Адгезионные технологии в получении трансдермальных терапевтических систем и планы импортозамещения ТТС на российском рынке

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VIII РОССИЙСКИЙ КОНГРЕСС ПЕРЕРАБОТЧИКОВ ПЛАСТМАСС

Moscow
April, 2017

Scientific Team

Dr. Mikhail Feldstein the «Guru of PSA» specialist, founder of Molecular theory of Adhesion

- 40 years of experience
- Developper of the P&G Strip (on behalf of Corium)
- Author of >100 patents and >100 articles (incl books)

Dr. Alexander Moscalets scientist, PSA-specialist

- 5 years of experience in adhesive systems
- Ph.D. in polymer physics & modelling of adhesive systems
- Righthand of Dr. Feldstein

Natalia Sherstneva scientist, PSA-specialist

- 8 years of experience in adhesive systems
- Coatings/Adhesives/Paints/Polymers/Pigments
- Ph.D. student

Kermen Bovaldinova scientist, PSA-specialist

- 8 years of experience in adhesive systems
- PSA and other Adhesives/Polymers/
- Ph.D. student

Dr. Tatiana Levada scientist, PSA-specialist

- 13 years of experience in adhesive systems
- Ph.D. in polymer chemistry & thechnology

RCC Group – маркетинговое агентство и венчурная компания

Definitions

Трансдермальная терапевтическая система (ТТС) — дозированная мягкая лекарственная форма для наружного применения в форме пластырей или плёнок, замедленно высвобождающая лекарственное средство.

Трансдермальная форма удобна тем, что пластырь (или плёнка для трансбуккального применения) наклеивается на кожу, и лекарство через верхние слои кожи (дерму) быстро проникает в кровь.

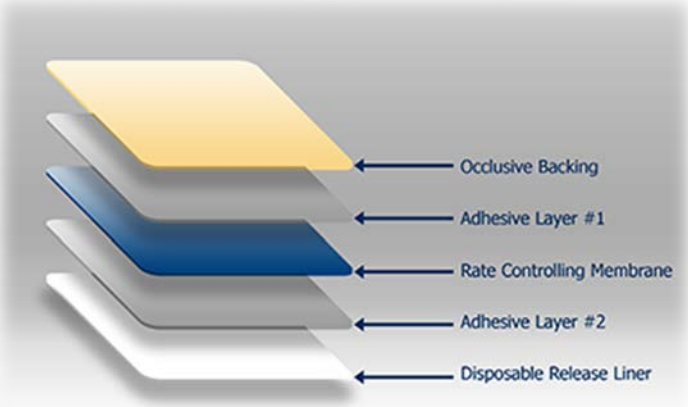
Преимущества ТТС: удобство применения, лекарство быстро попадает в кровь, возможность регулировать скорость высвобождения лекарства, возможность использовать гидрофильные и липофильные вещества и возможность моментального прекращения терапии.

Definitions

Trancedermal Therapeutic System (TTS)

It is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.

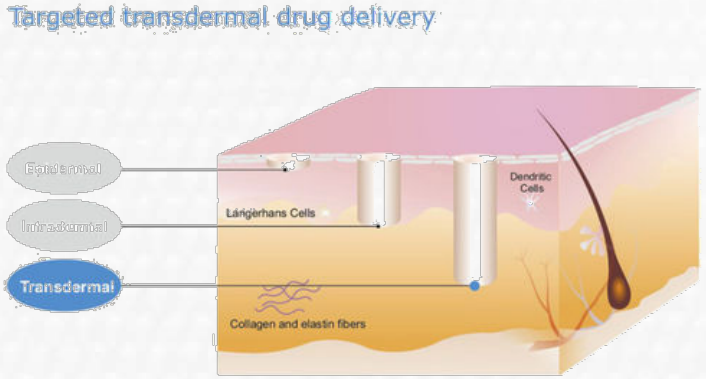


Pressure-Sensitive Adhesives (PSA)

Represent specific class of viscoelastic polymers.

They form strong adhesive joints with substrates of any chemical nature under application of a slight external pressure (comparable with a pressure by a finger) in the course of short contact time (1-5 sec).

PSA combine high fluidity under compressive force at the stage of adhesive bond formation with solid-like cohesive strength and elasticity under detaching force at the stage of debonding.



Transdermal drugs approved by the US FDA.*

Approval year	Drug	Indication	Product Name	Marketing company
1979	Scopolamine	Motion sickness	Transderm-Scop	Novartis Consumer Health (Parsippany, NJ)
1981	Nitroglycerin	Angina pectoris	Transderm-Nitro	Novartis (East Hannover, NJ)
1984	Clonidine	Hypertension	Catapres-TTS	Boehringer Ingelheim (Ridgefield, CT)
1986	Estradiol	Menopausal symptoms	Estraderm	Novartis (East Hannover, NJ)
1990	Fentanyl	Chronic pain	Duragesic	Janssen Pharmaceutica (Titusville, NJ)
1991	nicotine	Smoking cessation	Nicoderm, Habitrol, ProStep	GlaxoSmithKline (Philadelphia, PA), Novartis Consumer Health (Parsippany, NJ) Elan (Gainesville, GA)
1993	Testosterone	Testosterone deficiency	Testoderm	Alza, Mountain View, CA
1995	Lidocaine/epinephrine (iontophoresis)	Local dermal analgesia	Iontocaine	Iomed (Salt Lake City, UT)
1998	Estradiol/norethidrone	Menopausal symptoms	Combipatch	Novartis (East Hannover, NJ)
1999	Lidocaine	Post-herpetic neuralgia pain	Lidoderm	Endo Pharmaceuticals (Chadds Ford, PA)
2001	Ethinyl estradiol/norelgestromin	Contraception	Ortho Evra	Ortho-McNeil Pharmaceutical (Raritan, NJ)
2003	Estradiol/levonorgestrel	Menopausal symptoms	Climara Pro	Bayer Healthcare Pharmaceuticals (Wayne, NJ)
2003	Oxybutynin	Overactive bladder	Oxytrol	Watson Pharma (Corona, CA)
2004	Lidocaine (ultrasound)	Local dermal anesthesia	SonoPrep	Echo Therapeutics (Franklin, MA)
2005	Lidocaine/tetracaine	Local dermal analgesia	Synera	Endo Pharmaceuticals (Chadds Ford, PA)
2006	Fentanyl HCl (iontophoresis)	Acute postoperative pain	Ionsys	Alza, Mountain View, CA
2006	Methylphenidate	Attention deficit hyperactivity disorder	Daytrana	Shire (Wayne, PA)
2006	Selegiline	Major depressive disorder	Emsam	Bristol-Myers Squibb (Princeton, NJ)
2007	Rotigotine	Parkinson's disease	Neupro	Schwarz Pharma (Mequon, WI)
200[illegible]	Rivastigmine	Dementia	Exelon	Novartis (East Hannover, NJ)

