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## Pharmaceutical excipients: A regulatory aspect

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### Abstract

The purpose of this study is to understand the regulatory aspects of pharmaceutical excipients and its role in a dosage form. In earlier days, excipients were considered as inactive ingredients but with the passage of time, the pharmaceutical scientists learned that excipients are not inactive and have an impact on the manufacture, quality, safety and efficacy of drug(s) in a dosage form. The active drug can't be administered alone and the amount of excipients in a formulation is greater than that of drug(s). Hence, excipients act as important partner in a dosage form and affect various properties viz. absorption, efficacy, safety, bioavailability, solubility, stability, dissolution etc. in a formulation. Previous data revealed that the excipients can also produce some serious adverse effects but the regulatory control regarding the use of excipients are still not clear as compared to Active Pharmaceutical Ingredients (API's). There is a strong need of regulation and legislation for excipients so as to avoid the unnecessary adverse effects and interaction with the drug(s). So, there is a strong need to evaluate the excipients with respect to toxicity, preclinical trial, compatibility studies etc. before inclusion in a formulation.

**Keywords:** Excipients, preclinical evaluation, good manufacturing practice, preclinical studies, side-Effects.

### Introduction

Drugs are always administered in the form of a dosage form that generally consist of a drug (or drugs) together with a varying number and different proportion of other substances called excipients. Excipients are added to the formulation in order to facilitate the preparation, patient compliance and properties of dosage form. Excipients includes mainly disintegrating agents, diluents, lubricants, suspending agents, coloring agents, flavouring agents, emulsifying agents, chemical stabilizers etc<sup>[1]</sup>. Initially, excipients received little attention but this has changed over recent years not just because these items are seen as another opportunity for cost savings but also offers opportunity for introducing new dosage form. Excipients affects the various properties viz. absorption, efficacy, safety, bioavailability, solubility, stability, dissolution etc. in a formulation and have been increasingly used as a key element in improving product branding and also consists of design of more patient friendly dosage form. They are responsible for product performance and enable the drug to give desired pharmacological action. The regulatory guidelines have made it mandatory that all constituents of a drug formulation should be compliant and tested as per current cGMP regulations for safety and efficacy of drug<sup>[2, 3]</sup>

### Experimental Section

The secondary data used in the study was obtained from various official reports published by drug regulatory agencies and internet. The study is of descriptive type and method used is the description.

### Origin and sources of excipients

Excipients are derived from various sources:

- Mineral sources e.g. Talc, Calcium silicate, Silica, etc.
- Animal sources e.g. Shellac, gelatin, Magnesium stearate, Lactose etc.
- Vegetable sources e.g. Starches, Cellulose, sugar, alginates, etc.
- Semi synthetic origin e.g. Cellulose derivative like Hydroxypropylmethylcellulose (HPMC), etc.
- Synthetic origin e.g. polyvinylpyrrolidone, polyethylene glycol, Cross povidone etc.

### **Requirement for inclusion of an excipient in drug formulation:**

The incorporation of certain excipients in formulation is deemed to be undesirable, for example, inclusion of mercurial preservatives, and the inclusion of benzyl alcohol in parenteral products for use in children, the use of benzoic acid esters in injections and sulfites and bisulfites. If it is intended to use any of them, then, a full justification will be required. The function of each excipient is to be explained and the inclusion of material is justified<sup>1</sup>.

Compatibility data should establish the suitability of combination of excipients. Stability studies are also necessary where an unusual excipient is chosen, or where an established excipient is chosen for dosage form that results in its administration by a novel excipient, will need to be supported by data similar to those required for new drug, with full supporting data including composition, function and safety. Novel excipient includes the components of the matrix in prolonged release products, new propellants and new permeability enhancers. In all cases quality of excipient has to be described adequately and shown to be satisfactory but particular attention needs to be given to antimicrobial preservatives should be shown to be effective in appropriate tests to demonstrate antibacterial and antifungal activity<sup>[4, 5]</sup>.

