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REVIEW ARTICLE

Excipients in pharmaceuticals: mechanisms of hypersensitivity and the role of global pharmacovigilance

Ruba Malkawi[1] · **Lora Altahrawi**[2]

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Abstract

Excipients are important inactive components in drug formulations that ensure stability, bioavailability, and patient compliance. However, emerging evidence suggests that certain excipients, once considered inert, can cause hypersensitivity reactions in certain individuals. Such reactions include mild erythema due to systemic anaphylaxis and create clinical challenges that are difficult to handle. This review presents a systematic review of the existing literature on excipient hypersensitivity, with specific attention paid to commonly implicated excipients such as polyethylene glycol (PEG), parabens, and tartrazine. Hypersensitivity mechanisms (immune-mediated [IgE, T-cell] and non-immune) are discussed, along with their clinical features and diagnostic challenges. In addition, geographic variations in reporting are discussed, which in turn focus on the role of pharmacovigilance in the reduction of risk. Geographic variations in excipient hypersensitivity reporting are also discussed, highlighting disparities in pharmacovigilance efforts across different regions. This review also discusses recent work, regulatory issues, and desensitization protocols for the control of hypersensitivity reactions. Persistent surveillance and individual strategies are needed to enhance patient safety in the context of excipient-induced hypersensitivity.

Keywords Excipients hypersensitivity · Polyethylene glycol (PEG) · Pharmacovigilance · IgE-mediated reactions · T-cell mediated hypersensitivity · Anaphylaxis

1 Introduction

Excipients are inactive ingredients in pharmaceutical products that have crucial functions in drug formulations (Patel et al. 2020). Among their many applications, they enhance stability, regulate release, and improve palatability and appearance. Although excipients have traditionally been consider as inactive components, some studies now point to the possibility that they may cause adverse reactions in some subjects by triggering excipient hypersensitivity (Bruusgaard-Mouritsen et al. 2022).

Historically, excipients have been of natural origin, including honey, wax, and plant extracts, the use of which has been recorded since the early periods of Egyptian and Greek medicine. Currently, the pharmaceutical industry uses a large number of synthetic and natural excipients, each formulated for a particular purpose (Table 1) ((Petrovska 2012; Metwaly et al. 2021)).

Based on our studies, excipient hypersensitivity is one of the topics that is largely ignored within the pharmaceutical sciences, even though an increasing number of hypersensitivity reactions due to non-active materials of the drug substance are emerging. Although excipients are critical components for drug stability and delivery, their ability to cause adverse reactions, from mild cutaneous irritation to anaphylaxis, is inadequately discussed in the literature to date. Our review also points out the requirement to give a new importance to excipient hypersensitivity, particularly in considering the growing complexity of drug formulations and the ubiquitous use of excipients like polyethylene glycol (PEG), parabens, and artificial pigments. Greater knowledge of these hypersensitivity reactions is essential to ensure patient safety, inform regulatory guidelines, and move towards personalized medicine.

✉ Ruba Malkawi
r.malkawi@jadara.edu.jo

Lora Altahrawi
Lora.altahrawi2@dmu.ac.uk

[1] Jadara University, Pharmacy Department, P.O.Box 733, Irbid 21110, Jordan

[2] Leicester School of Pharmacy, Faculty of Health and Life Sciences, De Montfort University, Leicester, UK

Table 1 Classification of Excipients and Their Functions in Pharmaceuticals (Caballero et al. 2982; Seth et al. 2024)

Excipients Category	Common Examples	Function in Formulation	Potential for Hypersensitivity
Preservatives	Parabens, Benzyl Alcohol	Prevent microbial growth	High
Dyes and Colorants	Tartrazine, Red Dye 40	Improve appearance, aid identification	Moderate to High
Stabilizers	Polyethylene Glycol (PEG), Polysorbate 80	Maintain chemical stability	High
Binders and Fillers	Lactose, Starch	Bulking agent	Moderate
Sweeteners	Aspartame, Sorbitol	Improve taste	Low
Lubricants	Magnesium Stearate	Facilitate tablet manufacturing	Low

1.1 Excipients hypersensitivity

Excipient hypersensitivity refers to a clinical manifestation in which a patient experiences an unanticipated adverse effect after exposure to one or more excipients in the drug products. Both mild and severe types are possible, ranging from skin rash to anaphylaxis, and could create huge diagnostic and clinical management difficulties for patients (Caballero et al. Aug. 2021).

Recent studies have demonstrated that hypersensitivity reactions to excipients can occur through immune-as well as non-immune-mediated pathways (Pintea, et al. 2021). Immune-mediated responses are characterized by the activation of the immune system of the host, in particular, IgE antibodies or T-cell responses. In contrast, non-immune-mediated reactions could involve direct irritant effects or pharmacological effects that do not involve the immune system. Although the exact prevalence of excipient hypersensitivity is difficult to ascertain, it is increasingly recognized in clinical practice as a cause of unexplained drug reactions (Han et al. 2022). Table 2 provides examples of in vivo case studies of excipient hypersensitivity that generated relevant clinical responses. It offers specific examples of the presentation and management of excipient-associated hypersensitivity in various patient groups.

Purpose Through real-life case studies, this table presents the effects of hypersensitivity to excipients, with important clinical and personal repercussions. Specific examples illustrate how excipient-related hypersensitivity manifests and is controlled in a variety of patient groups.

Table 3 summarizes the clinical manifestations of excipient hypersensitivity categorized by organ system, along with the most implicated excipients:

1.2 Common excipients linked to hypersensitivity

Several excipients have been found to be potential allergens, some of which are more often associated with hypersensitivity reactions. The main offenders are preservatives, dyes, stabilizers, and other frequently used excipients (Viggiani, et al. 2019).

Table 2 Case Studies of Notable Excipients-Induced Hypersensitivity (Caballero et al. 2982; Seth et al. 2024)

Excipients Involved	Patient Details	Reaction Type	Outcome	Reference
PEG in COVID-19 vaccine	45-year-old male, history of allergies	Anaphylaxis (IgE-mediated)	Immediate administration of epinephrine, full recovery	Filon, et al. 1623)
Parabens in topical cream	32-year-old female, eczema	Contact dermatitis (T-cell mediated)	Resolved with discontinuation of cream, corticosteroid treatment	Rafi, et al. 2024)
Lactose in oral antibiotics	28-year-old male, lactose intolerance	GI upset (Non-immune-mediated)	Switch to lactose-free formulation, symptoms resolved	JanssenDuijghuijsen et al. 2024)
Tartrazine in soft drinks	50-year-old female, asthmatic	Asthma exacerbation (Non-IgE-mediated)	Symptoms managed with bronchodilators, dietary restrictions	Ardern et al. 2001)
Polysorbate 80 in biologic	65-year-old male, cancer patient	Anaphylaxis (IgE-mediated)	Hospitalized, switched to alternate therapy, desensitization attempted	Galateanu et al. 2023)

Table 3 Clinical manifestations of excipient hypersensitivity categorized by organ system

Organ System	Clinical Manifestations	Common Implicated Excipients
Skin	Urticaria, Contact Dermatitis, Angioedema	Parabens, PEG, Dyes, Formaldehyde
Respiratory	Asthma exacerbation, Bronchospasm, Anaphylaxis	Tartrazine, Sulfites, Polysorbate 80
Gastrointestinal	Nausea, Vomiting, Diarrhea, Abdominal pain	Lactose, Mannitol, Sodium Benzoate
Systemic	Anaphylaxis, Hypotension, Multi-organ involvement	PEG, Polysorbate 80, Gelatin

1.2.1 Preservatives

Adding preservatives to pharmaceutical formulations helps avoid microbial contamination and preserves them for a longer time (Teshome et al. 2022). However, they are also one of the most frequent provocateurs of hypersensitivity. Benzyl alcohol, which is currently used in inhalant and injectable formulations, has been implicated in local and systemic allergic reactions (Tripp et al. 2021). Parabens, which are commonly used in creams, lotions, and ophthalmic solutions, have been linked to delayed hypersensitivity reactions in susceptible individuals. Recently, case reports have shown the occurrence of contact dermatitis with topical preparations of parabens (Fisher 1975).