Prausnitz MR, Langer R. Transdermal drug delivery. Nature biotechnology. 2008;26(11):1261-1268. doi:10.1038/nbt.1504.

Background

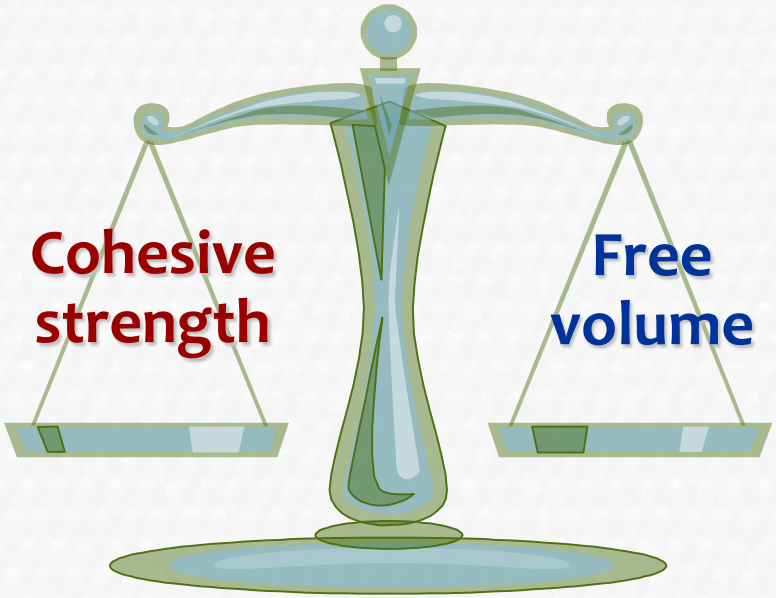
- Rubbers,
- Polyisobutylene (PIB),
- Styrene-isoprene-styrene triblock copolymer (SIS),
- Acrylic copolymers,
- Vinyl acetate – ethylene copolymers,
- Silicone rubber.

All the PSAs are **hydrophobic.**
Their common disadvantage is a lack of adhesion towards wet substrates.

Medical and industrial PSA Applications
Require development of **hydrophilic** adhesives, capable of moisture absorption.

Mechanisms of PSA

Glasses | **Viscoelastic polymers** | Liquids



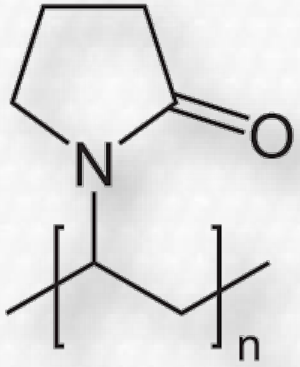
Main approaches to PSA formulation

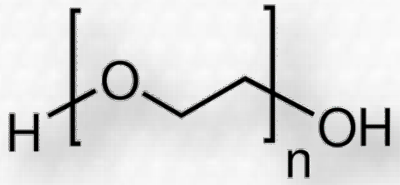
Традиционные методы получения ЧДА:

1. Химический синтез высокоэластичных полимеров с температурой стеклования в интервале от – 40 до – 100 ° С;
2. Химическая модификация липких полимеров;
3. Смешение липких гидрофобных полимеров с гидрофильными абсорбентами влаги.

Пример модельного PSA на основе комплекса ПВП – ПЭГ показывает,что новые PSA могут быть получены простым смешением нелипких полимеров и олигомеров.

Polymer – Oligomer Complexes:





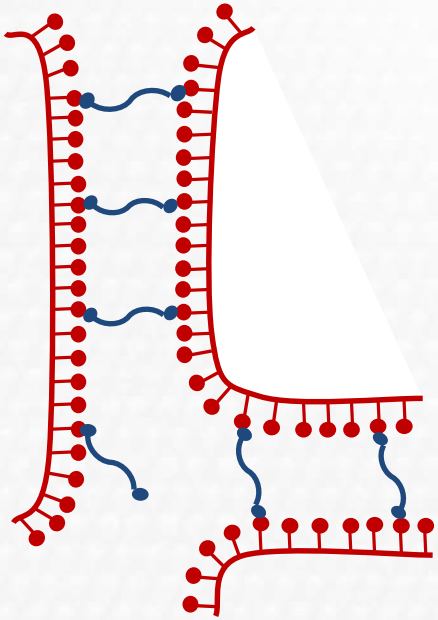
m ≈ 10 000
n = 9 – 10

Free volume:

