Croda Pharma

Super Refined™ solutions for transdermal drug delivery systems

October 2022

Smart science to improve lives™

CRODA

Agenda

- Introduction to Croda Pharma
- Croda technology
- Case studies

Our journey to Croda Pharma

1925

Croda was founded

Decades of **Smart science to improve lives™** across consumer and health ingredients

2000 onwards

Ongoing investments in high purity excipients

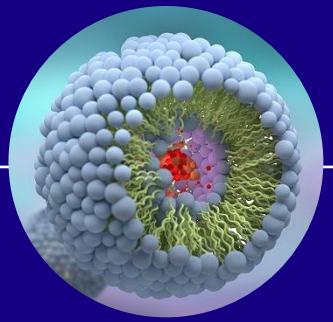
2018

Biosector acquisition, industry leading vaccine adjuvants

2020

Avanti® Polar Lipids
Part of Croda International Plc

Acquisition of world leading lipid portfolio



2021

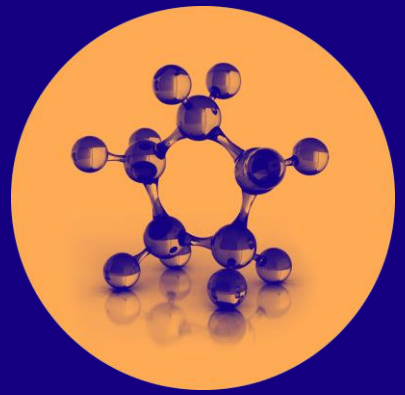
Global investments in pharma +£100m – a commitment to advancing expertise

2022

Our Health Care business becomes

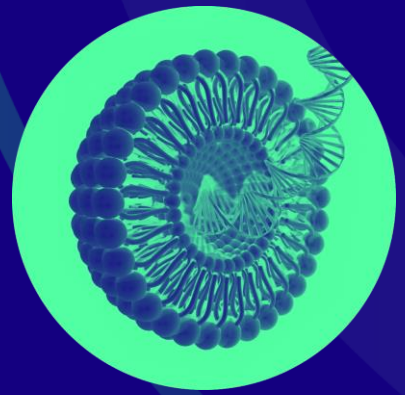
Croda Pharma

Croda Pharma platforms

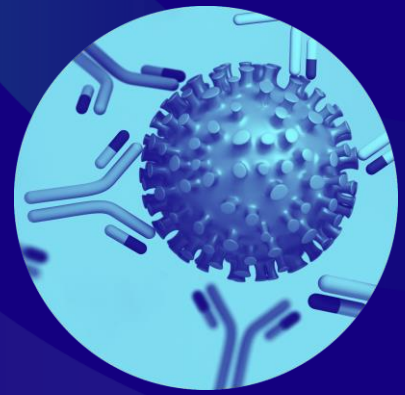


Small Molecule Delivery

Protein Delivery



Nucleic Acid Delivery



Adjuvant Systems

Human and Veterinary Health

Consumer Health

We combine our **technical expertise** with **regulatory knowledge** to help our customers market innovative products with **consumer relevant claims**, alongside supporting **formulation development challenges** within the Consumer Health market.

Excipient solutions for:

OTC
(*Over-the-Counter*)

Nutraceutical supplements

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Our expertise

Innovation

Enabling breakthrough innovation

Formulation

Unique blend expertise

Application

Focused scientific endeavors

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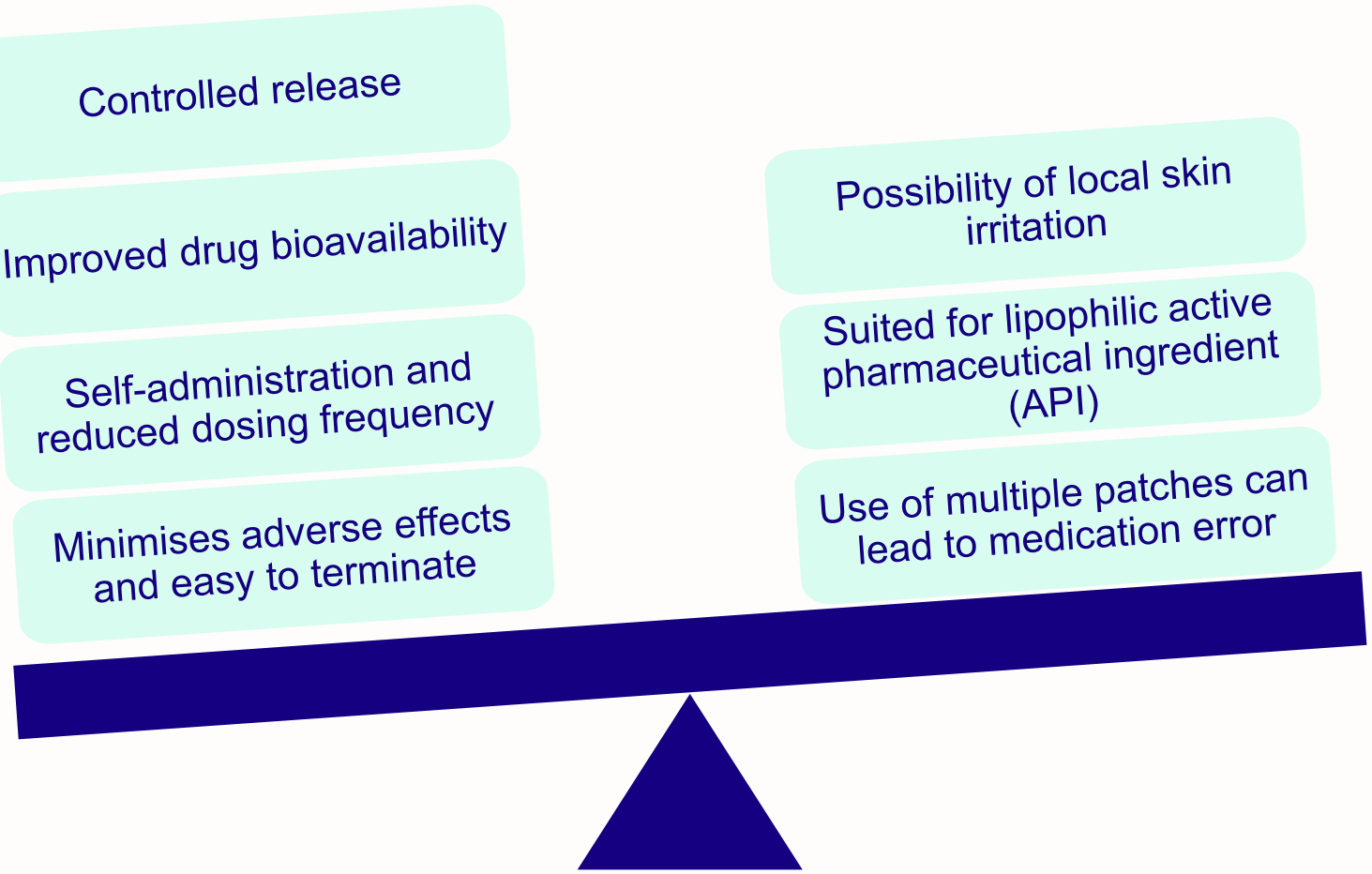
Advantages and disadvantage of transdermal delivery sytems (TDS)



Transdermal patch design

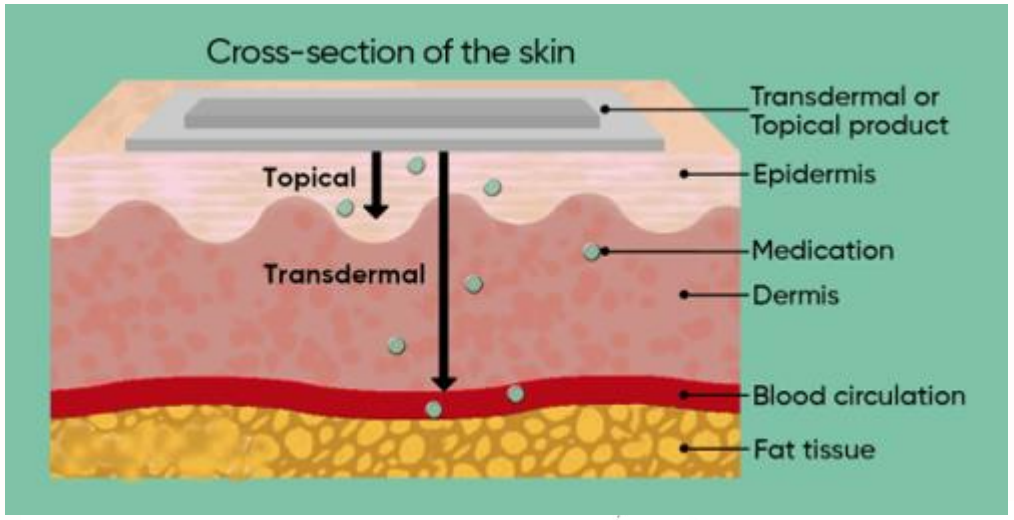
Purpose: Deliver specific dose of medication through the skin into the systemic circulation for therapeutic effects.

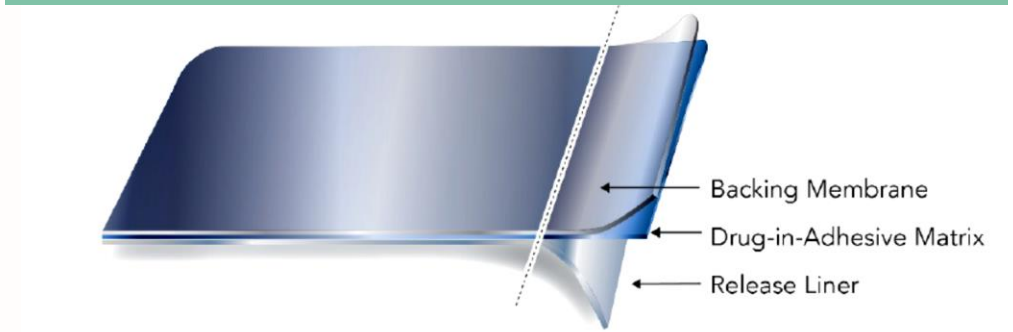
Generations of transdermal drug delivery system:

1st: Delivery candidates must be low-molecular weight, lipophilic, and efficacious at low-doses

2nd: Employed conventional **chemical enhancers** and electrically assisted methods like iontophoresis

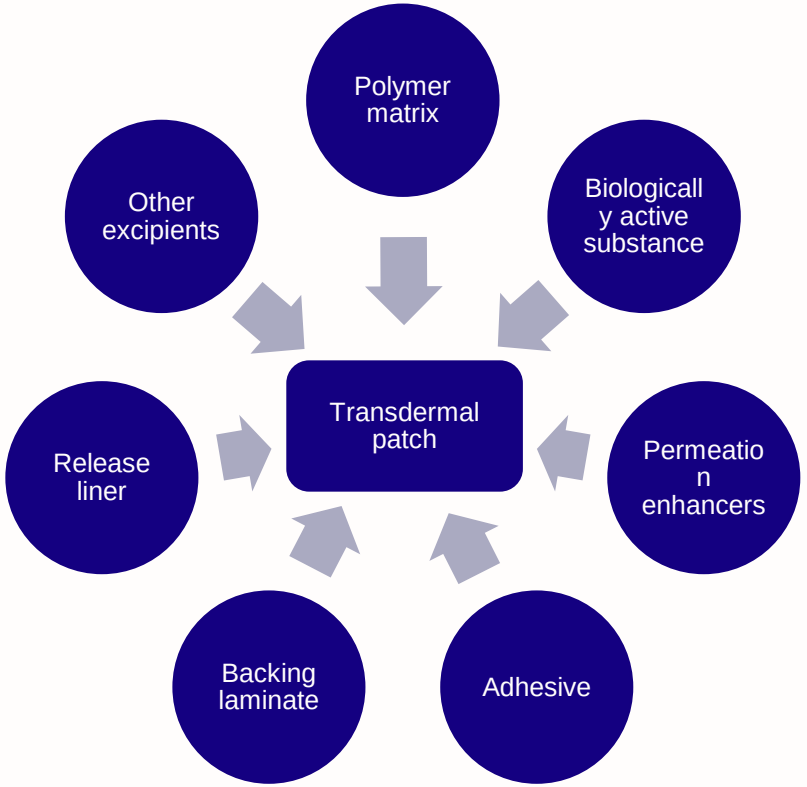
3rd: Usage of **novel chemical enhancers**, electroporation, microneedles, thermal ablation or microdermabrasion





Transdermal & Topical Delivery Systems- Product development & quality considerations, Guidance for Industry, USFDA, November 2019 https://www.science-community.org/en/node/175244 Prausnitz MR and Langer R. Nat Biotechnol 2008; 26(11): 1261-8.

