

**Delayed hypersensitivity reactions caused by drug excipients: A literature review****Short title: Drug excipients allergy****Caballero ML, Quirce S**

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**Abstract**

The European Medicines Agency (EMA) defines excipients as the constituents of a pharmaceutical form apart from the active substance. Delayed hypersensitivity reactions (DHRs) caused by excipients contained in the formulation of medications have been described. However, there are no data on the prevalence of DHRs due to drug excipients. Clinical manifestations of allergy to excipients can range from skin disorders to life-threatening systemic reactions.

The aim of this study was to perform a literature review on allergy to pharmaceutical excipients and to collect the DHRs described with different types of medications, specifically due to the excipients contained in their formulations. The cases reported were sorted alphabetically by type of medication and excipient, in order to obtain a list of the excipients most frequently involved for each type of medication.

**Key words:** Allergy, delayed hypersensitivity reaction, drug hypersensitivity reaction, excipient, pharmaceutical excipients.

## Resumen

La Agencia Europea de Medicamentos define los excipientes como los componentes de una forma farmacéutica diferenciados del principio activo. Se han descrito reacciones de hipersensibilidad retardada causadas por los excipientes contenidos en la formulación de medicamentos. Sin embargo, no hay datos sobre la prevalencia de dichas reacciones. Las manifestaciones clínicas de la alergia a los excipientes pueden ir desde trastornos de la piel hasta reacciones sistémicas que ponen en peligro la vida.

El objetivo de este estudio fue realizar una revisión de la literatura sobre la alergia a los excipientes farmacéuticos y recopilar las reacciones de hipersensibilidad retardada descritas con diferentes tipos de medicamento, debido solo a excipientes contenidos en sus formulaciones. Los casos se clasificaron alfabéticamente por tipo de medicamento y excipiente, con el fin de obtener una lista de los excipientes más frecuentemente implicados con cada tipo de medicamento.

**Palabras clave:** Alergia. Excipiente. Excipientes farmacéuticos. Reacción de hipersensibilidad retardada. Reacciones de hipersensibilidad a medicamentos.

## Introduction

The European Medicines Agency (EMA) defines excipients as the constituents of a pharmaceutical form different from the active substance [1]. From a pharmaceutical point of view, an excipient is an inert substance added to a drug to change solubility or the kinetics of absorption, improve stability, influence palatability, or create a distinctive appearance. Hypersensitivity reactions to excipients may lead to a false-positive diagnosis of drug allergy [2].

The aim of this study was to perform a literature review on delayed hypersensitivity reactions (DHRs) to pharmaceutical excipients by using the electronic search engine PubMed/MEDLINE to identify potentially relevant studies published in peer-review journals until December 2019. The cases were sorted alphabetically by type of medication and excipient, in order to obtain a list of the most frequently excipients involved for each type of medication.

## **DHRs reported with different type of medications due to excipients**

The excipients involved in the DHRs described in this review article are shown in Table 1 and 2. A link to PubChem Database of the National Center for Biotechnology Information (NCBI-PCD) for the description of each excipient (Table 3) and a summary of the concentrations used to test each excipient (Table 4) are provided.

### **Antiepileptic drugs (AEDs)**

#### ***Carboxymethylcellulose (CMC)***

Reactions with unrelated products due to CMC [3] (Table 2). A drug reaction with eosinophilia and systemic symptoms (DRESS) caused by Tegretol (carbamazepine) (CMC-containing) was reported. Subsequently, the patient experienced eczematous rashes following the intake of pills containing paracetamol and a Non-steroidal anti-inflammatory drug (NSAID). Because both, patch-test (PT) and skin prick test (SPT), to CMC were negative, an oral provocation test with a cumulative dose of 1.115 mg of CMC was performed under hospital surveillance, inducing a generalized eczematous rash on the following day.

