

# Delayed Hypersensitivity Reactions Caused by Drug Excipients: A Literature Review

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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 record the DHRs described with various 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 apart 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-reviewed 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 involved excipients for each type of medication.

## DHRs Due to Excipients Reported With Various Types of Medications

The excipients involved in the DHRs described in this review article are shown in Tables 1 and 2. A link to the 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

### *Carboxymethylcellulose*

DHRs to unrelated products due to carboxymethylcellulose (CMC) have been reported [3] (Table 2). A patient who developed drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome caused by carbamazepine (Tegretol, CMC-containing) subsequently experienced eczematous rashes following the intake of pills containing paracetamol and a nonsteroidal anti-inflammatory drug (NSAID). Because the results of both the patch test and the skin prick test (SPT) were negative for CMC, an oral provocation test with a cumulative dose of 1.115 mg of CMC was performed under hospital surveillance. The patient developed a generalized eczematous rash on the following day.

## Antihistamines

### *Propylene Glycol*

Propylene glycol (PG), an emollient and emulsifier found in cosmetics, medications, and food, was 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 this allergen. Optimal patch test concentrations and reading intervals have been a topic of debate for many years because PG causes both irritant contact dermatitis and allergic contact

dermatitis (ACD), and it is often difficult to differentiate between these types of reactions. The most recent update for the American Contact Dermatitis Society's core series recommends testing only with 100% PG. The confounding characteristics of patch tests to PG increase the relevance of an accurate interpretation. Crescendo reactions, which show little or no activity at 48 hours but become stronger at 96 hours, suggest contact allergy. Decrescendo reactions, which present weakly at 48 hours but disappear by 96 hours, are probably irritant reactions [4].

In the present review, reactions due to PG are reported with antihistamines, anxiolytics, lubricants, topical medications, and ultrasound gels.

DHRs with antihistamines and other unrelated products due to PG (Table 2) have also been documented, as follows:

- ACD with positive patch test results to PG. A sensitized patient improved significantly after switching to a PG-free topical corticosteroid. However, since dermatitis flared annually during seasonal rhinitis, it was discovered that the patient used oral antihistamines, which also contained PG [5].
- Eczematous lesions or rash with positive patch test results to PG. Dermatitis improved after switching to a PG-free topical corticosteroid. Two flare-ups of the patient's rash during seasonal use of oral cetirizine syrup led to the discovery that the antihistamine formulation contained PG [6].
- Atopic dermatitis treated with topical corticosteroids and oral antihistamines, without improvement. The patient had a positive patch test result to PG, and the skin lesions resolved after switching to a PG-free hydroxyzine syrup [6].

## Anxiolytics

### *Propylene Glycol*

DHRs due to PG have been observed with unrelated products [7] (Table 2). The patient experienced systemic contact dermatitis after administration of injectable diazepam (Valium) and with a lubricant K-Y Jelly during a gynecological examination. Both products contained PG. The patch test result to PG was positive.

## Corticosteroids

### *Benzalkonium Chloride*

Three cases of systemic allergic reactions induced by benzalkonium chloride (BAC) have been described after the use of a mometasone nasal spray. Patient histories and the positive results of the patch tests performed in 2 of the patients point to a diagnosis of type IV hypersensitivity reactions due to BAC [8].

### *Carboxymethylcellulose*

DHRs reported with unrelated products due to CMC [3] (Table 2) took the form of flexural dermatitis 3 days after an intra-articular injection of a betamethasone dipropionate preparation (CMC-containing) and, a few months later,

Table 1. Excipients Involved in the Delayed Hypersensitivity Reactions Reported With Different Type of Medications

Type of Medication	Excipient							
AEDs	CMC [3]							
Antihistamines	PG [5,6]							
Anxiolytics	PG [7]							
Corticosteroids	BAC [8]		CMC [3]					
Insulin	Metacresol [10,11]		Zinc [12]					
Local anesthetics	SMB [13,14]							
Lubricants	PG [15]							
Mineral supplements	Sunset Yellow FCF [16]							
NSAIDs	Colloidal silica [17]							
Ophthalmic products	BAC [18,19]		Thimerosal [20-23]					
Parenteral medications	BnOH [24]							
Topical medications	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]
Ultrasound gels	Imidazolidinyl urea [45]	MDBGN [46,47]	PG [48-50]					
Vaccines	Formaldehyde [51]							
Wound dressings	CMC [3]		Colophonium [52]					

Abbreviations: AEDs, antiepileptic drugs; BAC, benzalkonium chloride; BnOH, benzyl alcohol; CMC, carboxymethylcellulose; DSS, dioctyl sodium sulfosuccinate; MDBGN, methyl dibromo glutaronitrile; NSAIDs, nonsteroidal anti-inflammatory drugs; PEG, polyethylene glycol; PG, propylene glycol; SMB, sodium metabisulfite; SSO, sorbitan sesquioleate.

maculopapular rash affecting the trunk 24 hours after taking piroxicam pills (CMC-containing). Patch testing to CMC was negative, although the SPT revealed an infiltrated, erythematous reaction after 24 hours.