- Length and flexibility of non-covalent crosslinking PEG chains, acting as spasers;
- Low T_g of PEG;
- Concentration of terminal OH-groups

Cohesive strength:

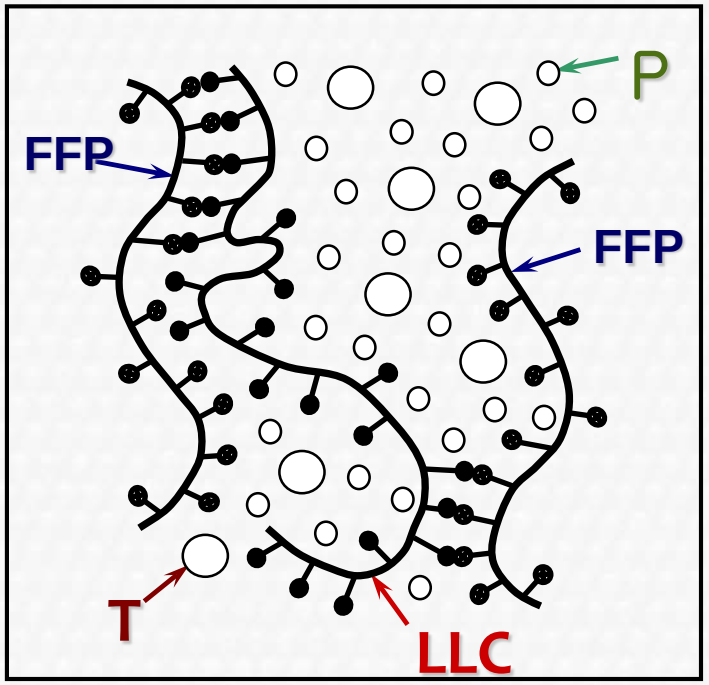
- Amount and strength of interpolymer bonds;
- Long PVP chain entanglements



High molecular weight PVP is a film-forming polymer.
Oligomeric PEG is non-covalent cross-linker and plasticizer.

Interpolymer Complexes

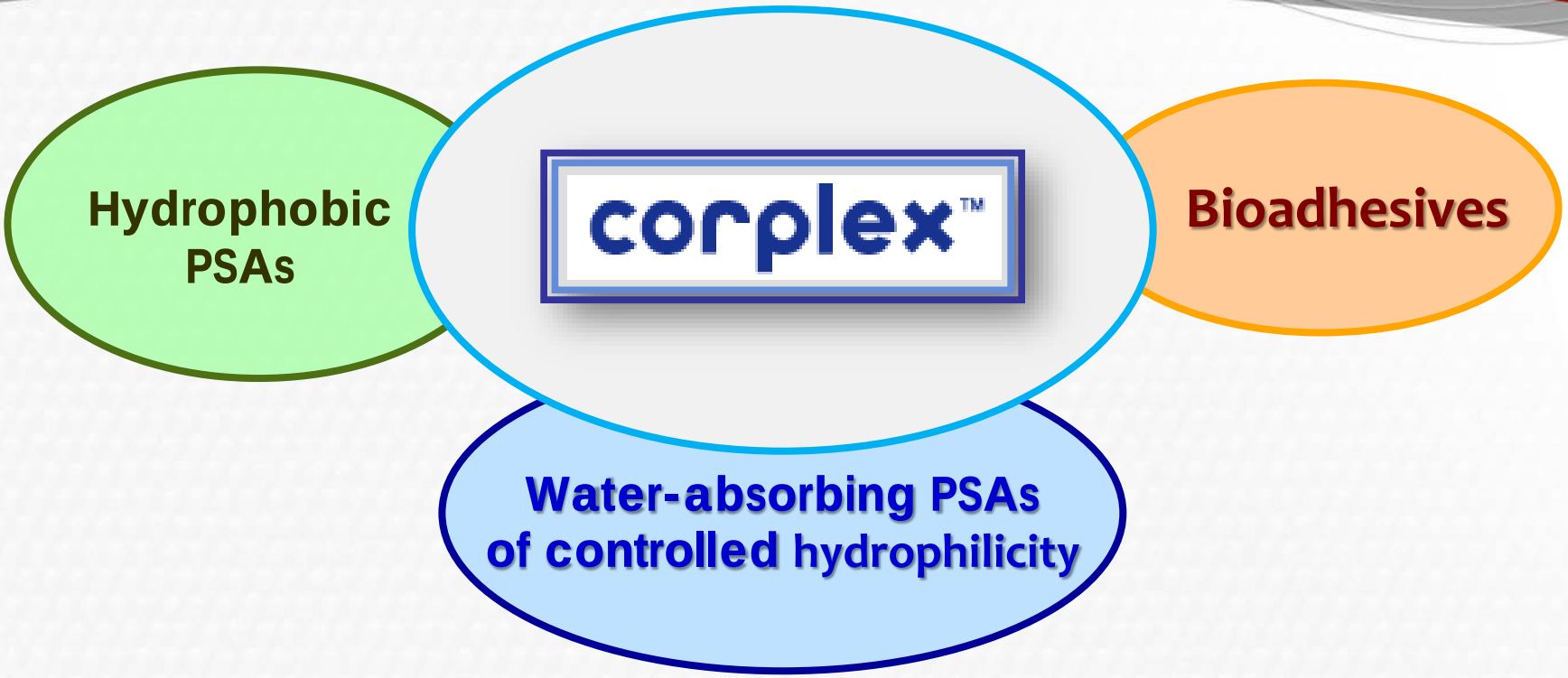
Formed between complementary macromolecules, bearing reactive groups in recurring units of long chains.



