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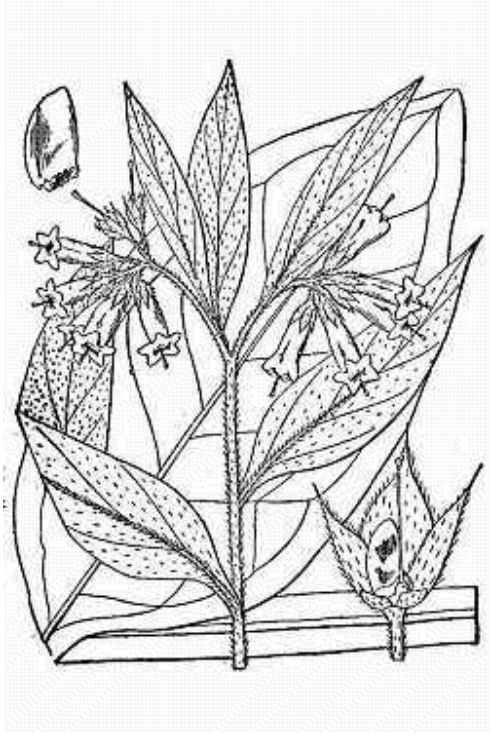
Allantoin

A safe and effective skin protectant

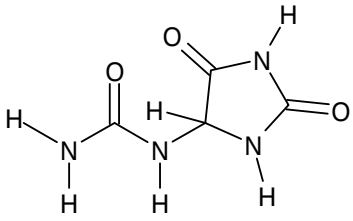


1. Overview

Allantoin, as a natural compound derived from *Symphytum officinale*, has long been known for its beneficial effects on skin. It is an active compound with keratolytic, keratoplastic, soothing and healing properties largely used in cosmetic, topical pharmaceutical and veterinary products.
Allantoin is an anti-irritating and non-toxic agent listed in *United States Pharmacopeia*, *European Pharmacopoeia, Merck Index* and *British Pharmacopoeial Codex. FDA* recognizes allantoin as a skin protectant active ingredient for over-the-counter (*OTC)* human use.

2. Chemical structure

Structural formula:



Empirical formula: $C_4H_6N_4O_3$
Molecular weight: 158.12

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3. Codex and names

CTFA/JSCI name:	Allantoin
INCI name:	Allantoin
EINECS name	Urea, (2,5-Dioxo-4-Imidazolidinyl)-
CAS number:	[97-59-6]
EINECS number:	202-592-8
JSCI number:	S0016

4. Specifications data

Appearance:	powder
Colour:	white
Odour:	odourless
Identification:	corresponds to C.T.F.A. IR spectrum
Assay:	99.0% min
Nitrogen:	35.0% – 35.5%
pH *(0.5% water solution)**:***	3.5 – 6.5
Loss on drying:	0.2% max
Sulphated ash:	0.1% max
Sulphate:	200 ppm
Chloride:	50 ppm
Heavy metals (Pb):	less than 10 ppm
Glycoluril:	less than 0.2%
Total viable count:	Less than 1000 cfu/g
Shelf life:	5 year in original packing

The analytical methods are available on request.

5. General description

Allantoin is a functional compound with mild *keratolytic* and *keratoplastic* action on skin. Although the biochemical mechanism of its keratolytic action has not been yet determined, allantoin soften and loosen keratin by disrupting its structure, thereby facilitating desquamation of the cornified cells on the top layer of skin. Removal of these dead cells exposes the new, soft skin underneath and makes the underlying layers of skin tissue more accessible to the other ingredients of the formulation.
Allantoin, as a result of increased corneocytes desquamation, is capable of modifying the dynamic homeostasis that exists within the epidermis, inducing basal cells proliferation. As a consequence, the skin surface is smoothed and softened while dull cells are removed.
Unlike all other keratolytic exfoliating agents that may also irritate the skin, Allantoin clean dead tissue and stimulate epidermal renewal process without any adverse effect.

Allantoin is classified by FDA OTC panel as a *skin protectant*, it is considered useful especially for individuals sensitive to topical products because, it forms complexes with a variety of sensitizing agents rendering them nonsensitizing. Allantoin helps to alleviate the skin-irritations effects of several cosmetic raw materials like surfactants, preservatives and acidic or alkaline materials.

