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Review Article

PHARMACEUTICAL EXCIPIENTS: GLOBAL REGULATORY ISSUES

Dinesh Kumar, Harish Dureja*

Department of Pharmaceutical Sciences, M.D. University, Rohtak India , 124 001.

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*Corresponding author
Harish Dureja

Email :
harishdureja@gmail.com

ABSTRACT

An excipient may be defined as an ingredient that is intentionally added to a drug for purposes other than the therapeutic or diagnostic effect at the intended dosage. Excipients have functional roles in pharmaceutical dosage forms which include the suitable form of consistency, modulating solubility and bioavailability of active ingredients, enhancing stability of the active ingredients in finished dosage form and many others. In most of the developed countries, the excipients are regulated as an active pharmaceutical ingredient. In Europe, it is assumed that novel excipients need to be evaluated as new chemical entities. In United State, the Food and Drug Administration assesses and permits use excipients as part of new drug application. The lack of harmonized international regulatory guidelines leads to the formation of the International Pharmaceutical Excipients Council (IPEC) in 1991. The IPEC was found to calibrate with different countries like Japan, Europe and China to address prevalent industry concerns related to the international harmonization of excipients standards, the introduction of useful new excipients to market place, and development of safety evaluation guidelines for the excipients. In the present study, an attempt has been made to investigate global issues governing regulations of pharmaceutical excipients.

Key words: pharmaceutical excipient, regulatory guidelines, IPEC

INTRODUCTION

An excipient is an inactive substance used as a carrier for the active ingredient of a medicine; in addition, excipients can be used to aid the process by which a product is manufactured. In general, the active substances may not be easily administered and absorbed by the human body; they need to be put in some appropriate form. In such cases, the active substance is dissolved or mixed with an excipient. Excipients are used to bulk up formulations with very potent active ingredients, to allow for convenient and accurate dosage. Excipients can be used as binder, disintegrants, dilatants, lubricants, glidants, emulsifying-solubilizing agents, sweetening agents, coating agents, antimicrobial preservatives, and so forth. In addition to their functional performance, ideally, excipients are now known to have defined functional roles in pharmaceutical dosage forms (Baldrick, 2007). These functions include: modulating solubility and bioavailability of the active ingredient(s); enhancing stability of the active ingredient in finished dosage forms; helping active ingredients to maintain preferred polymorphic form or conformation; maintaining pH and osmolarity of liquid formulations; acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders, tablet disintegrants; preventing aggregation or dissociation; modulating the immunogenic response of active ingredients (e.g., adjuvants) and many others (Bhattacharya *et al.*, 2006) .

Excipients are from various origins: animal (e.g. lactose, gelatin, stearic acid), plant (e.g. starches, sugar, cellulose, and arginates), mineral (e.g. calcium phosphate, silica) and synthetic (e.g. PEGs, Polysorbates, Povidone, etc). Their origin and use do not often guarantee the quality required by the pharmaceutical industry, however, these substances need analytical controls. In order to carry out the numerous functions, new classes

Table I. Classification of pharmaceutical excipients

Chemical classification	Roles to enhance
Water, alcohols, ether, esters, carboxylic acids	Compliance dose precision and accuracy
Glycerides and waxes	Stability
Carbohydrates (mono-, di-,and polysaccharides)	Manufacturing
Hydrocarbons and halogen derivatives	Tolerability
Polymer (natural and synthetic)	Dis-aggregation
Minerals	Dissolution
Proteins	Controlled release
Various preservative, Dyes, Sweeteners, etc.	Absorption

Table II. Regulatory classification of excipients in Europe

Classification of excipients	Regulatory status
Common excipients	No binding regulation available (IPEC PQG GMP-Guide for Pharmaceuticals Excipients)
Specific excipients	EC Directive 2001/83 amended by Directive 2004/27/EC
Fully synthetic polymers	Draft
Certain excipients	
Novel excipients	EC Directive 2001/83 amended by Directive 2004/27/EC Draft

of excipients have now become available, which can be derived from old and new materials either alone or in combination. Presently, more than one thousand different materials are used in the pharmaceutical industry to fulfill the various requirements such as diluents, bulking agents, etc. (Pifferi and Restani, 2003).