### **Antihistamines**

#### ***Propylene glycol (PG)***

PG, an emollient and emulsifier found in cosmetics, medications, and food, has been granted the dubious honor of being named the American Contact Dermatitis Society's Allergen of the Year for 2018. Contact, systemic, and irritant cutaneous reactions have been documented for PG. Optimal patch-test concentration and reading intervals have been a topic of debate for many years because of the fact that PG causes both irritant contact dermatitis and allergic contact dermatitis (ACD), and it is often difficult to

differentiate these types of reactions. The most recent update for the ACDs core series recommends testing only with 100% PG. The confounding characteristics of PTs to PG increase the relevance of an accurate interpretation. Crescendo reactions, which show little or no reaction at 48 hours but subsequently develop a stronger reaction at 96 hours, suggest contact allergy. Decrescendo reactions, which present weakly at 48 hours but disappear by 96 hours probably are irritant reactions [4].

In the present revision reactions due to PG have been described in the following type of medications: antihistamines, anxiolytics, lubricants, topical medications and ultrasound gels.

Reactions with antihistamines and other unrelated products due to PG (Table 2).

- ACD with positive PT to PG. A sensitized patient improved significantly after switching to a PG-free topical corticosteroid (CS). However, since dermatitis flared annually during seasonal rhinitis, it was discovered the patient used oral antihistamines which also contained PG [5].

- Eczematous lesions or rash with positive PT to PG. Dermatitis improved after switching to a PG-free topical CS. Flare-up of his rash twice during seasonal use of oral cetirizine syrup led to discover that the formulation of antihistamine contained PG [6].

- Atopic dermatitis treated with topical CS and oral antihistamines, without improvement. The patient had a positive PT to PG, and experienced a complete resolution of skin lesions after switching to PG-free hydroxyzine syrup [6].

## **Anxiolytics**

### ***PG***

Reactions with unrelated products due to PG [7] (Table 2). A systemic contact dermatitis after the injectable Valium (diazepam) administration and formerly, during a

gynecologist examination using the lubricant K-Y Lubricant Jelly, (both containing PG), have been described. PT to PG was positive.

## CS

### *Benzalkonium chloride (BAC)*

Three cases of systemic allergic reactions induced by BAC after the use of a mometasone nasal spray, have been described. The histories of the patients and the positive results of the PTs performed to two of the patients, point to a diagnosis of type IV hypersensitivity reactions due to BAC [8].

### *CMC*

Reactions with unrelated products due to CMC [3] (Table 2). Flexural dermatitis 3 days after an intra-articular injection of a betamethasone dipropionate preparation (CMC-containing), and few months later, maculopapular rash of the trunk 24 hours after taking piroxicam pills (CMC-containing). PT to CMC was negative however, the SPT showed an infiltrated, erythematous reaction after 24 hours.

## Insulin

DHRs to insulin do not appear to have been reported, these reactions usually occur to the components added to insulin preparations [9].

### *Metacresol*

- Injection site reactions (ISRs) independently of the type of human insulin used. PTs were positive to human, pork and isophane insulins, and to metacresol, present in all the insulins tested [10].

- A patient tolerating Humalog (insulin lispro) started using an insulin pump and began to experience itchy at the injection sites. When returning to injections with Novolog

(insulin aspart) the lesions disappeared. Analyzing insulins compounds, metacresol was present in different doses. PT to metacresol was positive [11].

### ***Zinc***

Local cutaneous hypersensitivity reactions in two patients after injection of insulin preparations. Patients noticed the appearance of pruritic, erythematous, papular lesions at each injection site 24 hour after injection. Zinc-insulin and zinc sulphate induced transformation and proliferation of peripheral-blood lymphocytes from these patients and the production of a specific leucocyte inhibitory factor. Intradermal tests (IDTs) to zinc were positive in both patients [12].

### **Local anesthetics**

#### ***Sodium metabisulfite (SMB)***

- Severe edema of the face and neck 2 hours after the injection of a local dental anesthetic (Neo-Lidocaton) containing SMB, not originally declared by the manufacturer [13]. PTs to both the anesthetic and SMB gave delayed positive responses.

- A case of a systemic DHR following a subcutaneous injection of a local anesthetic SMB-containing has been described [14]. The patient developed a generalized eczematous rash on trunk and limbs 3 days after the injection. PT to SMB was positive.

### **Lubricants**

#### ***PG***

Three cases of patients who acquired allergic contact dermatitis from different types of exposure to the lubricant K-Y Lubricating Jelly (PG-containing), have been described

[15]. In the two first cases, the patients also experienced reactions with other unrelated products due to PG (Table 2):

- Severe vulvitis after contact with K-Y Lubricating Jelly, severe dermatitis after the application of a cocoa butter product on the abdomen to prevent stretch marks, and dermatitis flares after the application of certain CS creams and the ingestion of salad dressings containing PG, have been described.

