

Excipients: The Real Players behind Robust Formulation

Hitesh Chavda*, Suresh Kumar Neerumalla, Axay Patel, Sanjay Poptani

Department of Formulation and Development, R&D Centre, Gowrie Research Pvt Ltd (B&S Group), Vadodara - 391740, Gujarat, INDIA.

The backbone of any successful robust pharmaceutical product is built on their excipients. Excipients show a vital role in the dosage form design. Excipients do not have therapeutic activity, however, they influence the therapeutic activity of active pharmaceutical ingredient (API) through formulation characteristics. Please note inactive ingredients are clearly not reliably inert in their biological activity and thus should not be listed as such. A more suitable and concise term is excipient.

A bad or wrong excipient selection can even lead to several issues. In Australia, in the late 1960s, epileptic patients who were taking phenytoin capsules experienced intoxications due to the replacement of diluent, calcium sulphate with lactose in the capsule formulation. This substitution, considered to be harmless, give rise to in an increase of the mean serum concentration of phenytoin by a factor of 4.5, which is large for a narrow therapeutic index drug such as phenytoin. This happens due to the solubility of excipients in water. Calcium sulphate (dehydrate) is very slightly soluble in water whereas as lactose is freely soluble in water. Therefore, in the original capsule formulation, calcium sulphate performed as a matrix former and prolonged the release of the phenytoin, whereas lactose triggered an immediate and considerable release of phenytoin beyond the toxic threshold.¹⁻² Misperception between excipients can also have a serious outcome. Toxic cough syrup case refers to a 2007 scandal in which Panamanian pharmaceutical manufacturers formulated cough syrup using diethylene glycol which they understood to be glycerin. Diethylene glycol is a

cheaper alternative to glycerin for industrial applications, however, it is nephrotoxic. As reported by The New York Times 365 deaths from the poison, 100 of which have been confirmed so far.³ In India and Bangladesh, in 1990-1992 paracetamol syrup in which diethylene glycol was substituted for propylene glycol caused 236 deaths.⁴ In USA, 71 adults and 34 children died in 1937 after taking a drug “Elixir Sulfanilamide” to treat a variety of ailments, from gonorrhea to sore throat. The investigators from the US Food and Drug Administration (FDA) identified the solvent, diethylene glycol, used in formulation as the killer.⁵ In pediatric population the presence of benzalkonium chloride in antihistaminic drugs leads to bronchospasms, aspartame (sweetener) leads to headaches and seizures. The presence of propylene glycol in neonates leads to hyper-osmolality and lactic acidosis.⁶ Benzyl alcohol toxicity in neonates was reported in 1980. A gasping syndrome was reported in premature infants.⁷ At this time in the United States, bacteriostatic water and sodium chloride injections contained 0.9% benzyl alcohol. The infants received injections from flushes and/or medicines which were reconstituted with the water and sodium chloride. The pathways involved in the metabolism, benzyl alcohol is oxidized to benzoic acid and then in the liver it is conjugated with glycine and finally excreted as hippuric acid in the urine. In premature babies this metabolism pathway is immature, and as a result these infants accumulated benzyl alcohol and leads to toxicity.⁷

Excipients selection for a drug product is a key step in drug development. The selection

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Correspondence:

Dr. Hitesh Chavda

Department of Formulation and Development, R&D Centre, Gowrie Research Pvt Ltd (B&S Group), Vadodara - 391740, Gujarat, INDIA. Phone: +919427472354 E-mail: hitcvd@gmail.com



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of excipients for the particular pharmaceutical product is a very critical step and it depends upon the API, route of administration, dosage form and other factors. Definitely, the properties like bioavailability and stability of the ultimate dosage form are greatly dependent on the excipients selected, their concentration and interaction with both the API and each other. A thorough knowledge of excipients is crucial for scientists. Furthermore, the evolution of novel forms of drug delivery has brought about an increase in the total of the excipients being used. Scientists must study stability and compatibility issues, pharmacokinetic aspects, permeation characteristics, drug delivery platform, segmental absorption performance, intellectual property concerns etc. while choosing an excipient for development of robust formulation. APIs cannot be administered as such; therefore they are formulated in suitable dosage forms for the several reasons. These reasons may be dose accuracy and consistency, patient compliance, bioavailability enhancement, aesthetics and side effects reduction. Excipients are the essential necessities to these reforms allowing formulation scientists to accomplish their set objectives.

