GATTEFOSSÉ

Rectal Drug Delivery

With Lipid Excipients

Oral | Topical | **Rectal** | Vaginal | Parenteral

People make our name

ABOUT GATTEFOSSÉ

Gattefossé is a leading provider of excipients and formulation solutions to healthcare industries worldwide. Our company history - of over 140 years - is built on a commitment to our customers to deliver the highest quality products and technical support. In parallel to developing innovative formulation applications, Gattefossé has worked diligently to guarantee the pharmaceutical qualification of its excipients.

GATTEFOSSÉ EXCIPIENTS

The lipids and fatty acids used in the production of Gattefossé excipients are derived strictly from raw materials of vegetable origin.

Excipients are obtained by the esterification of fatty acids with alcohols - glycerol, polyglycerol, propylene glycol and polyethylene glycol - and by the alcoholysis of vegetable oils and fats with glycerol, polyethylene glycol and propylene glycol.

Expertise in oleo-chemistry has enabled the development of a range of functional excipients with different thermal, rheological and textural properties and a wide spectrum of solubility characteristics.

RECTAL DRUG DELIVERY

Lipid excipients can be used to formulate suppositories, creams, ointments and foams.

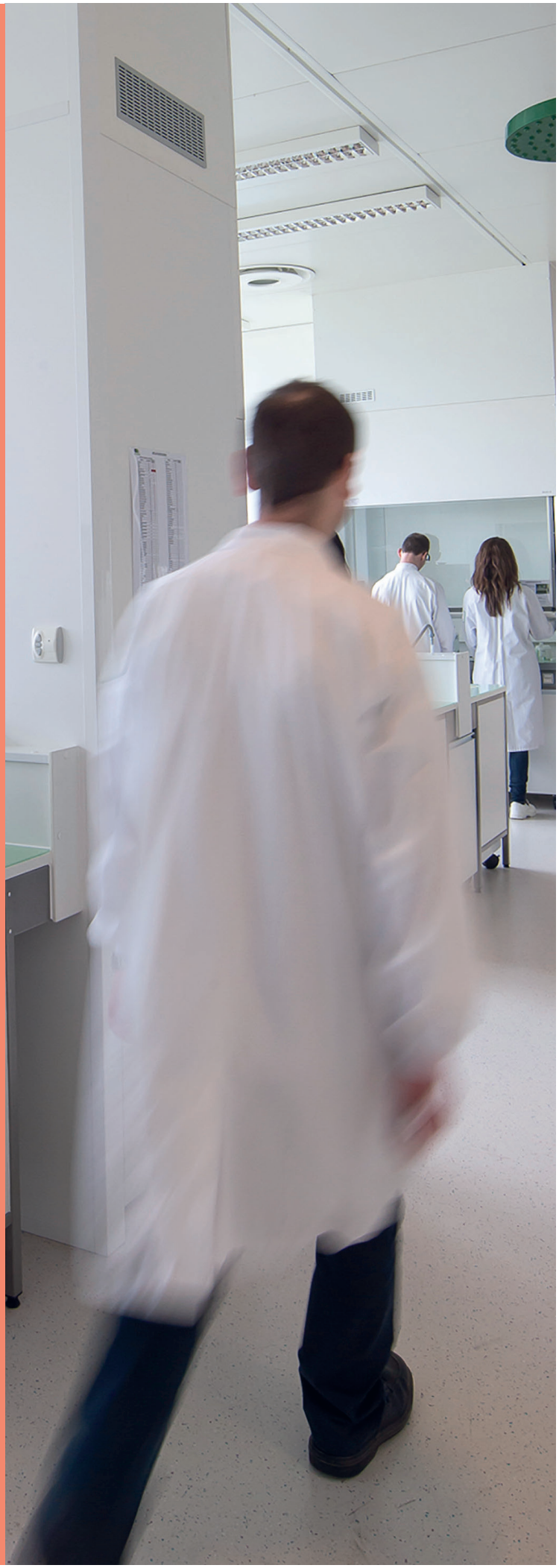
Suppocire® is our well-established brand of semi-synthetic hard fat bases comprising fatty acid esters. Their physicochemical properties have been optimized to provide excellent drug delivery for both solid and liquid active pharmaceutical ingredients (APIs), across a range of water solubility.

Gattefossé can help you identify the appropriate suppository base optimized for your API and manufacturing equipment. We also provide advice on formulating to obtain physicochemical stability and performance and solve manufacturing or quality issues.

Our excipients are extremely safe and many are used in internationally approved and marketed products.

ABBREVIATIONS

ANSM: Agence Nationale de la Santé et du Médicament (French Health Authority) **API:** Active Pharmaceutical Ingredient; **Ch.P.:** Chinese Pharmacopœia; **DMF:** Drug Master File (Type IV); **EP:** European Pharmacopœia; **FDA:** Food and Drug Administration; **IID:** USA FDA Inactive Ingredient Database; **IPEC:** International Pharmaceutical Excipient Council; **ISO:** International Organization for Standardization; **JP/JPE:** Japanese Pharmaceutical Excipients; **PEG:** Polyethylene Glycol; **USP-NF:** US Pharmacopœia-National Formulary.