1.2.2 Dyes and colorants

Colorants have many applications in pharmaceuticals for enhancing the aesthetic nature of products. 1,4-dioxane, is a yellow synthetic dye that is among the most frequently referenced excipients that trigger hypersensitivity [especially in persons with aspirin-induced asthma (Weisbrod et al. 2023)]. A study published in the Cochrane Database of Systematic Journal also emphasized the argumented impact of tartrazine in aggravating asthma and provoking a cutaneous reaction (urticaria) in atopy-prone individuals (Ardern et al. 2001).

1.2.3 Stabilizers and surfactants

Excipients (e.g., polysorbates and polyethylene glycol (PEG) act as stabilizers and surfactants in multiple drug formulations. Specifically, PEG has attracted attention in recent years following the onset of hypersensitivity reactions to COVID-19 vaccines (Katz et al. 2022). According to a systematic study, PEG-induced anaphylaxis, although uncommon, is a serious threat to individuals with pre-existing PEG sensitivity (Sellaturay et al. 2021). Similarly, polysorbates, structurally related to PEG, have been associated with hypersensitivity to injectable biologics; especially (Stone, et al. 1540).

1.2.4 Other excipients

Additional excipients that have been linked to hypersensitivity include.

Lactose as a common additive that may trigger reactions in lactose-intolerant persons (Pelto et al. 1998). As mannitol is injectable, it has been implicated in both immune- and non-immune-mediated reactions, especially in patients with underlying mast cell disorders (Buhari et al. 2015). Gelatin, a component of both vaccines and capsules, is associated with IgE-mediated hypersensitivity reactions, especially in patients with a previous exposure to gelatin allergy (Nucera, et al. 2017). Table 4 presents an overview of the most significant studies concerning excipient sensitivity, site, and mechanism.

2 Mechanisms of Hypersensitivity: Immune and Non-immune Pathways

The pathophysiological mechanisms of excipient hypersensitivity are complex, characterized by immune-mediated or non-immune-mediated reactions. Understanding these mechanisms is of great importance for both diagnosis and treatment the hypersensitivity mechanism is illustrated in the following chart. (Figure 1).

2.1 Immune-mediated hypersensitivity

Immune-mediated reactions can be divided into two main categories.

IgE-Mediated Reactions: These are produced when the immune system generates IgE antibodies against excipient(s). After further exposure, the excipient binds to IgE on mast cells and triggers the release of histamine and other inflammatory mediators. The effect is an immediate hypersensitivity response, which may take the form of urticaria, angioedema, or anaphylaxis. Recent work has reported that excipients, such as PEG and gelatin, can induce IgE-mediated anaphylactic responses in susceptible subjects (Abbas et al. 2023).

T-Cell Mediated reactions: Delayed hypersensitive reactions (e.g., contact dermatitis) are usually driven by T cells.

Table 4 Summary of Key Studies on Excipients Hypersensitivity

Excipients Studied	Type of Hypersensitivity	Clinical Manifestations (Location)	Mechanisms Involved	Additional Comments	Ref
Polyethylene Glycol (PEG) in COVID-19 vaccines	IgE-mediated anaphylaxis	Systemic: urticaria, angioedema, respiratory distress (whole body, skin, lungs)	IgE-mediated immediate hypersensitivity	First large-scale documentation of PEG-related anaphylaxis following COVID-19 vaccines. Suggests importance of PEG testing before vaccination in at-risk populations	Picard, et al. 2021a)
Tartrazine (synthetic dye)	Non-IgE-mediated (asthma exacerbation)	Respiratory: bronchospasm, asthma exacerbation (lungs)	Non-immune histamine release, mast cell degranulation	Tartrazine linked to worsening asthma symptoms in individuals sensitive to aspirin. Patients with asthma and aspirin sensitivity are at higher risk	Ardern et al. 2001)
Lactose (filler)	Gastrointestinal intolerance (non-immune)	Gastrointestinal: bloating, diarrhea, cramps (GI tract)	Lactase deficiency (non-immune intolerance)	Commonly seen in individuals with lactose intolerance. Important to differentiate between lactose intolerance and immune-mediated hypersensitivity	Pelto et al. 1998)
Parabens (preservatives) in cosmetics and topical drugs	Delayed-type hypersensitivity (Type IV)	Cutaneous: contact dermatitis (skin)	T-cell mediated delayed hypersensitivity	Patch testing is recommended for diagnosis. Reaction time is delayed, often appearing 48–72 h after exposure	Torfs and Brackman 2020)
Polysorbate 80 (stabilizer in biologics)	Anaphylaxis (IgE and non-IgE-mediated)	Systemic: urticaria, bronchospasm, hypotension (whole body)	IgE and non-IgE mechanisms (direct mast cell activation)	Documented in biologics and vaccines, especially in cancer therapy. Cross-reactivity with PEG can occur	Akarsu et al. 2020)
Benzyl Alcohol (preservative in injectables)	Irritant and allergic contact dermatitis (non-immune and immune)	Cutaneous: local swelling, redness at injection site (skin, subcutaneous tissues)	Irritant and possible T-cell mediated delayed hypersensitivity	Commonly found in injectable drugs, especially anesthetics. Reactions can be localized but may involve systemic effects	Tripp et al. 2021)
Gelatin (used in vaccines and capsules)	IgE-mediated anaphylaxis	Systemic: generalized urticaria, angioedema, gastrointestinal and respiratory involvement	IgE-mediated immune response	Frequently occurs in individuals with food allergies (gelatin) or those with previous reactions to vaccines. Anaphylaxis is rare but severe	Dreskin, et al. 2016)
Mannitol (filler and stabilizer in injectable drugs)	Non-immune-mediated hypersensitivity	Gastrointestinal: nausea, vomiting, diarrhea (GI tract); Systemic: flushing, headaches	Osmotic effects, non-IgE-mediated mast cell activation	Mannitol hypersensitivity reactions are non-immune and often involve GI upset and non-specific systemic symptoms	Tenny et al. Jun. 2024)

Table 4 (continued)

