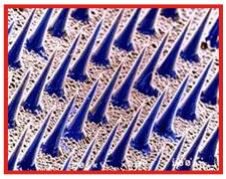
Topical efficacy index: skin permeability to COX inhibition (IC50)

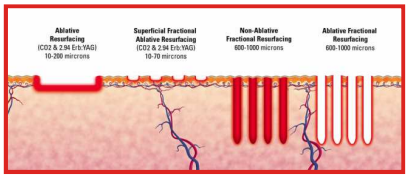
NSAID	COX IC50 [μM]	Efficacy Index (Dose Absorbed : COX)
Ketoprofen (KP)	2.26	550
Diclofenac (DC)	3.12	450
Indomethacin (IM)	4.16	215
Flurbiprofen (FP)	3.97	5.45
Salicylic Acid (SA)	2.08	0.16

Hisamitsu Pharmaceutical Co. Ltd.

Finally

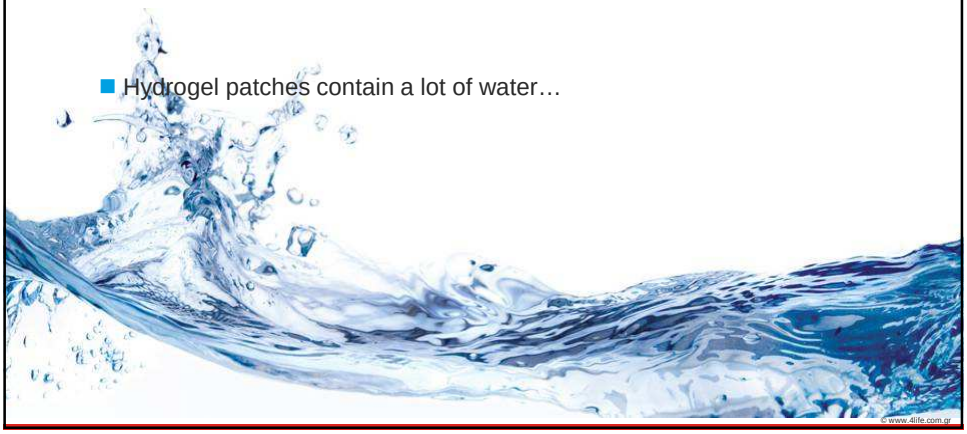
- The number of (trans)dermal drugs in the past 30 years is ca. **ONE** new drug approval every 1.5 years only
- The NCE trend is clearly **BIOLOGICS** instead of SMEs, but passive delivery is limited to ~ 500 Da
- Minimal invasive technologies – **ACTIVE DELIVERY** – is a clear tend (iontophoresis, sonophoresis), microneedles, laser poration, …





Hydrogels to enable active delivery!

- Biologics love water (at least to some extent)
- Minimal skin “damage“ generates hydrophilic pathways
- Hydrogel patches contain a lot of water…



Thank you for your time!

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