Transdermal excipients selection criteria



- Selection of patch design
- Solubility between API and excipient blend
- Physical and chemical compatibility between API and excipient blend
- Impact of excipient blend on skin permeation
- Impact of excipient blend on non-drug substance related impurities
- Impact of excipients on adherence for duration of wear period

Sree Raju N et al. Chapter 2 - Transdermal and bioactive nanocarriers, Editor(s): Arun Nanda, Sanju Nanda, Tuan Anh Nguyen, Susai Rajendran, Yassine Slimani, In Micro and Nano Technologies, Nanocosmetics, Elsevier, 2020, Pages 17-33.

Transdermal API - patches

API	MW	Log P	MP (°C)
Tulobuterol	227.7	3.08	89-91
Nitroglycerin	227.1	1.62	13.5
Nicotine	162.2	1.20	90
Estradiol	272.4	4.01	173-179
Isosorbide dinitrate	236.1	1.31	70
Fentanyl	336.5	4.05	83-84
Clonidine	230.1	2.28	130
Testosterone	288.4	3.32	155
Oxybutynin hydrochloride	394.0	4.68	129-130
Scopolamine	303.4	-1.20	59

- Low molecular weight; NMT 500 Daltons
- Moderate oil solubility log *P* = 1-4
- Low melting point; NMT 200°C
- Potent having dose <20mg/day
- Non-irritating and non-sensitising
- Low oral bioavailability

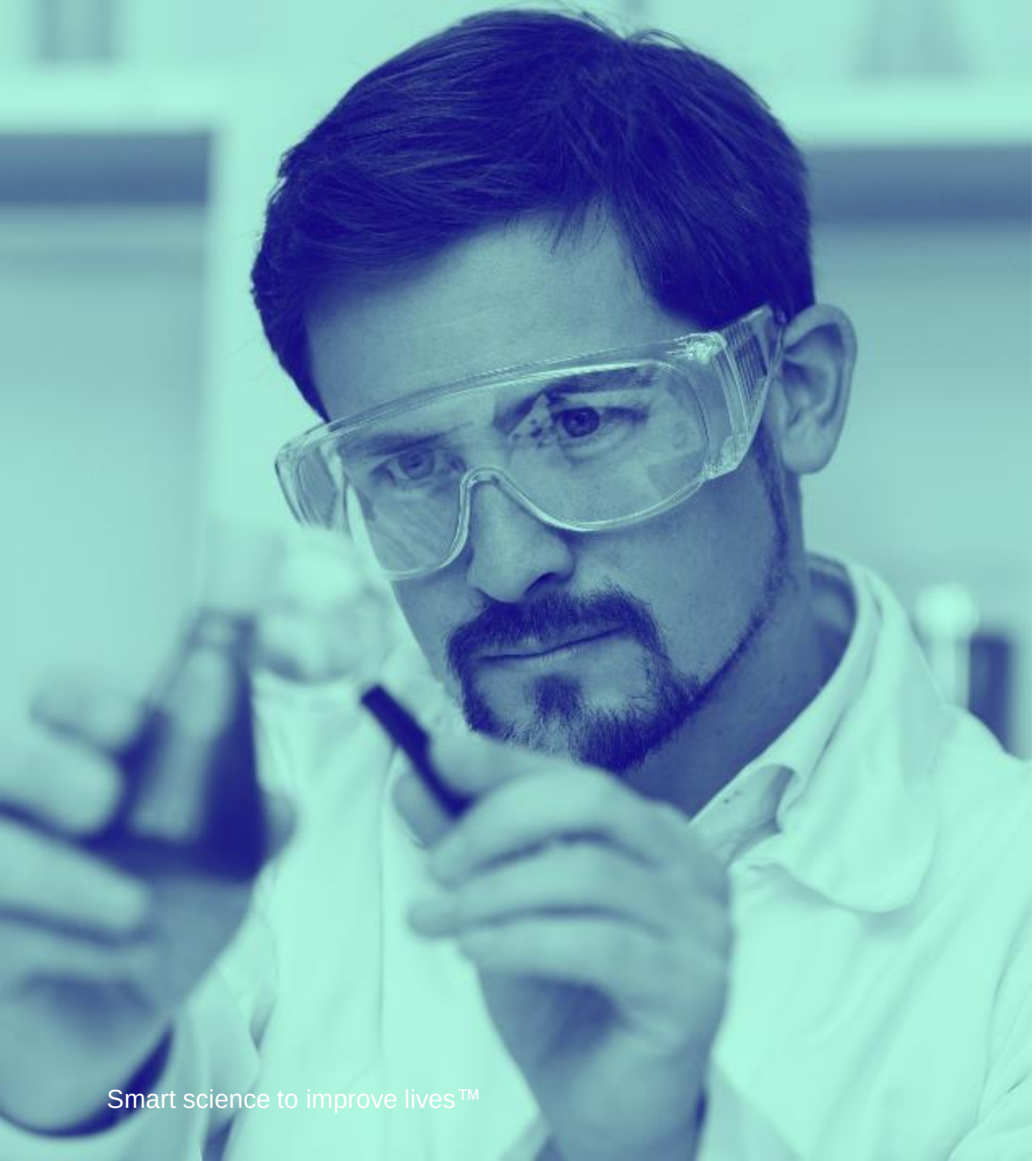
Wester RE, et. Al. Percutaneous absorption.Mecchanisms=Methodology=Drug-delivery, New York. 107-23 (1983)
Bos JD, et. At. Exp. Dermatol., 9, 165-9 (2000)
Flyn GL., et. Al., J. Pharm Sci , 39, 1043-50 (1986)
Yano T, et. Al., J. Pharm.Sci., 61, 838-52(1972)
Scheuplein RJ, et.al.,J.Invest. Dermatol, 52,63-70, (1969)
Michaels AS, et.al.,AlChe J.,21,985-96, (1969)
T.Watanabe,Drug delivery system,22,450-7,(2007)

Croda technology

Our **Super Refined™** range ensures that your formulations are stable, effective and consistent.

- Variety of products which offer:
  - ✓ Excellent API solubility
  - ✓ Excellent oxidation stability
  - ✓ Excellent hydrolysis stability
  - ✓ Low cellular irritation
  - ✓ Better skin permeation enhancement
  - ✓ Reduced odour impact
- Multicompendial - meets standards of international pharmacopoeias; USP/NF, Ph. Eur., JP/JPE, and ChP
- Excipients with a DMF submitted to the Chinese Health Authorities (CDE)
- Global manufacturing infrastructure, expert regulatory support and application know-how

Smart science to improve lives™



Our values

- **Wide range of excipient chemistries**
- **Solubility data - experimental**
  - Testing across a wide range of API and excipient chemistries
- **Solubility data - theoretical**
  - Use of Hansen solubility parameters (HSP) spheres for theoretical solubility prediction
  - Experimental data to support excipient HSP parameters (not just SMILES)
  - Linking HSP theoretical to Smax experimental data
- **Excipient stability**
  - Batch to batch and overtime consistency

Transdermal delivery system - Croda portfolio

Product	Chemical description	Category	Monograph compliance	Dosage route	Max potency*****	Function
Super Refined™ Oleic Acid	Oleic acid	Fatty acid	Ph. Eur., NF, JPE, *DMF	TF-ER TS	9.6 MG 22 MG	Permeation enhancer, solubiliser
Super Refined DEGEE	Diethylene glycol monoethyl ether	Ether	USP/NF, Ph Eur.	TG TS	5% 430 MG	Permeation enhancer, solubiliser
Super Refined DMI	Dimethyl Isosorbide	Carbohydrate, sugars and derivatives	*DMF	TS	None listed	Permeation enhancer, solubiliser
Super Refined Propylene Glycol	Propylene glycol NF	Glycols	NF, JP, *DMF	TF-ER TG	58.13 MG 20%	Permeation enhancer, plasticiser***, solubiliser
Super Refined Oleyl Alcohol	Oleyl alcohol	Fatty alcohol	NF	TF TF-ER TG TS	6.11 MG 7.45 MG 1.5% 6.12 MG	Permeation enhancer, solubiliser
Super Refined Oleyl Oleate	Oleyl oleate	Emollient ester	JPE	TS	30 MG	Permeation enhancer, solubiliser
Super Refined Polysorbate 80**	Polysorbate 80	Ethoxylated sorbitan esters	Ph. Eur., NF, JP, *DMF	TS	None listed	Permeation enhancer, surfactant
Super Refined PEG 400	Polyethylene glycol 400	Glycols	Ph. Eur., NF, JP, ChP, +DMF (grade LTG)	TS	None listed	Plasticiser****, solubiliser
Super Refined IPP	Isopropyl Palmitate	Emollient esters	NF, JPE; *DMF	TF-ER	187.5 MG	Permeation enhancer, solubiliser
Super Refined PGML	Propylene Glycol Monolaurate	Glycol esters	NF, Ph. Eur.	TS	None listed	Solubiliser
Cithrol™ GMO HP	Glyceryl Oleate	Glyceryl esters	NF, Ph. Eur.	TF-ER	18.8 MG	Permeation enhancer

*DMF submitted to the Chinese Authorities (CDE)
+ DMF in process of being submitted to the Chinese Authorities (CDE)
**Ref: i) Naveed et al. Trop. J. Pharm. Res., 10(3), 281-288, (2011); ii) Taghizadeh SM et al. J. Adv. Res, 6(2), 155-162, (2015).
***Ref: Panda et al. Int. J of Biological macromolecules, 6, 295-302, (2014)
****Gupta et al. Int. J. Pharm, Sci. Drug Res, 1(1), 46-50, (2009)
***** As listed on FDA IID inactive ingredients list
TG- Transdermal, Gel; TS- Transdermal, System; TF-ER- Transdermal Film, Extended release

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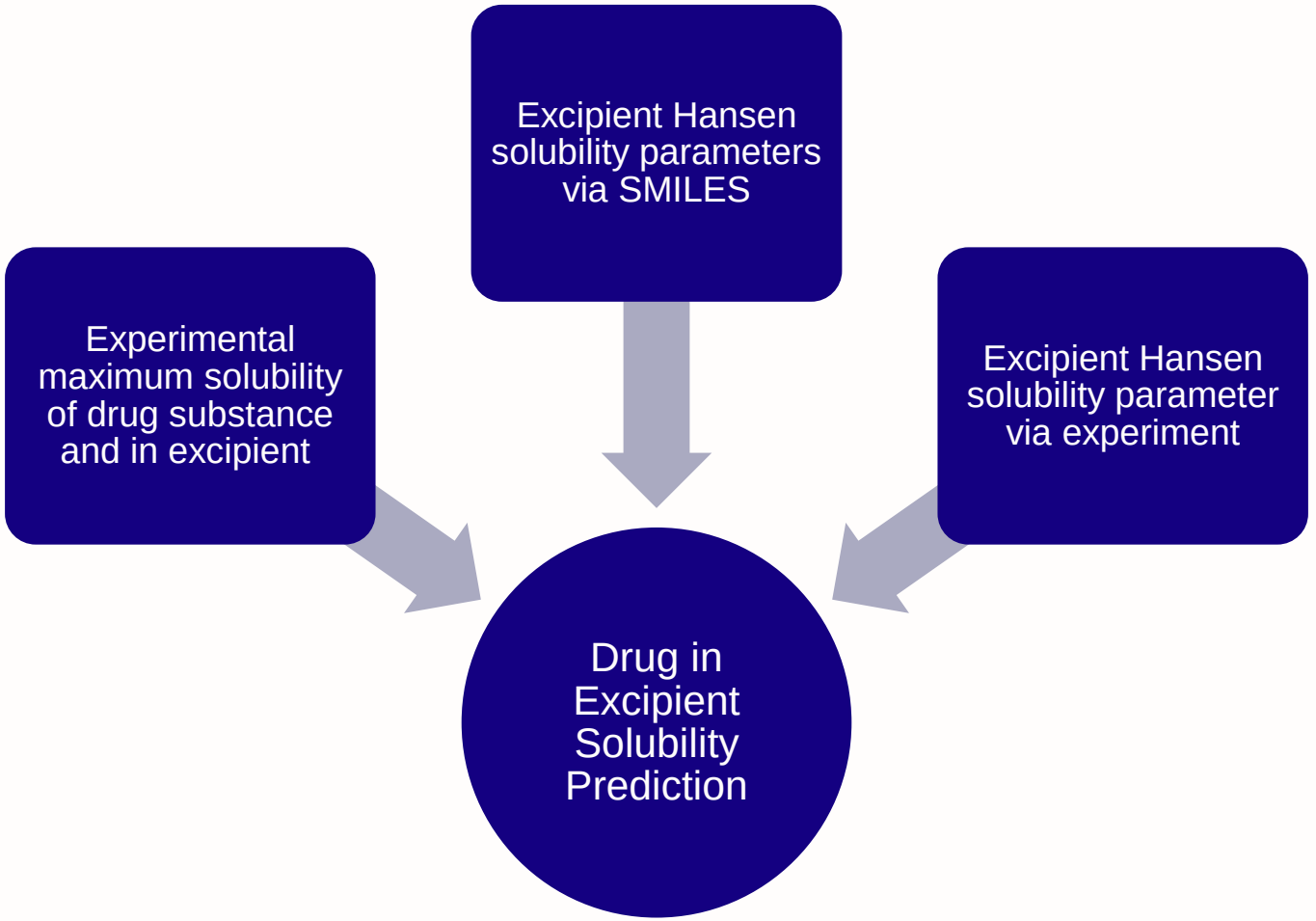
Transdermal delivery system - Croda portfolio