"Ladder-Like" Interpolymer Complex

- **FFP-Polybase**
- **LLC-Polyacid**
- **P – Plasticizer**
- **T – Tackifier**

CORPLEX® ADHESIVES



- Mixture of non-adhesive hydrophilic polymers
- Easy production
- Easy control of performance properties
- Abundance of the PSAs for various applications

CORPLEX™ Technology Classification Guide

SWELL RATIO LOG SCALE

2 4 6 8 10 100 1000

COMPLEX TYPE: FFP-LLC-Plasticiser → FFP-CLC-LLC → PVP-PEG

HYDROPHOBIC → HYDROPHILIC

NON ABSORBING → ABSORBING

DRY SKIN APPLICATION → WET MUCOSAL APPLICATIONS

TRANSDERMAL → TRANSDERMAL/MUCOSAL → MUCOSAL

Solid State

Film Forming Liquid

Liquid Fill

Dissolving Film

Aqueous Gel

Molecular design of novel PSAs with tailored properties

- Becomes possible due to well defined function of each component in blend;
- Novel PSA production has been achieved by simple mixing the components in solution or in melt;
- Adhesive and mechanical properties of PSAs can be tuned by the change of component concentrations in blend;
- Water-absorbing capacity of composite PSAs, their swelling and solubility in water are governed by parent polymer hydrophilicity;
- Tack of parent polymers is not required;
- A wide variety and accessibility of functional polymers, which are capable to serve as parent components of PSA composites.

Functional polymers, suitable for novel PSA formulating

Polymer 1	Polymer 2	Type of bonding
-COOH, -PhOH, $-SO_3H$	$-NH_2$, -NHR , $-NR_2$	Electrostatic
-OH	-OH, -C-O-C-, $-CONH_2$, -CONHR, $-CONR_2$-$CONH_2$, -CONHR, $-CONR_2$	Hydrogen
$-COO^-$	$-NH_3^+$, $-NH_2R^+$, $-NHR_2^+$, $-NR_3^+$	Ionic

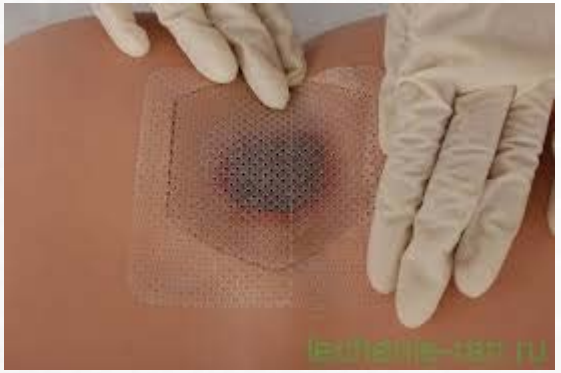
Transdermal Therapeutic Systems

The project team develop the Transdermal Therapeutic Systems based on original hydrophilic PSA since 1991.

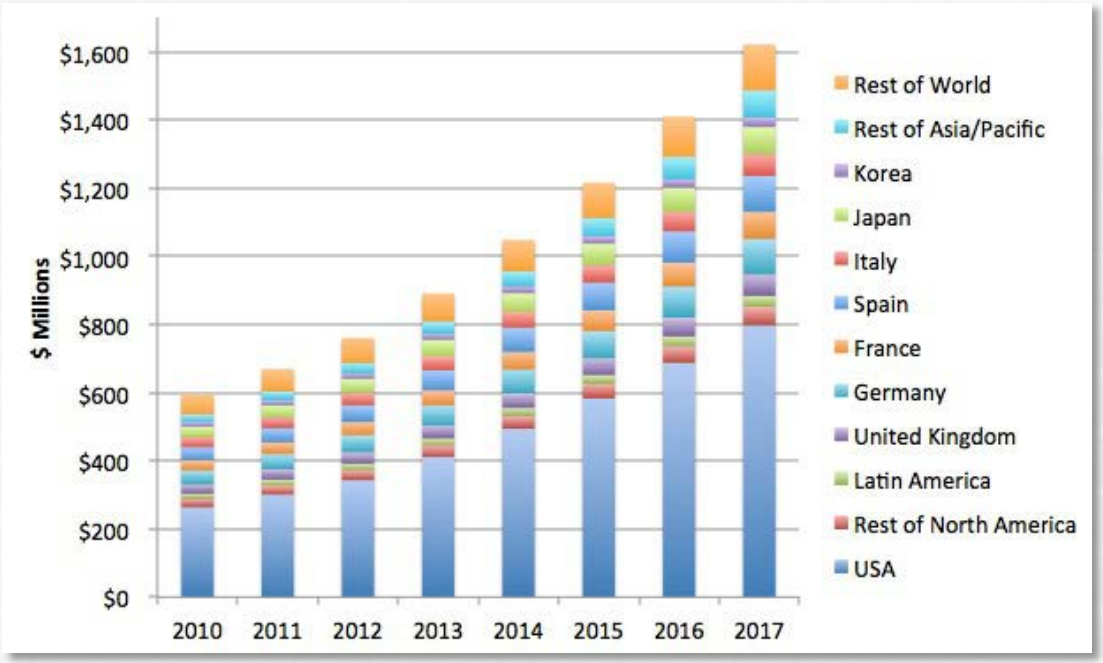
Our group has implemented several significant projects in this area with international pharmaceutical companies.

According to some data, the TTS market is doubling annually in the last three years.

We are ready to develop about five new systems in an year in collaboration with the Swiss pharmaceutical company or independently.