- A severe pruritic dermatitis of the penis and scrotum 24 hours after the patient had intercourse his wife who used K-Y Lubricating Jelly as a vaginal lubricant and formerly, severe ACD to Halog (halcinonide) (PG-containing), have been also reported in the literature.

- The third case described was an allergic contact dermatitis after the exposure to the electrolyte jelly Spectra 360 (PG-containing) used in a transcutaneous nerve-stimulating device and to K-Y Lubricating Jelly, used as substitute.

### **Mineral supplements**

#### ***Sunset Yellow FCF***

A severe skin reaction 24 hours after beginning treatment with Ferrograd (ferrous sulphate) containing Sunset Yellow FCF was described [16]. PTs were performed with the European standard series resulting positive for orange disperse, present in the iron formulation as Sunset Yellow.

### **Non-steroidal anti-inflammatory drugs (NSAIDs)**

#### ***Colloidal silica***

Generalized cutaneous eruption reported with Voltarene (diclofenac). PT to Voltarene was positive. The investigation study of cross-reactivity with other NSAIDs non-

structural related showed positive PTs to Piroxen (piroxicam), Oki (ketoprofen) and Indocid (indometacin), in which colloidal silica was present. PT to colloidal silica was positive [17].

### **Ophthalmic products**

#### ***BAC***

- Allergic contact conjunctivitis in a patient after treatments with two prednisolone ophthalmic solutions, first with Prednefrin and with secondly Inflammase Forte, which with intensified the edema and conjunctivitis [18]. Both preparations contain BAC. PTs were positive with the two preparations and strongly positive to BAC.

Two cases of contact allergy due to BAC after treatment with Propine (dipivefrin hydrochloride) and Timoptol (timolol maleate) were described [19]. PTs were in both positive to BAC.

#### ***Thimerosal***

A total of 38 patients were studied because of ocular redness, irritation, and corneal changes apparently related to soft contact lens wear. Solutions containing thimerosal had been used by all of the patients for lens care, and 31 responded to an ocular challenge with a thimerosal-preserved lens lubricant. Twenty-seven of these 31 also reacted to thimerosal PTs. Hypersensitivity to thimerosal was assumed to be responsible of the clinical findings [20,21].

In another study performed with 36 patients with thimerosal-induced follicular allergic contact conjunctivitis, 18 of them had been using thimerosal-containing eye drops and 13 used thimerosal-containing solutions for their contact lenses. All patients showed positive PTs to thimerosal [22].

- A patient with a two-year history of episodes of dermatitis, eyelids swelling and burning eyes, and treated with various eye drops without resolution, showed positive PTs to thimerosal, phenylmercuric borate and the thimerosal-containing eye drops he used. Phenylmercuric borate hypersensitivity was interpreted assumed as a cross-reactivity with thimerosal, due to presence of a mercury compound in both allergens [23].

### **Parenteral medications**

#### ***Benzyl alcohol (BnOH)***

ACD due to BnOH after injection of sodium tetradecyl sulfate, a sclerosing agent used for the treatment of varicose veins. PT to BnOH was positive [24].

### **Topical medications**

#### ***Ascorbyl tetraisopalmitate***

Severe ACD caused by ascorbyl tetraisopalmitate (an ester-modified ascorbic acid agent) contained in Atopiclair, a non-steroidal anti-inflammatory cream used for the management of atopic dermatitis [25]. PTs were performed with the ingredients of the cream provided by manufacturer. The PT to ascorbyl tetraisopalmitate was positive. Vitamin C from food was well tolerated by the patient.

#### ***BnOH and Isopropyl palmitate***

Reaction with Visderm cream (amcinonide) due to BnOH and isopropyl palmitate [26]. PTs were positive to the cream and these two excipients.

#### ***Cetostearyl alcohol***

ACD due to cetostearyl alcohol in hydrocortisone butyrate lipocream [27]. The only constituent of the cream to which patient reacted showing positive PTs was cetostearyl

alcohol (Lanette O), which is a component of lanolin and which cross-reacts with wool alcohols and PTs resulted also positive.