The excipients are set out according to their class and the chemical function that can contribute their reactivity. The first category is the approved excipient, which are used in the pharmaceutical industry. Second is intermediate excipients (essentially new excipients), covers compounds obtained by means of the structural modification of the excipients already approved or those already used in the food or cosmetic industries. Third category covers new compounds, never previously used in the pharmaceutical field and it is growing rapidly due to the present interest in modern high productivity. The chemical classification and role of various excipients are tabulated in table I. In Europe, the excipients are also classified on the basis of regulatory consideration, such as common excipient did not need any binding regulation. The regulatory classification of excipient is presented in table II. Regulation of the excipients differs from one country to another. In the present study, global regulatory issues governing pharmaceutical excipients are investigated.

REGULATORY ISSUES IN DIFFERENT COUNTRIES

Pharmaceutical excipients have a vital role in drug formulations. The safety assessment of pharmaceutical excipient is the major issues in different countries (DeMerlis, 1999). The regulatory considerations in different countries are as follows:

Food and drug administration

FDA defined an excipient as "any component of a drug product other than active ingredient" (21CFR218.3(C) (b)). FDA has also defined new excipient "as any ingredient that are intentionally added to therapeutic and diagnostic product, but which (a) are not intended dosage (b) are not fully qualified by existing safety data. The regulation of drug inactive ingredients initiated after the sulfanilamide disaster, in which 107 people died as a result of the use of an inactive ingredient and dramatized the need to establish drug

Table III. Specifications for starting material

No	Name
1	Description: Name, internal code, Pharmacopoeial references, approved suppliers
2	Sampling and testing directions
3	Qualitative and quantitative requirements with acceptance limits
4	Storage condition and precaution
5	Maximum period of storage before examination

safety before marketing and provide the impetus to pass the Federal Food, Drug and Cosmetic Act of 1938. Inactive ingredients (21CFR 330.1 and 330.10) are considered separately from active ingredients and need to be suitable and safe. To assist in developing drug products to pharmaceutical industry FDA is updating "Inactive Ingredients Database" quarterly on its website. The industry can use this information to assist in developing drug products (Steinberg *et al.*, 2001). There are 400 excipient monographs listed in the USP28-NF23, in which 32 new monographs are admitted in 2005. The approval mechanism for an excipient according to U.S law: Approval of a food additive petition under 21 CFR 171; As contained in a New Drug Application (NDA) approval for a specific drug product and for a particular function and for a particular function or use in that dosage form (Steinberg and Kinoshipa 2007).

An excipient can only be considered if it has been used in the FDA approved list or generally recognized as safe (GRAS) list. Under 21CFR 211, excipient as with active drug substances, are required to be manufactured under current Good Manufacturing Practices (GMP). The FDA does not review excipients separately from formulations. They are only approved as part of the IND or NDA. For a novel excipient, the manufacturer must essentially develop the same amount of safety data required for new active ingredient (Chang, 2007). FDA address the safety testing for the novel and potential excipient through "Nonclinical Studies for Development of Pharmaceutical Excipients" which address safety related issues under an IND or NDA in support of proposals for the use of excipients in new drug products.

European legislation

In Europe, the European Council (EC) has published the different directives related to medicinal product for human use. These directives provide the legal basis for the marketing of medicinal products. Colouring matters shall satisfy the requirement of directive 78/25/EEC and 94/36/EC (color for use in foodstuff), in addition, colouring matters in medicinal product have to comply with the specification to the directive 95/45/EC. The residual solvent in pharmaceutical excipients should be in accordance with ICH guidelines (DeMerlis, 1999; Robertson, 1999).

For a novel excipient, a dossier should be established containing the same data as required for new active substance. The marketing authorization of new excipient guidance is given by the European Union; Wray, pharmalicensing.com), In addition, the regulation for the inclusion of antioxidants and antimicrobial preservatives in medicinal products, the requirements vary depending upon whether or not the excipient is listed in the European Pharmacopeia or a member state Pharmacopeia. Stability data should be provided as ICH Q1A "Note for Guidance on stability testing of new drug substances and products" (CPMP/ICH/ 2736/99). The test procedure and acceptance criteria for new drug substance (CPMP/ICH/ 367/96) are not necessary.

The regulation 91/356/EEC described the principles and guidelines of GMPs for the medicinal products for human use, which are used for manufacturing authorization and as a basis for inspection. The regulation described various documentation requirements for starting material including excipients such as written procedures, records and standard operating procedures (Table III) (DeMerlis, 1999).