Excipients Studied	Type of Hypersensitivity	Clinical Manifestations (Location)	Mechanisms Involved	Additional Comments	Ref
Propylene Glycol (solvent in oral, topical, and injectable drugs)	Delayed-type hypersensitivity (Type IV)	Cutaneous: eczema-like reactions, contact dermatitis (skin)	T-cell mediated delayed hypersensitivity	Propylene glycol is a common solvent in topical formulations, especially antifungals and corticosteroids. Skin patch testing can confirm diagnosis	Choi et al. 2021)
Chlorhexidine (preservative and antiseptic)	Immediate-type hypersensitivity (Type I)	Cutaneous: urticaria; Respiratory: anaphylaxis (skin, lungs)	IgE-mediated immune response	Anaphylaxis due to chlorhexidine is increasingly reported, particularly in surgical settings or dental procedures where antiseptics are used	Fernandes et al. 2019)
Ethanol (solvent in liquid oral medications)	Irritant and allergic contact dermatitis	Cutaneous: localized redness, stinging, or burning (skin)	Non-immune irritant reactions; rare allergic mechanisms	Mainly an irritant, but can trigger allergic contact dermatitis in sensitive individuals	Lachenmeier 2008)
Tween 80 (Polysorbate 80, emulsifier)	IgE-mediated and non-IgE anaphylaxis	Systemic: anaphylaxis, bronchospasm, hypotension (whole body)	IgE-mediated immune response, non-IgE mast cell degranulation	Widely used in vaccines and biologics. Cross-reactivity with PEG is reported. Anaphylaxis rates are higher in biologic therapies	Schwartzberg and Navari 2018)
Sulfites (preservatives in injectable and oral drugs)	Non-IgE-mediated asthma exacerbation	Respiratory: wheezing, shortness of breath, asthma (lungs)	Sulfite-sensitive bronchoconstriction, non-immune histamine release	Sulfites have been known to worsen asthma, especially in those with a predisposition to sulfite sensitivity. Reactions range from mild to severe	Vally and Misso 2012)
Formaldehyde (preservative in vaccines and cosmetic products)	Delayed-type hypersensitivity (Type IV)	Cutaneous: contact dermatitis (skin)	T-cell mediated delayed hypersensitivity	Mostly linked to contact dermatitis in topical applications, but hypersensitivity to formaldehyde in vaccines has been reported, albeit rarely	Malinauskiene et al. 2015)
Sodium Benzoate (preservative in oral medications)	Non-IgE-mediated hypersensitivity	Gastrointestinal: abdominal pain, bloating (GI tract); Respiratory: wheezing (lungs)	Direct irritation of mucosal surfaces, non-IgE histamine release	Found in many oral formulations, especially in liquid medicines and soft drinks. Intolerance or sensitivity more common than true allergy	Rathee, et al. 2023)

In such instances, the excipient becomes a hapten, reattaches to skin proteins, and causes a delayed hypersensitivity reaction. This form of hypersensitivity is usually attributed to the use of preservatives such as parabens or formaldehyde-releasing agents. A research paper published in 2023 was about excipient-induced delayed hypersensitivity, especially from topical formulations (Tramontana et al. 2023).

2.2 Non-immune mediated hypersensitivity

Hypersensitive non-immune mechanisms do not require an adaptive immune system, but mediate reactions via other biochemical pathways. For example:

Direct Irritant Effects: Certain excipients can irritate the skin/mucosal surfaces directly. For example, benzyl alcohol has been demonstrated to induce transient local irritation around injection sites in susceptible subjects. Histamine Release: Some excipients induce histamine release without the requirement of IgE. This process, termed non-IgE-mediated histamine release, can cause the following symptoms: itching, swelling, and flushing. Mannitol, a diluent used in injectable drug formulations, has been linked to this response (Joshi and Khan 2021). In non-IgE-mediated reactions, excipients directly stimulate mast cells, causing histamine release without specific antibody involvement. These reactions may occur via the direct action of excipients on mast cell membranes or through activation of alternative inflammatory pathways. This leads to symptoms similar to IgE-mediated reactions but occurs without sensitization or prior exposure (Mouri et al. 2022).

3 Clinical manifestations of excipients hypersensitivity

Clinical manifestations of excipient hypersensitivity are greatly different based on the underlying mechanism, the kind of excipient, and the patient's health status. Symptoms can target multiple organ systems and can occur acutely or late (Caballero and Quirce 2020).

3.1 Cutaneous reactions

Cutaneous manifestations are among the most frequent signs of excipient hypersensitivity. These can include:

Urticaria (hives): Acute onset allergic reactions, especially those mediated by IgE, are commonly manifested as hives. Data have shown that PEG and parabens are frequent provocateurs of urticaria in susceptible individuals (Akin et al. 2022).

Angioedema: Circumpatient edema of deeper skin layers, specifically in perioral regions, can occur with hives and is life-threatening if it occurs in the airway (Caballero et al. 2021).

Contact Dermatitis: Hypersensitivity related to delayed reaction, on the most frequent occasions the skin is erythematous, itchy, and inflamed, is often attributed to topical excipients, such as parabens or colorants (Choi et al. 2021).

3.2 Respiratory reactions

Excipients can cause respiratory symptoms, especially in people with a history of asthma or respiratory disease. For example, tartrazine has been recently reported to induce asthma symptoms in more sensitive individuals. An excipient hypersensitivity study published in 2022 found that exposure to dyes and preservatives leads to a dramatic increase in respiratory symptoms (Giancaspro and Kligerman 2023).

3.3 Gastrointestinal reactions

Excipient hypersensitivity may also affect the gastrointestinal tract, specifically in patients with food allergy. Lactose, for instance, may lead to GI discomfort in lactose-intolerant individuals. In the most severe manifestations, hypersensitivity to gelatin in both oral and injectable preparations may cause nausea, vomiting, and abdominal pain (Vighi et al. 2008).

3.4 Anaphylaxis

Anaphylaxis is the most serious form of excipient hypersensitivity and must be treated with immediate medical help (Fischer et al. 2018). Excipient-induced anaphylaxis has been documented to be increasing, especially in the case of products containing PEG and polysorbate (Stone, et al. 1540). A recent systematic review identified over 50 cases of anaphylaxis triggered by excipients in vaccines, biologics, and intravenous medications (Bruusgaard-Mouritsen et al. 2022).

4 Diagnostic challenges in excipient hypersensitivity

Excipient hypersensitivity diagnosis is difficult to perform because of the heterogeneity of excipients used in pharmaceuticals and the lack of specificity of symptoms (Table 5). The following diagnostic tools are commonly used.

Patch Testing: Patch testing, the most common method of detecting delayed hypersensitivity reactions has a premise of exposing small amounts of suspected excipients to the skin and looking for dermal responses up to 48–72 h. This is particularly valuable for the diagnosis of contact dermatitis caused by preservatives and dyes (Woodruff and Botto 2022).

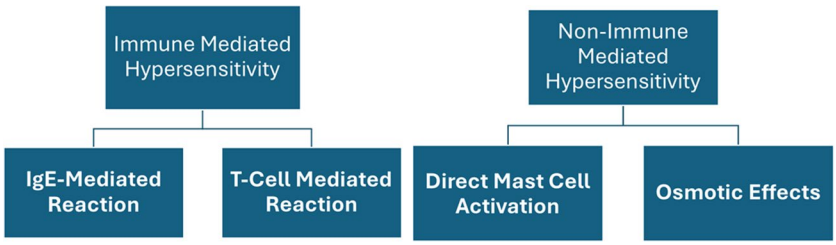

Fig. 1 Mechanisms of Hypersensitivity

Skin Prick and Intradermal Testing: These tests are used for the detection of immediate hypersensitivity reaction by applying small doses of the excipient topically and assessing whether an allergic reaction occurs. Nevertheless, these assessments are restricted by the lack of availability of purified excipients for the assessment (Singh et al. 2021).