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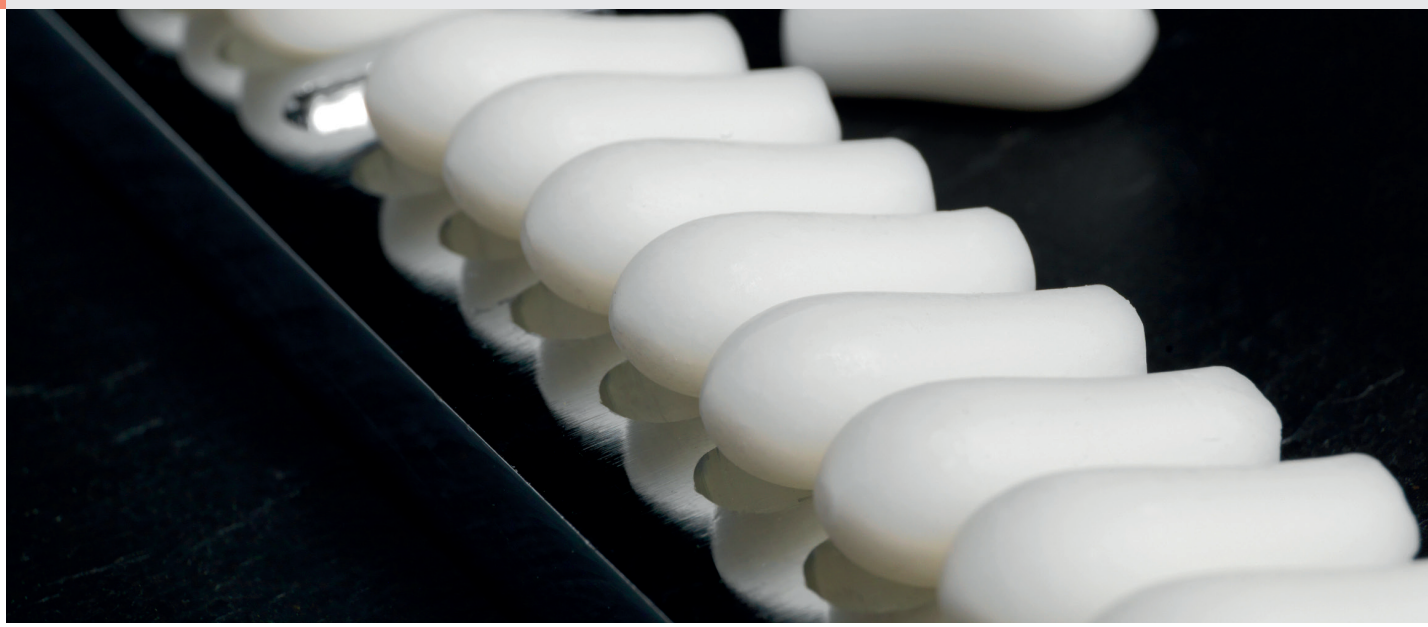
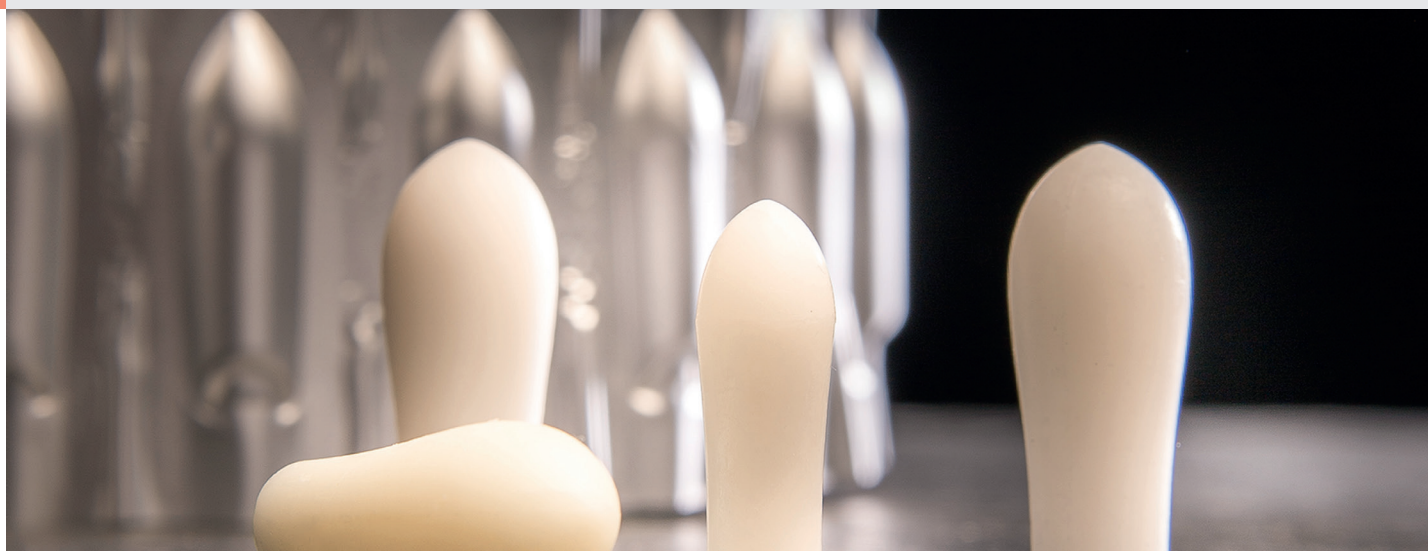


Introduction



Your reliable partner for suppository development

With 60 years of experience in the manufacturing of suppository bases, Gattefossé supplies customers with the highest quality excipients and technical support for formulation, scale-up and production.