Table IV. Data required for safety evaluation of excipients

No	Evaluation of excipients
1	Toxicity –acute;
2	Toxicity-sub acute
3	Toxicity-chronic
4	Effect on reproduction
5	Dependency
6	Antigenicity
7	Mutagenicity
8	Carcinogenicity
9	Local irritation (human patch test)

(1-4, 7: mandatory); (1-8: foreign data are acceptable); (9: a domestic trial required)

Table V. Comparative regulatory guidelines for safety pharmacology

Safety Issues	ICH	U.S. FDA	EMEA/CPMP	JAPAN/MHW
Safety assessment of pharmaceuticals	M3 non clinical safety studies for the conduct of human clinical trials for pharmaceuticals	Guidelines for industry: nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals	-	The new drugs division's notification no. /99: guidelines for toxicity studies of drugs
Safety assessment of biotech therapeutics	S6 preclinical safety evaluation of biotechnology-derived pharmaceuticals	Guidance for industry: providing clinical evidence of effectiveness for human drug and biological products	Note for guidance on comparability of medicinal products containing biotechnology-derived protein as a drug substance	-
Safety pharmacology	Guidance for industry: S7A safety pharmacology studies for human pharmaceuticals	Guidance for industry: S7A safety pharmacology studies for human pharmaceuticals	CPMP: note for guidance on safety pharmacology studies in medicinal product development	Notification no.4-guidelines for general pharmacology
QT interval (Heart rate)	Safety pharmacology studies for assessing the potential for delayed ventricular Repolarization(QT interval prolongation)by human pharmaceuticals	-	CPMP points to consider the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal product	-

Japan legislatio

The regulation of pharmaceutical excipients in Japan does not differ markedly from other countries. The Pharmacopoeia of Japan (JP) and the Japanese Standard of Pharmaceutical Ingredient (JSPI) issue guidelines on regulatory provision on excipients. JP resides in the pharmaceutical affair bureau of the Ministry of Health, Labour and Welfare organization (MHLW). The monographs contained in JP establish mandatory standards for the most widely used excipients.

Table VI. IPEC Excipients Guidelines

	Oral	Mucosal	Trans dermal	Topic	Parenteral	ihalation/ Intranasal	Ocular
APPENDIX 1 (for exposures of less then 2 weeks)							
Base set							
Application site evaluation	-	A	A	A	A	A	
Acute dermal toxicity	A*	A	A	A	A	A	A
Chromosomal damage	A	A	A	A	A	A	A
Eye irritation	A	A	A	A	A	A	A
Acute oral toxicity	A	A	A	A	A	A	A
Skin sensitization	A	A	A	A	A	A	A
Acute Parenteral Toxicity	-	-	-	-	A	-	-
Acute inhalation toxicity	B**	B	B	B	B	B	B
Bacterial gene mutation	A	A	A	A	A	A	A
Pulmonary sensitization	-	-	-	-	-	A	-
Photo toxicity/ photo allergy			A	A	-	-	-
Skin irritation	A	A	A	A	A	A	A
28-day toxicity (2 species)	A	A	A	A	A	A	A
ADME-intended	A	A	A	A	A	A	A
APPENDIX 2 (for exposures of 2-6 weeks)							
Teratology (rat/rabbit)	A	A	A	A	A	A	A
90 day toxicity	A	A	A	A	A	A	A
Genotoxicity assays	A	A	A	A	A	A	A
Additional assays	B	B	B	B	B	B	B
APPENDIX 3 (for exposures greater than 6 weeks)							
I generation reproduction	A	A	A	A	A	A	A
Chronic toxicity	B	B	B	B	B	B	B
Carcinogenicity	B	B	B	B	B	B	-
Photo carcinogenicity	-	-	B	B	-	-	-

A*, required; B**, conditional.

The quality and safety of the excipient is evaluated by a sub-committee on pharmaceutical excipient of the Central Pharmaceutical Affair Council (CPAC) concurrently with the approval process undertaken from pharmaceuticals and Medical Devices Evaluation Center (PMDE) with a part of the National Institute of Health Sciences (Baldrick, 2007; Uchiyama, 1999).

There are several reference materials that must be attached to an application for approval of a new pharmaceutical product containing new excipients. The list of safety data required for new excipient is given in Table IV. All applications require information concerning the reasons for the excipient inclusion in the preparation, precedents of use and description of quality standards. It is necessary to provide information on the origin and development of the excipient, including a description of its uses overseas and its characteristics as well as comparison with other excipients and data related to stability and safety as well (Uchiyama, 1999).