## Insulin

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

### Metacresol

- Injection site reactions have been reported, independently of the type of human insulin used. Patch test results were positive to human, pork, and isophane insulins and to metacresol, which is present in all the insulins tested [10].

- A patient tolerating insulin lispro (Humalog) started using an insulin pump and began to experience itching at the injection sites. The lesions disappeared when the patient returned to injections with insulin aspart (Novolog). Analysis of the insulin

compounds revealed that metacresol was present in different doses. Patch testing to metacresol was positive [11].

### Zinc

Local cutaneous hypersensitivity reactions were reported in 2 patients after injection of insulin preparations [12]. The patients reported pruritic, erythematous, papular lesions at the injection site 24 hours after injection. Zinc insulin and zinc sulphate induced transformation and proliferation of peripheral blood lymphocytes from these patients and production of a specific leucocyte inhibitory factor. Intradermal tests to zinc were positive in both cases.

## Local Anesthetics

### Sodium Metabisulfite

- Severe edema of the face and neck developed 2 hours after the injection of a local dental anesthetic (Neo-Lidocaton) containing sodium metabisulfite (SMB), which was not originally declared by the manufacturer [13]. Patch

**Table 2.** Excipients Involved in the Delayed Hypersensitivity Reactions Reported With Unrelated Products

Type of Product	Excipient
Antiepileptic drugs, analgesics, and NSAIDs	Carboxymethyl-cellulose [3]
Antihistamines and topical corticosteroids	Propylene glycol [5,6]
Anxiolytic and lubricant	Propylene glycol [7]
Corticosteroids and NSAIDs	Carboxymethyl-cellulose [3]
Lubricant, stretch marks cream, corticosteroid creams, and salad dressings	Propylene glycol [15]
Lubricant and corticosteroid cream	Propylene glycol [15]
Topical medication and deodorant	Parabens [32]
Ultrasound gels and sunscreen lotion	Imidazolidinyl urea [45]
Wound dressing and a thyroid hormone	Carboxymethyl-cellulose [3]

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

testing to both the anesthetic and SMB yielded delayed positive responses.

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

## Lubricants

### *Propylene Glycol*

Three cases of patients who acquired ACD from different types of exposure to the lubricant K-Y Jelly (PG-containing) have been reported [15]. In the first 2 cases, the patients also experienced DHRs with other unrelated products due to PG (Table 2):

- The reactions reported were severe vulvitis after contact with the lubricant, 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 corticosteroid creams and the ingestion of salad dressings containing PG.

**Table 3.** Links to the PubChem Database of the National Center for Biotechnology Information (NCBI-PCD) for the Description of the Excipients Involved in the Delayed Hypersensitivity Reactions Reported

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

- Severe pruritic dermatitis affecting the penis and scrotum 24 hours after the patient had intercourse with his wife, who used a vaginal lubricant. The patient had previously experienced severe ACD to halcinonide (Halog, PG-containing).
- The third case of ACD occurred after exposure to an electrode gel (Spectra 360, PG-containing) used in a transcutaneous nerve-stimulating device and to K-Y Jelly, which was used as substitute.

## Mineral Supplements

### Sunset Yellow FCF

A severe skin reaction occurred 24 hours after beginning treatment with ferrous sulphate (Ferrograd) containing Sunset Yellow FCF [16]. Patch testing performed with

the European standard series yielded positive results for disperse orange, which was present in the iron formulation as Sunset Yellow.

## Nonsteroidal Anti-inflammatory Drugs

### Colloidal Silica

A generalized cutaneous eruption was reported with diclofenac (Voltarene). Patch testing to Voltarene was positive. The investigation of cross-reactivity with other, non-structurally related NSAIDs showed positive patch test results with piroxicam (Piroxen), ketoprofen (Oki), and indomethacin (Indocid), in which colloidal silica was present. Patch testing to colloidal silica was positive [17].