We provide:

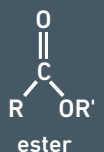
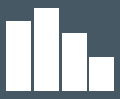
- A wide range of Suppocire® grades suitable for different API and manufacturing equipment
- Bases with consistent physicochemical characteristics and high batch-to-batch reproducibility
- An extensive formulation database
- Expertise in formulation, product performance testing, scale-up, industrial production and trouble-shooting

Our commitment to quality

+ **Suppocire® bases conform to relevant Pharmacopœia monographs (EP, USP-NF, JP/JPE, ChP.)**
+ **Manufacturing sites are certified ISO 9001/2008**
+ **Implementation of IPEC Good Manufacturing Practice Guidelines**
+ **Certification by French Healthcare Authority (ANSM)**
+ **Customer audit policy**

Understanding the nomenclature of the Suppocire® range

Each Suppocire® has a specific composition which determines the main physicochemical properties of the base – such as its melting range and hydroxyl value. These characteristics constitute part of the nomenclature of the Suppocire® range along with other features including the type of synthesis reaction and the presence of additives.

				-OH
Suppocire®	**Chemical reaction**	**Melting range**	**Specific composition**	**Hydroxyl value**
Gattefossé trademark for suppository bases See also our **Japocire®** range compliant to Japanese pharmacopœia See also our **Ovucire®** range of bases for vaginal pessaries.	**Type of esterification** **Prefix 'N'**: direct esterification between fatty acids and glycerol (-) no prefix: interesterification of hydrogenated palm oil and hydrogenated palm kernel oil	**Melting point or drop point** From low 32.5°C to high >40°C **AI < A < B < C < D**	**When composition includes an additive** **GP:** contains glyceryl monostearate and PEG stearate **P:** contains PEG esters **S/S2:** modified monoglyceride content **L:** contains lecithin **X:** contains emulsifier	**Indicates level of free hydroxyl group** **M** indicates a low hydroxyl value (<15) (-) no prefix indicates a standard value (>15)
Suppocire®	**N**	**AI**	**S**	**10**

Example of nomenclature

Suppocire® NAI 25 is made by direct esterification, it has a low melting point and a medium hydroxyl value of 20 - 30, it does not contain any additives.

Suppocire® AML is made by interesterification, it has a low melting point and a low hydroxyl value of ≤ 10, it contains lecithin as an additive.

The Suppocire® range

Suppocire® bases are semi-synthetic hard fat bases comprising fatty acid esters. Their physicochemical properties have been optimized to provide excellent drug delivery for both solid and liquid APIs, across a range of water solubility.

Advantages of Suppocire®

- **+ Proven safety and mucosal tolerance**
- **+ Excellent drug dispersion and physicochemical stability**
- **+ Narrow melting range for high performance *in vivo***
- **+ Solidification behavior adapted for a wide range of manufacturing equipment**
- **+ Conformity to internationally recognized pharmacopœias (EP, USP-NF, JP/JPE, ChP.)**

Selecting the base that delivers the best physicochemical stability, drug dispersion and release for a particular active ingredient is critical.
For advice on the selection of the right base and technical assistance please contact your local Gattefossé representative.

PRODUCT NAME	Melting point Capillary tube (°C)	Drop point Mettler (°C)	Hydroxyl value (mg KOH/g)
SUPPOCIRE® AIML	32.5-36.5	33.0-35.0	≤10
SUPPOCIRE® AML	34.0-38.0	35.0-36.5	≤10
SUPPOCIRE® BM	35.0-39.0	36.0-37.5	≤10
SUPPOCIRE® BML	35.0-39.0	36.0-37.5	≤10
SUPPOCIRE® CM	35.6-39.6	37.8-39.8	≤10
SUPPOCIRE® AM	34.0-36.0	35.0-36.5	≤10
SUPPOCIRE® AS2	34.0-38.0	35.0-36.5	15-25
SUPPOCIRE® AS2X	34.0-38.0	35.0-36.5	15-25
SUPPOCIRE® BS2X	35.0-39.0	36.0-37.5	15-25
SUPPOCIRE® A	34.0-38.0	35.0-36.5	20-30
SUPPOCIRE® BP	Not available	35.0-37.0	30-50
SUPPOCIRE® AP	Not available	33.0-35.0	30-50
SUPPOCIRE® AGP	34.5-36.5	34.5-37.5	40-50
SUPPOCIRE® NA	33.0-36.5	34.5-36.5	20-30
SUPPOCIRE® NA 15	33.5-35.5	Not available	5-15
SUPPOCIRE® NAIS 10	37.0-39.0	Not available	5-15
SUPPOCIRE® NAI 25	33.5-35.5	34.5-36.5	20-30
SUPPOCIRE® NAI 25 A	33.0-35.0	33.2-35.2	20-30
SUPPOCIRE® NAL	33.5-37.5	34.5-36.5	20-30
SUPPOCIRE® NB	35.0-39.0	36.5-38.5	20-30
SUPPOCIRE® NBL	35.0-39.0	36.0-38.0	20-30
SUPPOCIRE® NAS 50	33.5-35.5	Not available	40-50

All products are available in pellet form, 200 g samples and 20 kg pack size.