### ***Chlorocresol and PG***

Two cases of ACD with Dermovate cream (17-clobetasol propionate) due to chlorocresol and PG were described [28]. PTs were positive to chlorocresol and PG.

### ***Diocetyl sodium sulfosuccinate (DSS)***

ACD after treatment with Esperson gel (desoximetasona) due to DSS was described [29]. PTs performed with the excipients of Esperson both gel and ointment supplied by the manufacturer, showed a strong positive result to DSS.

### ***Edetic acid (EDTA)***

A case of ACD to EDTA as excipient contained in the formulation of Locacorten-Vioform paste was described [30]. PTs were positive to sodium edetate.

### ***1,2,6-Hexanetriol***

ACD after treatment with a fluocinonide cream due to 1,2,6-hexanetriol was described [31]. PTs performed with the cream ingredients showed positive reaction to 1,2,6-hexanetriol.

### ***Parabens***

Three patients experienced ACD after the application of Cortaid cream (hydrocortisone acetate) containing methyl and butyl parabens [32]. PTs to the cream and a paraben mix (Hollister-Stier Laboratories) were strongly positive. However, negative PTs were obtained to the various cream ingredients aside from the parabens. As author commented, one patient was of particular interest since he displayed the so-called “paraben paradox”. The patient had applied the cream to his left axilla for an irritated excoriation. He subsequently developed a widespread dermatitis of the left axilla, chest, and upper abdomen requiring systemic corticosteroid treatment.

Two weeks after the dermatitis had subsided, he used a deodorant spray (parabens-containing) to both axillae. Only the previously involved left axilla flared. The right axilla remained uninvolved. Such event is an example of that paraben-sensitive individuals can use paraben-containing topical applications providing the skin that is not previously eczematized, nor has been the site of a previous dermatitis. For this reason, in order to obtain a positive reaction by PTs on normal skin, author recommended a concentration of 15% parabens, at least fifteen times stronger than the parabens concentrations used in topical medications or cosmetics (usually less than 1%) [32].

### ***Polyethylene glycol (PEG)***

The incidence of contact sensitivity to PEGs of different molecular weight among 120 patients with suspected topical medicament sensitivity was 6.7%, as reported [33]. In a more recent study to investigate the prevalence of ACD caused by PEG in 836 patients, 4.2% patients showed positive PTs to PEG, and this sensitivity was almost exclusively related with nitrofurazone allergy [34].

In relation to nitrofurazone preparations, several cases of reactions has been described after the use of Furacin (PEG-containing):

- ACD reactions due to PEG were described in two patients [35]. PTs to PEG 300 and 400, were strongly positives.
- A case of eczema following the use of Furacin was described [36]. PTs to PEG 300 and 400, were positive.
- A case of worsening dermatitis after the application of Furacin was described [37]. PTs to PEGs mix, PEG 300 and PEG 400, were positive.
- Five cases of ACD with local eczematous lesions 24-48 hours after application of Furacin were reported [38]. PTs to PEG were positive in three patients.

### ***Propyl gallate***

A case of ACD due to propyl gallate contained in desonide cream (Locapred) was described [39]. PTs were both positive to the cream and propyl gallate.

### ***PG***

Three cases of local ACD to Zovirax (aciclovir) cream, were described [40]. PTs were positive to the entire product and negative to aciclovir. Regarding PTs to PG, two patients were negative one at concentrations 2% and the other at 5% in petrolatum (pet), but positive the first patient at 5% pet and the second at 10% glycerin. PTs performed to the third patient were positive to PG both at 5% pet and 10% aqueous (aq). These cases illustrate the frequency of false negative reactions to PG, suggesting PG should be used at concentrations 10-20% or in other vehicles than pet as glycerin or aq solution.

### ***SMB***

Two cases of ACD due to SMB as a compound of Trimovate cream were described [41]. PTs to SMB were positive in both patients.

### ***Sodium sulfite***

A case of ACD due to sodium sulfite contained in a ketoconazole cream (Nizoral) has been described [42]. PTs were strongly positive to the cream, to an identical control cream base (without the active ingredient ketoconazole) and to sodium sulfite.