China and Australia legislation

China's State Food and Drug Administration (SFDA) control the excipient regulation. SFDA treat excipients like APIs, requiring clinical study data, drug master file data and good manufacturing practices certificates. The regulation established new GMP and manufacturing rules for excipients produced in China and new requirements for obtaining an import license for pharmaceutical excipient ingredient produced outside China. Under the guidelines, excipient manufacturers would require to provide additional detailed

information concerning the manufacture of pharmaceutical ingredient and specific additional data to substantiate the excipient safety for its intended use. The regulation would apply to new excipients and commonly used compendial excipients. SFDA revised his excipient regulations in 2007, after a serious tragedy in panama in which more than 100 people died after administration of a syrup having glycerin as an excipient adulterated with the diethylene glycol. Then SFDA revised his excipient regulation with harmonization with international agencies like IPEC (Schoneker, 2007).

In Australia, the regulation of new excipient is controlled under the Australian Regulatory Guidelines for Complementary medicines (ARGCM). New substances, which are excipients, will usually be evaluated *via* the same route as the products in which they are to be used. The *British Pharmacopoeia* (BP) is the official standard for regulatory purposes in Australia. The new active pharmaceutical ingredient is evaluated by drug safety and evaluation branch (DSEB). Data requirement for the registration of medicines evaluated by the DSEB have been closely aligned with European Union data required for applications for marketing authorization of a medicine. The comparative regulatory guidelines for safety pharmacology are tabulated in Table IV (Gad, 2004).

INTERNATIONAL PHARMACEUTICAL EXCIPIENT COUNCIL (IPEC)

The purpose of IPEC is to encourage the harmonization of different standards for manufacturing and use of pharmaceutical excipient, develop improved consumer safety in the manufacture and use of pharmaceutical excipient, and introduction of new pharmaceutical excipient. There are various national excipient regulation registration systems they have not yet to be internationally harmonized. The lack of regulatory provision is to be identified by IPEC. IPEC is an industrial association with worldwide pharmaceutical, chemical and food processing firm, which develop, manufacture, sell and use of pharmaceutical excipient. IPEC comprise three regional organizations-US, Europe and Japan. IPEC have same objective regarding the International Harmonization of Excipient Standards. The IPEC's main function is to introduction of novel excipient to market place and development of safety evaluation guidelines. The Safety Committee of IPEC (SCIPEC) includes qualified scientist which develops safety testing of the excipient. The guidelines are based on chemical and physical properties of the excipient, review of the scientific literature, exposure, condition (Including dose, dose duration, frequency, route and user population), and absence or presence of pharmacological activity. The IPEC proposed the guidelines for the safety evaluation of new excipients and good manufacturing guide for bulk pharmaceutical excipients. The guidelines provide sufficient data to define safe condition of use of new excipients. The excipient toxicity guidelines are summarized in table VI, which were developed with reference to the FDA proposed implementation document (Steinberg *et al.*, 1996; Rios, 2006. ICH has approved guidance documents on technical requirements for drug products containing new ingredients. Excipients are controlled closely by defined specification, or monographs, compiled in three major Pharmacopoeias in the U.S., Japan, and Europe. Pharmacopoeial Harmonization also helps to avoid unnecessary delays in the regulatory process, while ensuring their quality, safety, and efficacy. Pharmacopoeial Discussion Group (PDG) established in 1989, harmonization may be carried out retrospectively for existing monographs or chapters or prospectively for new monographs. At present 25 of the 35 general chapter and 39 of the 62 excipient monograph have been harmonized.

CONCLUSION

Pharmaceutical excipients are additives used in the formulation of pharmacologically active drugs and can be viewed as any ingredient of a medicinal product other than the active ingredient. From an International regulatory point of view, it is assumed that novel excipients need to be evaluated as new chemical entities. The lack of harmonized

international regulatory guidelines led to the formation of the International Pharmaceutical Excipients Council (IPEC) in 1991. This industry association, with European, U.S., and Japanese membership has championed the international standardization of excipients, the introduction of useful new excipients, and the development of safety evaluation guidelines. The International Conference on Harmonization (ICH) and Pharmacopoeial harmonization are other association working on harmonization of excipients. Harmonization will lower the cost of goods and the trade barrier and will standardize the regulatory approval process.

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