## Ophthalmic Products

### *Benzalkonium Chloride*

A patient developed allergic contact conjunctivitis after treatment with 2 BAC-containing prednisolone ophthalmic solutions, first with Prednefrin and second with Inflamase Forte, which intensified the edema and the conjunctivitis [18]. Patch tests were positive in both cases and strongly positive with BAC.

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

### *Thimerosal*

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

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

– In the case of a patient with a 2-year history of episodes of dermatitis, eyelid swelling, and burning eyes treated with various eye drops without resolution, positive patch test results were recorded for thimerosal, phenylmercuric borate, and the thimerosal-containing eye drops he used. Phenylmercuric borate hypersensitivity was considered to be due to cross-reactivity with thimerosal owing to presence of a mercury compound in both allergens [23].

## Parenteral Medications

### *Benzyl Alcohol*

ACD due to benzyl alcohol has been reported after injection of sodium tetradecyl sulfate, a sclerosing agent used for the treatment of varicose veins. Patch testing with benzyl alcohol was positive [24].

## Topical Medications

### *Ascorbyl Tetraisopalmitate*

Severe ACD is reported to have been caused by ascorbyl tetraisopalmitate (an ester-modified ascorbic acid agent) contained in Atopiclair, an NSAID used for the management of atopic dermatitis [25]. Patch tests were performed with the ingredients of the cream provided by manufacturer. The patch test to ascorbyl tetraisopalmitate was positive. Vitamin C from food was well tolerated by the patient.

### *Benzyl Alcohol and Isopropyl Palmitate*

A reaction was reported to amcinonide (Visderm cream) due to benzyl alcohol and isopropyl palmitate [26]. Patch testing was positive to the cream and to both excipients.

### *Cetostearyl Alcohol*

ACD due to cetostearyl alcohol has been reported after use of hydrocortisone butyrate lipocream [27]. The only constituent of the cream to which the patient reacted (positive patch test results) was cetostearyl alcohol (Lanette O), which is a component of lanolin and cross-reacts with wool alcohols.

### *Chlorocresol and Propylene Glycol*

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

### *Diocetyl Sodium Sulfosuccinate*

ACD after treatment with desoximetasone (Esperson gel) due to dioctyl sodium sulfosuccinate has been reported [29]. Patch testing performed with the excipients of Esperson in both gel and ointment supplied by the manufacturer showed a strong positive result to dioctyl sodium sulfosuccinate.

### *EDTA*

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

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

ACD has been reported after treatment with a fluocinonide cream due to 1,2,6-hexanetriol [31]. Patch testing performed with the ingredients of the cream confirmed a positive reaction to 1,2,6-hexanetriol.

### *Parabens*

Three patients experienced ACD after the application of hydrocortisone acetate cream (Cortaid) containing methyl and butyl parabens [32]. Patch tests to the cream and a paraben mix (Hollister-Stier Laboratories) were strongly positive. However, the results of patch tests were negative to the various ingredients other than the parabens. As the 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 irritated excoriation. He subsequently developed 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 (paraben-containing) on both axillae. Only the previously involved left axilla flared. The right axilla remained unaffected. Such an event illustrates that paraben-sensitive individuals can use paraben-containing topical applications providing the skin is not previously eczematous or has not been the site of a previous dermatitis. For this reason, in order to obtain a positive reaction in patch tests on normal skin, the author recommended a concentration of 15% parabens, at least

15 times stronger than the paraben concentrations used in topical medications or cosmetics (usually less than 1%) [32].

### *Polyethylene Glycol*

The incidence of contact sensitivity to polyethylene glycol (PEG) of different molecular weights in 120 patients with suspected sensitivity to topical medication was 6.7% [33]. In a more recent study to investigate the prevalence of ACD caused by PEG in 836 patients, 4.2% had positive patch test results to PEG; this sensitivity was almost exclusively associated with allergy to nitrofurazone [34].

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

- ACD due to PEG was reported in 2 patients [35]. Patch test results to PEG 300 and 400 were strongly positive.
- A case of eczema following the use of Furacin was described [36]. Patch test results to PEG 300 and 400 were positive.
- A case of worsening dermatitis after the application of Furacin was described [37]. Patch test results to PEG 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]. The results of the patch test to PEG were positive in 3 patients.

### *Propyl Gallate*

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

### *Propylene Glycol*

Three cases of local ACD to acyclovir cream (Zovirax) have been described [40]. Patch test results were positive to the entire product and negative to acyclovir. As for patch testing with PG, the results were negative for 2 patients, one at a concentration of 2% and the other at a concentration of 5% in petrolatum (pet), although the result was positive for the first patient at 5% pet and the second at 10% glycerin. Patch tests performed in a 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 that PG should be used at concentrations of 10%-20% or in vehicles other than pet such as glycerin or aq solution.