Medical applications of PSAs



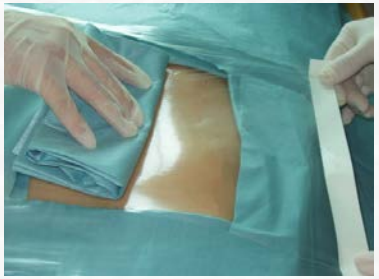
Source: MedMarket Diligence

Medicine applications of thermoswitchable PSAs

Applications

Traditional

- Removable patches and bandages
- Veterinary patches
- Specialized medical devices



Innovative

- Patches for transdermal drug delivery
- Wearable sensors for monitoring the human condition

Advantages of our new adhesive:

1. **Reversible loss of tack**
2. **Hydrophilicity**
3. **Ease of fabrication**
4. **Absence of toxicity**

Patent application (PCT/RU2013/001107 от 11.12.2013)

Hydrophilic PSA Applications: “Smart” Teeth Whitening Strips

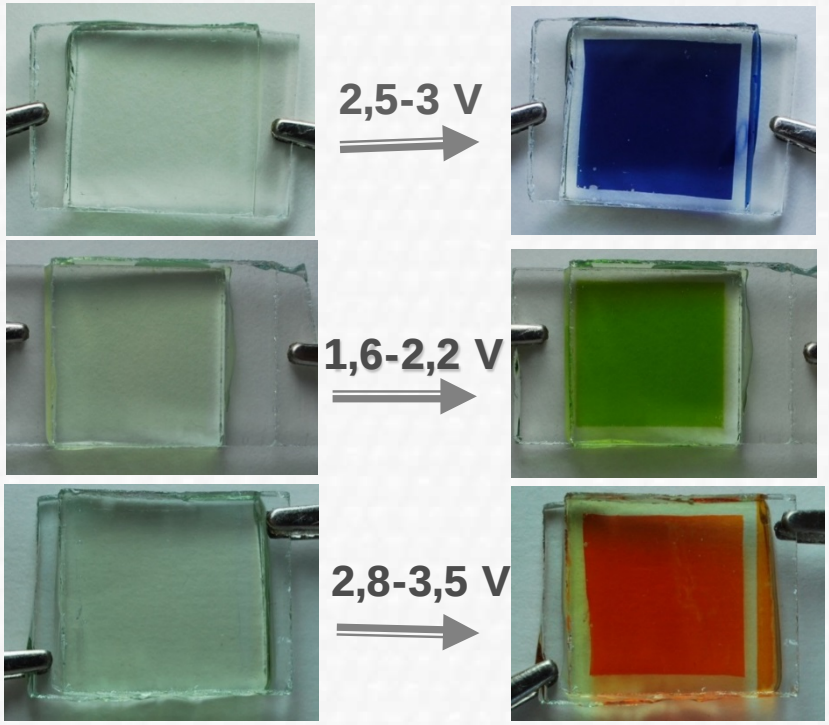
Our group, led by Prof. **M. Feldstein**, is author of P&G white strips technology.

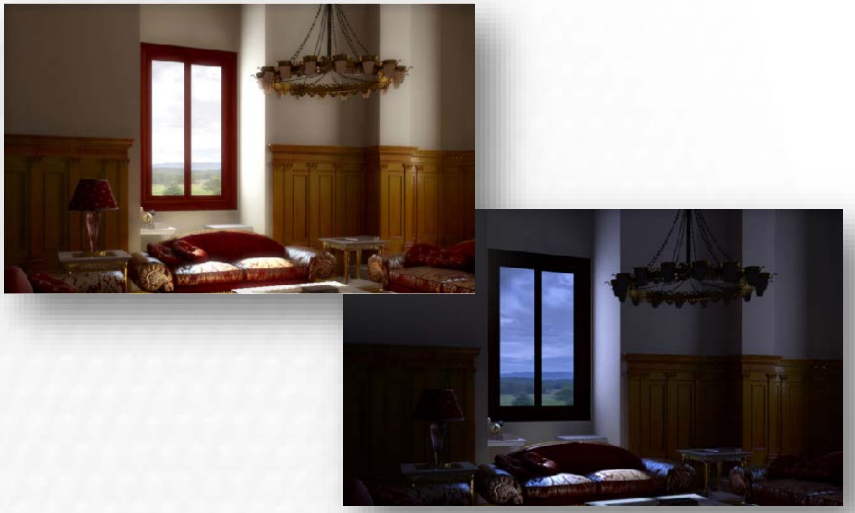
The market volume in this segment is about $ 20 billion an year.

Over last few years the project team significantly improved a new generation of strips which display much stronger adherence to teeth but exhibit no adhesion towards other mucosal tissues in the mouth (e.g. tongue, lips, gums and palate).

New electrochromic PSAs

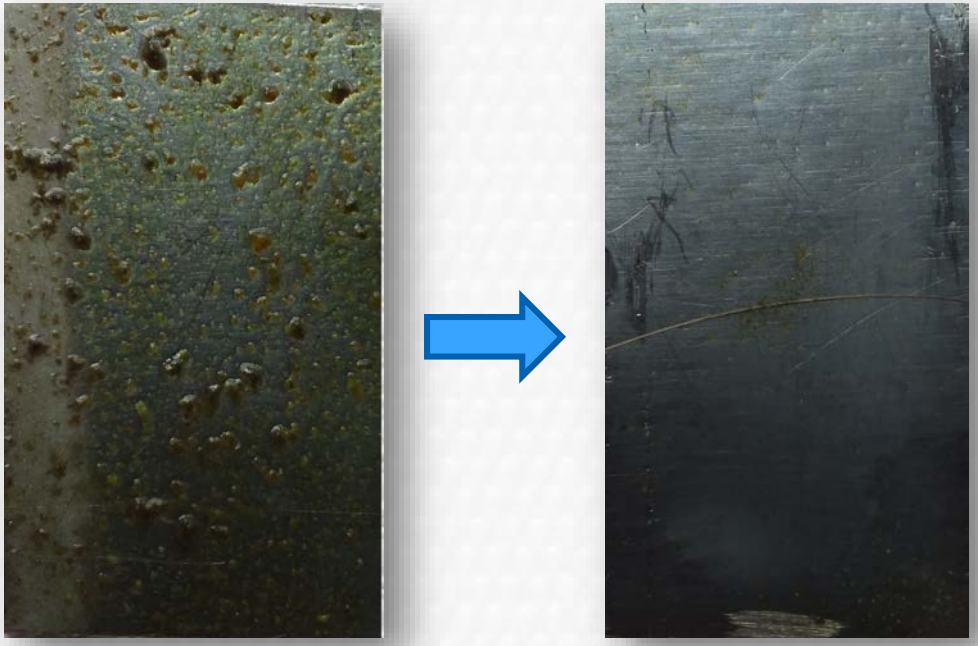
- Our team has developed adhesives electrochromic technology, which holds great promise in a number of industries.