Alternative dosage forms for rectal drug delivery

In addition to Suppocire® bases, Gattefossé offers a range of excipients for the formulation of rectal creams, ointments and foams.

Our emulsifiers are highly effective with therapeutic compounds commonly used in rectal therapy, including challenging combination API treatments. They deliver excellent stability, tolerability and optimized application properties.

We can help with advice on excipient selection, formulation optimization, sensorial and texture analysis and manufacturing scale-up.

Creams	Ointments	Foams
Tefose® 63 **Tefose® 1500**	**Labrafac™ Lipophile WL 1349** and **Compritol® 888 Pellets**	**Tefose® 63** **Gelot™ 64**
Excellent soft texture and non-irritant properties	Emollient and non-irritant properties	Light texture with good spreadability
Widely used in anti-hemorrhoid and pain relief treatments applied on mucosal membranes		Used in anti-inflammatory treatments

Rectal formulation and characterization

Customers choose Gattefossé because our expertise accelerates formulation development and production. Our technical staff provides support for a wide range of formulation objectives.

- Improve drug release
- Improve drug absorption
- Improve physicochemical stability
- Improve unit dose size

- Improve mucosal tolerance and patient acceptability
- Improve quality of finished dosage form
- Formulate multiple active ingredients
- Match properties of market reference

Formulators in our application laboratories specialize in the development and characterization of suppositories. European Pharmacopœia methods as well as in-house validated methods are used to evaluate the physical properties and drug release performance of suppository units.

Common physical assays:

- Mechanical resistance
- Slip-melting point
- Liquefaction time

Drug release from suppository units can be assessed by dissolution testing with specialized equipment.

We support customers' scale-up and production transfer with the generation of thermorheograms to determine the optimal blister filling temperature.

Case study 1#: Improving drug release efficacy

Paracetamol (acetaminophen) is the most commonly used antipyretic drug for children.

Pediatric suppositories are generally available in several dose strengths to enable weight based dosing. This case study illustrates the 300 mg paracetamol suppositories often prescribed for children of 15 kg - 24 kg.

For a fast-acting antipyretic effect, drug release from the suppository unit must be efficient.

Paracetamol is not soluble in hard fat bases – therefore it is dispersed into the base. The 300 mg paracetamol suppository units were made with Suppocire® NAI 25 A.

Suppository formulation: 2 gram unit

Paracetamol..... 300 mg

Suppocire® NAI 25 A..... 1700 mg

Suppository units meet the requirements for mechanical resistance, slip-melting point and liquefaction time.

The *in vitro* testing of drug release performance is not mandatory in suppository development. However, when a drug needs to reach the systemic circulation it is important to evaluate drug diffusion and dissolution from the suppository base. Dissolution testing provides an indication of *in vivo* performance with respect to drug diffusion, dissolution and subsequent absorption across the rectal mucosa. For paracetamol, these are important criteria to ensure a fast-acting antipyretic effect.

Dissolution testing shows the drug release performance of Suppocire® NAI 25 A compared to three market references (300 mg / 2 g unit).

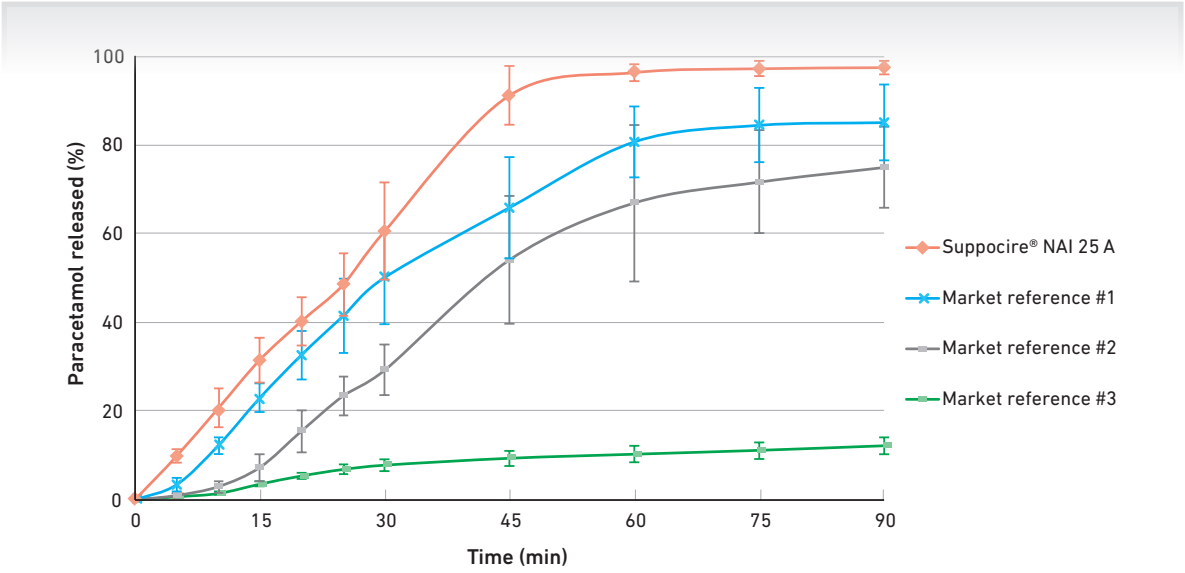
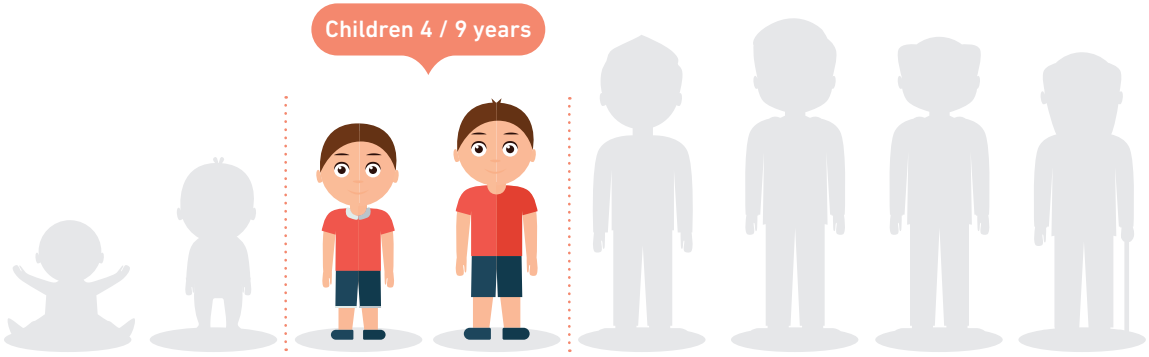


