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Review

An Overview of Pharmaceutical Excipients: Safe or Not Safe?

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ABSTRACT

A medicine consists of 2 fundamental parts: the active pharmaceutical ingredient and the excipient. Most, if not all, medicines could not be made without the use of excipients. In the early times, the safety of excipients was overlooked and no specific safety tests were generally conducted. This fact has been changed over times and is currently being recognized that the excipient's toxicity is not negligible, because its direct interaction with the active pharmaceutical ingredient or between other excipients may occur, leading to a potential change in the relationship between effectiveness and toxicity. This review is intended to address the general status of the pharmaceutical excipients and to describe the safety assessment. As a summary, this review suggests the interest of simplifying the formulations as much as possible and the interest of reducing the number of excipients necessary to strictly meet the required functions. The risk/benefit ratio of an excipient should be always evaluated on the basis of not only its production/quality but also of its safety. Further research according to Good Manufacturing Practices, Guiding Principles in Toxicology Assessment, Good Laboratory Practices, and Good Distribution Practices requirements are needed and are fundamental for health safety, contributing to a comprehensive picture of this matter.

Introduction

A pharmaceutical excipient is by definition a substance or a group of substances that completes a volume of agglomerating a mixture, which serves as a vehicle and incorporates active pharmaceutical ingredients (APIs); the word itself is defined in some of the features of a pharmaceutical excipient. Examples of excipients include absorption enhancers, coloring agents, emulsifiers, extenders, diluents, fillers, flavors, preservatives, wetting agents, solvents, and sustained release matrices. An ideal excipient is one that provides the volume, the uniformity, and the dose of the API in the medicine throughout the production process to the administration by the patient.

At the beginning of time, specifically at the beginning of the production and handling of medicines, excipients have been described as inert substances that were added to the API only to achieve the required consistency to the formulation. Therefore, several natural products were used in formulating medicines, such as honey as well as other simple substances, which are still used today, such as lactose.[1,2]

Over the years, the use of excipients was considered as the addition of simple vehicles (e.g., syrups). Nowadays, pharmaceutical excipients are more than just simple substances added to complete a total volume formulation; these substances require numerous guarantees to the safety and efficacy of the medicine, such as ensure stability throughout the formulation process to the administration of the medicine by the patient. They also may guarantee that the dose is administered and delivered with the same precision and accuracy that is established for that API in particular, thus making the medicine administration more adequate and reflecting positive results in terms of patient adherence to therapy.

The progress of pharmaceutical technology has made possible the assessment of the excipients from its origin, estimating their behavior in a mixture with other excipients and APIs, where it is possible to check their status. This fact results in a formulation which has the ability to improve the bioavailability and efficacy of the API, whenever necessary.[3-6]

With the advancement of pharmaceutical technology, new drug delivery systems evolved to provide better results: sustained release systems, liposome formulations, and mixtures of various excipients are some examples. The addition of excipients to the API provides the final product with a wide range of functions for the formulation. Excipients must be added appropriately to a dosage

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form so that it can conveniently be administered enterally, parenterally, or topically.[1,2,7-12]

Pharmaceutical excipients perform multiple functions, such as to complete the volume of the formulation, ensure stability by protecting the API, improve the precision and API dose accuracy in the product, improve bioavailability, facilitate the API administration by both improving the organoleptic characteristics or produce a final pharmaceutical form more pleasant, and, finally, to improve the acceptance of the treatment by the patient. It should be noted that the safety and effectiveness of excipients depends on these functions mentioned above. The most important function of any excipient is to ensure the safety and efficacy of the medicine throughout the formulation, the storage period, and during and after its administration.[13-26] The toxicity of excipients (intrinsic or specific toxicity) is not a simple issue for several reasons: first, the large number of excipients and their diversity of chemical profiles or sources or technological functions and, second the presence or probability of occurrence of secondary products and contaminants.

Excipients are no longer considered inert substances because they can interact with the API, lowering their titer. They also can generate undesirable impurities or alter the absorption, distribution, metabolism and excretion (ADME) and, ultimately, reduce the bioavailability of the API. They are assessed as functional and essential substances added to a modern pharmaceutical formulation. However, there is still no common and equitable order in the world for the safety of the excipients used in the pharmaceutical industry.