Allantoin is recognized a valuable cell-regenerating and healing agent which stimulates healthy tissue formation. Althought the mechanisms of healing action are not completely clear yet, it is supposed that *Allantoin* causes a local and temporary multiplication of leukocytes.

Allantoin speed up *wound healing* by assisting the regeneration of cells of damaged epithelium, by stimulation of cell granulation and fibrinolysis of damaged tissue. For its keratolytic activity acts as chemical debrider of necrotic tissue, cleansing up the areas where applied.
Approved by the FDA for the treatment of cold sores and fever blisters, Allantoin provides a number of functions optimal for reducing the severity of an outbreak and promoting healing.

It's also an active ingredient proven safe and effective in the treatment of xerosis, psoriasis, seborrheic dermatitis or dandruff symptoms. Allantoin has not antiseptic properties.

Allantoin showed the moisturizing and keratoplastic properties of urea, that constitute a part of allantoin molecule, at ten time lower concentrations. Another benefit versus urea, is represented by its better stability in solution, in fact the hydrolisis of urea in neutral or alkaline environment produce ammonium hydroxide and ammonia.

6. Epidermis renewal process

Epidermal cells are mostly represented by keratinocytes. These cells undergo considerable physical transformation in the course of moving from the basal layer to the outer surface of the stratum corneum. Keratinocytes originate in the basal layer of the epidermis as living, nucleated cells, that migrate upward. In the upper layers they increase in size, become angular and flatten, undergo increased protein synthesis. At last they lose internal structural organization and fluid contents, and harden by process of keratinization becoming in the compact mass of dead cells that forms the stratum corneum, called corneocytes.
Each corneocyte consists of closely packed arrays of keratin filaments, without nucleus with thickened membrane. This flattened polyhedric cells are stacked on the top of one other, embedded in a lipid-enriched intercellular matrix in what has been described as a "brick and mortar" arrangement.
This process of continual proliferation and differentiation, followed by cornification continuosly produce new inert corneocytes at the base of the stratum corneum. To balance this build-up of corneocytes and mantain skin thickness, the stratum corneum must ultimately shed cells or desquamate. Desquamation is a process designed to slowly degrade the stratum corneum cohesive forces allowing the surface corneocyte to easily detach, without compromising tissue integrity.
Perturbations in the desquamatory process result in the dry-flaky skin condition. The process of desquamation is crucial to the mantenance of the stratum corneum barrier tissue. By continually shedding corneocytes, the skin can withstand the accumulative mechanical and chemical damage, which naturally occurs and hence mantain a functional barrier.
Allantoin for its keratolytic activity cause the lough of external corneocytes, facilitating the renewal process of epidermis, the stratum corneum remain fully functioning in the face of continual environmental damage and mantain a healthy skin condition.

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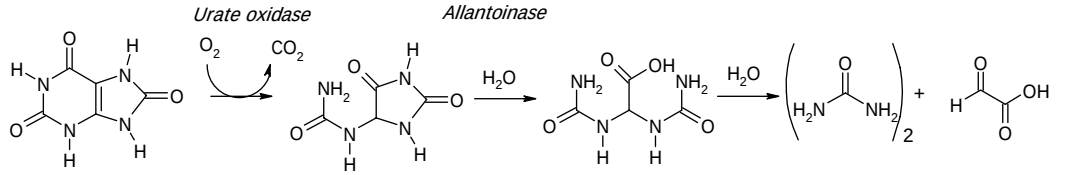
7. Origin

Allantoin is a metabolic intermediate of a wide variety of organisms, from bacteria, to vegetals and animals.
Allantoin is the oxidation product of *uric acid* mediated by the enzyme urate oxidase. Uric acid is the metabolic end product of purine degradation excreted in the urine in primates; bird, reptiles and insects excrete uric acid as crystals.
In mammalians other than primates, that are lacking in urate oxidase, uric acid is oxidized to *Allantoin* which is excreted. Allantoin is hydrolized to *Allantoic acid* in teleost fish, while certain cartilagious fishes and amphibians, which possess enzyme allantoicase, convert allantoic acid to *urea*, that is excreted.
Allantoin was found in fetal allantoic fluid and in the urine of pregnant women.



Allantoin was also found in many plant species in combination with other natural compounds, particularly in the leaves and roots of comfrey.