A carefully-selected excipient may lessen manufacturing costs, may amplify patient experience, etc. An excipient must suit the proposed dosage form, establish organoleptic properties, obey pharmacopeial regulations, easily available and work excellently. It should work well with equipment. Determining factors may include the amount of drug needed, the proposed use of the drug, prevailing environmental conditions, excipient potential toxicity and its origin.⁸

There are diverse types of excipients and their requirements. Excipients may be a single chemical entity (include organic and inorganic acids, their salts, sugars, alcohols, etc.), may have experienced physical treatments (like micronization), may have chemically converted (like modified starch) or mixtures of chemically related components (like polyol esters). Mixed excipients are preparations that are ready-for-use, like ready-made coating materials. Commonly used excipients are listed in Figure 1.

The quantity of excipient to be used in the formulation may be referred from Handbook of Pharmaceutical excipients,⁹ Joint FAO/WHO Expert Committee on Food Additives (JECFA),¹⁰ Inactive Ingredients Database (IID),¹¹ etc. Information on inactive ingredients present in FDA-approved drug products is provided by the Inactive Ingredient Database by FDA which can be used by industry as a support in the development of drug products. For different drug development purposes, once an inactive ingredient has appeared in an approved



Figure 1: Commonly used excipients for solid, liquid and semisolid products.

drug product database for a particular route of administration, the inactive ingredient is not considered new and may necessitate a less extensive review the next time it is included in a new drug product. According to 21 CFR 210.3(b)(8), an inactive ingredient is any component of a drug product other than the active ingredient.¹² Novel excipient is a material or composition that has not been previously used in an approved drug product in the US (i.e. not listed in FDA IID) or that has been previously used in an approved drug product but which it is desired to employ for a new route of administration, or a higher level of use that has been previously listed in the IID.¹³ A novel excipient can also be defined as a new co-processed excipient made from two or more previously approved excipients. Generally Recognized As Safe (GRAS) excipient is any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use or unless the use of the substance is otherwise excepted from the definition of a food additive.¹⁴ The International Pharmaceutical Excipients Council (IPEC), a pharmaceutical regulatory non-profit, develops, implements, and promotes global use of appropriate quality, safety, and functionality standards for pharmaceutical excipients and excipient delivery systems. IPEC functions as a primary international resource on excipients for its members, governments, and public audiences.¹⁵ A group of industry experts from European Fine Chemical Group (EFCG), IPEC Europe, IPEC Americas, European Association of Chemical Distributors (FECC), and Pharmaceutical Quality Group (PQG) have worked

together since 2008 on the development of a certification scheme for excipients suppliers now known as EXCIPACT™. The EXCIPACT™ scheme provides for an independent certification of manufacturers and suppliers of excipients as a means of ensuring patient safety, improving assurance of supplier quality, while minimizing the overall supply chain costs.¹⁶

Implementation of Quality-by-Design (QbD) for a drug product drives the need for QbD approach for the excipient. Presently there is no specific industry for pharmaceutical excipients. The majority of pharmaceutical excipients are generally provided by chemical or food industries. Specifications are generally not provided by the pharmaceutical market. QbD consideration may encourage pharmaceutical manufacturers choices for excipient selection to choose excipients which are manufactured under well-defined controls, well characterized for a variety of functionalities, possess good batch uniformity, high-quality grade specifically designed for the pharmaceutical purpose and are supplied by authenticated manufacturers.¹⁷

As per report “Global Pharmaceutical Excipients Market Growth, Trends and Forecasts (2017 - 2022)” published by MarketResearch.com the global market of pharmaceutical excipients is anticipated to reach USD 9.3 billion by the end of 2020, rising at a CAGR of about 7.2% from 2014 to 2021.¹⁸

It is important that scientists ensure that they have fully investigated excipients to be used for the development of the most robust formulation, as excipients are the backbone and real players.

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