Those problems may be overcome by adopting and carefully adhering to good manufacturing practices (GMPs) similar to those for active principles. The methods used to guide the safety assessment and regulations are still different in Europe, the United States, and Japan. The purpose of this review is to describe the safety standards for excipients used in the formulation of the medicine. It is generally recognized that existing human data for some excipients can substitute for certain nonclinical safety data, and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies outlined in literature, but it should be analyzed case-by-case.

Safety Assessment

Excipients constitute about 90% of the total volume of a medicine, and as such the probability of changing API's molecular structure is very high if the manufacturing or transport conditions are not appropriate. Thus, global regulatory agencies require routine testing of pharmaceutical excipients—to ascertain and verify the identity, purity, traceability of batches at any moment, resistance, and quality—which have become essential for the production of safer and more effective medicines.[27]

The manufacturer must evaluate the safety of excipients before their access to the pharmaceutical market.[28] Fortunately, the intrinsic toxicity of excipients is becoming much rare because they are usually chosen from among the materials noted for being very nearly pharmaco-toxicologically inert.

This review will describe the excipient safety guidelines from 3 regulatory agencies: the US Food and Drug Administration (FDA), the European Medicines Agency, and the Japanese Ministry of Health, Labour, and Welfare. Those agencies operate under different rules for a common goal: the safety of excipients used by the pharmaceutical industry.[29-47]

Pharmaceutical Excipients Safety Assessment

The use of an excipient in a pharmaceutical formulation begins by relying on the precedence of use. The safety assessment is done through 2 options: the excipient has precedence of use or the excipient has no precedence of use.[48-50]

Excipient With Precedence of Use

The excipient has already been used in a pharmaceutical product, a food additive, or any product with human exposure, that is, where previously safety tests were carried out. These excipients are already registered in a pharmaceutical product and usually are included in the pharmacopoeias.

Excipient With No Precedence of Use

The excipient has never been used in any product and therefore safety tests are required. Each regulatory authority has its own way of acting.[38,39,42,51,52]

Food and Drug Administration

FDA has an excipient database for consultation, Inactive Ingredient Database, where it is possible to consult the excipient's historical precedence of use.[32,33,53]

European Medicines Agency

There is no list of ingredients for quick consultation. A review of excipients with the precedence of use is generally made by a drug compendium in each country. For example, in France there is the "Dictionnaire Vidal," in Germany the "Die Rote Liste," or in UK "The Electronic Medicines Compendium."[29,54]

Japanese Ministry of Health, Labour, and Welfare

In Japan, there is a precedence of use dictionary for consultation—the Japanese Pharmaceutical Excipients Dictionary.

FDA and Japanese Ministry of Health, Labour, and Welfare list excipients that have been previously used in drug formulations, with the description of its characteristics, and the maximum dose used in diverse routes of administration.[29]

International Pharmaceutical Excipients Council (IPEC) recommends that the GMP principles follow the "IPEC-PQG Excipient Guide" for all excipients. If the excipient to be used does not have precedence of use, this material is considered as a new excipient.

New Excipients

A new excipient is considered as a material to be used in a drug product for the first time or it will be used by a new route of administration according to ICH Guideline M4. In other words, a new excipient is a substance that is not present in the Inactive Ingredient Database, United States Pharmacopeia-National Formulary (USP-NF), European Pharmacopoeia (Ph. Eur), Japanese Pharmacopoeia (JP), "Handbook of Pharmaceutical Excipients," or "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete." An excipient with previous chemical change—however small—is considered as a new excipient by the industry.

When there is an excipient that has never been used in any pharmaceutical formulation, there are several guidelines imposed by the regulatory authorities to allow its use. FDA has the "Nonclinical Studies for Development of Pharmaceutical Excipients" and the USP-NF 26 General Chapter <1074 > "Excipient Biological Safety Evaluation Guidelines," while IPEC has the "New Excipient Evaluation Guidelines" and "The Proposed Guidelines for the Safety Evaluation of New Excipients."

It is important to consult these documents to assess the safety of a chemical agent to be used as an excipient.