### ***Sorbitan sesquioleate (SSO)***

In a study to investigate the relevance of SSO as sensitizer performed with 112 dermatitis patients, 8.9% patients showed positive PTs to SSO, 0.9% to sorbitan monooleate, and 1.8% to both. Of the SSO-positive patients 75% were using topical CS preparations emulsified with sorbitan derivatives or sorbitol, and 15.4% of the sorbitan-positive patients exhibited a concurrent CS allergy, confirming the association between sorbitan emulsifiers, CS use and the ACD development [43].

In this sense, a case of ACD to CS preparations was described in a patient with history of intolerance to various topical preparations [44]. PTs were positive to Dermovate ointment and cream, with an irritant reaction to Betnovate N ointment. PTs to the constituents of the three preparations were performed. Only the PT to SSO was positive.

## **Ultrasound gels**

### ***Imidazolidinyl urea***

Reactions with unrelated products due to imidazolidinyl urea [45] (Table 2). A reaction after the first application of ultrasound gel (Meditec SRL) and formerly, with a sunscreen lotion (Avon), have been described. PTs were positive to triethanolamine, the gel and the sunscreen (both containing imidazolidinyl urea). PTs with the components of the sunscreen provided by the manufacturer, were positive to triethanolamine and imidazolidinyl urea.

### ***Methyldibromo glutaronitrile (MDBGN)***

Reactions in two patients after application of gels containing the preservative Euxyl K 400 (MDBGN-containing). For one patient, SPT to the gel was negative but positive PTs with gel and Euxyl K 400 [46]. In the second patient, PTs were positive to Euxyl K 400, MDBGN and the gel, that manufacturer confirmed contained Euxyl K 400 [47].

### ***PG***

- ACD after application of Aquasonic 100 gel (PG-containing). PT was positive to PG [48].
- Eczematous local reaction after Geleco gel (PG-containing) application. PTs were performed with the gel and its preservatives, and PG resulted positive [49].
- ACD after Ultra/Phonic Conductivity Gel application. PTs with the gel, its PG compounds, and a commercial PG, were positive [50].

## **Vaccines**

### ***Formaldehyde***

Systemic ACD on the anterior chest and shoulders 48 hours after IM injection of influenza vaccine Agriflu (formaldehyde-containing) in the right deltoid muscle. PT to formaldehyde was positive [51].

## **Wound Dressings**

### ***CMC***

Reactions with unrelated products due to CMC [3] (Table 2). A patient with intolerance to a wound dressing (CMC-containing) for leg ulcers developed a chronic generalized urticaria. Chronologically, the urticaria had appeared when pills containing levothyroxine (a thyroid hormone) had been introduced. IDTs performed with CMC were positive.

### ***Colophonium***

ACD due to a modified colophonium present in the hydrocolloid dressing Combiderm [52]. PTs were positive to this dressing and to a modified colophonium derivative, glyceryl rosinate, however not to the unmodified gum rosin or colophonium 20% pet. as in the standard series. The reaction to glyceryl rosinate probably represent cross-sensitivity with the modified colophonium derivative used in Combiderm, the presence (but not the exact nature) of which was showed by the manufacturer. As authors' conclusions, for patients where ACD from hydrocolloid dressings is suspected and colophonium tests negative, PT to modified colophonium derivatives should be performed. Furthermore, as the complete composition of wound dressings is often

unknown, is necessary advocate requirements for labelling of those and in fact all medically used devices.

### **Conclusions**

The number and variety of reported cases of DHRs caused by the excipients highlights the importance that all the excipients contained in the formulation of a medication should be listed in the package insert, thus avoiding the need to request to the manufacturers the compounds list. An accurate labeling of the preparations and the standardization of the excipients nomenclature could facilitate the diagnosis of the allergic reactions and the implementation of safe avoidance strategies to prevent future reactions in the sensitized patients.

Finally, it would be very useful to provide to patients allergic to excipients a list of commercial products that contain the trigger component as well as the alternatives, since the excipients may be present in drugs that may be needed throughout life.

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**Table 1.** Excipients involved in the delayed hypersensitivity reactions reported with different type of medications.