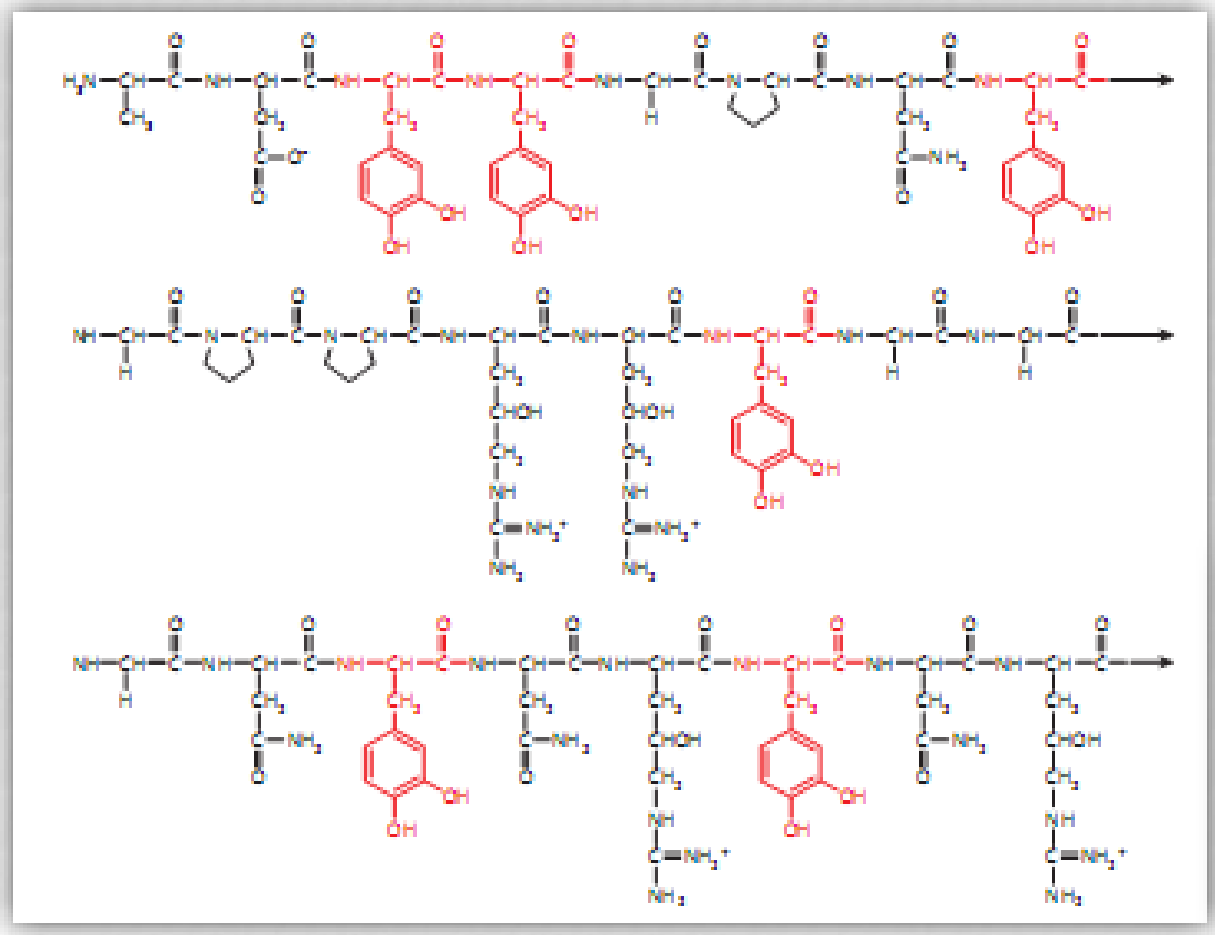
New application of antifouling PSA

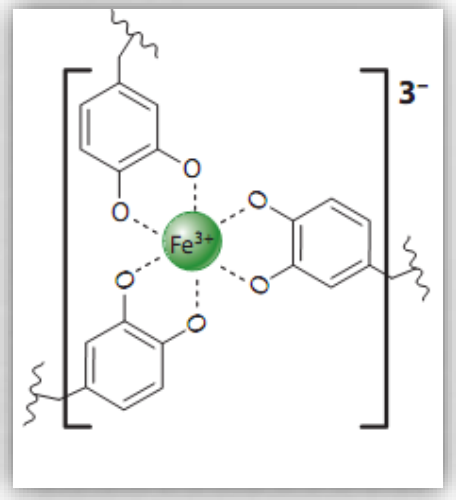
Our team has obtained competitive solution: antifouling coatings for preventing fouling of ship hulls and underwater marine structures.

