Great expectations in new excipients

29 September 2015

As companies grapple with patent cliffs, reduced healthcare spending and increasingly stringent regulations, drug development has become more challenging. New excipients could offer much-needed opportunities, but how can you make the right choice? Dr Rajsekhar Paul, senior scientist at Novartis, shares his views.

Pharmaceutical excipients are a heterogeneous group of materials, and differ in their origin, chemistry, physico-chemical properties and functionality. The most commonly used chemicals of this class are sugars, starches or modified starches, minerals, cellulose and its derivatives, fats, and oils or solvents. All these materials have a long history of use in pharmaceuticals, food and cosmetic applications. But with the transition from simple formulations to drug delivery systems, the demand for synthetic or semi-synthetic functional polymers (such as acrylates, ethoxylated compounds or polyvinylpyrrolidone grades) has increased tremendously. Today, as the pharmaceutical industry has to deal with the patent cliff, reduced healthcare spending and more stringent regulations, drug development has become difficult. But new excipients offer opportunities. A novel excipient could help to reformulate approved drugs to improve the quality and safety of the medicine, or to reduce its manufacturing costs. Despite the number of modified and co-processed excipients to have come to the market recently, almost all manufacturers refrain from their development because the process takes time, requires resources and is associated with high failure risks.

World Pharmaceutical Frontiers: How do you think formulation development has changed in the past ten years or so?

Dr Rajsekhar Paul: I can clearly see a trend. There's a formulation change in many aspects. First of all, the active pharmaceutical ingredient is coming up in many novel formats. For biologics, we've seen change in the regime from monoclonal antibodies to multivariations of antibody formats. Yet, these molecules pose specific challenges during development and commercialisation. In many diseases, gene and cell therapy are combined in the development of promising therapies. This is being considered a biologics formulation, but the mode of administration is also very diverse. Now, coming back to our standard biologics formulation of monoclonal antibodies, the formulation part is changing. It's coming to different formats of primary packaging devices. In order to extend product life cycle for injectable therapeutics, a product's presentation is moving from a vial to a prefilled syringe presentation. A prefilled syringe helps to increase dosing accuracy, convenience and safety; enhance patients' quality of life; and reduce patient time in the clinic. Prefilled syringes is an area with an expected growth of about 15% a year.

How have these trends affected excipient development?

In formulation research, people are looking for more stable formulations with extended life cycle and longer shelf life. Apart from stabilities, the development and testing of new excipients require a multidisciplinary understanding of technical, safety, quality and regulatory aspects. The technical complexities associated with drug development have increased over the years. This is mainly due to the challenges associated with the drug solubility problems, complex drug actives and stabilisation of the active ingredient. Most of the time, the current array of excipients in approved products is not sufficient to formulate challenging molecules, forcing pharmaceutical scientists to explore new

excipients. International pharmacopoeias had defined the list of purposes for which certain excipients are used. Many excipients have more than one use, which can be an advantage since it reduces the number of excipients needed and minimises the risk of interactions between them. Cross-reference to published scientific reviews of the safety of materials used as excipients in a drug formulation is acceptable to the regulators. More reviews are becoming available for materials used as excipients. Few examples of recently popularly reviewed and commonly used materials are the PEG - polysorbates (tweens) and sugars such as sucrose or trehalose. For example, the roles of polysorbates in biopharmaceutical formulations require this surfactant to maintain its intact structure. It is essential to choose the appropriate method of evaluations in order to assess the content, stability and compatibility of a formulation. Tweens can potentially degrade, resulting in the formation of lauric acid.

When it comes to choosing an excipient, what are the most important considerations?

The manufacture of the excipient itself can be a complex process, and considerable ingenuity and formulation expertise are required to produce a product that will be stable during storage, transport and handling, yet will release its active pharmaceutical ingredient as required once ingested. An in-depth knowledge of the physical, chemical and biological behaviour of the excipients is essential. The stability study with the protein is very important with regard to drug product quality perspective. It is crucial to monitor whether the product is stable longer term when formulated with the selected excipient. Also, a parallel monitoring of the self-degradation of the excipient is important. Excipients can be stable; however, certain molecules have their own degradation mode and chemical pathways depending on their structures. Accelerated stress studies at higher temperature and relatively shorter duration can already hint at the product's stability together with the combined effect of the excipient formulated in it. Physico-chemical parameters are analysed, such as purity of monomeric entity, viscosity and increase in particulate matter content per container. When coming to the real clinical trial, and when presented with a patient who has an adverse reaction, it is important to be aware that reactions may not always be due to the active ingredient.

What happens if you choose the wrong excipient?

Wrong excipients can create adverse activities in a patient's body. They are more likely to occur if the patient has an existing sensitivity to similar ingredients, is on multiple medicines or when the quantity of excipients may be high relative to body weight, for example, in premature babies. Excipients present in their current and past medication history should also be considered. This will help to rule out which ingredients may be causing the adverse effects. For a formulation perspective, wrongly chosen excipients can sometimes generate particles after administration in a patient's body. A compatibility study should be established beforehand with the injection or infusion materials that are in potential contact with the biologics. A sound and well-designed preformulation study would certainly be helpful to predict a stable formulation in most cases ahead of time.

In terms of the newer excipients on the scene, how do they compare with more traditional ones?

Due to limited physico-chemical and pharmacokinetic properties of the widely existing excipients, certain drugs present formulation challenges and may require either the discovery of new excipients or new applications of existing excipients. Novel excipients may be advantageous in their formulation, manufacture and marketing. In formulation, these excipients may increase solubility, enhance flow properties during delivery by reducing viscosity, require

smaller quantities, decrease environmental concerns and improve stability. Health authorities have an excipient database, which is basically an approved excipient list for pharmaceutical companies. There are certain hurdles in introducing a new excipient, mostly because of the regulatory consequences in the industry. Regulatory agencies require new excipients to undergo a series of toxicology tests, which may be costly. Few new excipients of new chemical entity have been introduced into the market, primarily because of the economic hurdles associated with toxicology testing.

How do you think the excipient space is going to change in the next ten years?

I think novel excipients research is a very interesting field. Design of new excipients by computational modelling and simulations are being done in early-phase research labs. Substantial electrostatic interactions can occur between oppositely charged excipients and drugs. Negatively charged excipients may not be compatible with positively charged drugs or excipients, and positively charged excipients can interact with negatively charged drugs and excipients. Based on the Henderson-Hasselbalch equation, alkalinising agents and acidifiers can influence the micro-environment pH significantly, and may have a major influence on drug solubility for acidic and basic drugs. I think that with the growing complexity of delivery devices, people are looking now for much more stable and simplified formulations. Patient convenience is a crucial issue while taking injectables. Delivery of highly concentrated drug formulation is challenging. Success stories can be told in many aspects of the drug products, from the robust formulation and manufacturing process to smooth scale-up and process validation, to strong regulatory acceptance and market-share domination in their therapeutic areas. Paying attention to pharmaceutical excipients and their regulatory issues, is an indispensable initial step to the success of drug products.