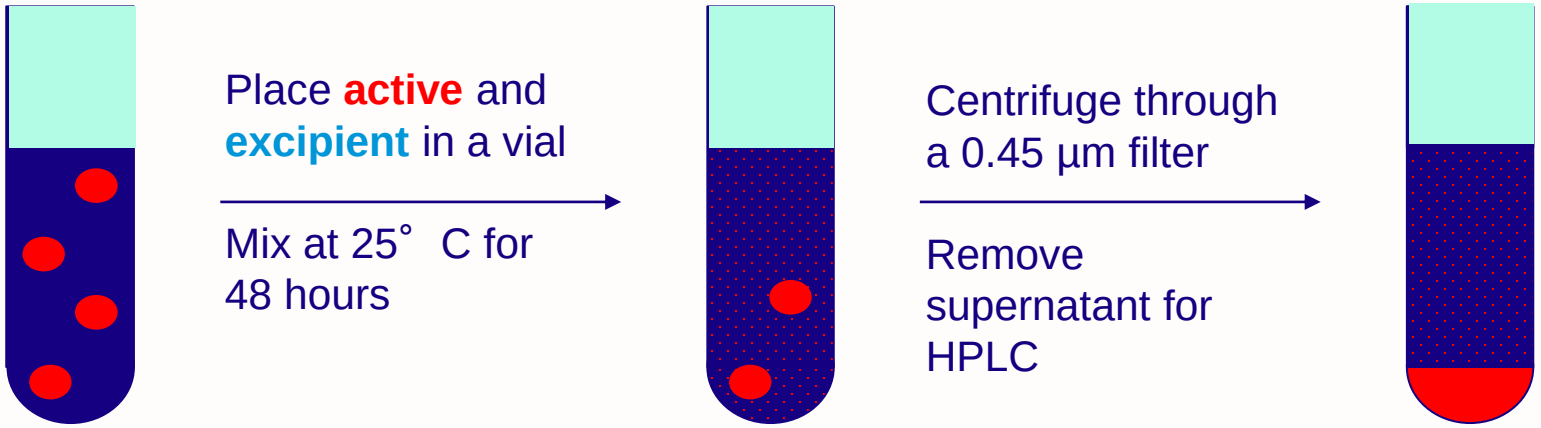
Product	INCI Name	Category	Monograph compliance	Dosage route	Max potency	Function
Crodamol™ DA Pharma	Diisopropyl adipate	Emollient esters	JPE, *DMF	TG	1.5%	Plasticiser, solubiliser
Super Refined™ Castor Oil	Castor oil	Vegetable oils	NF, JP, *DMF	TS	None listed	Plasticiser, solubiliser
Super Refined Sesame Oil	Sesame oil	Vegetable oils	NF, Ph. Eur., JP, *DMF	TS	None listed	Permeation enhancer*, solubiliser
Super Refined Olive Oil	Olive oil	Vegetable oils	JP	TS	None listed	Permeation enhancer*, solubiliser
Super Refined Ethyl Oleate	Ethyl oleate	Emollient esters	Ph. Eur.	TF-ER	15 MG	Permeation enhancer, solubiliser
Super Refined GTCC	Medium-chain triglycerides	Emollient esters	JPE, Ph. Eur., NF, ChP, *DMF	TS	None listed	Solubiliser
Super Refined IPM	Isopropyl myristate	Fatty acid ester	JPE, NF, Ph. Eur, *DMF	TS TF TF-ER TG-M	7.25 MG 58.08 MG 20.4 MG 1%	Permeation enhancer, solubiliser
Super Refined Isostearic Acid	Isostearic acid	Fatty acids	JPE	TS	None listed	Permeation enhancer**, plasticiser, solubiliser
Super Refined Hexyl Laurate	Hexyl laurate	Emollient esters	JPE	TS	None listed	Solubiliser
Span™ 80 HP	Sorbitan Monooleate	Sorbitan esters	NF, Ph. Eur.	TS	2.33 MG	Permeation enhancer, solubiliser
Span 20 HP	Sorbitan Monolaurate	Sorbitan esters	NF, Ph. Eur., JPE, ChP, *DMF	TS	None listed	Permeation enhancer, solubiliser

***Ref:** i) Lakshi et al. Int. Res. J. Pharm, 8(9), 9-17, (2017); ii) Dinda SC & Ratna JV. Indian J Pharm Sci, 68(3), 313-316, (2006); iii) Cizinauskas V. Molecules, 22, 1536, (2017).
****Ref:** US patent Application (#20050020552).
TG- Transdermal, Gel; TS- Transdermal, System, TF-ER- Transdermal Film, Extended release; TG-M- Transdermal gel, metered

Drug substance solubility platform



Solubility platform experimental drug substance in excipient



Example actives tested

- Anti-bacterials
- Anti-cancer
- Anti-fungals
- Anti-virals
- Cannabinoids
- Decongestants
- Hormones
- Pain relief
- Vitamins

Typical excipients tested

- PEGs
- Polar liquids (Super Refined™ DMI, Super Refined™ DEGEE, Super Refined™ Propylene Glycol)
- Oils
  - Esters
  - Long chain triglycerides
  - Fatty alcohols and acids
- Surfactants
  - Water soluble
  - Oil soluble

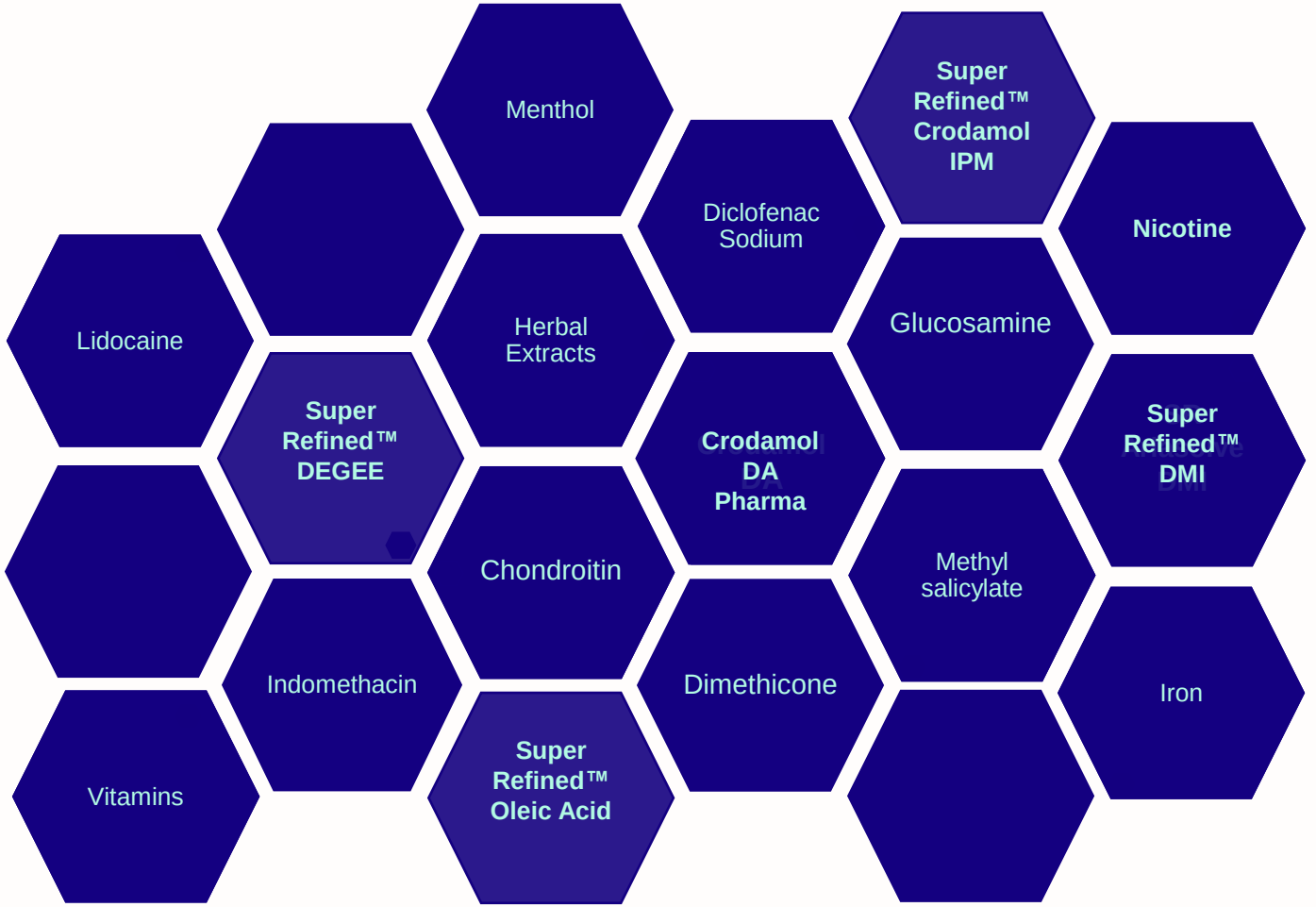
Solubility platform - example of experimental HSP

Acetaminophen solubility prediction

- Example fully theoretical HSP, HSP with improved excipient parameters with experimental data and fully experimental maximum solubility data

Solubility ranking	Fully theoretical HSP	Experimental HSP for theoretical solubility prediction	Experimental maximum solubility
1	Super Refined™ PEG 300	Super Refined PEG 400	Super Refined PEG 400 (219.2 mg/g)
2	Super Refined Propylene Glycol	Super Refined CCMG 400	Super Refined PEG 300 (172.6 mg/g)
3	Super Refined GTCC	Super Refined PEG 300	Super Refined Propylene Glycol (123.6 mg/g)
4	Super Refined P35 Castor Oil	Super Refined Propylene Glycol	Super Refined CCMG 400 (105.0 mg/g)

Solubility platform

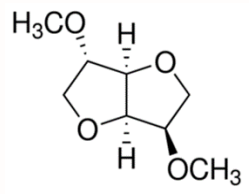


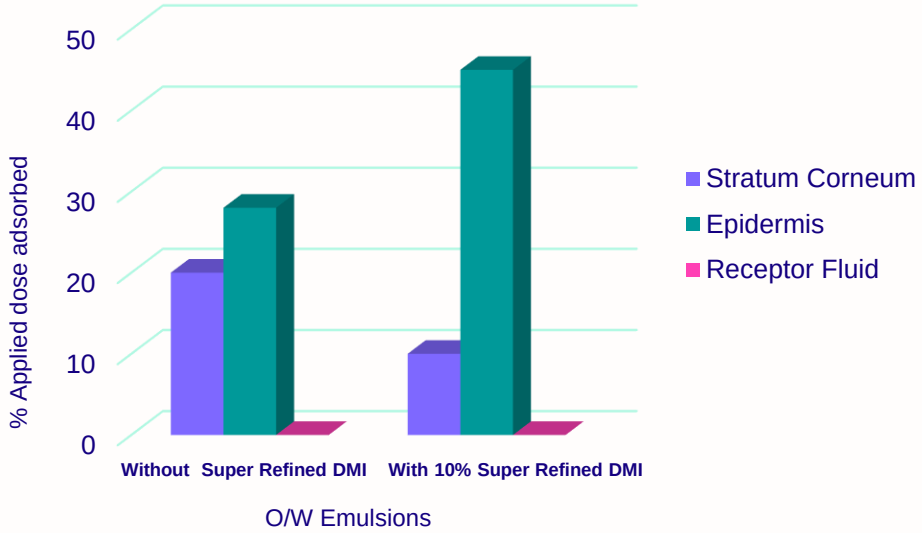
Super Refined™ DMI

HIGHLY PURIFIED DIMETHYL ISOSORBIDE

Features

- Solvent for poorly soluble hydrophilic and hydrophobic actives
- Enhances formulation and API stability
- Epidermal permeation enhancer
- Improves spreading of viscous materials
- Reduced cellular irritation





Topical delivery efficacy of a hydrophilic active in two O/W formulations, one with and one without Super Refined DMI.