Figure 1. Dissolution testing of 300 mg paracetamol suppositories (n=6) in pH 7.4 at 37°C (USP type IV apparatus; drug assayed by UV-spectrophotometry).

Suppocire® NAI 25 A delivers 60% drug release after 30 minutes compared with 50% for reference 1, 30% for reference 2 and only 8% for reference 3.

Suppocire® NAI 25 A guarantees excellent drug release properties for a fast-acting antipyretic effect.



Case study #2: Matching a market reference product

Ibuprofen suppositories are prescribed or available over-the-counter to relieve acute pain and inflammation. Drug release needs to be efficient to ensure fast-onset of the therapeutic effect.

Suppositories are generally available in several dose strengths to enable weight based dosing in children. This case study illustrates 125 mg ibuprofen suppositories often prescribed for children between 12 kg – 20 kg weight.

To provide equivalent *in vitro* and *in vivo* performance a generic suppository should match the originator in terms of weight, dose, hardness, melting point, liquefaction time, drug release profile, aspect and stability (shelf-life).

Based on the physicochemical properties of ibuprofen and the target dose, Suppocire® BM was selected for formulation development.

Suppository formulation: 1 gram unit

Ibuprofen ..... 125 mg

Suppocire® BM..... 875 mg

Physical tests of Suppocire®-ibuprofen units

	Requirement	Suppocire® BM	Market reference
		Physical tests are performed 48 hours after formulation	
Mechanical resistance	> 1.8 – 2.0 kg	3.2 kg	5.2 kg
Slip-melting point	< 37°C	35.6°C	35.3°C
Liquefaction time	< 20 min	3 min 30	4 min 30

Suppocire® BM – Ibuprofen suppositories meet the required physical performance specifications.

Subsequent dissolution testing shows that drug release from the Suppocire® BM base closely matches the market reference product. This result confirms that the difference in mechanical resistance observed in the physical tests has no impact on the performance of the suppository unit and that Suppocire® BM will provide good *in vivo* performance.