Oral Challenges: In situations where additional tests are negative, an oral challenge can be carried out under medical supervision. The patient was given increasing amounts of the suspected excipient with the aim of detecting a hypersensitivity reaction. Although it is the best diagnostic test, it has the potential to cause life-threatening reactions such as anaphylaxis (Emons et al. 2731). Recent work has highlighted the requirement for more dependable diagnostic tools to diagnose excipient hypersensitivity. According to a 2023 paper published in The Journal of Allergol, many previously available diagnostic tests are non-specific and can provide either false-negative or false-positive results (Brockow, et al. 2023).

5 Recent Research and Advances in Excipients Hypersensitivity

Recent reports have greatly helped to elucidate excipient hypersensitivity, with particular attention given to immune phenomena and to the identification of candidate high-risk excipients. Immunological and pharmacological progress has enabled us to understand the molecular mechanisms involved in hypersensitivity reactions and the corresponding genetic predispositions (Venturini Díaz et al. 2022).

5.1 PEG and polysorbates in COVID-19 vaccines

Over the last few years, notable progress has been made towards the attention paid to PEG and polysorbates as triggers of anaphylactic reactions in COVID-19 vaccines (Ieven et al. 2021). A study published in The New England Journal of Allergy Clin Immunol Pract reported several cases of PEG-induced anaphylaxis after vaccination. This has resulted in increased attention being paid to excipients in vaccine formulations and the search for improved desensitization protocols for patients with PEG hypersensitivity (Picard, et al. 2021b).

5.2 Role of genetic predisposition

Relevant studies have identified polymorphisms in genes such as **HLA-DRB1**, **IL-4R**, and **FCER1A**, which are involved in immune response regulation and have been associated with allergic reactions to excipients like PEG and parabens (Kim et al. 2010). Moreover, variations in **CYP450 enzymes** can influence drug metabolism, potentially exacerbating hypersensitivity responses to excipients. Genetic screening may offer a personalized approach to prescribing medications, helping identify patients at risk and allowing for the selection of alternative excipients. Greater attention must be given to excipient hypersensitivity due to the

Table 5 Diagnostic Tools for Excipients Hypersensitivity

Diagnostic Tool	Purpose	Excipients Tested	Advantages	Limitations
Patch Testing	Identify delayed-type hypersensitivity	Parabens, dyes, preservatives	Specific for T-cell mediated responses	Limited to cutaneous reactions; only for topical exposures
Skin Prick Testing	Detect immediate-type hypersensitivity	PEG, gelatin, chlorhexidine	Fast, simple to perform	Limited availability of excipients for testing
Oral Challenge Test	Confirm non-IgE or IgE-mediated reactions	Multiple excipients, including fillers	Gold standard for confirmation	Risk of severe reactions, labor-intensive
Intradermal Testing	Detect low-level IgE-mediated reactions	PEG, Polysorbate	Sensitive to small quantities	Can provoke severe reactions

increasing complexity of drug formulations and widespread use of excipients such as PEG, parabens, and artificial dyes.

5.3 Novel formulations

Pharmaceutical corporations are now regularly examining the utilization of new formulations with the aim of minimizing hypersensitivity reactions. Since then, recent advances in nanotechnology have resulted in the introduction of excipient-free formulations, including biologics (Cha, et al. 2017). Nanotechnology is emerging as a promising solution for developing excipient-free drug formulations. **Nanoparticle-based drug delivery systems**, including lipid nanoparticles, polymeric micelles, and dendrimers, offer a means to enhance drug solubility and stability without relying on conventional excipients (Hassan et al. Sep. 2020). These nanoscale carriers can provide controlled drug release, improve bioavailability, and protect active pharmaceutical ingredients from degradation. Moreover, surface modifications of nanoparticles can enhance drug targeting, reducing the need for additional stabilizers or preservatives. Research is actively exploring **self-assembling nanocarriers** and **biodegradable nanomaterials** as viable substitutes for traditional excipients (Yang et al. 2015). For instance, **nanoemulsions** and **solid lipid nanoparticles** have shown significant potential in reducing hypersensitivity reactions while maintaining drug efficacy. Clinical trials are currently evaluating the safety and effectiveness of these novel formulations in comparison to traditional excipient-containing drugs. Current clinical trials are investigating excipient-free biologics and injectable therapies to assess their efficacy and safety. For example, efforts to create PEG-free monoclonal antibodies and polysorbate-free vaccines have shown promising results in reducing adverse reactions while maintaining therapeutic value (Zhang et al. 2020). These advancements represent a crucial step toward safer formulations for hypersensitive patients.

6 Regulatory considerations

Regulatory agencies, such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA), play a significant role in the safety of excipients. Agencies of this nature require detailed testing and labeling of pharmaceutical excipients, in particular those that have been implicated in the induction of hypersensitivity reactions.

6.1 Labeling requirements

According to the FDA, excipients, especially those associated with hypersensitivity, must be prominently presented in drug labels. Recent changes to the FDA guidelines put a particular focus on labeling the excipients (e.g., PEG, lactose, gelatin) so that it is possible to make informed choices both for patients and health care providers with regard to pharmaceutical treatment (FDA 2024b). Table 6 outlines the global recommendations for excipients used in pharmaceuticals, with emphasis on hypersensitivity issues. It focuses the focus of regulatory entities on the safety of their patients and provides valuable information on labeling procedures that help avoid adverse reactions.

6.2 Pharmacovigilance

Pharmacovigilance has an important function in assessing adverse reactions to excipients (Hamid et al. 2022). Healthcare workers are advised to submit cases of excipient hypersensitivity to national databases, including the FDA's Spontaneous Reporting System (FAERS) or the European Union EudraVigilance (European Medicines Agency (EMA). 2024; FDA 2024a). Recently, attention has been drawn towards the role of pharmacovigilance in the detection of new excipients potentially associated with adverse effects in susceptible persons. The heat map in Fig. 2 illustrates the disparity in the reporting of excipient hypersensitivity across various regions. These differences emphasize the worldwide demand for public health measures and education with regard to the risk associated with ubiquitous pharmaceutical excipients.

6.3 Geographic distribution and epidemiology of excipient hypersensitivity

The distribution of patients with hypersensitivity to excipients is characterized by strong geographic variability, as illustrated in the heat map below (Fig. 2) (Buhari et al. Jul. 2015). The highest number of reports are related to North America and Europe, presumably due to strengthened pharmacovigilance and increased use of medications that carry potentially harmful excipients, such as polyethylene glycol (Stevenson and Simon 1981). In contrast, regions like Africa and South America showed fewer reports, which may be attributed to underreporting or differing medication profiles (Rafi, et al. 2024; Stevenson and Simon 1981; WHO 2002). Geographic variations in excipient hypersensitivity reporting reveal significant disparities worldwide. In North America, reports of PEG-induced anaphylaxis have surged by **40%** over the past decade, highlighting the growing concern regarding its widespread use in pharmaceutical and vaccine formulations (Turner et al. 1176). Europe has documented **an estimated 5,000 cases annually** related to hypersensitivity reactions from excipients such as polysorbate 80 and sulfites. Meanwhile, underreporting in Africa and South

America remains a critical issue, with only **1,200 cases per year** recorded across both regions, suggesting a potential gap in pharmacovigilance and healthcare infrastructure. Pharmacovigilance data further indicate that **up to 30% of unexplained anaphylaxis cases** may be attributed to excipients, underscoring the need for increased awareness and reporting mechanisms (Doña et al. 2024). Incorporating such quantitative data strengthens the epidemiological analysis, providing a clearer understanding of global trends and informing future regulatory strategies.