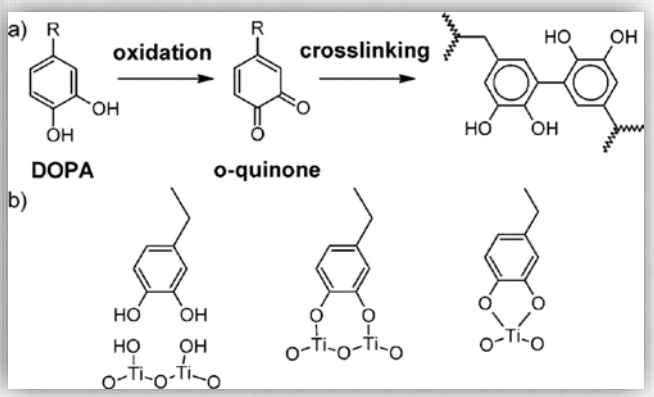


At the bottom: the control plate (A) and coated with anti-fouling coating PP2 (B) - after 2 months of the experiment in standing water.

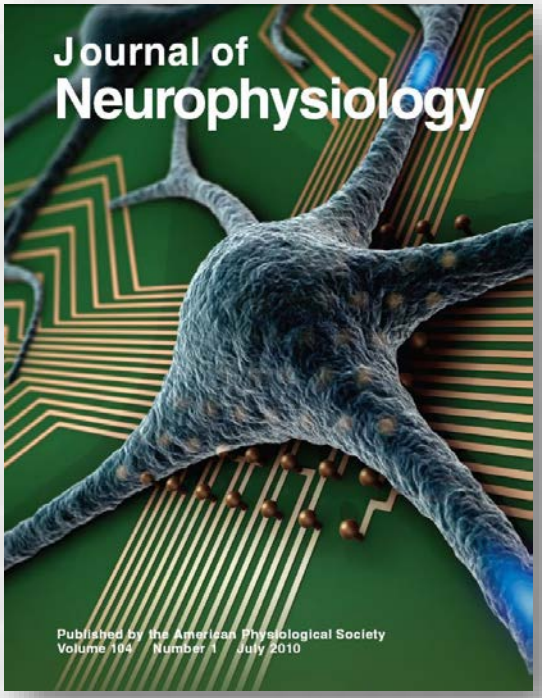
Mechanism of metal ship hull fouling with marine mollusces





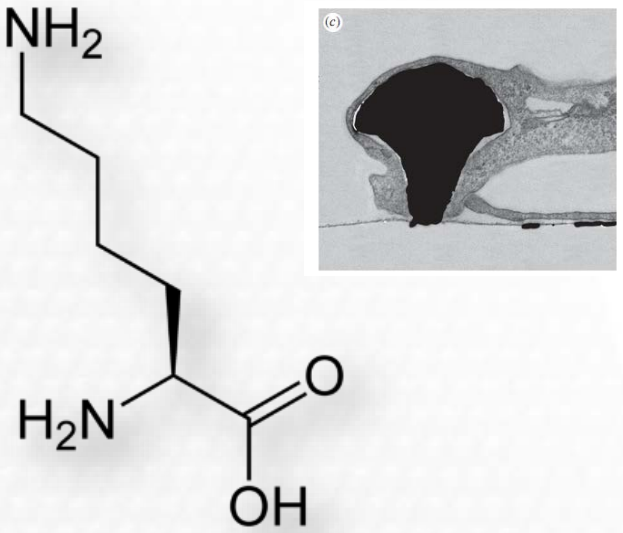


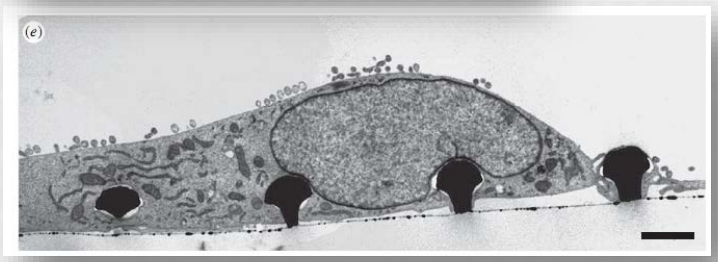
New hybrid PSAs for cognitive technologies