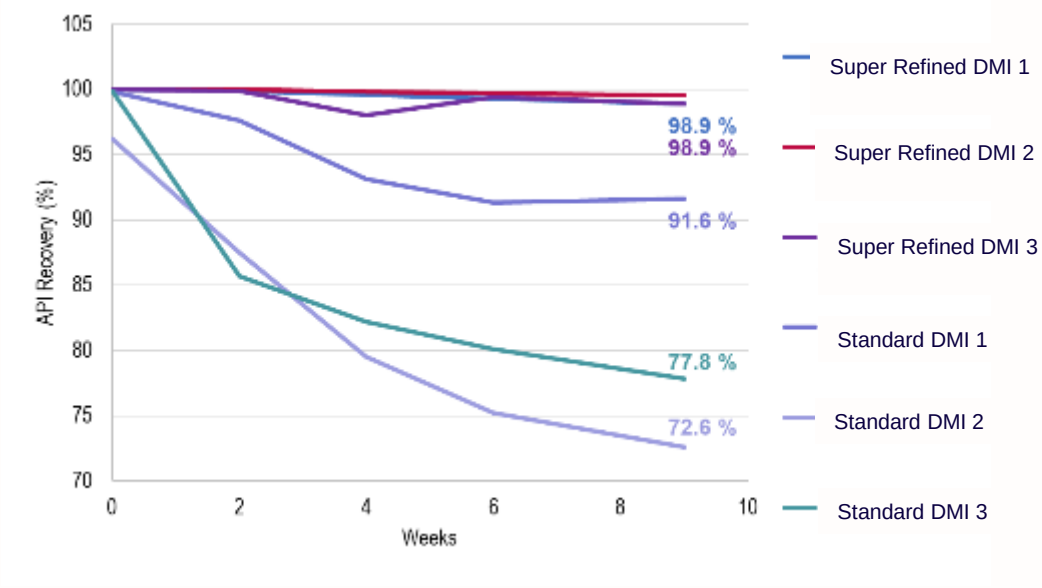
Expanding your permeation options with Super Refined DMI, supporting data:

Penetrating solvent: Addition of just 10% Super Refined™ DMI to a formulation can result in a 15% increase in the amount of active delivered into the epidermis, and almost a 50% increase in active permeation into the stratum corneum.

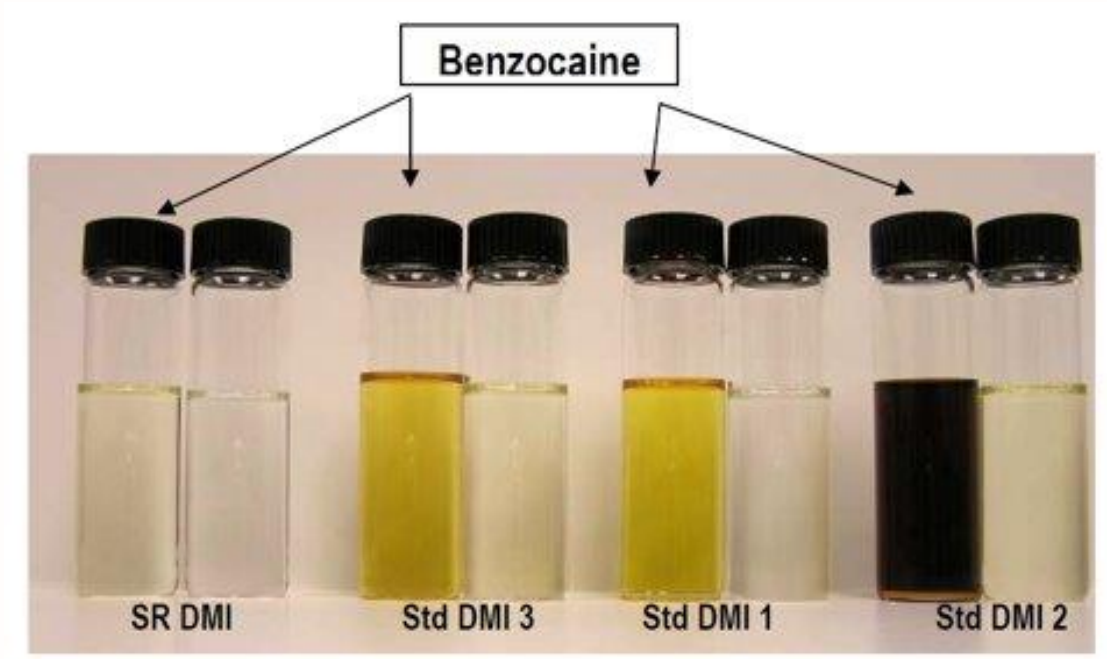
Super Refined™ DMI

API stability

- 1% w/w benzocaine in Super Refined DMI vs standard grade DMI
- Samples incubated at 50ºC for 9 weeks
- Samples dissolved in acetonitrile for analysis
- Detection method: HPLC at 0, 2, 4, 6, 9 weeks



API recovery (%) Super Refined™ DMI vs standard DMI; 1% Benzocaine at 9 weeks 50°C



Super Refined DMI vs standard DMI samples;
1% Benzocaine at 9 weeks 50°C

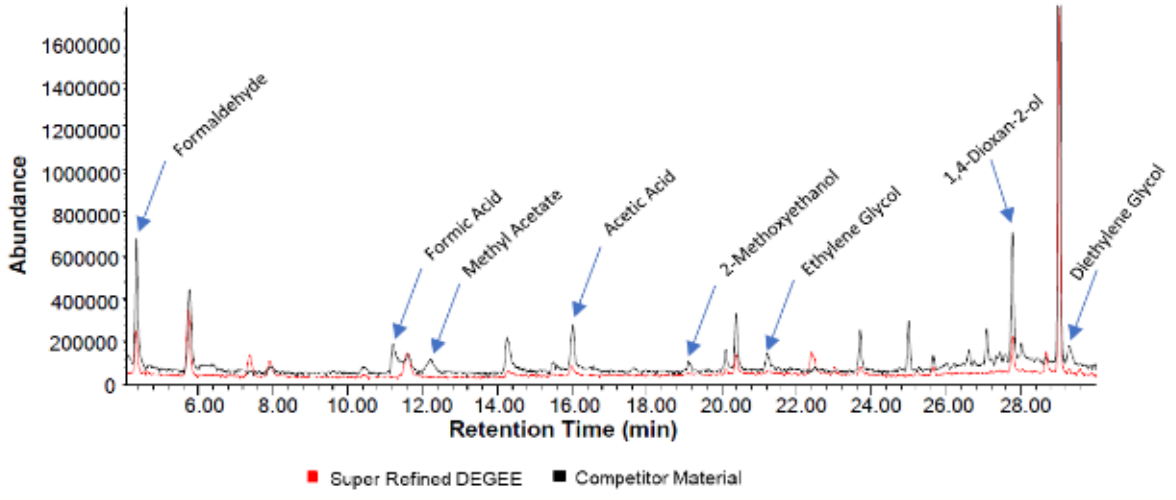
Super Refined™ DEGEE

HIGH PURITY DIETHYLENE GLYCOL MONOETHYL ETHER

Features

- Permeation enhancer
- Excellent solubilising properties, ideal for solubilising poorly water soluble APIs
- FDA IID Listed for topical and transdermal applications
- Multi-compendial
- Reduced impurity profile
- Potential to reduce odour impact
- Improved API and formulation stability

Reduced impurity profile



- HS-GCMS was used to qualitatively analyse the volatile impurity profiles of **Super Refined DEGEE** and a standard compendial competitor material

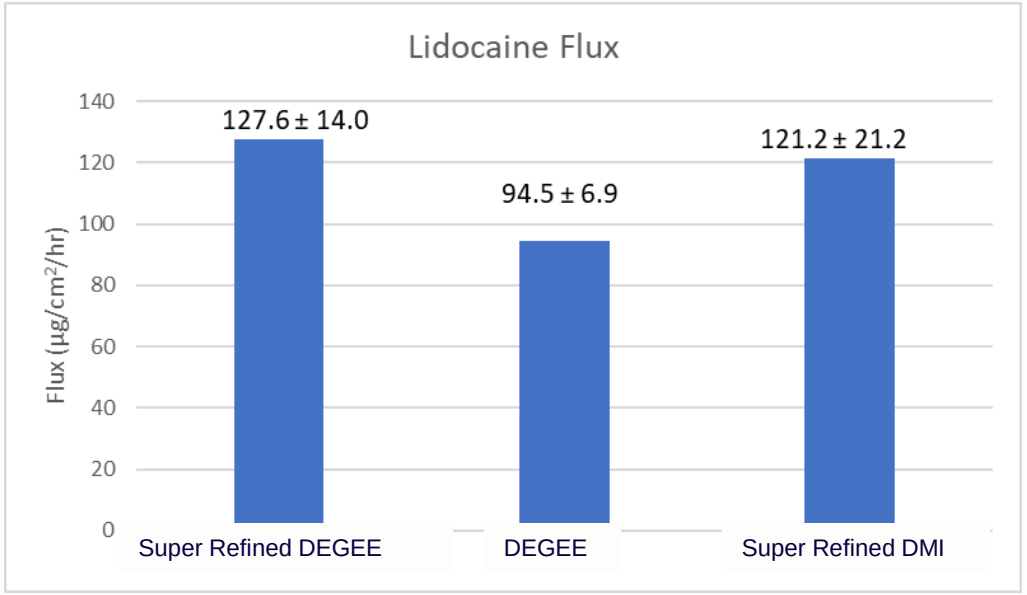
- Impurity peaks were identified by matching retention times and mass spectra of the identified peaks to standards and those referenced in the NIST Research Library

Super Refined™ DEGEE

Expanding your permeation options with Super Refined DEGEE supporting data:

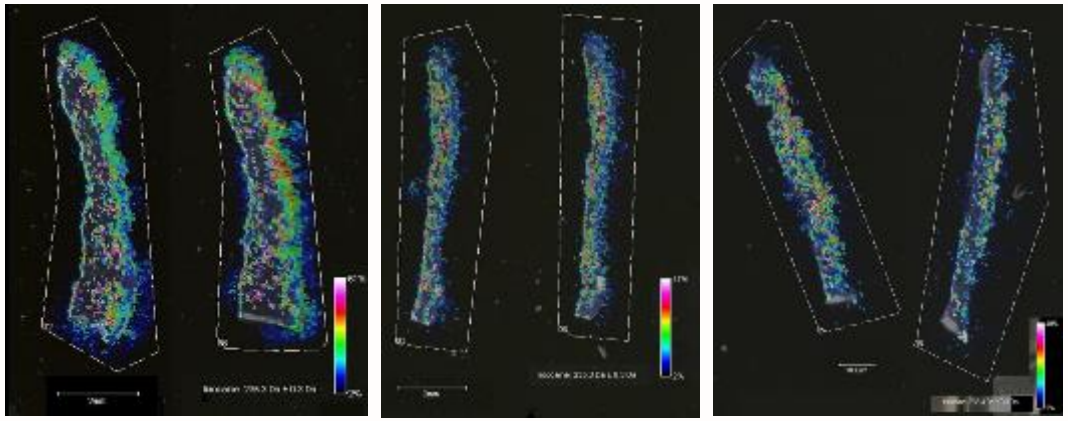
Permeation enhancer effect: Lidocaine

- 0.8% solution of Lidocaine prepared in 15% Super Refined DEGEE, DEGEE and Super Refined DMI respectively, in water
- Skin permeation study using human cadaver skin
- Detection method: HPLC at 1-8h and 24h



Flux of Lidocaine in each permeation enhancer tested

MALDI MS imaging results



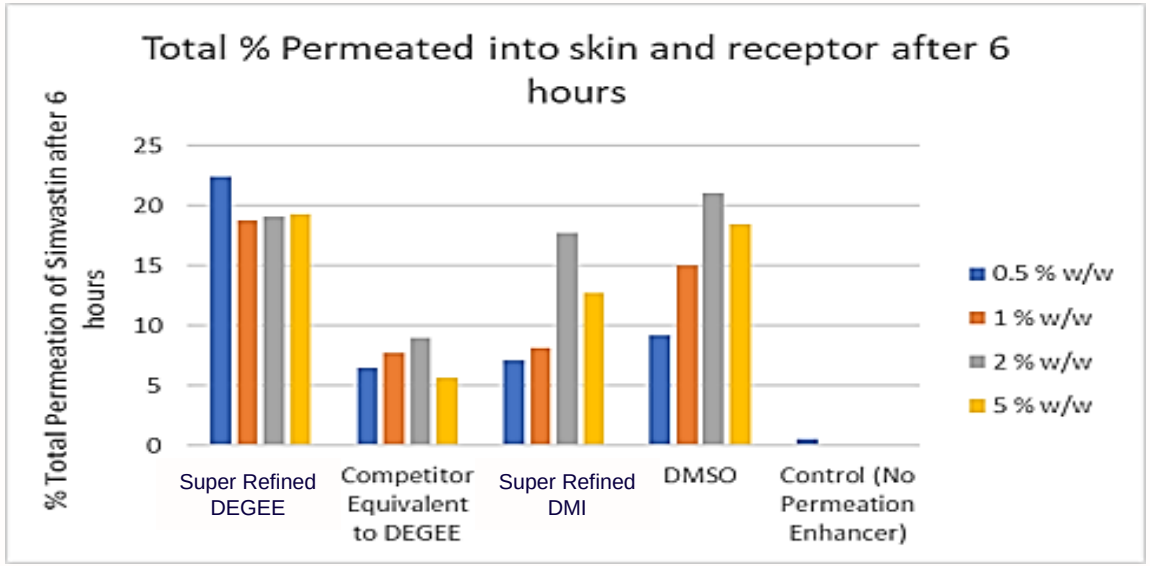
Super Refined DEGEE having stronger signal in the upper layers of the skin