7 Management of excipients hypersensitivity

The management of excipient hypersensitivity involves a combination of avoidance strategies, pharmacological treatment, and desensitization protocols in some cases (Fig. 3 illustrate a chart where confirm how to handle the hypersensitivity).

7.1 Avoidance strategies

The best solution to treat excipient hypersensitivity is to eliminate the implicated excipient. This could involve the use of substitute drug(s) that do not contain contentious excipient(s) (Gelincik, et al. 2793). For example, to prevent vaccines, biologics, or other injectables including, PEG (Mouri et al. 2022). Similarly, lactose-intolerant individuals may require lactose-free formulations.

7.2 Pharmacological treatment

Mild hypersensitivity to antihistamines and corticosteroids can be used to treat symptoms. In cases of more serious responses, such as anaphylaxis, it is necessary to administer epinephrine immediately. Recently, biologics, such

Table 6 Regulatory Guidelines on Excipients in Pharmaceuticals (FDA, EMA)

Regulatory Body	Guidelines on Labeling	Excipients Subject to Special Regulation	Notes on Hypersensitivity
FDA (U.S.)	Requires detailed excipients labeling for all drugs	PEG, Lactose, Tartrazine, Parabens	Alerts for excipients with known allergenic potential
EMA (Europe)	Mandatory for all excipients in drug formulations	PEG, Polysorbates, Preservatives, Dyes	Similar rules to FDA, with additional focus on hypersensitivity reports
MHRA (UK)	Excipients must be listed if present above a threshold	PEG, Gelatin, Mannitol, Lactose	Guidelines updated after COVID-19 vaccine hypersensitivity reports
TGA (Australia)	Comprehensive excipient labeling, especially for injectables	Propylene Glycol, PEG, Dyes	Focus on excipient reactions in both topical and injectable formulations

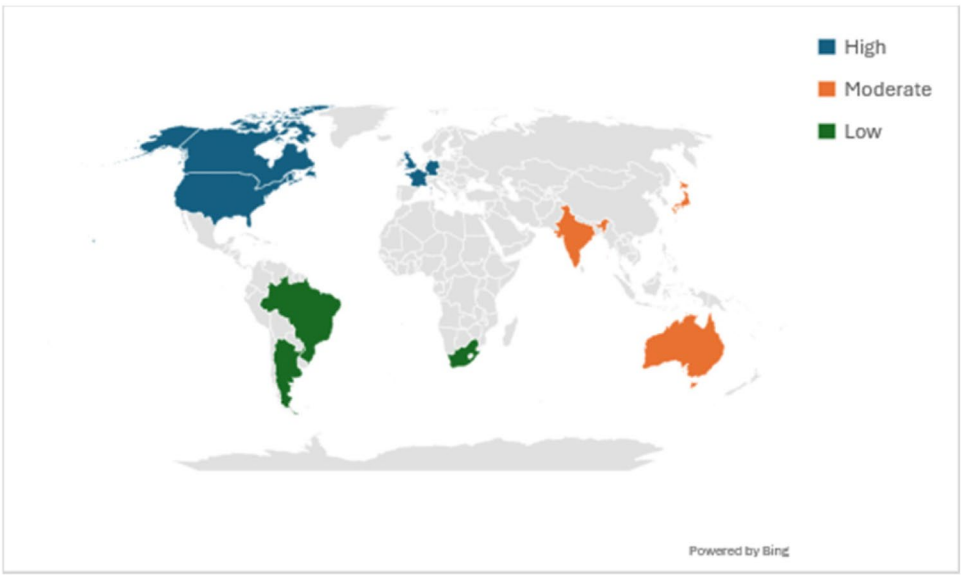

Fig. 2 Geographic distribution of excipient hypersensitivity reports

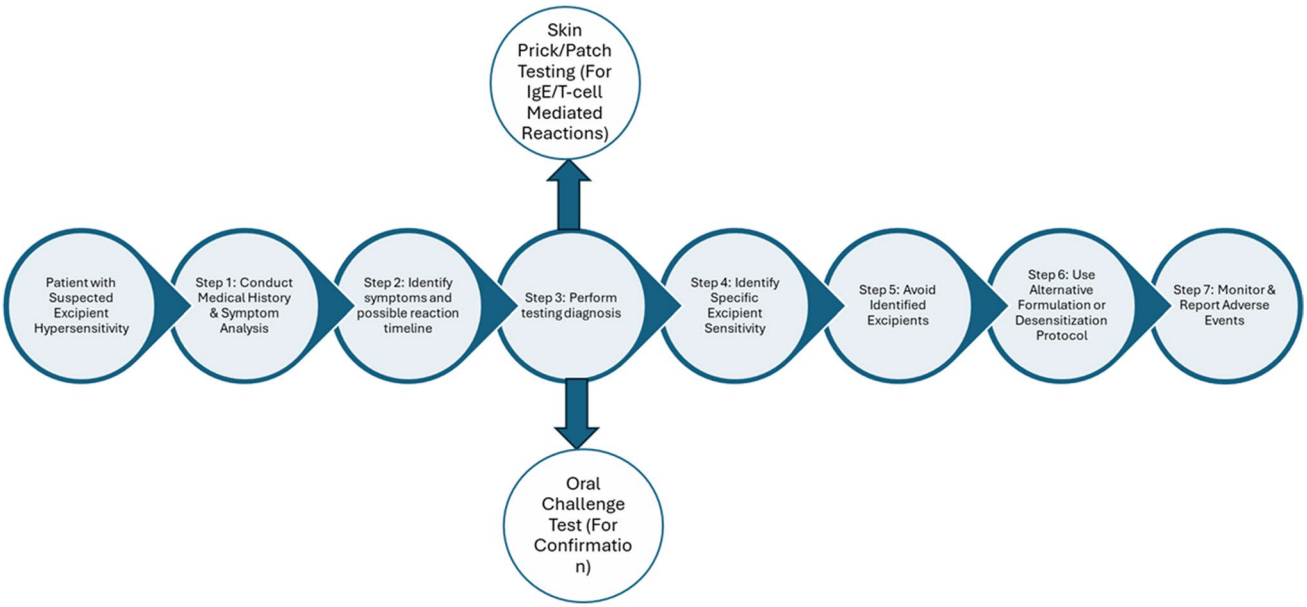

Fig. 3 Management of Excipient-Induced Hypersensitivity

as omalizumab, have been investigated for the prevention of anaphylaxis in patients with excipient hypersensitivity (Bruusgaard-Mouritsen et al. 2022).