Plant species with highest amount of Allantoin

Scientific name	Common name	Part of the plant
Symphytum officinale	*Comfrey*	*13,000 ppm in Leaf; 6,000-8,000 ppm in Root*
Aesculus hippocastanum	*Horse Chestnut*	*in Bark*
Agrostemma githago	*Cockle, Corn Cockle, Corn-Pink*	*in Sprout Seedling*
Arctostaphylos uva-ursi	*Bearberry, Uva Ursi*	*in Plant*
Aristolochia debilis	*Chinese Birthwort*	*in Root*
Beta vulgaris subsp. vulgaris	*Beet, Beetroot, Garden Beet,*	*in Root*
Borago officinalis	*Borage*	*in Sprout Seedling*
Brassica napus var. napobrassica	*Rutabaga, Swede, Swedish Turnip*	*in Root*
Brassica rapa var. rapa	*Rapini, Seven Top Turnip, Turnip*	*in Root;*
Camellia sinensis	*Tea*	*in Plant*
Coffea arabica	*Coffee*	*in Leaf*
Datura metel	*Hindu Datura*	*in Seed*
Glycine max	*Soybean*	*in Seed*
Lupinus albus	*White Lupine*	*in Sprout Seedling*
Oryza sativa	*Rice*	*in Seed*
Pisum sativum	*Pea*	*in Shoot*
Plantago major.	*Common Plantain*	*in Plant*
Prunus cerasus	*Sour Cherry*	*in Stem*
Pueraria pseudohirsuta	*Chinese Kudzu*	*in Root*
Solanum tuberosum	*Potato*	*in Plant*
Trifolium pratense	*Cowgrass, Peavine Clover, Purple Clover*	*in Sprout Seedling*
Triticum aestivum.	*Wheat*	*in Embryo*
Vigna mungo	*Black Gram*	*in Seed*
Zea mays	*Corn*	*in Seed*

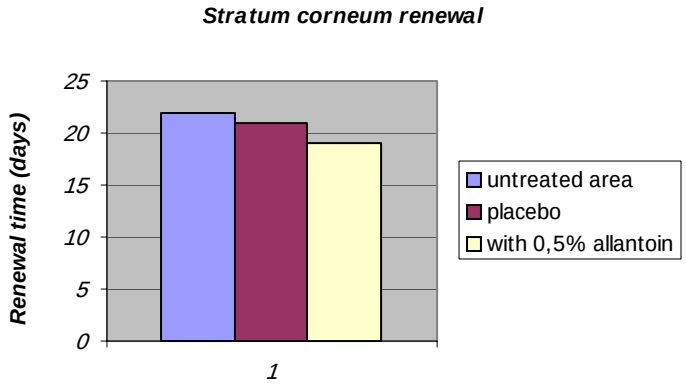
Allantoin was synthetically obtained by different chemical routes, mainly by oxidation with permanganate of uric acid, heating dichloroacetic acid and urea and by a condensation process between glyoxylic acid and urea.

8. History

The earliest reported use of allantoin topically was in form of poultices made of comfrey (the botanical name *Symphytum officinale* derived from greek *symphyein* which means "grow together, to unite", possibly referring to its wound healing effect). The roots and leaves of this perennial herb are reported to contain from 0,6 to 1% allantoin and has a long hystory of use in the treatment of wounds and ulcerous conditions of the skin.
Many authors in the past centuries reported the impressive effects of the rootes of comfrey on ulcers and gangrenes: Turner in *Herball* (1568), John Parkinson (the apothecary of King James I), in his *Theatrum Botanicum* (1640), Tournefort, in his *Compleat Herbal* (1716).
In 1790 Vaquelin demonstrated the presence of allantoin in the fetal fluids of many animals. Allantoin had been available by a synthetic process since 1838.
The use of allantoin in topical creams has been reported in scientific journals since the 1930s.
During the Korean war was established that allantoin occurring in fly larvae and maggot secretions, infestating the soldier wounds, was responsible of their more rapid wound healing.