K – decalysine

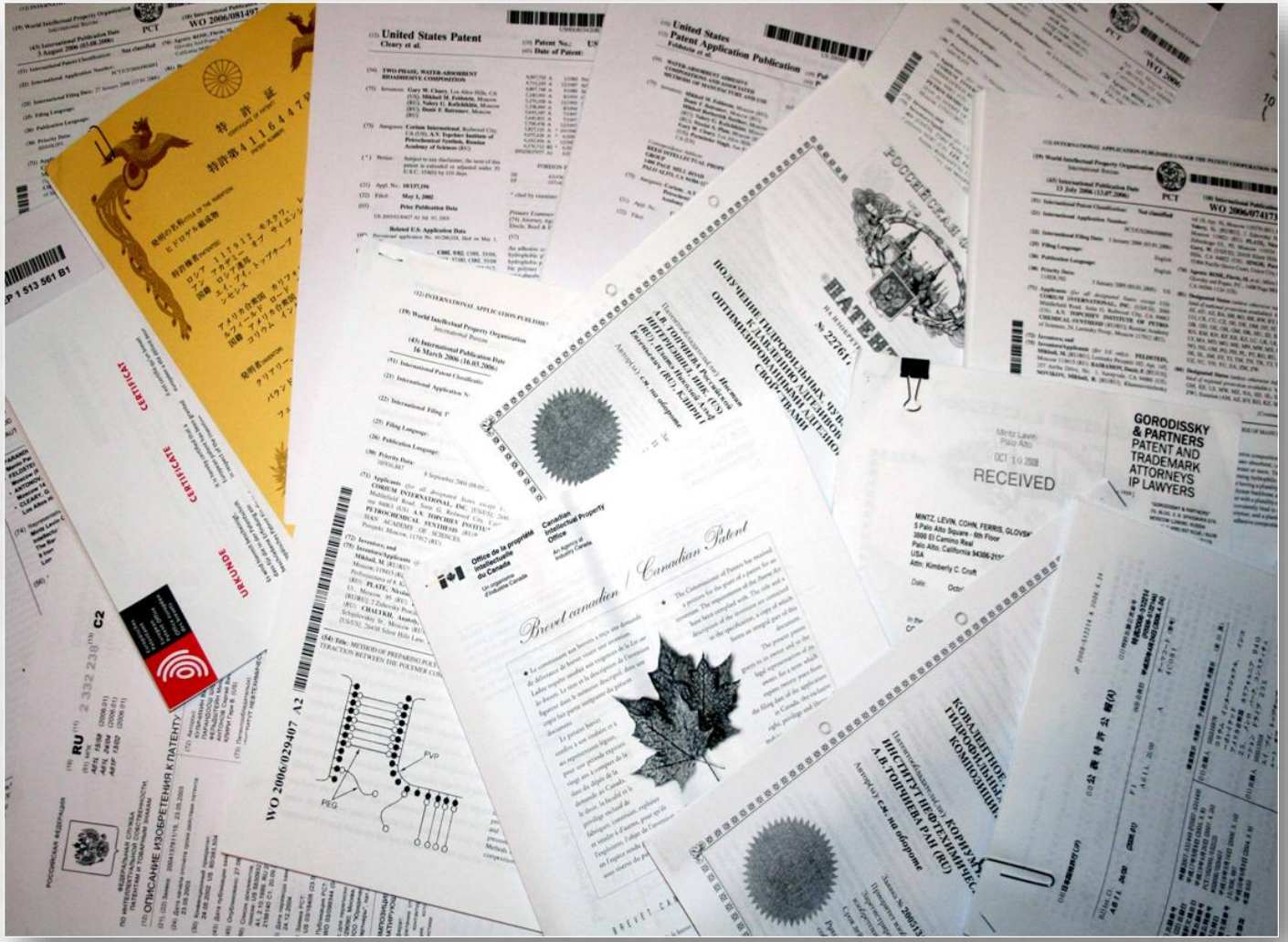
Engulfment promoting polypeptide (EPP): CKKKKKKKKKKPRGDMPRGDMPRGDMPRGDM, MW = 3630 g/mol





Electroconductive hybrid bio-PSAs for monitoring of neural activity

Our IP is aproved by patents of 96 countries



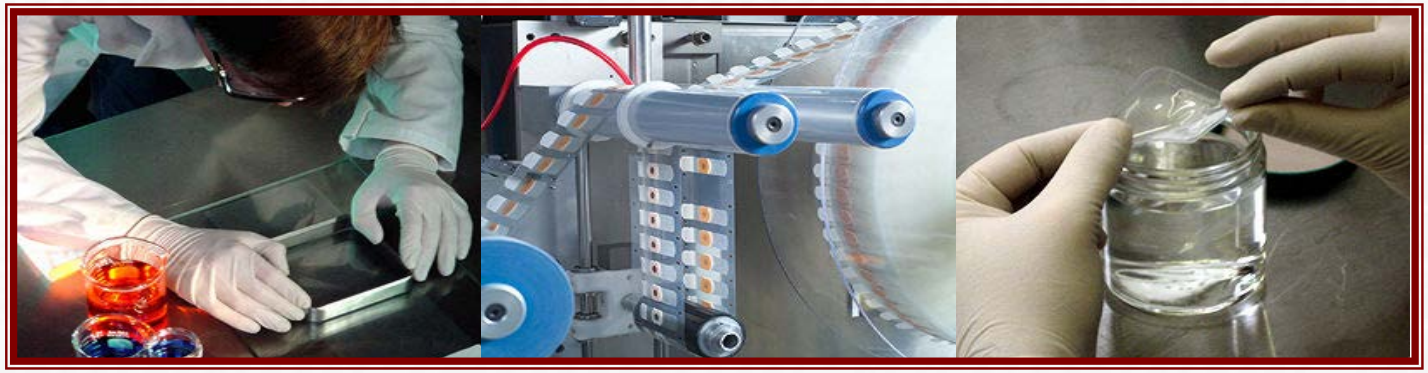
Possible partner opportunities

Our Company has a broad portfolio of innovative PSA materials and products ready to be commercialized:

- Super water absorbing adhesive hydrogels;
- Moisture-absorbing ulcer, wound and burn adhesive dressings;
- Painlessly removable skin and mucosal PSAs;
- Tooth-whitening strips with targeted adhesion toward teeth and the lack of tackiness to tongue, gums and palate;
- Wide spectrum of oral and tooth-care PSA products;
- Electro-conducting and electrochromic PSAs;
- Transdermal patches with enhanced drug delivery;
- Adhesive films for sublingual controlled drug delivery;
- Bio-inspired and mussel-inspired PSAs for assembling metal and glass substrates;
- Hybrid bioPSAs based on polypeptides and proteins for monitoring neural cell signals.

Основные итоги

- Впервые установлены молекулярные структуры, ответственные за чувствительную к давлению адгезию полимеров.
- Впервые разработан метод молекулярного конструирования новых PSA контролируемой гидрофильности и влагопоглощающей способности, основанный на простом смешении широкого круга гидрофильных полимеров.
- Положено начало новой отрасли промышленности адгезионных композиционных материалов.



Thank you for your attention!

“RUSSIAN ADHESIVES”
invites proposals from interested companies for any forms of cooperation in bringing to the market new generations of innovative PSA materials and products

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