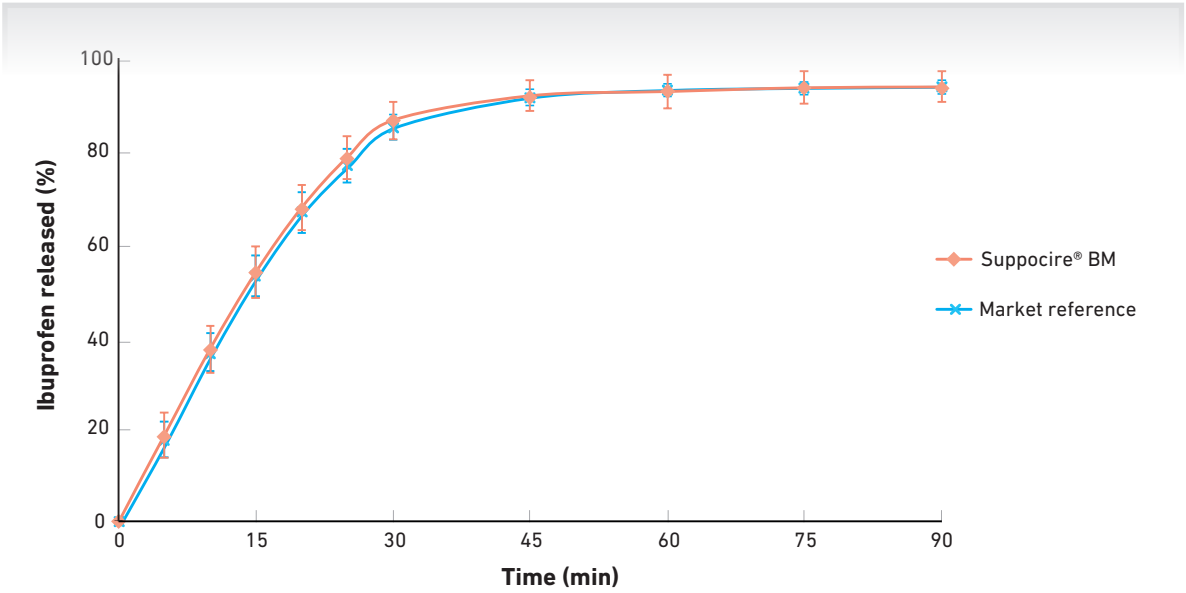
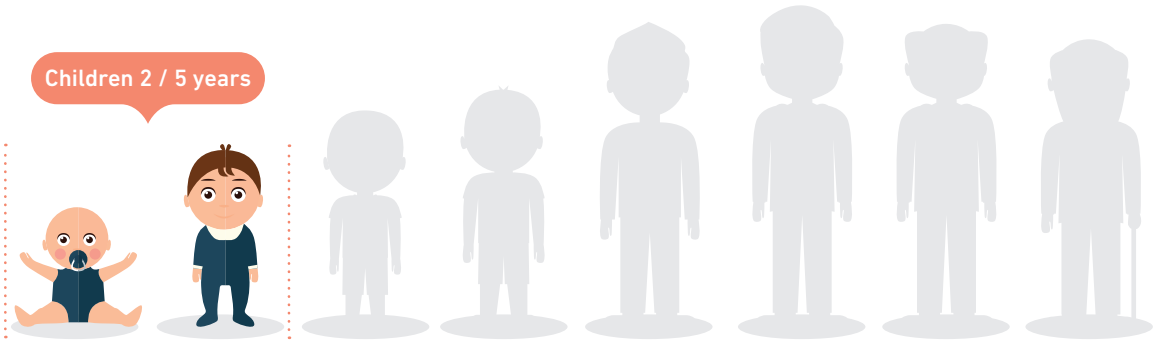


Figure 2. Dissolution testing of 125 mg ibuprofen suppositories (n=6) in pH 7.2 at 37°C (USP type IV apparatus; drug assayed by UV-spectrophotometry).



Case study #3: Improving physicochemical stability

Hydrocortisone acetate - lidocaine hydrochloride suppositories are commonly prescribed for the acute treatment of hemorrhoids.

Formulations are designed to maximize contact between the melting suppository mass and the rectal mucosa; as such zinc oxide and aluminum hydroxyacetate are often combined in the hard-fat base to maintain the drug in a structured network.

Multiple-active ingredient formulations can be associated with physicochemical stability issues.

Our formulators were asked to assess the quality of an existing product and improve the physicochemical stability of the formulation.

The reference product showed visible signs of fat bloom and on physical testing, a slip melting point of 45°C was measured. This high value is an artifact due to the high viscosity of the melted mixture which contains a large amount of powder (25% by weight). As the suppository unit melts it forms a viscous liquid which does not readily slip, as such a significantly higher temperature is required to trigger the slip-melting point.

This high viscosity can be reduced by formulating with a suppository base that has better properties for the dispersion of large amount of powders, ie. Suppocire® AM.

Based on the physicochemical properties of ibuprofen and the target dose, Suppocire® AM was selected for formulation development.

Suppository formulation: 2 gram unit

Hydrocortisone acetate..... 5 mg

Lidocaine hydrochloride .... 60 mg

Zinc oxide..... 400 mg

Aluminum hydroxyacetate 50 mg

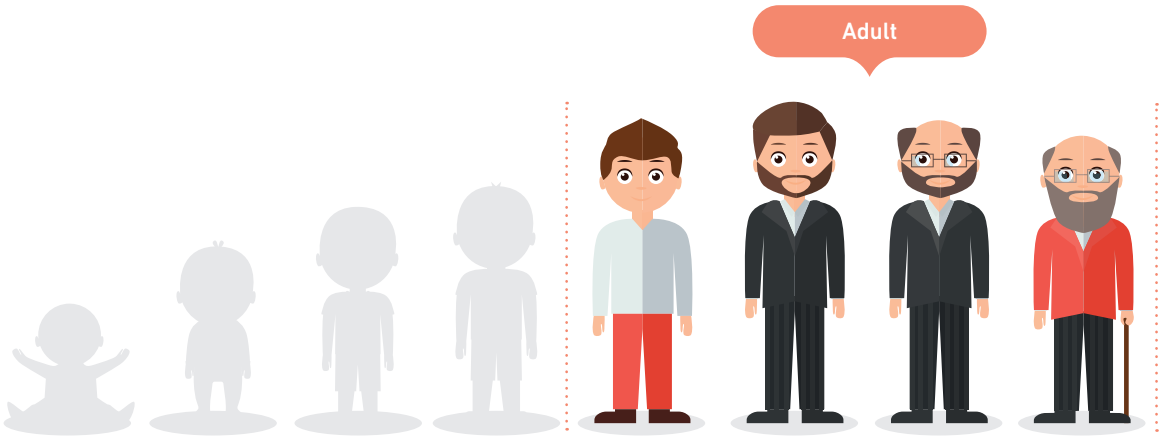
Suppocire® AM..... 1685 mg

Visual assessment of the Suppocire® AM suppository units showed smooth and glossy units with no fissures, no fat bloom and no surface drug crystallization.