9. Efficacy studies

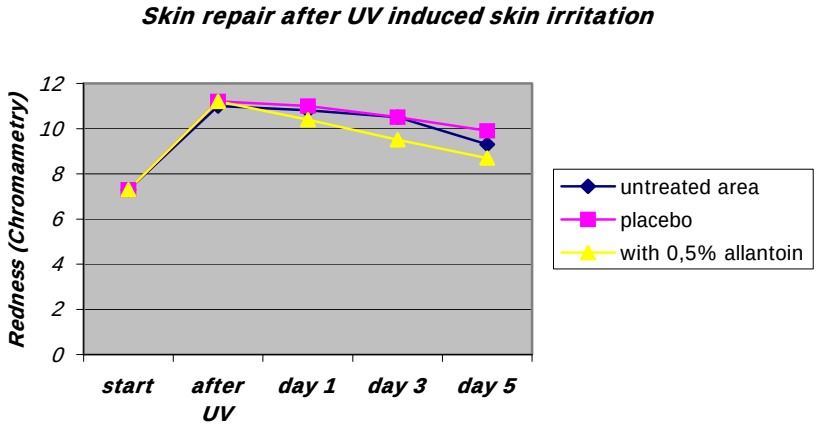
Detailed efficacy studies have been conducted on allantoin (2001, Hetting) to evaluate its cell proliferation effect, soothing effect and moisturizing effect.



The study, conducted on 20 volunteers, showed that the renewal of the stratum corneum is significantly faster when this was treated with a cream containing 0,5% allantoin.

The soothing effect of allantoin was tested, on 20 volunteers for each test, after:

- UV-induced irritation
- Chemically induced irritation;
- Mechanically induced irritation.



The data obtained showed the significantly enhanced decrease of redness of the skin after UV exposure.

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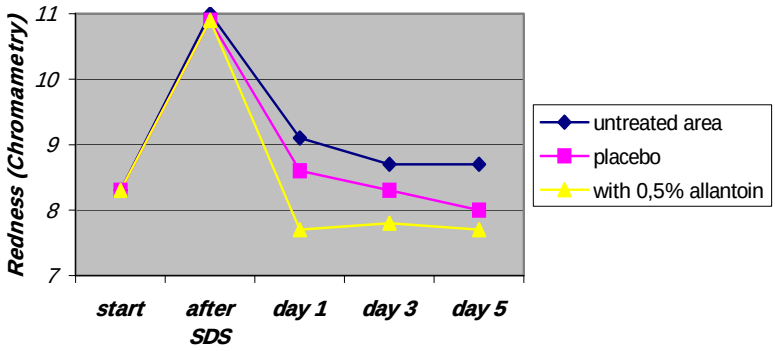
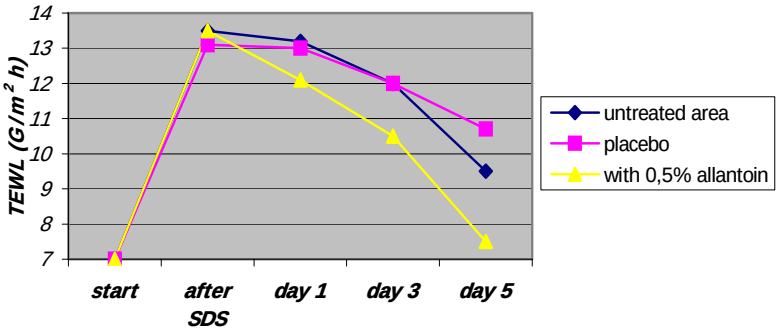
Skin repair after sodium dodecyl Sulfate-induced skin irritation (redness)

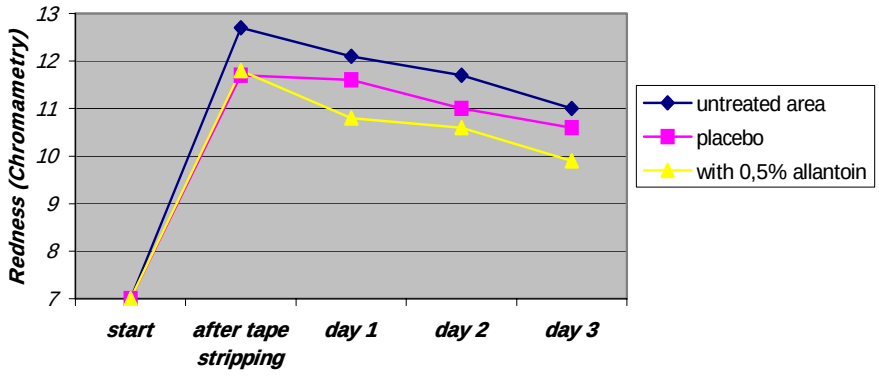


Skin repair after Sodium Dodecyl Sulfate-induced skin irritation (TEWL)