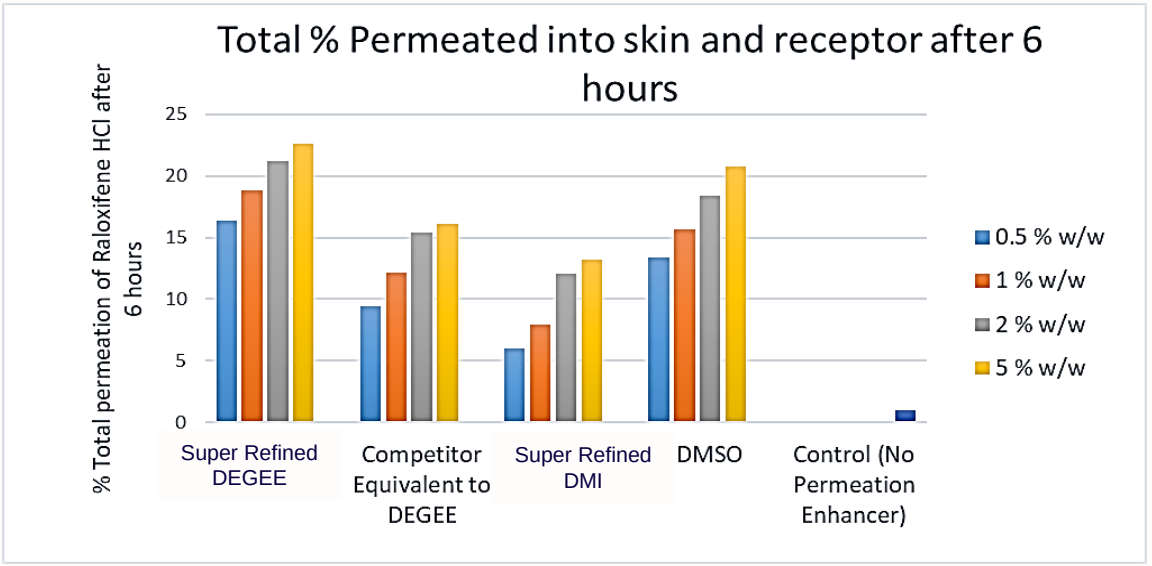
MALDI MS image of lidocaine in two sections obtained from
A: Super Refined™ DEGEE; **B**: DEGEE and
C:Super Refined™ DMI treated skin samples

Super Refined™ DEGEE

Permeation enhancer effect - simvastatin and raloxifene HCl (1% active gel)

- 1% Simvastatin and Raloxifene HCl gels containing Super Refined DEGEE, Super Refined DMI, competitor equivalent to Super Refined™ DEGEE and DMSO as permeation enhancers
- Concentrations tested: 0.5, 1, 2 and 5% w/w
- *Ex vivo* skin permeation using pig skin as barrier medium
- Detection method: HPLC





Super Refined DEGEE outperforms DMSO in terms of **Simvastatin and Raloxifene HCl** permeated into and through the skin. Super Refined DEGEE and Super Refined DMI are both less damaging to the skin.

Super Refined™ PEG 400

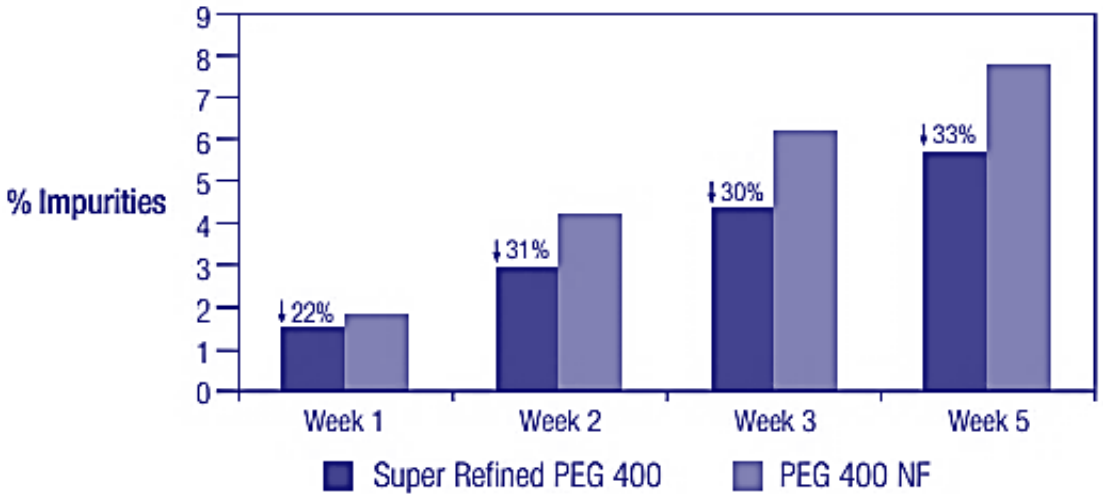
HIGHLY PURIFIED POLYETHYLENE GLYCOL 400

Features

- Multi-compendial
- Odourless, colourless viscous liquid
- Extremely low impurity profile
- Increases active stability
- Low peroxide value and low residual EO
- Effective when formulating with highly sensitive and unstable

API stability

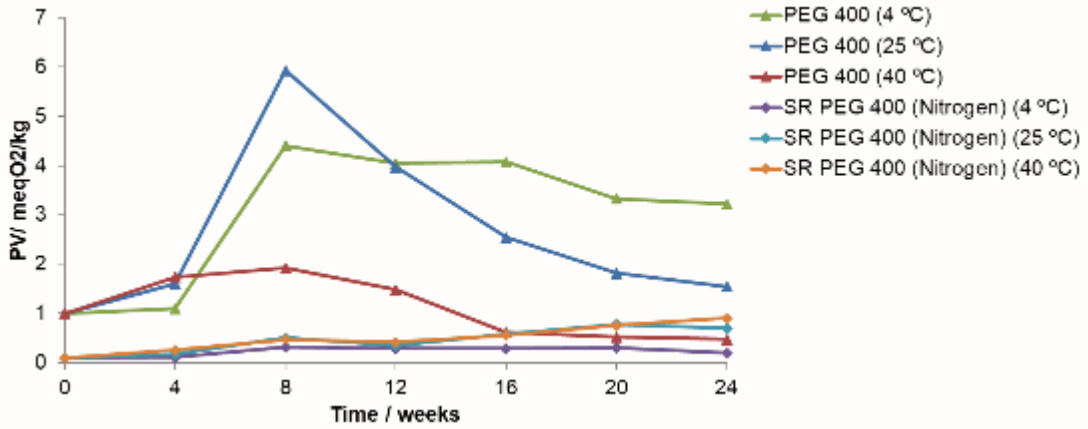
- Indomethacin was dissolved in standard pharmaceutical grade PEG and Super Refined PEG 400
- The samples were then subjected to accelerated stability conditions and analysed by high performance liquid chromatography (HPLC) to determine the amount of degradation of the active

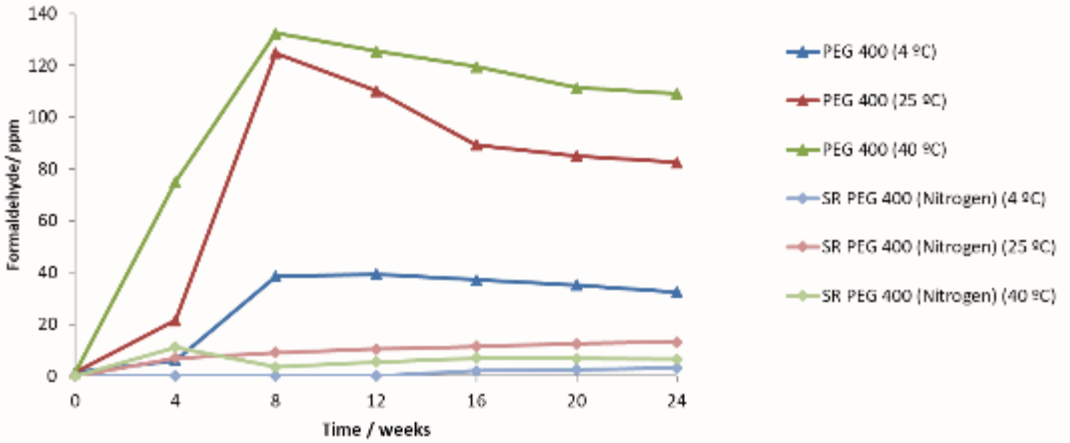


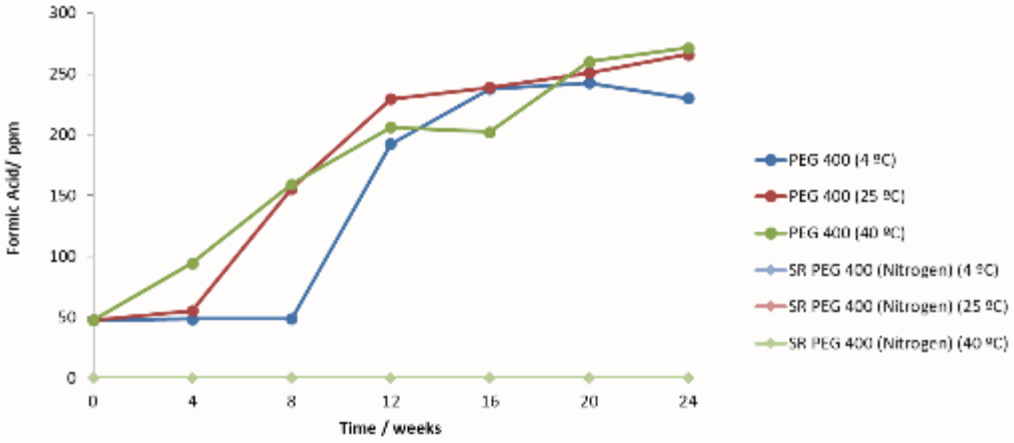
Super Refined PEG 400 consistently yielded a lower percent of impurities over the length of 4-week study. By week 4, the impurity profile of Super Refined PEG 400 was 33% less than the indomethacin dissolved in standard compendial PEG 400 NF.

Super Refined™ PEG 400

Excipient stability: peroxide value







- Low peroxide value in Super Refined PEG 400 for a 24-week study duration as compared to standard PEG 400
- High peroxides results in formaldehyde formation as evident in standard PEG 400. Significant increase as compared to Super Refined PEG 400
- Formaldehyde eventually becomes formic acid. Significantly higher levels in standard PEG 400 but barely detectable in Super Refined PEG 400

Crodamol™ DA Pharma

DIISOPROPYL ADIPATE

Features

- Provides excellent skin spreadability with no stickiness or tackiness
- Enhanced API and formulation stability
- Provides moisturising effect and improves skin texture

Stability

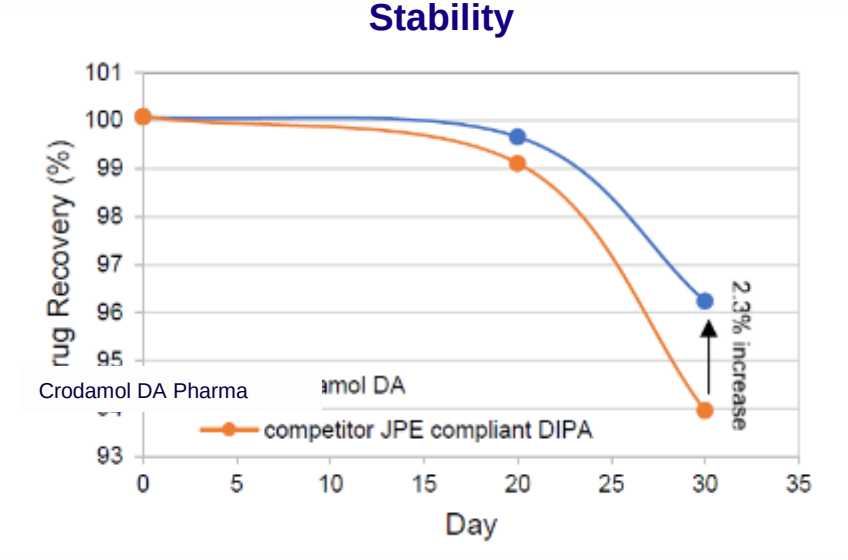


Figure 1: recovery of lidocaine in Crodamol DA Pharma compared to standard compendial grade of diisopropyl adipate over 30 days at 60°C