Type of medication	Excipients							
<b>AEDs</b>	CMC [3]							
<b>Antihistamines</b>	PG [5,6]							
<b>Anxiolytics</b>	PG [7]							
<b>CS</b>	BAC [8]	CMC [3]						
<b>Insulin</b>	Metacresol [10,11]	Zinc [12]						
<b>Local anesthetics</b>	SMB [13,14]							
<b>Lubricants</b>	PG [15]							
<b>Mineral supplements</b>	Sunset Yellow FCF [16]							
<b>NSAIDs</b>	Colloidal silica [17]							
<b>Ophthalmic products</b>	BAC [18,19]	Thimerosal [20-23]						
<b>Parenteral medications</b>	BnOH [24]							
<b>Topical medications</b>	Ascorbyl tetraisopalmitate [25]	BnOH [26]	Cetostearyl alcohol [27]	Chlorocresol [28]	DSS [29]	EDTA [30]	1,2,6-Hexanetriol [31]	
	Isopropyl palmitate [26]	Parabens [32]	PEG [35-38]	Propyl gallate [39]	PG [28,40]	SMB [41]	Sodium sulfite [42]	SSO [44]
<b>Ultrasound gels</b>	Imidazolidinyl urea [45]	MDBGN [46,47]	PG [48-50]					
<b>Vaccines</b>	Formaldehyde [51]							
<b>Wound dressings</b>	CMC [3]	Colophonium [52]						

Abbreviations: AEDs, antiepileptic drugs; BAC, benzalkonium chloride; BnOH, benzyl alcohol; CMC, carboxymethylcellulose; CS, corticosteroid; DSS, dioctyl sodium sulfosuccinate; EDTA, Edetic acid; MDBGN, methyldibromo glutaronitrile; NSAIDs, non-steroidal anti-inflammatory drugs; PEG, polyethylene glycol; PG, propylene glycol; SMB, sodium metabisulfite; sorbitan sesquioleate (SSO).

**Table 2.** Excipients involved in the delayed hypersensitivity reactions reported with unrelated products.

Type of product	Excipients
AED, analgesic and NSAID	CMC [3]
Antihistamines and topical CS	PG [5,6]
Anxiolytic and lubricant	PG [7]
CS and NSAID	CMC [3]
Lubricant, stretch marks cream, CS creams and salad dressings	PG [15]
Lubricant and CS cream	PG [15]
Topical medication and deodorant	Parabens [32]
Ultrasound gels and sunscreen lotion	Imidazolidinyl urea [45]
Wound dressing and a thyroid hormone	CMC [3]

Abbreviations: AEDs, antiepileptic drugs; CMC, carboxymethylcellulose; CS, corticosteroid; NSAID, non-steroidal anti-inflammatory drug; PG, propylene glycol.

**Table 3.** Links to PubChem Database of the National Center for Biotechnology Information (NCBI-PCD) for the description of the excipients involved in the delayed hypersensitivity reactions reported.