7.3 Desensitization protocols

For patients needing a drug with an offending excipient, desensitization protocols can be considered (Kang et al. 2022). A sort of desensitization uses titration of the drug that is given in fractional steps to develop tolerance. This methodology has been successfully applied to patients with PEG or polysorbate hypersensitivity who require COVID-19 vaccination. A paper in the Blood Journal reported desensitization in more than 90% of patients with PEG-related anaphylaxis (Swanson, et al. 2019). Table 7 lists the desensitization protocols used to control hypersensitivity reactions to essential excipients. It describes the achievements and provides case studies about drugs for which such protocols have been successfully used, highlighting the implications of desensitization for patients and patients who need specific therapies.

8 Future research directions

Although the field has made tremendous progress in understanding excipient hypersensitivity, there are still several topics which require urgently attention to the furtherance of patient safety and treatment effect. Next studies are warranted to improve the accuracy of diagnostic devices, investigate the genetic influence over excipient hypersensitivity, and create drug formulations with minimal or no excipients. The following subsections outline key research directions that will contribute to these advancements.

8.1 Advancements in diagnostic testing

There is a demand for more accurate and specific diagnostic tests for the precise identification of excipient hypersensitivity. Future studies should concentrate on the design of in vitro assays to identify immune responses to excipients as precisely as possible and on discovering biomarkers to predict hypersensitivity.

8.2 Personalized medicine

Personalized medicine has huge potential in the management of excipient hypersensitivity. Genetic testing can identify individuals who are at an increased risk of hypersensitivity to excipients and can lead to tailored treatment approaches based on alternative excipients (Goetz and Schork 2018).

8.3 Excipient-free formulations

The rational design of excipient-free drug formulations, especially biologics, is a stimulating field of study. Improvements in drug delivery systems (e.g.,

Table 7 Desensitization Protocols for Excipients-Induced Anaphylaxis

Excipients	Desensitization Protocol Used	Success Rate	Example Drugs	Comments
PEG (Polyethylene Glycol)	Gradual increase of vaccine doses over time	90% success	mRNA COVID-19 vaccines	Desensitization primarily for high-risk patients
Polysorbate 80	Incremental dose escalation of biologic therapy	85% success	Monoclonal antibodies, vaccines	Cross-reactivity with PEG should be assessed
Gelatin	Slow oral tolerance build-up through gelatin ingestion	70% success	Vaccines, encapsulated drugs	Primarily used for patients with known gelatin allergy
Mannitol	Stepwise increase of exposure through oral administration	80% success	Injectable drugs	Typically used in non-life-threatening reactions
Chlorhexidine	Gradual exposure with skin patches	75% success	Surgical antiseptics	Used in patients requiring surgery with known allergies

nanoparticles and liposomes) could decrease the use of conventional excipients, with a consequent lower risk of hypersensitivity episodes (Yang et al. 2015). The development of excipient-free formulations poses significant challenges due to the essential roles that excipients play in ensuring drug stability, bioavailability, and manufacturability. Excipients prevent drug degradation, enhance solubility, and improve patient adherence. Removing them entirely could compromise drug effectiveness and increase formulation costs (Marasini et al. 2022).

However, recent advancements are making excipient-free formulations more feasible. Innovations in **nanotechnology**, **liposomal drug delivery systems**, and **biologic therapies** aim to reduce or replace traditional excipients (Zhang et al. 2020). Liposomal formulations, for instance, allow for drug encapsulation without requiring stabilizers or preservatives, minimizing hypersensitivity risks (Dedeloudi et al. 2022). Similarly, **nanoparticles and protein-based carriers** are being explored as alternative delivery mechanisms that eliminate the need for synthetic excipients.

Current clinical trials are investigating excipient-free biologics and injectable drugs to assess their efficacy and safety. For example, efforts to create PEG-free monoclonal antibodies and polysorbate-free vaccines have shown promising results in reducing adverse reactions while maintaining therapeutic efficacy (Kozma et al. 2023). These advancements represent a crucial step towards safer drug formulations for hypersensitive patients.

9 Conclusion

Excipients are important ingredients in the preparation of pharmaceutical products; however, their ability to induce hypersensitivity in some people is increasingly becoming a clinical problem. With a deeper understanding of the roles of immune and non-immune cells, recent developments in diagnostic testing, and personalized therapeutic strategies, excipient hypersensitivity management is undergoing transformation. Future research on safer formulations and genetic susceptibility will play an important role in decreasing the incidence of hypersensitivity reactions and in the safe use of drugs for every patient.

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Author contribution **Ruba Malkawi** contributed significantly to the conceptualization and design of the study. She led the literature review on excipients and their mechanisms of hypersensitivity, ensuring a comprehensive evaluation of existing research. Ruba also provided expertise in pharmacology and immunology, guiding the interpretation of findings related to hypersensitivity reactions. She took part in drafting and critically revising the manuscript to ensure it adhered to scientific rigor and clarity. **Lora Altahrawi** played a crucial role in analyzing data on global pharmacovigilance practices and their integration into hypersensitivity case management. She contributed to synthesizing data and highlighting trends in regulatory frameworks across different regions. Lora was also responsible for editing and refining the manuscript, ensuring coherence and alignment with the article's objectives. Her input strengthened the sections focusing on international pharmacovigilance and its implications for patient safety.

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References

Abbas, M, Moussa, M and Akel, H (2023) Type I hypersensitivity reaction. StatPearls, 4, 14, 1–20. Accessed: Oct. 18, 2024. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK560561/

Akarsu A, Soyer O, Sekerel BE (2020) Hypersensitivity reactions to biologicals: from bench to bedside. Curr Treat Options Allergy 7(1):80. https://doi.org/10.1007/S40521-020-00242-2

Akin C et al (2022) Acute urticaria and anaphylaxis: differences and similarities in clinical management. Front Allergy 3(6):840–999. https://doi.org/10.3389/FALGY.2022.840999

Ardern K, Ram FSF, Lasserson TJ (2001) Tartrazine exclusion for allergic asthma. Cochrane Database Syst Rev 2001(4):1–30. https://doi.org/10.1002/14651858.CD000460

Brockow, K. (2023) Guideline for allergological diagnosis of drug hypersensitivity reactions: s2k guideline of the german society for allergology and clinical immunology (dgaki) in cooperation with the german dermatological society (ddg), the association of german allergologists (äda), the german society for pediatric allergology (gpa), the german contact dermatitis research group (dkg), the german society for pneumology (dgp), the german society of otorhinolaryngology, head and neck surgery, the austrian society,. Allergol Select 7:122-139. https://doi.org/10.5414/ALX02422E

Bruusgaard-Mouritsen MA, Nasser S, Garvey LH, Krantz MS, Stone CA (2022) Anaphylaxis to excipients in current clinical practice: evaluation and management. Immunol Allergy Clin North Am 42(2):250. https://doi.org/10.1016/J.IAC.2021.12.008

Buhari GK et al (2015) Immediate-type hypersensitivity reactions due to antituberculosis drugs: A successful readministration protocol. Ann Allergy Asthma Immunol 115(1):39–44. https://doi.org/10.1016/j.anai.2015.04.015

Caballero ML, Quirce S (2020) Delayed hypersensitivity reactions caused by drug excipients: A literature review. J Investig Allergol Clin Immunol 30(6):400–408. https://doi.org/10.18176/JIACI.0562

Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone CA (2021) Hidden Dangers: Recognizing Excipients as Potential Causes of Drug and Vaccine Hypersensitivity Reactions. J Allergy Clin Immunol Pract 9(8):2982. https://doi.org/10.1016/J.JAIP.2021.03.002

Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone CA (2021) Hidden dangers: recognizing excipients as potential causes of drug and vaccine hypersensitivity reactions. J Allergy Clin Immunol Pract 9(8):2968–2982. https://doi.org/10.1016/J.JAIP.2021.03.002

Cha Y et al (2017) Drug repurposing from the perspective of pharmaceutical companies. Br J Pharmacol 175(2):180. https://doi.org/10.1111/BPH.13798

Choi C, Vafaei-Nodeh S, Phillips J, de Gannes G (2021) Approach to allergic contact dermatitis caused by topical medicaments. Can Fam Physician 67(6):419. https://doi.org/10.46747/CFP.6706414

Dedeloudi A, Siamidi A, Pavlou P, Vlachou M (2022) Recent advances in the excipients used in modified release vaginal formulations. Materials 15(1):335. https://doi.org/10.3390/MA15010327

Doña I, Torres MJ, Celik G, Phillips E, Tanno LK, Castells M (2024) Changing patterns in the epidemiology of drug allergy. Allergy 79(3):613–628. https://doi.org/10.1111/ALL.15970

Dreskin SC et al (2016) International consensus (ICON): allergic reactions to vaccines. World Allergy Organ J 9(1):40. https://doi.org/10.1186/S40413-016-0120-5

Emons J, van Gunst M, Liem O, Landzaat L, Arends N (2020) Improving successful introduction after a negative food challenge test: how to achieve the best result? Nutrients 12(9):2731. https://doi.org/10.3390/NU12092731

European Medicines Agency (EMA) (2024) EudraVigilance. Accessed: Oct. 18, 2024. [Online]. Available: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/pharmacovigilance-research-development/eudravigilance

FDA (2024a) FDA's Adverse Event Reporting System (FAERS). Accessed: Oct. 18, 2024. [Online]. Available: https://www.fda.gov/drugs/surveillance/fdas-adverse-event-reporting-system-faers

FDA (2024b) FDA's Labeling Resources for Human Prescription Drugs. Accessed: Oct. 18, 2024. [Online]. Available: https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

Fernandes M, Lourenço T, Lopes A, Santos AS, Santos MCP, Barbosa MP (2019) Chlorhexidine: a hidden life-threatening allergen. Asia Pac Allergy 9(4):29–40. https://doi.org/10.5415/APALLERGY.2019.9.E29

Filon FL et al (2022) Allergic reactions to COVID-19 vaccination in high-risk allergic patients: the experience of trieste university hospital (North-Eastern Italy). Vaccines (Basel) 10(10):1623. https://doi.org/10.3390/VACCINES10101616/S1

Fischer D, Vander Leek TK, Ellis AK, Kim H (2018) "Anaphylaxis", Allergy Asthma. Clin Immunol 14(2):66. https://doi.org/10.1186/S13223-018-0283-4

Fisher AA (1975) Allergic paraben and benzyl alcohol hypersensitivity relationship of the 'delayed' and 'immediate' varieties. Contact Dermatitis 1(5):281–284. https://doi.org/10.1111/J.1600-0536.1975.TB05436.X

Galateanu B et al (2023) Allergy in cancer care: antineoplastic therapy-induced hypersensitivity reactions. Int J Mol Sci 24(4):38–86. https://doi.org/10.3390/IJMS24043886

Gelincik A et al (2020) Diagnosis and management of the drug hypersensitivity reactions in Coronavirus disease 19: An EAACI Position Paper. Allergy 75(11):2793. https://doi.org/10.1111/ALL.14439

Giancaspro G, Kligerman JS (2023) Excipient lung disease in a patient with preexisting chronic thromboembolic disease. Radiol Cardiothorac Imaging 5(4):23–59

Goetz LH, Schork NJ (2018) Personalized medicine: motivation, challenges and progress. Fertil Steril 109(6):693. https://doi.org/10.1016/J.FERTNSTERT.2018.05.006

Hamid AAA, Rahim R, Teo SP (2022) Pharmacovigilance and its importance for primary health care professionals. Korean J Fam Med 43(5):295. https://doi.org/10.4082/KJFM.21.0193

Han J et al (2022) Hypersensitivity reactions to small molecule drugs. Front Immunol 13(5):1016–1730. https://doi.org/10.3389/FIMMU.2022.1016730/BIBTEX

Hassan H et al (2020) Acyclovir-Loaded Solid Lipid Nanoparticles: Optimization, Characterization and Evaluation of Its Pharmacokinetic Profile. Nanomaterials 10(9):1–17. https://doi.org/10.3390/NANO10091785

Ieven T, Van Weyenbergh T, Vandebotermet M, Devolder D, Breynaert C, Schrijvers R (2021) Tolerability of polysorbate 80–containing COVID-19 vaccines in confirmed polyethylene glycol–allergic