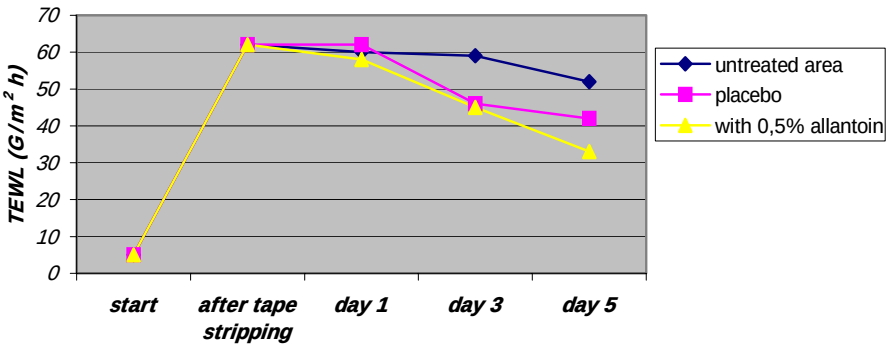


The data obtained after chemically induced irritation caused by the surfactant sodium dodecyl sulfate measuring both redness of the skin and also transepidermal water loss (TEWL), showed a significant soothing effect of allantoin.

Skin repair after tape strip-induced skin irritation (redness)



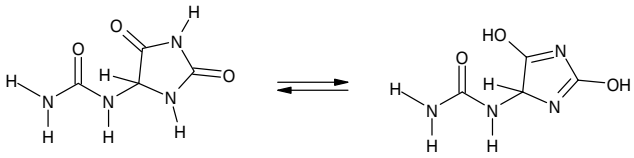
Skin repair after tape strip induced skin irritation (TEWL)



The data obtained for mechanical irritation, by evaluating redness of the skin and transepidermal water loss, have confirmed the soothing effect of allantoin.

10.Chemical physical properties

Allantoin is a fine white powder, odorless, tasteless with not less than 99% of pure active ingredient. It could be considered a purine derivative, with an open pyrimidine ring.
Allantoin exists in solution as a tautomeric mixture of ketonic and a enolic forms in equilibrium:



ketonic form enolic form

Allantoin possesses one chiral center, thereby exists in the two enantiomeric forms R and S. The synthetic product is a mixture (50:50) of the two enantiomers (R) and (S) in stable form as the that is optically inactive (racemic mixture). Optically active forms have been obtained by extraction procedures.
Allantoin crystallizes in monoclinic lamellae or prisms.
Thanks of its amino and carboxyl groups, *Allantoin* has an amphoteric nature.
Allantoin has a melting point varying between 225–230°C with decomposition.

11.Solubility

Allantoin is soluble in hot water, slightly soluble in cold water, glycerin and propylene glycol, very slightly soluble in alcohol and practically insoluble in apolar solvents, like mineral oil, dimethylisosorbide, ether and chloroform.

Solubility (g percent of solvent) of Allantoin in different solvents

Solvents	T (°C)	%
Water	25°C	0.5
Water	40°C	1
Water	70°C	3.5
Propylene glycol	25°C	0.1
Propylene glycol	70°C	0.5
Glycerol	25°C	0.05
Glycerol	70°C	0.4
Sorbitol	25°C	1
Propandiol-1,2	25°C	1
Ethanol	25°C	0.01
Ethanol 50%	25°C	0.3
Methanol	25°C	0.01
Sodium laureth sulfate 30%	20°C	0,8
Dimethylisosorbide	70°C	<0.01
Mineral oil	25°C	<0.01

12.Stability

A *0.5% aqueous solution* may be heated at 80°C for one hour without *Allantoin* showing any change. A lengthy boiling alkaline solution decompose in allantoic acid, then in urea and glyoxylic acid. Also strong alkaline solutions (pH>8) cause the decomposition of Allantoin. It's stability increase with the pH diminution.
Allantoin in dried powder is very stable alone or in dry preparations. When stored in well closed containers at room temperature <35°C, the guaranteed shelf-life is 5 years.

13.Applications

Allantoin for its properties may be used in a large number of cosmetic products and topical pharmaceuticals.