Physical test evaluation

	Requirement	Suppocire® AM	Market reference
		Physical tests are performed 48 hours after formulation	
Mechanical resistance	> 1.8 – 2.0 kg	4.4 kg	> 5.4 kg
Slip-melting point	< 37°C	36.2°C	**> 45°C**
Liquefaction time	< 20 min	6 min	7 min

Suppocire® AM is an excellent base for hydrocortisone - lidocaine delivering good physicochemical characteristics and stability that ensure excellent spreading properties *in vivo*.



Speed-up product development with Gattefossé

Selecting the right suppository base for the API

Careful selection of the right Suppocire® base ensures optimal physicochemical stability and drug delivery properties. Candidate bases are chosen based on consideration of the API physicochemical properties, manufacturing equipment and environmental conditions (ie. heat and humidity).

Gattefossé provides technical support for formulation and scale-up for APIs commonly formulated in suppository dose form. We also develop solutions for uncommon APIs (eg. probiotics) and traditional medicines.

Therapeutic class	Examples of APIs
Anti-inflammatory	Sodium diclofenac, ketoprofen, ibuprofen, piroxicam, niflumic acid, mesalazine
Laxative	Glycerin
Anti-pyretic	Paracetamol
Anti-hemorrhoid	Titanium dioxide/zinc oxide, hydrocortisone/lidocaine, ruscogenine/trimebutine

Dispersion and stability of colored powders/liquids (Traditional Chinese Medicines, essential oils...) can be improved by selection of the right base.

with the **wrong** suppository base

▸ *instability and phase separation during storage*

with the **right** suppository base

▸ *stable and homogenous dispersion during storage*

Formulation database: We offer access to an extensive database of standard formulations with common API that can help speed-up new product development.

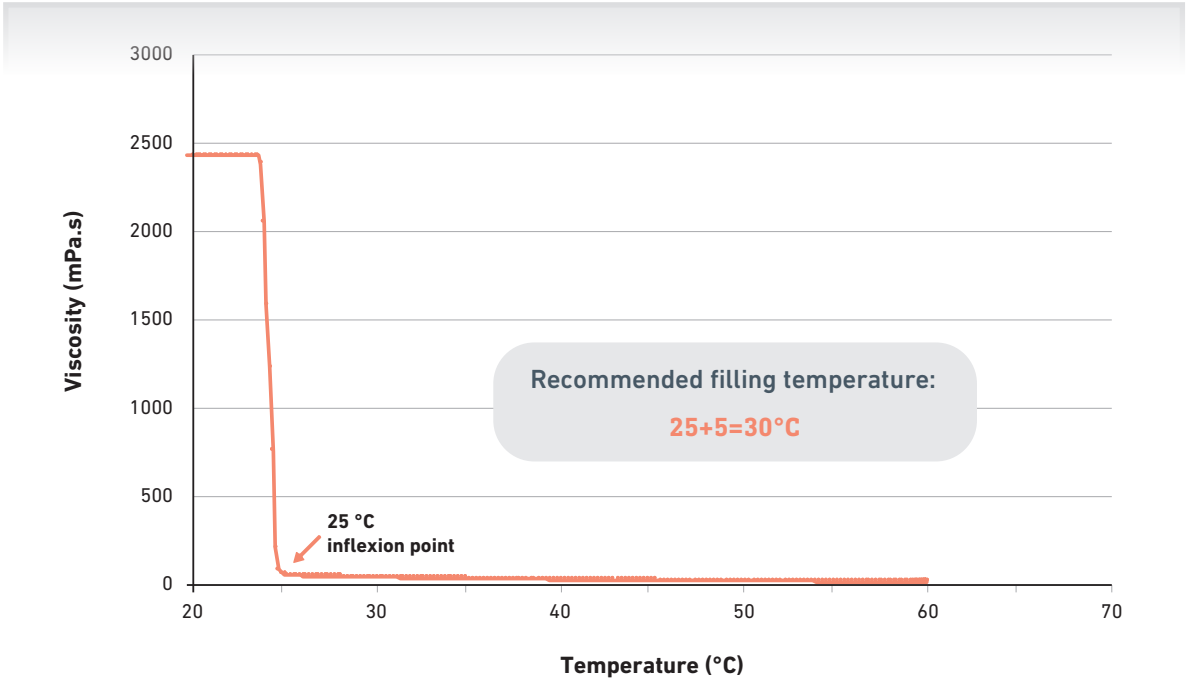
Optimizing production process parameters

Temperature is a critical parameter in the manufacturing of suppository units.

- Melting temperature of the base
- Temperature of the base when the API should be added
- Pouring/blister filling temperature

To assist in identifying these important parameters, Gattefossé provides formulation process sheets and a thermorheogram for each Suppocire® base.