patients. J Allergy Clin Immunol Pract 9(12):4472. https://doi.org/10.1016/J.JAIP.2021.09.039
JanssenDuijghuijsen L et al (2024) Changes in gut microbiota and lactose intolerance symptoms before and after daily lactose supplementation in individuals with the lactase nonpersistent genotype. Am J Clin Nutr 119(3):702–710. https://doi.org/10.1016/J.AJCNUT.2023.12.016
Joshi SR, Khan DA (2021) Non-IgE-mediated drug hypersensitivity reactions. Curr Allergy Asthma Rep 21(7):1–18. https://doi.org/10.1007/S11882-021-01018-7
Kang SY, Seo J, Kang HR (2022) Desensitization for the prevention of drug hypersensitivity reactions. Korean J Intern Med 37(2):270. https://doi.org/10.3904/KJIM.2021.438
Katz JS et al (2022) Emerging challenges and innovations in surfactant-mediated stabilization of biologic formulations. J Pharm Sci 111(4):919–932. https://doi.org/10.1016/J.XPHS.2021.12.002
Kim SH, Ye YM, Palikhe NS, Kim JE, Park HS (2010) Genetic and ethnic risk factors associated with drug hypersensitivity. Curr Opin Allergy Clin Immunol 10(4):280–290. https://doi.org/10.1097/ACI.0B013E32833B1EB3
Kozma GT et al (2023) Role of anti-polyethylene glycol (PEG) antibodies in the allergic reactions to PEG-containing Covid-19 vaccines: Evidence for immunogenicity of PEG. Vaccine 41(31):4561–4570. https://doi.org/10.1016/J.VACCINE.2023.06.009
Lachenmeier DW (2008) Safety evaluation of topical applications of ethanol on the skin and inside the oral cavity. J Occup Med Toxicol 3(1):40. https://doi.org/10.1186/1745-6673-3-26
Malinauskiene L, Blaziene A, Chomiciene A, Isaksson M (2015) Formaldehyde may be found in cosmetic products even when unlabelled. Open Med 10(1):328. https://doi.org/10.1515/MED-2015-0047
Marasini N et al (2022) Development of excipients free inhalable co-spray-dried tobramycin and diclofenac formulations for cystic fibrosis using two and three fluid nozzles. Int J Pharm 624(2):121–989. https://doi.org/10.1016/J.IJPHARM.2022.121989
Metwaly AM et al (2021) Traditional ancient Egyptian medicine: A review. Saudi J Biol Sci 28(10):58–23. https://doi.org/10.1016/J.SJBS.2021.06.044
Mouri M et al (2022) Serum polyethylene glycol-specific IgE and IgG in patients with hypersensitivity to COVID-19 mRNA vaccines. Allergol Int 71(4):512–519. https://doi.org/10.1016/J.ALIT.2022.05.007
Nucera E et al (2017) Anaphylaxis by antihistamine containing bovine gelatin: the utility of the basophil activation test in the diagnostic work-up. Adv Derm Allergology/PostępPy Dermatologii i Alergologii 34(3):280. https://doi.org/10.5114/ADA.2017.67851
Patel R, Barker J, Elshaer A (2020) Pharmaceutical Excipients and Drug Metabolism: A Mini-Review. Int J Mol Sci 21(21):82–24. https://doi.org/10.3390/IJMS21218224
Pelto L, Salminen S, Lilius EM, Nuutila J, Isolauri E (1998) Milk hypersensitivity–key to poorly defined gastrointestinal symptoms in adults. Allergy 53(3):307–310. https://doi.org/10.1111/J.1398-9995.1998.TB03892.X
Petrovska BB (2012) Historical review of medicinal plants' usage. Pharmacogn Rev 6(11):15. https://doi.org/10.4103/0973-7847.95849
Picard M et al (2021a) Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: A case series. J Allergy Clin Immunol Pract 10(2):625. https://doi.org/10.1016/J.JAIP.2021.11.021
Picard M et al (2021b) Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: A case series. J Allergy Clin Immunol Pract 10(2):624. https://doi.org/10.1016/J.JAIP.2021.11.021
Pintea I et al (2021) Hypersensitivity reactions to monoclonal antibodies: Classification and treatment approach (Review). Exp Ther Med 22(3):960. https://doi.org/10.3892/ETM.2021.10381
Rafi SM et al (2024) Understanding parabens – A literature review. Cosmoderma 4(8):40. https://doi.org/10.25259/CSDM_241_2023
Rathee P et al (2023) Polyphenols: natural preservatives with promising applications in food, cosmetics and pharma industries; problems and toxicity associated with synthetic preservatives; impact of misleading advertisements; recent trends in preservation and legislation. Materials 16(13):4793. https://doi.org/10.3390/MA16134793
Schwartzberg LS, Navari RM (2018) Safety of polysorbate 80 in the oncology setting. Adv Ther 35(6):767. https://doi.org/10.1007/S12325-018-0707-Z
Sellaturay P, Nasser S, Ewan P (2021) Polyethylene Glycol–nduced systemic allergic reactions (anaphylaxis). J Allergy Clin Immunol Pract 9(2):670–675. https://doi.org/10.1016/J.JAIP.2020.09.029
Seth S et al (2024) Excipient induced allergies in oral medications: unravelling the covert threat - a systematic review. Intern Med J 11(11):16–23. https://doi.org/10.1111/IMJ.16605
Singh S, Bohara A, Rai T (2021) Comparison of sensitivities of skin prick and intradermal tests with oral rechallenge test: a prospective interventional hospital-based study. Indian J Dermatol 66(1):59. https://doi.org/10.4103/IJD.IJD_554_19
Stevenson DD, Simon RA (1981) Sensitivity to ingested metabisulfites in asthmatic subjects. J Allergy Clin Immunol 68(1):26–32. https://doi.org/10.1016/0091-6749(81)90119-6
Stone CA et al (2019) Immediate hypersensitivity to Polyethylene Glycols and Polysorbates: more common than we have recognized. J Allergy Clin Immunol Pract 7(5):1540. https://doi.org/10.1016/J.JAIP.2018.12.003
Swanson HD et al (2019) Predicting success of desensitization after pegaspargase allergy. Blood 135(1):75. https://doi.org/10.1182/BLOOD.2019003407
Tenny S, Patel R, Thorell W (2024) Mannitol. StatPearls Publishing LLC 7(8):1–10
Teshome E, Forsido SF, Rupasinghe HPV, Olika Keyata E (2022) Potentials of natural preservatives to enhance food safety and shelf life: a review. Sci World J 5:99–110. https://doi.org/10.1155/2022/9901018
Torfs E, Brackman G (2020) A perspective on the safety of parabens as preservatives in wound care products. Int Wound J 18(2):232. https://doi.org/10.1111/IWJ.13521
Tramontana M, Hansel K, Bianchi L, Sensini C, Malatesta N, Stingeni L (2023) Advancing the understanding of allergic contact dermatitis: from pathophysiology to novel therapeutic approaches. Front Med (Lausanne) 10(5):118–180. https://doi.org/10.3389/FMED.2023.1184289
Tripp M, Ribeiro M, Kmiecik S, Go R (2021) A 'Rash' decision in anesthetic management: benzyl alcohol allergy in the perioperative period. Case Rep Anesthesiol 2021(8):885–823. https://doi.org/10.1155/2021/8859823
Turner PJ, Campbell DE, Motosue MS, Campbell RL (2020) Global trends in anaphylaxis epidemiology and clinical implications. J Allergy Clin Immunol Pract 8(4):1176. https://doi.org/10.1016/J.JAIP.2019.11.027
Vally H, Misso NLA (2012) Adverse reactions to the sulphite additives. Gastroenterol Hepatol Bed Bench 5(1):23
Venturini Díaz M, Vidal Oribe I, D'Elia Torrence D, Hernández Alfonso P, Alarcón Gallardo E (2022) New challenges in drug allergy: the resurgence of excipients. Curr Treat Options Allergy 9(3):291. https://doi.org/10.1007/S40521-022-00313-6
Viggiani F et al (2019) "Predictive value of skin testing with excipients for COVID-19 vaccines". Open Exploration 2:1 2 1 49–64 2024 https://doi.org/10.37349/EAA.2024.00028
Vighi G, Marcucci F, Sensi L, Di Cara G, Frati F (2008) Allergy and the gastrointestinal system. Clin Exp Immunol 153(1):13. https://doi.org/10.1111/J.1365-2249.2008.03713.X

Weisbrod DB, Caruana DL, Li D, Wan L, Szema AM (2023) A case report of allergic hypersensitivity to color additives in Slurpee® beverages. Yale J Biol Med 96(1):90. https://doi.org/10.59249/KGFT1011

WHO (2002) "The importance of pharmacovigilance.,". World Health Organization, 48

Woodruff CM, Botto N (2022) The role of patch testing in evaluating delayed hypersensitivity reactions to medications. Clin Rev Allergy Immunol 62(3):561. https://doi.org/10.1007/S12016-022-08924-2

Yang XF, Xu Y, Qu DS, Zhu J, Li HY (2015) Excipient-free, spray-dried powders for pulmonary aztreonam delivery. J Drug Deliv Sci Technol 28(7):7–10. https://doi.org/10.1016/J.JDDST.2015.04.005

Zhang Y, Mackenzie B, Koleng JJ, Maier E, Warnken ZN, Williams RO (2020) Development of an excipient-free peptide dry powder inhalation for the treatment of pulmonary fibrosis. Mol Pharm 17(2):632–644. https://doi.org/10.1021/ACS.MOLPHARMACEUT.9B01085