Cosmetic use

Allantoin is the most employed softener agent in cosmetics formulations. Allantoin and its derivatives constitute an effective and comprehensive group of compounds for the cosmetic treatment of the skin, so that a branch called *Allantoin-cosmetics* has been described by some authors.
The use of *Allantoin* is very cost effective as the concentrations required are quite low. The typical use in cosmetic products is between 0.1%-0.2%, but it may be increased to 0.5% and also 2%.
Allantoin could be used in every chemical-physical form except for the high pH formulations like depilatory (where allantoin decomposes) and totally lipidic preparations (where allantoin is insoluble).
Particularly emulsions, fluid or thickened, containing *Allantoin*, such as nutritive creams, day and night creams, has shown a moisturizing and softener effect.
Shaving, solar and lipcare preparations with allantoin have a soothing and regenerative effect.
The addition of allantoin to hand creams and lotions eliminates cracking keeping the skin smooth and elastic.
Preparations with allantoin correspond well to the requirement of new-born baby and children, whose skins are particularly sensitive.
For its keratolytic properties, Allantoin is also suggested for the treatment of hairs and of the scalp, particularly for antidandruff products.
Allantoin is also effective in promoting healing of inflammed and bleeding gums or periodontal tissue. It can be used in a variety of oral compositions such as toothpaste, gels, tooth powders, mouth sprays and mouth washes at concentrations of 0.1-1%.
The multiple uses of allantoin can be summarized as follows:

- Bath and shower gel
- Body lotions and creams
- Hand lotions and creams
- Facial lotions and creams
- Baby lotions and creams
- Suntan and sunscreen lotions
- After sun lotions
- Shaving soap foam
- Aftershave lotions
- Lipsticks
- Footcare
- Deodorants
- Antidandruff shampoo
- Oral care

A cosmetic formulary is available upon request.

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Dermatological uses

In topical pharmaceutical preparations the recommended doses of *Allantoin* dose are 0.5% to 2%. This proportion may be increased or decreased according to the use planned for the preparation, the nature and number of other ingredients.
The addition of allantoin to topical pharmaceutical preparations enhance the cleaning of the wound and its healing.
The spectrum of action of this preparations includes scratches, cuts, carbuncles, sores, persistent ulcers of various etiology and burns of various degree an origin (heat, X rays and sun rays). Acne, impetigo, psoriasis, eczemas, contact dermatitis of the hands, hypercheratosis, parodontosis and heat blisters in the mouth react well to medications with allantoin.
Internal and external haemorrhoids react equally well to suppositories and ointments containing allantoin.
In combination with various pharmaceutical substances, allantoin sinergizes their activity reducing at same time their side-effects, sensitizing, irritating or toxic properties. It is of no importance to the effectiveness of the product whether allantoin is present as a solution, suspension or powder.

In USA the labeling of drug products for over-the-counter (OTC) human use containing allantoin can states according to FDA: "temporarily protects minor cuts, scrapes, burns", "temporarily protects and helps relieve chapped or cracked skin and lips", "Helps protect from dryng effect of wind and cold weather".

No incompatibility with other ingredients has been described.
It is recommended to incorporate *Allantoin* with other hydrosoluble components in the aqueous phase of the preparation or to dissolve at 50°C in water. In case of preparation of an emulsion, add this aqueous phase to the oily phase stirring quickly.

O/W Emulsions with high content of Allantoin

The beneficial topical use of Allantoin in *cosmetics and personal care products*, and in *topical pharmaceutical products*, may remarkably increased when it's applied at concentrations of 1-2%.
In fact Allantoin, who has been classified from FDA as safe and effective ingredient for adult, children and infants in the concentration range from 0,5 to 2%, is usually used at level ≤ 0,5% for its slight solubility in cold water.
Allantoin at level above 0,5% is soluble in hot water (3,5% at 70°C, 1,5% at 50°C), but not at 25°C. At this temperature it forms a dispersion that need an adequate rheological stabilization to prevent sedimentation.
Stable O/W emulsions with high levels of Allantoin can be easily obtained by increasing viscosity of the water phase with a *rheology modifier* and using an *emulsifier system* that form lamellar liquid crystalline layers.