Hydrolytic stability

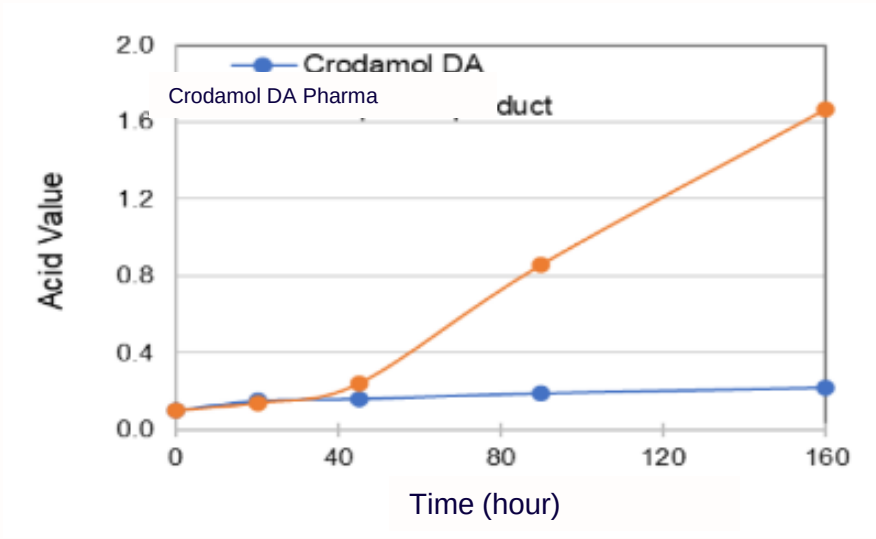
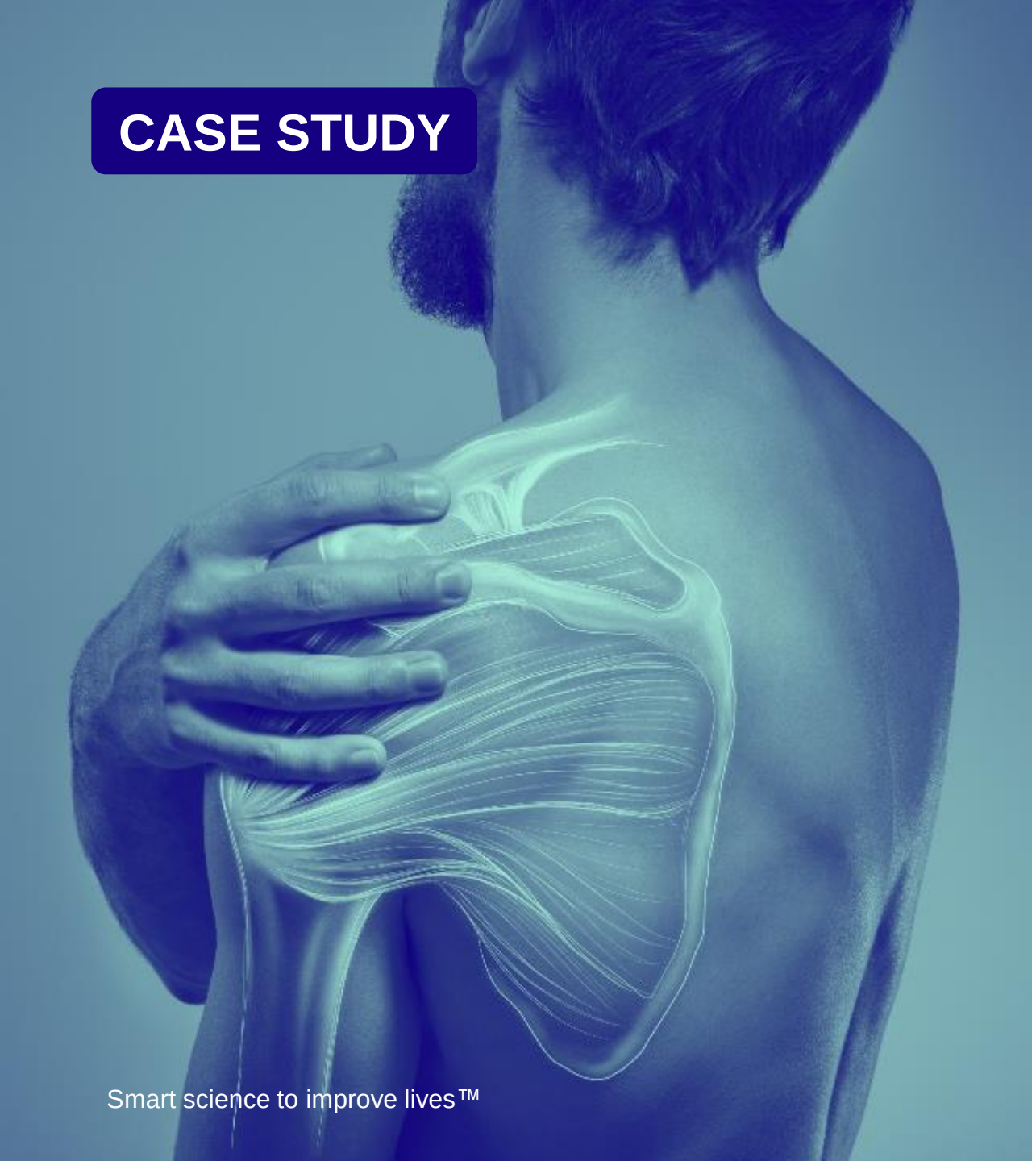


Figure 2: acid value of Crodamol DA Pharma and JPE compendial competitive product at 105°C for 160 hours

Claims for products

We aim to help our customers **formulate** medicines **with claims relevant to their customers**, **increasing** the **superiority of their product and brand**.



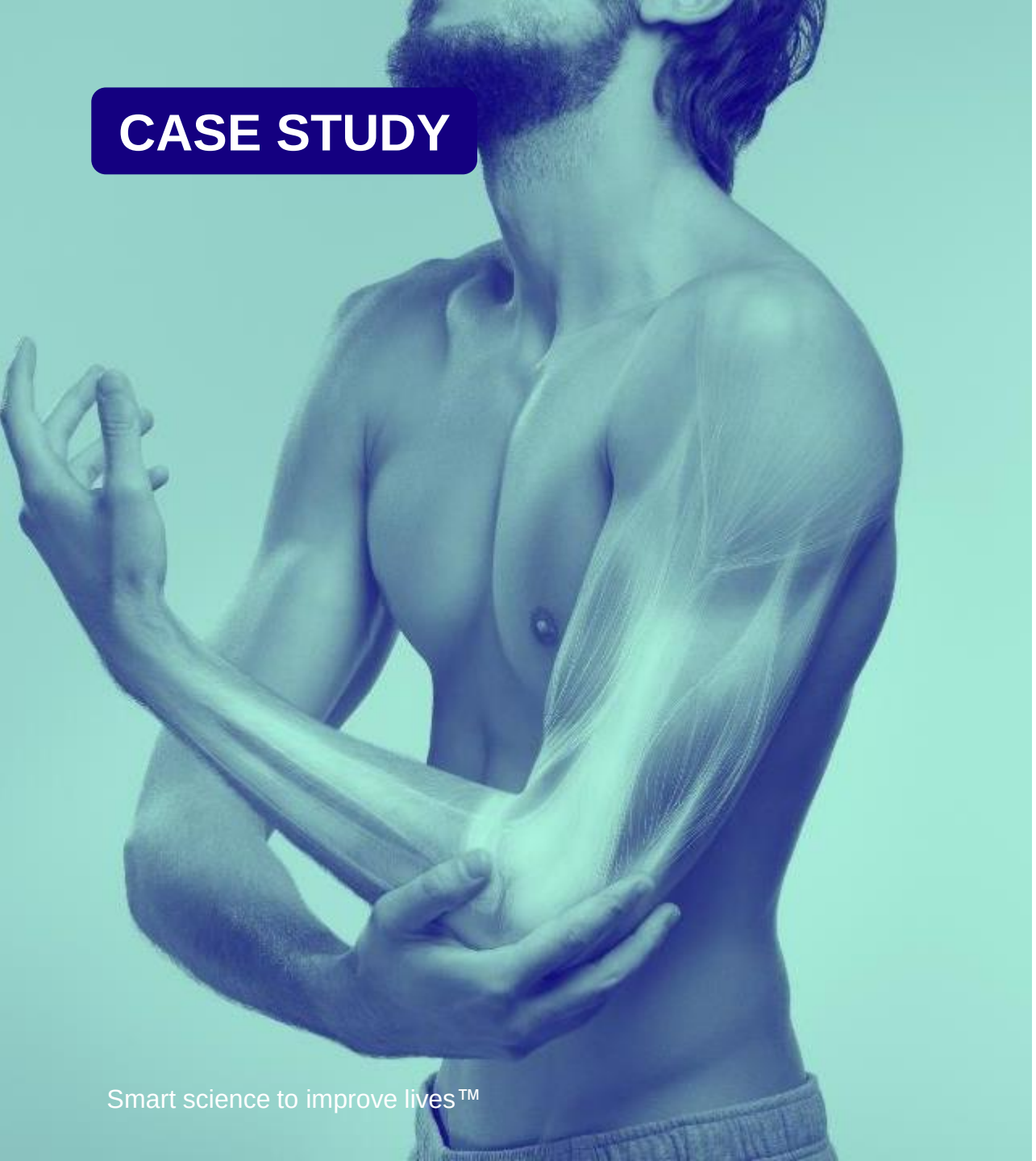
CASE STUDY

Muscle pain and tendinopathy

“I want fast acting, long lasting pain relief which I barely notice wearing”

Technical barriers

- Several excipients in combination required to achieve high drug solubility for long lasting effect
- Drug prone to oxidation in excipients
- Some key solubilising excipients have a strong unpleasant odour



CASE STUDY

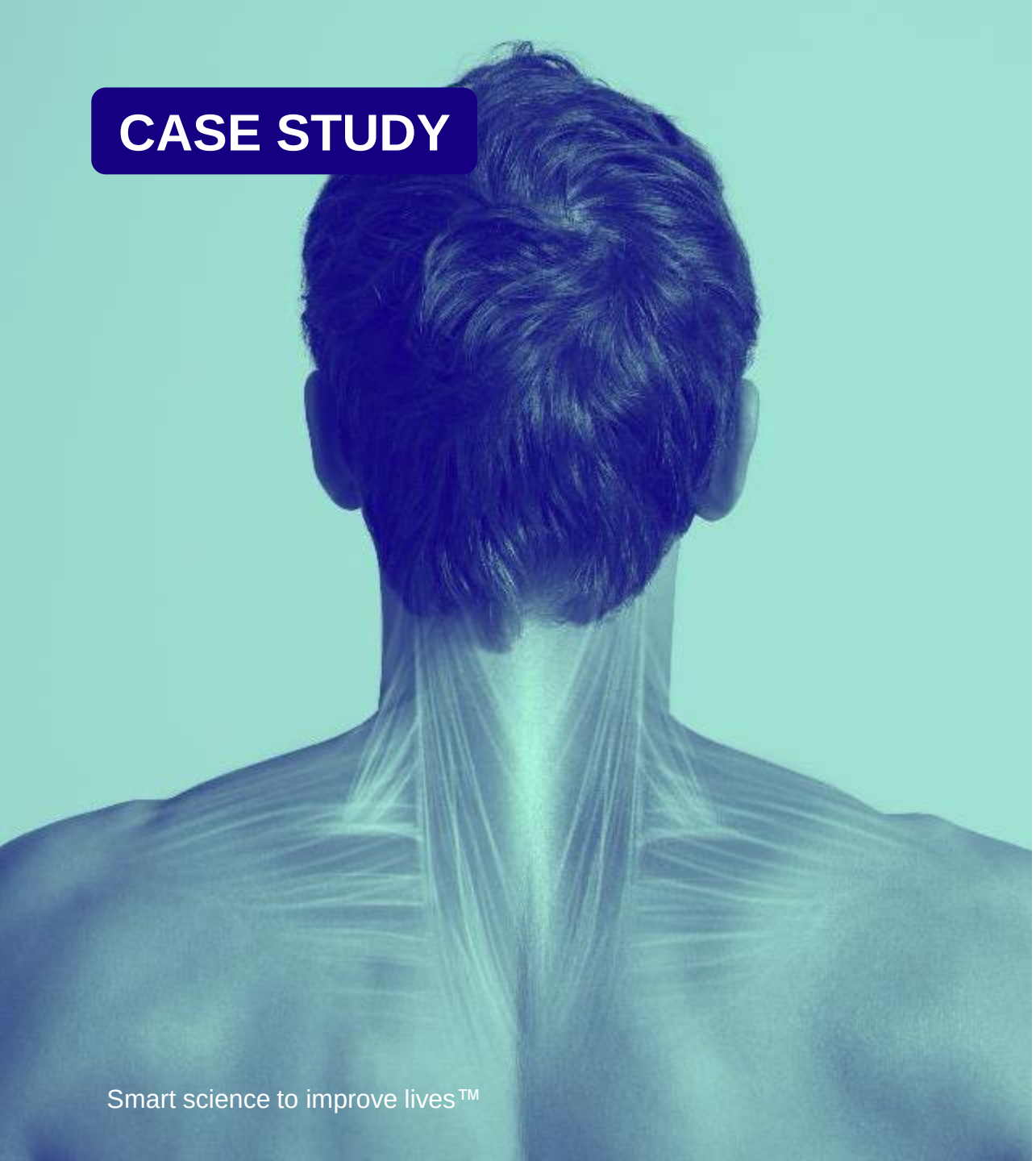
Smart science to improve lives™

Muscle pain and tendinopathy

Solutions

- **Super Refined™ PEG 400, Super Refined Castor Oil and Crodamol™ DA Pharma** offer the API solubility required when combined
- **Crodamol DA Pharma** is low in odour compared to competitor diisopropyl adipate
- **Super Refined Polysorbate 80** helps compatibilise the formulation excipients
- Croda's **Super Refined** excipients and **Crodamol DA Pharma** have superior stability, protecting the formulation from drug degradation

CRODA



CASE STUDY

Smart science to improve lives™

Muscle pain and tendinopathy

Pack claims

1. Odourless
2. Fast acting pain relief
3. Less frequent application

Did you know that Croda offers a wide range of polar and non-polar excipients in our Super Refined™ range?