<b>Excipient</b>	
<b>Ascorbyl tetraisopalmitate</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/10260680">https://pubchem.ncbi.nlm.nih.gov/compound/10260680</a>
<b>Benzalkonium chloride</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/13740">https://pubchem.ncbi.nlm.nih.gov/compound/13740</a>
<b>Benzyl alcohol</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/244">https://pubchem.ncbi.nlm.nih.gov/compound/244</a>
<b>Carboxymethylcellulose</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/24748">https://pubchem.ncbi.nlm.nih.gov/compound/24748</a>
<b>Cetostearyl alcohol</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/62238">https://pubchem.ncbi.nlm.nih.gov/compound/62238</a>
<b>Chlorocresol</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/1732">https://pubchem.ncbi.nlm.nih.gov/compound/1732</a>
<b>Colloidal silica</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/24261">https://pubchem.ncbi.nlm.nih.gov/compound/24261</a>
<b>Colophonium</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/substance/121147430">https://pubchem.ncbi.nlm.nih.gov/substance/121147430</a>
<b>Diocetyl sodium sulfosuccinate</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/23673837">https://pubchem.ncbi.nlm.nih.gov/compound/23673837</a>
<b>Edetic acid</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/6049">https://pubchem.ncbi.nlm.nih.gov/compound/6049</a>
<b>Formaldehyde</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/712">https://pubchem.ncbi.nlm.nih.gov/compound/712</a>
<b>1,2,6-Hexanetriol</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/7823">https://pubchem.ncbi.nlm.nih.gov/compound/7823</a>
<b>Imidazolidinyl urea</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/38258">https://pubchem.ncbi.nlm.nih.gov/compound/38258</a>
<b>Isopropyl palmitate</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/8907">https://pubchem.ncbi.nlm.nih.gov/compound/8907</a>
<b>Metacresol</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/342">https://pubchem.ncbi.nlm.nih.gov/compound/342</a>
<b>Methyldibromo glutaronitrile</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/61948">https://pubchem.ncbi.nlm.nih.gov/compound/61948</a>
<b>Polyethylene glycol</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/174">https://pubchem.ncbi.nlm.nih.gov/compound/174</a>
<b>Propyl gallate</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/4947">https://pubchem.ncbi.nlm.nih.gov/compound/4947</a>
<b>Propylene glycol</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/1030">https://pubchem.ncbi.nlm.nih.gov/compound/1030</a>
<b>Sodium metabisulfite</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/656671">https://pubchem.ncbi.nlm.nih.gov/compound/656671</a>
<b>Sodium sulfite</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/24437">https://pubchem.ncbi.nlm.nih.gov/compound/24437</a>
<b>Sorbitan sesquioleate</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/6433515">https://pubchem.ncbi.nlm.nih.gov/compound/6433515</a>
<b>Sunset Yellow</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/17730">https://pubchem.ncbi.nlm.nih.gov/compound/17730</a>
<b>Thimerosal</b>	<a href="https://pubchem.ncbi.nlm.nih.gov/compound/16684434">https://pubchem.ncbi.nlm.nih.gov/compound/16684434</a>

**Table 4.** Concentrations used to perform the skin tests with each excipient.

Excipient	Intradermal Test	Patch Test
Ascorbyl tetraisopalmitate		0.05% liquid paraffin or aq. [25]
BAC		0.1% aq. [8]; 1:750, 1:1000 aq. [18]
BnOH		5% pet. [24,26]
CMC	1 mg/ml [3]	Pure, 30% aq. and 30% pet. [3]
Cetostearyl alcohol		1,2 and 5% pet. [27]
Chlorocresol		2% pet. [28]
Colloidal silica		10% pet. [17]
Colophonium and modified colophonium glyceryl rosinate		20% pet. [52]
DSS		1% aq. [29]
EDTA		Sodium edetate 1% aq. or pet. [30]
Formaldehyde		1 and 10% aq. [51]
1,2,6-Hexanetriol		0.5, 2.5 and 5% pet. [31]
Imidazolidinyl urea		2% pet. [45]
Isopropyl palmitate		2% pet. [26]
Metacresol		5% pet. [10]
MDBGN		0.3% pet. [47]
Parabens		15% unspecified vehicle [32]
PEG		PEG 300 3% aq., PEG 400 (as is) [36]; PEGs mix 4% pet., PEG 300 4% pet. and PEG 400 (as is) [37]; PEG unspecified 4% pet. [38]
PG		30% aq. [6]; 5% aq. [7]; 10% aq. [28]; 5% pet., 10% glycerin or 10% aq [40]; 2.5% aq. [48]; 2,5,10 and 20% aq. [49]; 0.1,1,10% aq. and original [50]
SMB		5% pet. [13]; 1% pet. [14]
Sodium sulfite		0.2 and 2% aq. and 0.2,2 and 5% pet. [42]
SSO		20% pet. [43]; 10% unspecified vehicle [44]
Thimerosal		0.1% pet [22]
Zinc	70 µg (Zn <sup>2+</sup> ) (zinc sulphate solution) [12]	

Abbreviations: (aq.), aqueous; BAC, benzalkonium chloride; BnOH, benzyl alcohol; CMC, carboxymethylcellulose; DSS, dioctyl sodium sulfosuccinate; EDTA, Edetic acid; MDBGN, methyldibromo glutaronitrile; (pet.), petrolatum; PEG, polyethylene glycol; PG, propylene glycol; SMB, sodium metabisulfite; sorbitan sesquioleate (SSO).

Accepted Article