Rheology modifiers

The use of polimeryc hydrocolloids, such as Carbomer, as thickening and suspending agents represents the most important factor to stabilize the water phase of this O/W emulsion, containing a powder at level over the saturation point.
Allantoin at levels until 2% can be incorporated in the water phase after the emulsification, during the cooling phase at temperature above 50°C, with a good agitation to disperse the powder.
The polymer neutralization must be done only after the Allantoin addition. Neutralization increase the viscosity of the water phase, so Allantoin molecules result homogeneously suspended and stabilized in a 3-dimensional network structure, very stable also at lower temperature.
Neutralization must be done in such a manner that the pH of the final formulation must be between 4,5 and 5,8 , to better preserve the stability of Allantoin.

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Our suggested base formula made use of not less of 0,3% *Carbomer* (Carbopol 940), as emulsion instability at centrifugation (5,000 rpm for 30 min.) was observed at lower concentration.
Also other Carbomer types may be used (Carbopol ETD, Carbopol Ultrez 10), or other thickening polimers that don't need neutralization, such as *Sepigel 305* (Polyacrylamide and C13-14 Isoparaffin and Laureth-7,) or natural polymers (Xanthan gum, Hydroxyethylcellulose, Hydroxypropylcellulose).

Emulsifier system
Anionic emulsifier, or a *non ionic emulsifiers (ethoxylated, glucosidic* or *polymeric*). *Non ionic glucosidic emulsifiers*, such as Lauryl glucoside and Arachidyl glucoside, are very suitable for this formulation, for their ability to form lamellar liquid crystalline layers on the O/W interface that stabilize the water phase of the emulsion and help Allantoin to remain in suspension.
Polymeric emulsifiers, such as Pemulen TR-1, form a gel network in the water phase that physically stabilizes the emulsion, this gel matrix has an high suspending capability that hold in place Allantoin molecules.
The emulsion with polymerics, can be formed by addition of oil phase ingredients at a temperature at which all ingredients are liquid (70-75°C), to the water phase at about 50°C.

14.Toxicological data

Allantoin has a long history of safety. The *US Food and Drug Administration (FDA)* has classified *Allantoin* as a *Category I (safe and effective)* active ingredient skin protectant, based on the results of 200 Patch tests .Bibliography and experience did not show any toxic or allergic reactions or skin irritations following its use.
The toxicity tests conducted on allantoin had given the following results:

Acute oral toxicity (rats)
Thirty healthy rats, equally divided as to sex are used in this study. The test material is administered orally by a rigid stomach tube.
The oral LD_{50} is > 5000 mg/Kg (method Litchfield and Wilcoxon).
Allantoin must be considered only slightly toxic.

Acute dermal toxicity (rabbits)
Ten healthy rabbits of both sexes are used in this study. The test material is applied to the normal and abraded skin of animals.
The dermal (normal and abraded) LD_{50} is ≥ 5000 mg/Kg.

Primary skin irritation (rabbits)
The test material in powder and its saturated water solution (0.5%) are applied to the normal and abraded skin of healthy rabbits.
In both cases no irritation is observed, so the test material not can be considered a primary skin irritant.

Eye irritation (rabbits)
A saturated water solution of the test material is applied to the eyes of healthy rabbits without washout (Draize method).
No eye irritation is observed, so the test material not can be considered an eye irritant.

Mutagenicity
Non mutagenic by Ames test.

Patch test (humans)
Repeated patch tests on 200 healthy volunteers (Schwarz method) show no irritation and no sensitization.

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15.References

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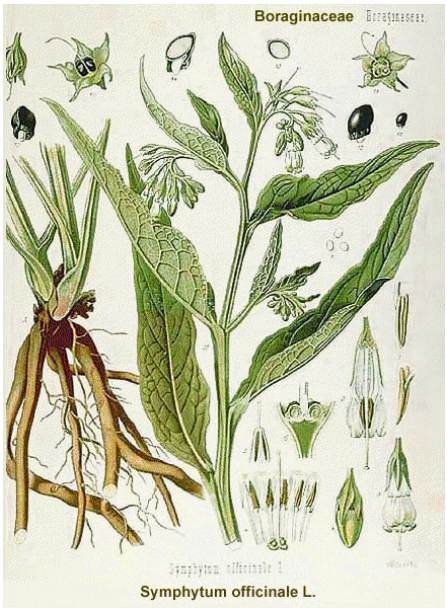

Symphytum officinale L.