### **Functions of excipients in a formulation**

Total amount of excipients used is greater than the amount of the active drug substance in a dosage form. Like drug substances, excipients are also derived from natural sources or are synthesized either by chemical or any other means. In earlier days, excipients were considered as inactive ingredients but with passage of time pharmaceutical scientists learned that excipients are not inactive and have a substantial impact in dosage forms. There is variability in the performance of an excipient both from batch to batch within a single manufacturer as well as between batches from different manufacturers. Now a day's excipients are known to have well defined functional roles in pharmaceutical dosage form. Their various functions are modulating solubility and bioavailability of the API's, enhancing stability of the active ingredient in finished dosage form, maintaining pH and osmolarity of liquid formulation, acting as an anti-oxidant, emulsifying agent, aerosols, tablet binders, disintegrates, lubricants and diluents. Excipients also interacts with the active principle in a formulated dosage form and provides a matrix that can affect critical quality attributes of drug substance, including stability and bioavailability. Excipients have a potential influence on finished dosage form, affect the safety and efficacy of a product<sup>[6-11]</sup>. Thus, Pharmaceutical companies have to be careful consideration for excipients while incorporating into a dosage form.

### **GMP and quality standard for excipients**

Excipients industry, which consist of hundreds of small companies faced with a strict regulatory framework, increasingly demanding quality standard and a customer base that expects added but increasingly improved services. If route of administration for the drug product containing the main excipient require high GMP further no evaluation is necessary. Otherwise nature of the excipient and its method of manufacture must be assessed because these factors can cause the required GMP level to increase. The inherent nature of an excipient and its production involves consideration of the excipients functionality in drug product, evaluation of

excipient's toxicity and the potential for cross contamination during its manufacturing. This inherent nature of excipient can raise the requirement for GMP compliance<sup>[12, 13]</sup>.

### **Tragedy due to lack of GMP**

In 1937, diethyleneglycol (DEG) was used to solubilize the antibacterial drug. The elixir contained 72% DEG, 10% sulfanilamide and about 15% water. DEG also improved the taste of the medication and made it esthetically pleasing to children. The first batch was distributed in September 1937. More than 100 children died from its consumption as a result of kidney failure. This incident induced the U.S. congress to pass the federal Food, Drug and Cosmetic Act of 1938. During period of 1995 to 1996, 88 Haitian children were poisoned from DEG contaminated glycerin used to make acetaminophen syrup. Similar toxicities from DEG contaminated products were reported in children in South Africa in 1972 and in Bangladesh in 1995. It is also reported that in 1990, cough syrup contaminated with solvents led to 47 deaths in Nigeria. Between 1986 and 1998 in India and Bangladesh, paracetamol syrup contaminated with diethylene glycol resulted in 236 reported deaths, while a similar case in 2006 Panamanian case, for example a Chinese factory was found to have exported diethylene glycol mislabeled as the glycerol suitable for use in medicines. The result was same 100 fatal poisonings<sup>[14-16]</sup>.

### **Need of a preclinical evaluation of excipients**

The development of excipient materials for use in challenge drug formulation represents a growing area for pharmaceutical companies. Such developments have been promoted by the increasing need for more sophisticated excipients and/ or new uses for established ones. The main concern is that how safe the material is? This is very important to know about the safety and efficacy because pharmaceutical excipients are no longer considered as inert substances. New Drug Development involves a range of preclinical studies to show efficacy and safety to support clinical trial work and product licensing safety studies include absorption, distribution metabolism, excretion, pharmacokinetic, genotoxicity, and carcinogenicity investigations within industry. Now a day, the use and safety of established and new excipient is given importance in new drug development process. In excipient development main aspects considered are chemical, manufacturing and preclinical data. Preclinical assessment in excipient development is influenced by non-availability of international guidelines on safety evaluation of excipients, list of approved excipients and lack of strategy for the preclinical assessment of excipients<sup>17</sup>. Excipients are not inert substances as considered earlier. They may have adverse toxicological reaction either by themselves or in drug formulation; this necessitates the preclinical evaluation of excipients before inclusion in a formulation. Instead of many functional roles in a drug formulation a number of adverse reactions like hypersensitivity, allergic or anaphylactic nature is caused by excipients. A preclinical study is more important in case of a novel excipient<sup>18</sup>. New excipient from an intermediate category include substances resulting from a structural modification of an 'approved' excipient, a recognized food additive, a structurally modified food additive, or a constituent of an over the counter (OTC) medicine. But according to guidelines prepared by Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) "Guidance for the industry nonclinical studies for safety evaluation of pharmaceutical excipients", a new excipient means any