Thermorheogram Suppocire® AM



Trouble-shooting: We can help you solve manufacturing and quality issues which are often attributable to inappropriate stirring time or speed, filling temperature, cooling conditions or selection of the suppository base.

Formulating alternative dosage forms for rectal drug delivery

Gattefossé provides technical support in the development and characterization of rectal creams, ointments and foam formulations.

Our self-emulsifying excipients combine lipophilic and hydrophilic surfactants with texture agents. These 'all-in-one' emulsifiers deliver soft, rich creams with excellent stability whatever the nature and concentration of oil. They also provide excellent mucosal tolerance and their safety is substantiated by decades of use in internationally approved pharmaceutical products.

Examples of simple formulations with optimized stability and texture are presented below.

Rectal cream formulation

Anti-hemorrhoid cream		
Excipient	**Function**	**W/W (%)**
Tefose® 1500	**O/W emulsifier**	**12.00**
Labrafil® M 2130 CS	**Oily phase**	**5.00**
Mineral oil	Oily phase	6.00
Demineralized water	Aqueous phase	64.10
Propylene glycol	Solubilizer	4.00
Methyl paraben sodium salt	Preservative	0.25
Propyl paraben	Preservative	0.15
Viscarin GP 209 NF	Gelling agent	2.50
Titanium dioxide	**API**	**2.00**
Zinc oxide	**API**	**2.00**
Lidocaine base	**API**	**2.00**

White cream
pH 9.1 ± 0.5
Viscosity ($50s^{-1}$ at 25°C): 4300 mPa.s

Rectal ointment formulation

Anti-hemorrhoid ointment		
Excipient	**Function**	**W/W (%)**
Compritol® 888 Pellets	**Thickener**	**2.00**
Mineral oil	Oily phase	14.00
Paraffin oil	Oily phase	80.75
Cod liver oil	**API**	**3.00**
Phenylephrine HCl	**API**	**0.25**
		100%

Rectal foam formulation

Emulsions with Tefose® 63 and Labrafil® M 1944 CS can be used with pressurized aerosol to make soft, rich foam. Please contact Gattefossé for further information about formulating foams.

Visit www.gattefosse.com to see topical formulation processes and to download our Topical Drug Delivery brochure

Regulatory information

Compliance to the EP, USP-NF, JPE and Ch.P pharmacopœias is summarized in the table below.

Type IV DMF for Gattefossé suppository bases is registered with the USA Food and Drug Administration.

Suppocire® grades	
Hard fat	**Pharmacopœia compliance**
SUPPOCIRE® A SUPPOCIRE® AM SUPPOCIRE® AS2 SUPPOCIRE® BM SUPPOCIRE® CM SUPPOCIRE® NA SUPPOCIRE® NA 15 SUPPOCIRE® NAI 25 SUPPOCIRE® NAI 25 A	Hard fat EP/NF/JPE/Ch.P
SUPPOCIRE® NAI 50 SUPPOCIRE® NAS 50	Hard fat EP/NF/JPE/Ch.P
SUPPOCIRE® NB	Hard fat EP/JPE/NF/Ch.P
Hard fat with additive	
SUPPOCIRE® AIML	Hard fat NF/JPE with additive (lecithin) Hard fat with additive EP
SUPPOCIRE® AML SUPPOCIRE® BML SUPPOCIRE® NAL SUPPOCIRE® NBL	Hard fat NF/JPE/Ch.P with additive (lecithin) Hard fat with additive EP
SUPPOCIRE® AS2X SUPPOCIRE® BS2X	Hard fat NF/JPE/Ch.P with additive (polysorbate) Hard fat with additive EP
SUPPOCIRE® AGP	Hard fat EP/NF/JPE with glycerol monostearate EP/NF and PEG -75 stearate NF
SUPPOCIRE® NAIS 10	Hard fat JPE with additive
Saturated polyoxylglycerides	
SUPPOCIRE® AP SUPPOCIRE® BP	Saturated polyglycolyzed glycerides

Topical route excipients

Product name	Chemical description / Pharmacopœia compliance
Compritol® 888 Pellets	Glycerol dibehenate EP Glyceryl dibehenate NF Glyceryl behenate Ch.P
Gelot™ 64	Mixture of glycerol monostearate EP/NF and PEG-75 stearate NF
Labrafil® M 1944 CS	Oleoyl macrogol-6 glycerides EP Oleoyl polyoxyl-6 glycerides NF
Labrafil® M 2130 CS	Lauroyl macrogol-6 glycerides EP Lauroyl polyoxyl-6 glycerides NF
Tefose® 63	Mixture of PEG-6 stearate (type I) NF and ethylene glycol palmitostearate EP/NF/JPE and PEG-32 stearate (type I) NF
Tefose® 1500	Mixture of PEG-6 stearate (type I) NF and PEG-32 stearate (type I) NF

Detailed Regulatory Datasheets are available for all our excipients. For further information please contact Gattefossé.

Technical support

Our Technical Centres of Excellence in France, India, China and USA are at your service to provide technical support.

We can provide advice on handling and formulating lipid excipients as well as straightforward formulation guidelines for oral, dermal, rectal and vaginal dosage forms as well as access to extensive databases comprising many validated placebo or model API formulations.

Please contact your local Gattefossé representative
or email us at:
infopharma@gattefosse.com

GATTEFOSSÉ

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