CRODA

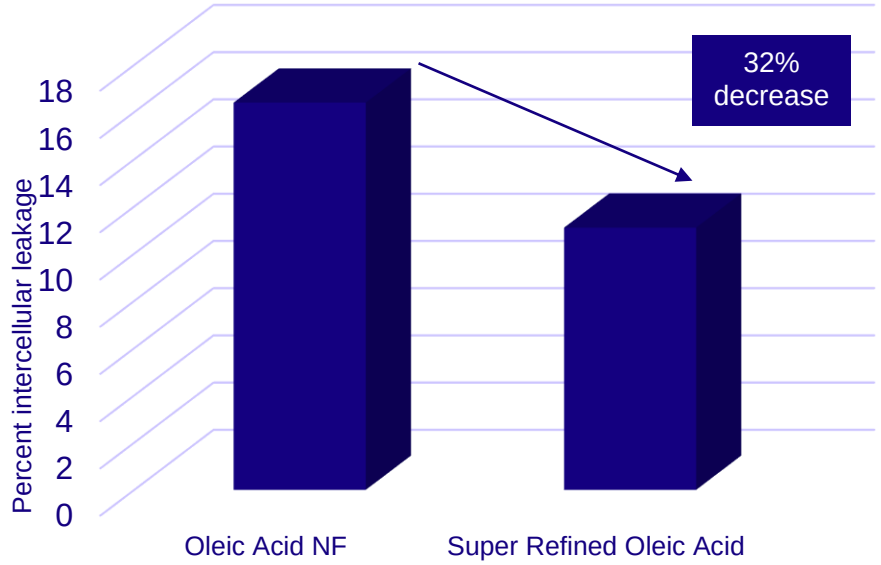
Super Refined™ Oleic Acid

HIGHLY PURIFIED OLEIC ACID

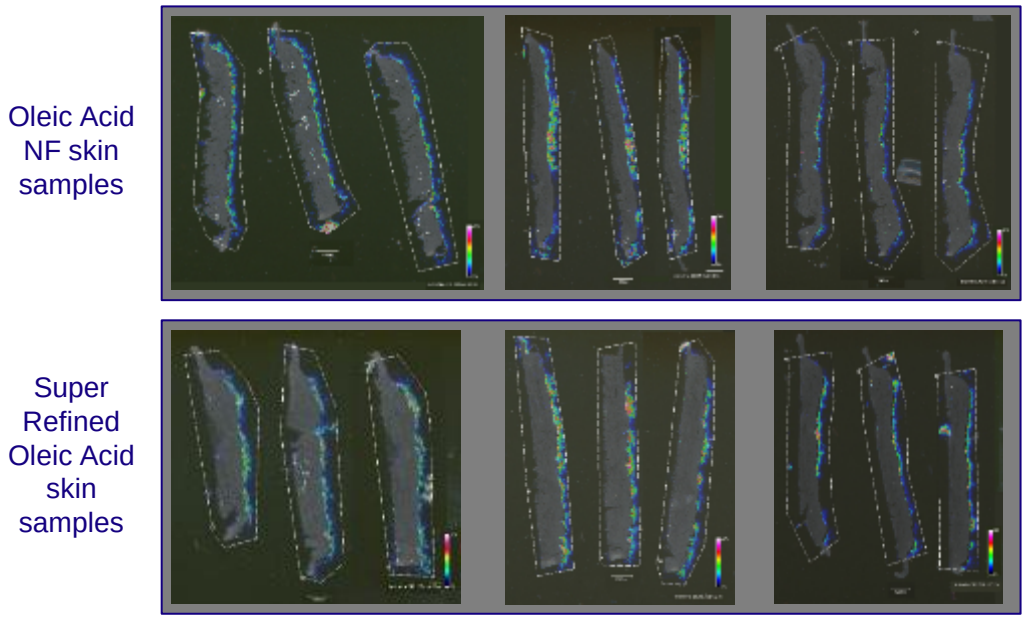
Features

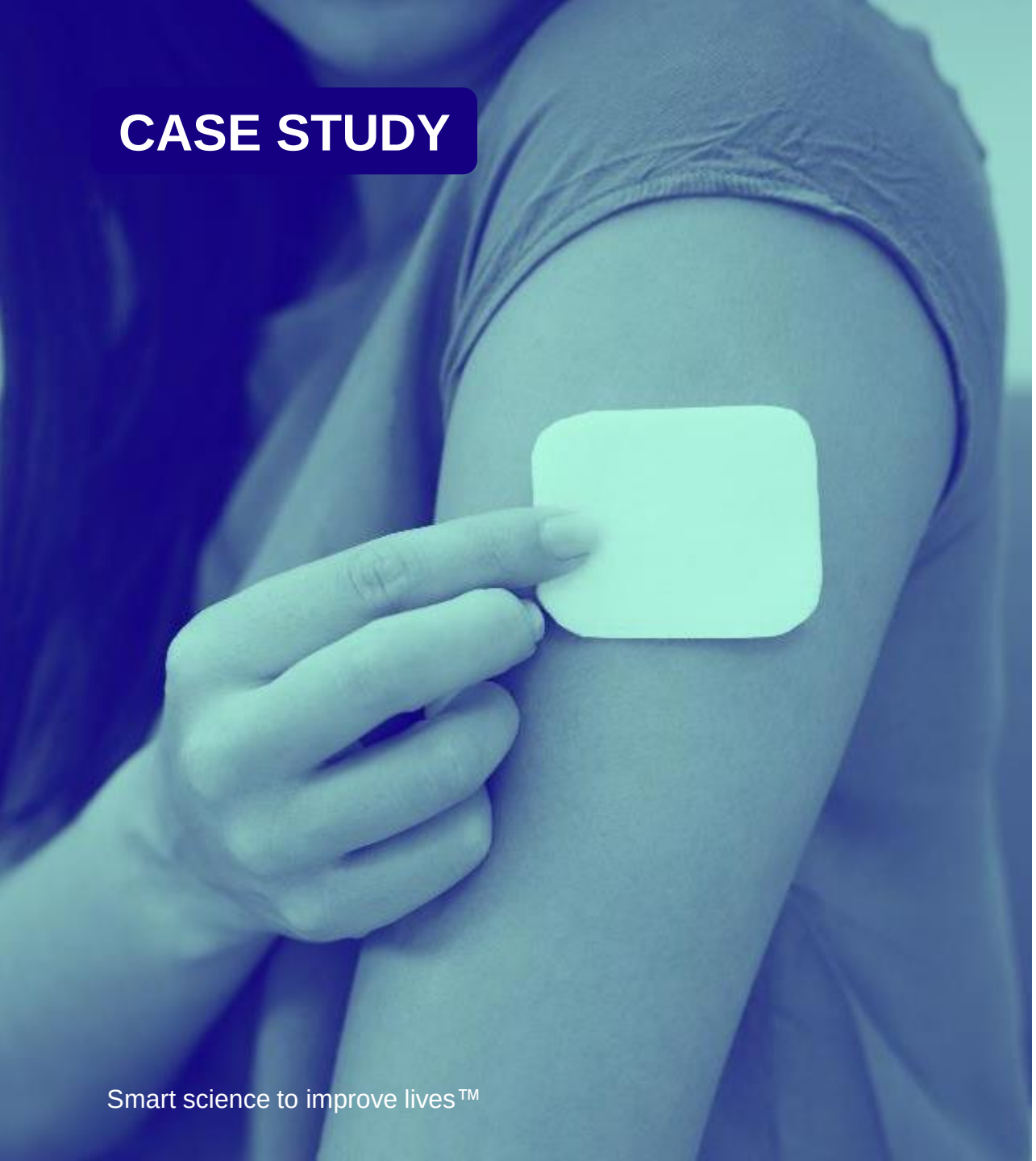
- Enhanced active and oxidative stability
- Reduced skin irritation
- Enhanced active membrane permeation

Reduced cellular irritation - TEP results



Permeation efficacy - MALDI images





CASE STUDY

Anti-inflammatory - local administration patch

“The customer wants a patch that stays in place”

Technical barriers

- Difficult to achieve balance of adhesive efficacy and sufficient API solubility
- Difficult to solubilise required dose
- permeation enhancer required to get active past the stratum corneum
- API prone to oxidation

Anti-inflammatory - local administration patch

Solutions

- **Super Refined™ Hexyl Laurate** compatibilises the oil based solvents and permeation enhancers with the adhesives and structural excipients
- **Super Refined Oleic Acid** offers API solubility and the required permeation enhancement
- **Super Refined Oleic Acid** prevents API degradation

CASE STUDY

Smart science to improve lives™

Anti-inflammatory - local administration patch

Pack claims

1. Sticks and stays in place
2. Fast acting pain relief
3. Less frequent application

Did you know that Super Refined™ Oleic Acid has been shown to be more “skin friendly” than standard oleic acid?

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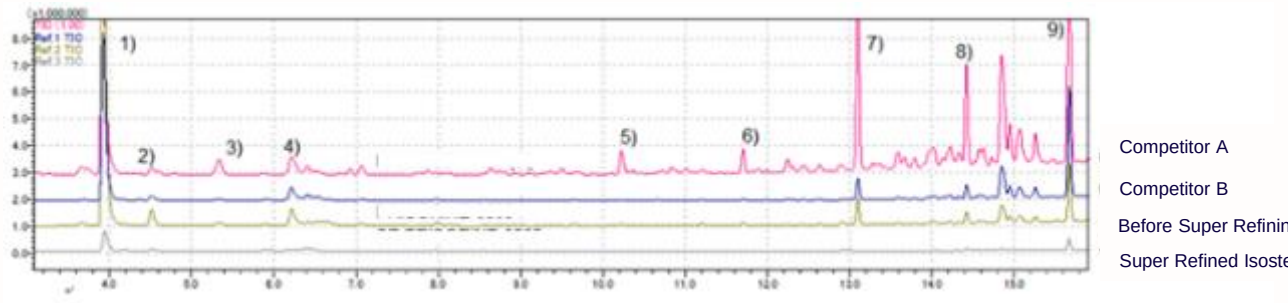
Super Refined™ Isostearic Acid

- Low viscosity
- Good extensibility, light texture
- Minimised skin irritation
- Enhanced API and formulation stability
- JPE compliance
- FDA IID Listed



1) Methyl Alcohol 2) Ethyl alcohol 3) Decane 4) Propyl alcohol 5) Tridecane
6) Tetradecane 7) Pentadecane 8) Hexadecane 9) Heptadecane

	Detected impurities		Competitor A	Competitor B	Before Super Refining	Super Refined Isostearic Acid
1	Methyl alcohol	lower alcohol	100	70	129	9
2	Ethyl alcohol	lower alcohol	100	97	250	36
3	Decane	hydrocarbon	100	9	21	0
4	Propyl alcohol	lower alcohol	100	92	101	4
5	Tridecane	hydrocarbon	100	2	5	0
6	Tetradecane	hydrocarbon	100	4	9	0
7	Pentadecane	hydrocarbon	100	11	11	0
8	Hexadecane	hydrocarbon	100	6	4	0
9	Heptadecane	hydrocarbon	100	38	17	3

CASE STUDY

Anti-inflammatory - local administration patch

“I want to put the patch where I need it, not just where it will stay on.”

