Excipients in the 21st century.

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Editorial

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Excipients are truly the Cinderellas of pharmaceutical formulation science; they do not get the glory, but without them, many of the therapeutic advances of the last 50 years would not have been possible. Almost all drug products contain excipients, and without them we could not have drug products that can be administered by or to the patient. However, what is concerning today is that there appears to be a lack of understanding of the properties of excipients and how they are best used in formulation and process design and development.

When I left pharmacy school, in another era and another country, I at least had an understanding of what an excipient was, and the types of formulations and processing. I had used several in my practical classes in pharmacy compounding. With minor exceptions, such as the course taught by the author of the commentary that appears in this issue; this is not taught in pharmacy school today, as far as I am aware. My first industrial job was with a generic/contract manufacturer. It was here that I really began to understand formulation and excipients; what could be done, and sometimes more importantly, what could not be done to achieve an acceptable product.

I worked with oral tablets, oral solution and suspension products, creams and ointments. While a lot of the tablet formulations were wet granulated, we were also manufacturing increasing numbers of formulations using direct compression. I got to understand a good deal about the properties and applications of the different excipients, including lactose, corn starch, microcrystalline cellulose, calcium phosphate dihydrate, magnesium stearate, stearic acid, talc and fumed silica. Later on, after I moved to another company, I worked with the formulation and design of powder-filled capsules, softgel capsules, suppositories, pessaries (vaginal suppositories) and injections and learned about the properties and application of even more excipients.

In those days, we did not have as good an understanding of the detailed properties of excipients as we do today in some ways. However, we knew how to use them, and the drugs were somewhat simpler; most were soluble (BCS I or III). Yes, we had some insoluble drugs such as griseofulvin, digoxin and the oral steroids, but we knew that we had to micronize them and process them in certain ways.

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Over the years, I have been fortunate in that I have been able to keep up with developments in the field of excipients and formulation. It has become apparent that not everyone realizes the importance of excipients. To many, formulation science is easy (like falling off a log), but I can tell you, from my own experience, that if that were the case, I would not be needed as a consultant in pharmaceutical formulation.

Today, as a consequence of combinatorial chemistry and high-throughput screening, we are able to design and create drug molecules that can bind very specifically to the intended receptor. However, this comes at a price; higher molecular weight and increased lipophilicity, both of which can mean decreased solubility, and often solubilities far lower than the drugs of yesteryear.

This has meant that we have had to adopt dissolution- and bioavailability-enhancing technologies beyond simple micronization more often. This is where a good understanding of excipients and the delivery technologies is of vital importance. We need to keep up with the development in understanding of our excipients; their uses and advantages as well as their disadvantages if we are to be successful in developing new formulations of potentially life-saving drugs.

In the past 50 years, there has been tremendous achievements and progress in the treatment of disease. There are new drugs and procedures that were in the realm of science fiction 50 years ago. For example, there are drugs to treat and effectively cure some viral diseases, there are gene editing techniques and gene therapy, and there has recently been the transplantation of the heart from a genetically engineered pig into a human patient. Some of these advanced therapeutic modalities will rely on excipients. Can we expect that yesterday's excipients will be sufficient for these new advanced therapies? I believe not! Going forward, we will need new chemical excipients to enable the development and commercialization of new advanced therapies.

In the field of excipients, we have not seen many new chemical excipients. Since approximately 1995 until the development of the COVID vaccines, we had only seen the introduction of five new chemical excipients:

- Sulfobutyl ether betadex sodium (Captisol® by Cydex; now part of Ligand)
- Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus® by BASF)
- Polyethylene glycol (15)-hydroxystearate (Solutol® HS 15 by BASF)
- Salcaprozate sodium (SNAC used in Eligen® technology by Emisphere)
- Fumaryl diketopiperazine (a component of Technosphere® inhaled insulin technology by MannKind)

The COVID mRNA vaccines are believed also to contain novel excipients which are fundamental to how they work and deliver the mRNA.

One of the major stumbling blocks to the introduction of new chemical excipients is the lack of a formal approval process for new excipients. They are only approved through a drug product marketing application. The US FDA Final Guidance document, the Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, May 2005 outlines the necessary studies for the different routes of administration. However, there is reluctance on the part of pharmaceutical companies to risk their potential blockbuster drug application on an unapproved excipient, unless there is a technical need which cannot be met any other way. IPEC-Americas has a New Excipient Evaluation Scheme. Under this scheme, the excipient safety/toxicology package is reviewed by a panel of independent toxicologists who indicate if, in their opinion, the safety/toxicology package would be acceptable to the FDA for the proposed route of administration and use level. However, it lacks the formal input from the US FDA and has not been used as much as had been hoped.

The US FDA recently (September 8, 2021) announced

a pilot program for the evaluation of new chemical excipients, and called for the submission of dossiers for novel excipients, including the results of the studies outlined in the May 2005 Guidance document, to allow the Agency to evaluate them with a view to setting up a more permanent program to asses new excipients. In this voluntary pilot scheme, the Agency will select two dossiers to evaluate in 2022 and a further two for 2023. At the end of the pilot program, there will be a review and a decision made as to whether or not the program will be continued on a permanent basis.

Let's hope the pilot program is a success, and that the program does become permanent, because patients' lives will depend on it!