### *Sodium Metabisulfite*

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

### *Sodium Sulfite*

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

### *Sorbitan Sesquioleate*

In a study to investigate the relevance of sorbitan sesquioleate (SSO) as a sensitizer performed with 112 dermatitis patients, 8.9% had positive patch test results to SSO, 0.9% to sorbitan mono-oleate, and 1.8% to both. Of the SSO-positive patients, 75% were using topical corticosteroid preparations emulsified with sorbitan derivatives or sorbitol, and 15.4% of the sorbitan-positive patients exhibited concurrent corticosteroid allergy, thus confirming the association between sorbitan emulsifiers, use of corticosteroids, and development of ACD [43].

In this sense, a case of ACD to corticosteroid preparations was described in a patient with a history of intolerance to various topical preparations [44]. Patch test results were positive to Dermovate ointment and cream, with an irritant reaction to Betnovate N ointment. In patch testing with the constituents of the 3 preparations, only the result to SSO was positive.

## **Ultrasound Gels**

### *Imidazolidinyl Urea*

DHRs due to imidazolidinyl urea with unrelated products were reported after the first application of ultrasound gel (Meditec SRL) in a patient who had previously reacted to sunscreen lotion (Avon) [45] (Table 2). Patch test results were positive with triethanolamine, the gel, and the sunscreen (both containing imidazolidinyl urea), and those with the components of the sunscreen provided by the manufacturer were positive to triethanolamine and imidazolidinyl urea.

### *Methyldibromo Glutaronitrile*

Reactions to methyldibromo glutaronitrile have been reported in 2 patients after application of gels containing the preservative Euxyl K 400 (methyldibromo glutaronitrile-containing). For one patient, the result of SPT with the gel was negative but the patch test results with gel and Euxyl K 400 were positive [46]. In the second patient, patch test results were positive to Euxyl K 400, methyldibromo glutaronitrile, and the gel, which was confirmed to contain Euxyl K 400 by the manufacturer [47].

### *Propylene Glycol*

- In ACD after application of Aquasonic 100 gel (PG-containing), patch testing was positive to PG [48].
- In a case of eczematous local reaction after application of Geleco gel (PG-containing), patch testing performed with the gel and its preservatives was positive for PG [49].
- Patch testing to assess ACD after application of Ultra/Phonic Conductivity Gel was positive for the gel, its PG compounds, and a commercial PG [50].

## **Vaccines**

### *Formaldehyde*

Patch testing was performed to assess systemic ACD on the anterior chest and shoulders 48 hours after intramuscular

injection of the influenza vaccine Agriflu (formaldehyde-containing) in the right deltoid muscle. The result was positive for formaldehyde [51].

## Wound Dressings

### Carboxymethylcellulose

DHR with unrelated products due to CMC [3] (Table 2) was reported in a patient who developed chronic generalized urticaria after application of a wound dressing (CMC-containing) for leg ulcers. Chronologically, the urticaria appeared when pills containing levothyroxine (a thyroid hormone) had been introduced. Intradermal testing with CMC was positive.

### Colophonium

ACD was reported to be due to a modified colophonium present in a hydrocolloid dressing (Combiderm) [52]. Patch testing was positive for this dressing and for a modified colophonium derivative, glyceryl rosinatate, but not for the unmodified gum rosin or colophonium 20% pet as in the standard series. The reaction to glyceryl rosinatate probably represents cross-sensitivity with the modified colophonium derivative used in Combiderm, the presence (but not the exact nature) of which was shown by the manufacturer. The authors concluded that in cases where ACD from hydrocolloid dressings is suspected and colophonium test results are negative, patch testing with modified colophonium derivatives should be performed. Furthermore, as the complete composition of wound dressings is often unknown, it is necessary to advocate mandatory labelling of the products used in these and all other medical devices.

## Conclusions

The number and variety of reported cases of DHRs caused by excipients highlights the importance of listing all the excipients contained in the formulation of a medication in the package insert, thus obviating the need to request the list of compounds from the manufacturer. Accurate labeling of the preparations and standardization of excipient nomenclature could facilitate the diagnosis of allergic reactions and the implementation of safe avoidance strategies to prevent future reactions in sensitized patients.

Finally, it would be very useful to provide to excipient-allergic patients with a list of commercial products that contain the trigger component, as well as alternatives, since the excipients may be present in drugs that have to be administered over a patient's lifetime.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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