inactive ingredients that is internationally added to therapeutic and diagnostic products, but it is believed that these inactive ingredients possess no therapeutic effect at the intended dosage, although they may act to improve product delivery (e.g. enhance absorption or control release of drug substance) and they are not fully qualified by existing safety data with respect to the currently proposed level of exposure duration of exposure or route of administration<sup>[19]</sup>.

### Adverse effects and safety concerns of pharmaceutical excipients

The most important part of a medicine as far as its weight is concerned, is constituted by its excipients, which have the important functions of guaranteeing the dosage, stability and bioavailability of the active principle. The components employed as excipients must present the characteristic required by this technological function but, as with any substance administered to human being, they must also correspond to suitable safety requirements. In past the importance of evaluating the possible adverse effect of excipient was underestimated. The safety profile of these substances is more deeply researched as record the toxicological aspect only if they are also employed in the food industry (anti-oxidants, sweeteners, coloring agents etc) toxicological committees (among which Joint Expert Committee on Food Additives a mixed committee of WHO/FAO) demand through studies in laboratory animals, with the intent of protecting the consumer's safety. Study of toxicity is not simple for several reasons mentioned below:

- The large number of substance on the market.
- Diversity of their chemical profiles, their sources.
- Their technological functions.
- The presence of secondary products and/or contaminated that may be true causes of adverse effects<sup>[14, 15, 20]</sup>,

### Results And Discussion

The traditional view point considering excipients as inert material is long outdated. Excipients now considered more likely new drug substances that require regulatory requirements like API's. Hence, there is a need of regulatory requirements for excipients before they are used in a particular dosage form. Several organizations have published guidance on excipients development, manufacture and control. Some addressed safety testing for new excipient and for existing excipients with a new use. Other addressed excipients manufacturing and Current Good Manufacturing Process (cGMP) requirements. Now a day excipients not only acts as fillers in a dosage form but can be true partners of API's and have a potential to enhance or adversely affect performance. In many countries tragedies have taken place in past due to the unknown toxicity of excipients and also due to mishandling of excipients during transportation. These tragedies draw the attention of regulators and field experts toward the quality of excipients. The various organizations are working in this field for providing the assurance to drug manufacturer for better quality of excipients. The role of excipients is increased in formulations the excipients functionality is latest necessity in pharmaceutical industry. There is a need to characterize an excipient as fully as possible. The true functionality test of excipients related to function must be approached. The actual function of excipient must be known before inclusion into a formulation.

The harmonization of excipients is other important field to remove the trade barriers and keeps the formulators to design

the formulation for worldwide acceptance by regulatory bodies. Many excipients are in different stage of the harmonization. Although the process of harmonization is slow, the efforts of various regulatory agencies, pharmacopoeias and industry organizations will have a very positive impact. Harmonization will lower the cost of goods, standardize the regulatory approval process and also lower the trade barriers.

### Conclusion

Excipients act as important partner in a dosage form and affect the properties of a formulation. In earlier days, excipients were considered as inactive ingredients but it was reported that they can also produce some serious adverse effects. However, the regulatory control regarding the use of excipients is still not clear as compared to Active Pharmaceutical Ingredients. There is a strong need of regulation and legislation for excipients so as to avoid the unnecessary adverse effects and interaction with the drug(s). So, excipients should go through the various evaluations viz. toxicity study, preclinical study, compatibility studies etc. before inclusion in a formulation. Hence, the regulatory bodies and industries should regularize the evaluation of excipients as that of APIs.

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