Technical barriers

- Patch flexibility is poor due to required excipients to solubilise sufficient API

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CASE STUDY

Anti-inflammatory - local administration patch

Solutions

- Moving from standard Isostearic Acid to Super Refined™ Isostearic Acid significantly increased patch flexibility

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CASE STUDY

Anti-inflammatory - local administration patch

Pack claims

1. Sticks on joints - flexible effective patch

Did you know Super Refined™ Isostearic Acid can be used as an even more oxidatively stable alternative to Super Refined™ Oleic Acid?

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Super Refined™ IPM

ISOPROPYL MYRISTATE

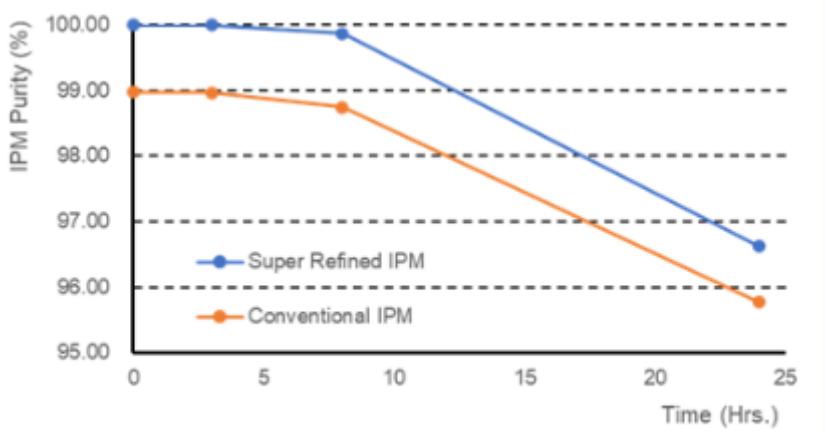


Figure 1: Hydrolysis stability

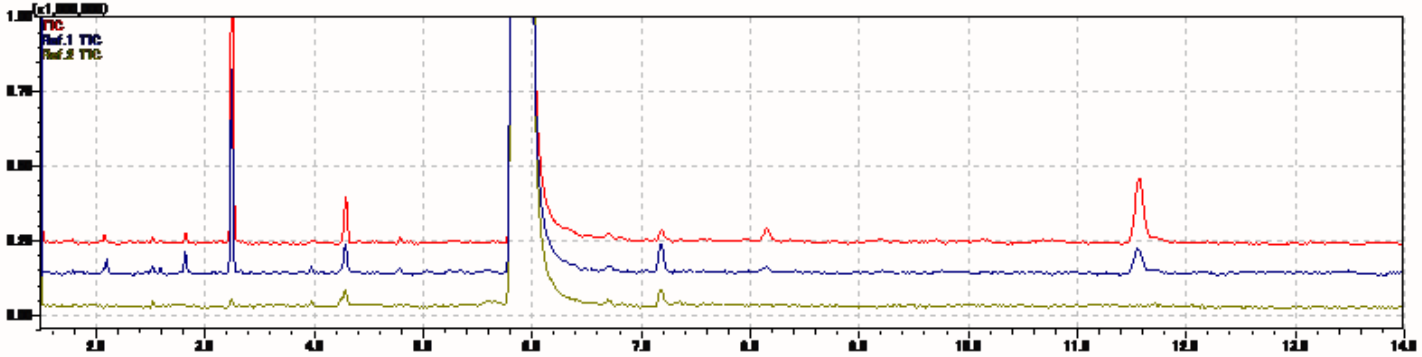


Figure 2: GC Chromatograms of Super Refined IPM
(a) Super Refined™ IPM, (b) competitor's JPE grades, (c) competitor's JPE grades

Very stable ester

Super Refined IPM has high purity compared with conventional grade of IPM. To demonstrate hydrolysis stability, 1 wt % H_2O was added in IPM and the samples were heated under 120℃, air bubbling (5 L/min.), using GC analysis to determine the IPM purity, and the test was conducted at multiple time points.

Low impurities

Super Refined IPM exhibited significantly less impurities compared to the competitor grades. Super Refining process significantly reduced the amount of isopropyl laurate (peak number 2), among other impurities.

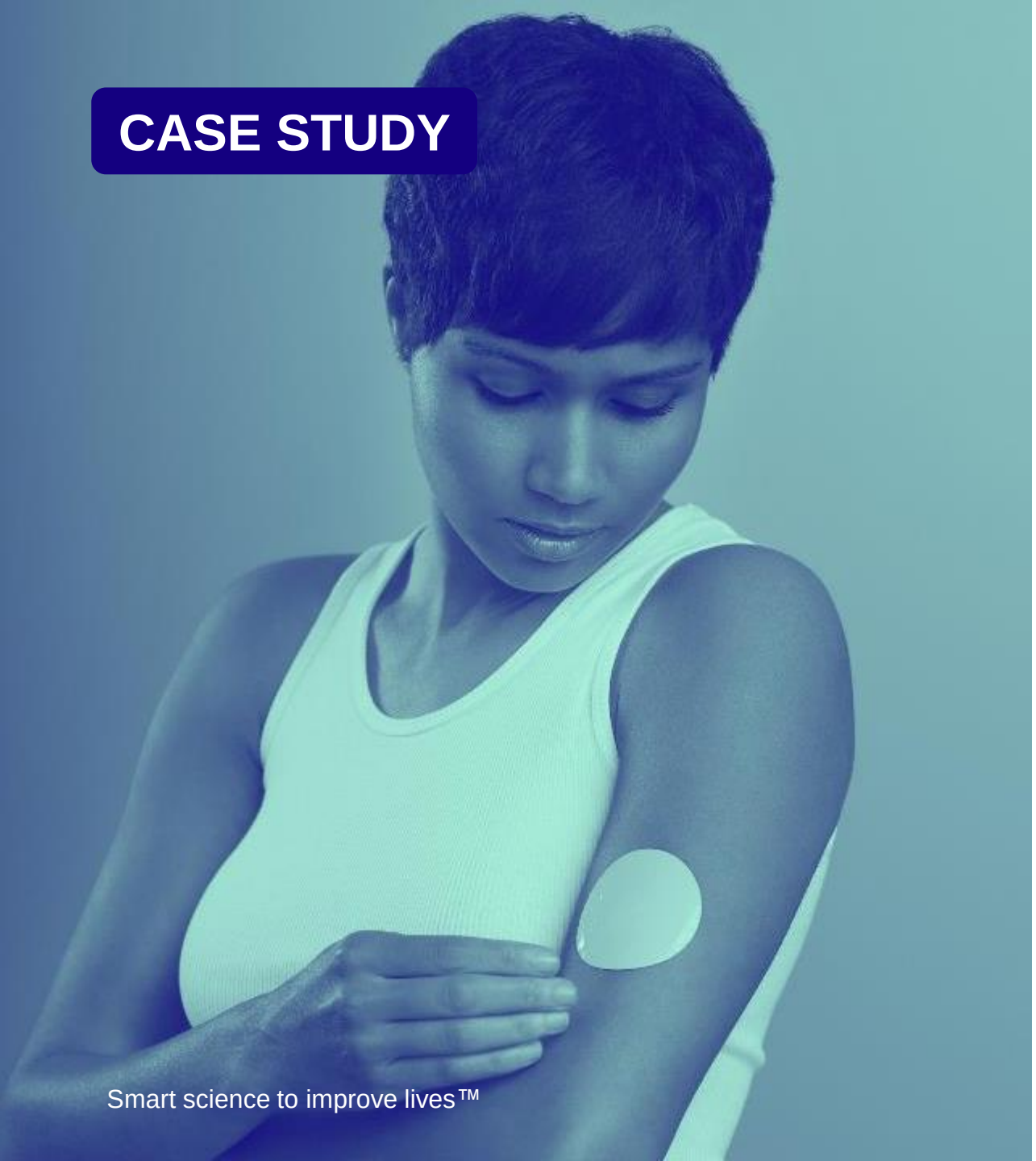
CASE STUDY

Antipsychotic - system administration patch

“We need long lasting persistent effects from each application”

Technical barriers

- Long term effectiveness of each patch is API solubility limited
- Need solubility enhancers with good patch excipient compatibility



Antipsychotic - system administration patch

Solutions

- Combination of Super Refined™ Sesame Oil and Super Refined IPM maximise API solubility
- Combination does not interfere with patch excipients and materials

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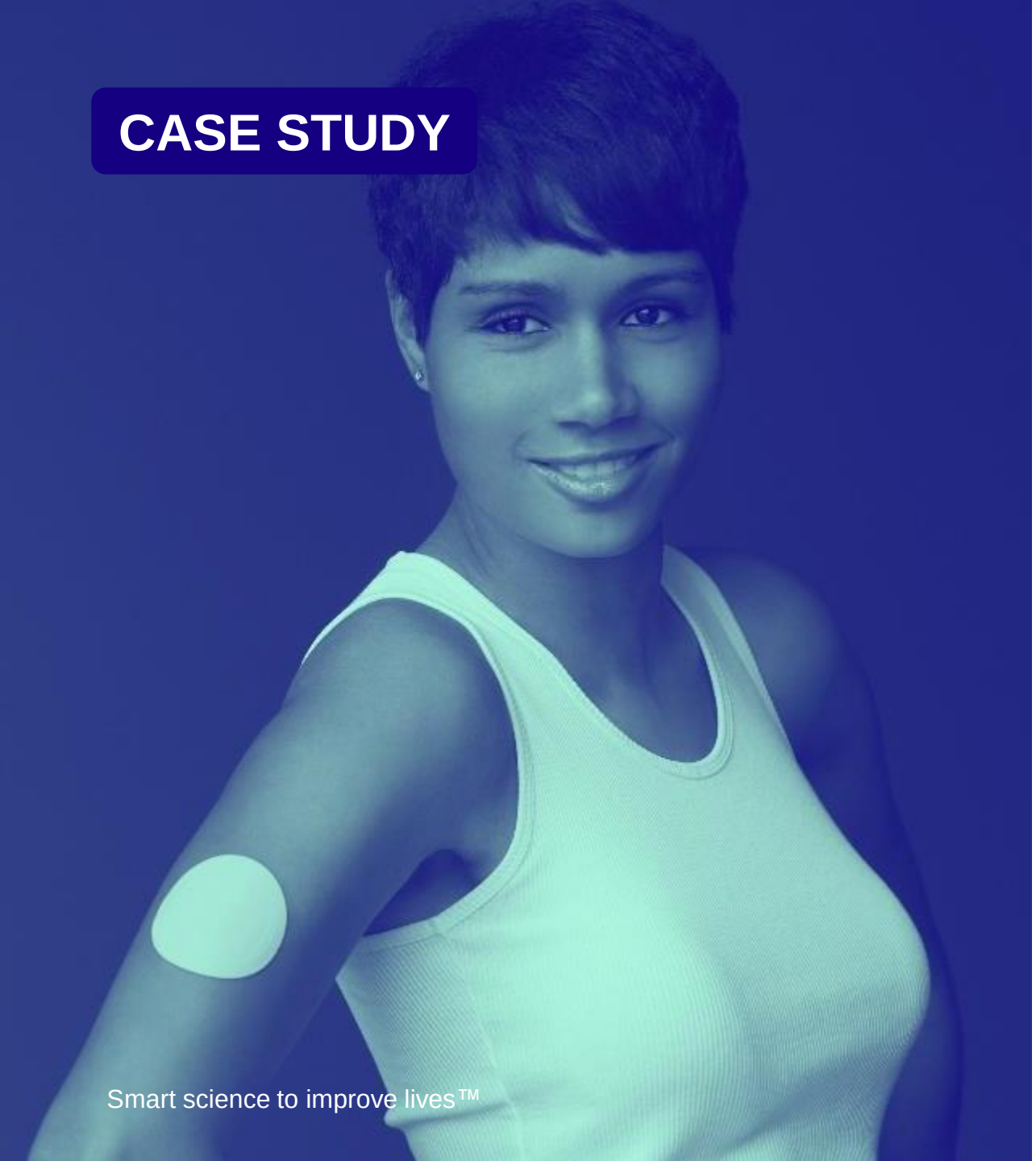


Antipsychotic - system administration patch

Pack claims

1. Long lasting application

Did you know that Croda offer a wide range of Super Refined™ vegetable oils and ester oils?

CRODA

Why work with us?

Create **tailored excipient solutions** directly in partnership with our scientists.

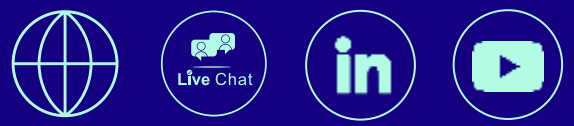
Tackle your stability challenges with **unparalleled purity excipients** across all administration routes.

Formulate and **troubleshoot faster** by working with our scientific experts during your development.

Prioritise **sustainability** and **integrity** by choosing Croda.

Croda Pharma

Thank you!



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