Excipients to the year 2025 – and beyond!

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ABSTRACT

The developments in pharmaceutical excipient science and technology since 1995 have been reviewed. The field of excipients science and technology has changed and continues to change. Some good progress has been made in such areas as harmonization of excipient pharmacopeial monographs, and the application of new analytical methods to better characterize excipients. However, progress in some other areas has been less satisfactory. There have been developments in other areas that have impacted excipients, such as Quality by Design, continuous manufacturing, the preponderance of poorly water-soluble new small molecule drug substances, and the introduction of biologic drug substances. It is likely that these developments will place more demands on our excipients and excipient manufacturers and suppliers. Looking ahead, excipients will continue to be in the spotlight. It is hoped that progress can be made in the development of an independent review of new chemical excipients to ease their introduction. Without new chemical excipients, it seems likely that the robust formulation of some future drug molecules may not be achievable. While new excipients for small molecule drug applications are needed, better and more effective excipients will also be needed for the formulation of biologic drug substances.

KEY WORDS: Excipients, future developments, variability, continuous manufacturing, regulatory approval

INTRODUCTION

In March 1995 a presentation was given at Rutgers University (1) on possible future developments in the field of excipients. This presentation was subsequently developed into a review paper (2). It is now almost 25 years since the presentation and subsequent publication of the paper and it is worth reviewing what has happened in the field of pharmaceutical excipients since 1995.

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This report will review the progress and changes that have occurred in the excipient field in the past almost 25 years, report on other developments that have impacted excipients, and also take a look into the future to try to anticipate likely changes that will impact excipients, from both excipient manufacturers' and excipient users' perspectives. In addition, other desirable developments will also be discussed.

What has been achieved/what has not been achieved since 1995/6

The original report (2) looked at possible future developments related to excipients in three categories:

- New excipients
- Particle engineering
- Other factors influencing excipients

New excipients

The 1996 paper (2) postulated that there would be few, if any, new chemical excipients introduced. This has largely been borne out in practice. As of the time of writing this report (Q2 2019), and as far as the author is aware, in the past ca. 25 years there had been five new chemical excipients introduced into the US market that have been used in commercial pharmaceutical finished products: sulfobutyl ether betadex sodium (Captisol® from Cydex; now part of Ligand Pharmaceuticals), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus® from BASF) Polyethylene glycol (15)-hydroxystearate (Solutol® HS 15 also from BASF), salcaprozate sodium (SNAC used in Eligen® technology from Emisphere Technologies) and fumaryl diketopiperazine (a component of Technosphere® technology from MannKind). It should be noted that, in the case of sulfobutyl ether betadex sodium and fumaryl diketopiperazine, and possibly for the other new excipients, the driver for accepting the new excipient was an unmet technical need that could not be solved using existing means. Recently, a new surfactant excipient based on novel chemistry has been announced (FM1000 from The Dow Chemical Company) for use in protein drug products (3, 4). However, at the time of writing, it was not known if this excipient has been used in either clinical or commercial drug products for human use.

Particle Engineering

The 1996 paper (2) also suggested that new grades of existing excipients would continue to be introduced to meet user requirements and the needs of new enabling technologies (e.g. hot-melt extrusion, spray dried amorphous dispersions, etc.). This has largely been the case. However, there are only so many variations which can be made to an excipient to achieve a new grade for it to continue to meet e.g. compendial specifications. If it no longer complies with the monograph specification, it becomes much more difficult to persuade potential users to use the excipient. There is an expectation on the part of regulatory authorities that, if a pharmacopeia monograph exists for the excipient, the excipient used in human medicines, both for investigational use or commercial sale, will comply with that monograph. It may be possible to modify the monograph, but this takes time and a monograph revision to extend the definition of the excipient may have to wait for the excipient to be included in a marketed product. There is the issue of potential excipient safety questions during product marketing authorization review, and there is also the need to develop a suitable specification which can be accepted by the regulatory agencies. However, with the current move to Quality by Design (QbD) (see below) the question of suitability of specification is a potential issue for all excipients since regulatory agencies now require that the suitability of the excipient for use in a product formulation be justified and simple acceptance of the compendial specification will likely not be sufficient.

In addition, the 1996 paper (2) suggested that co-processed excipients would be more likely to be introduced since their safety can be bridged to that of the individual components provided there has been no new covalent chemistry introduced during the co-processing. This has largely been the case with several co-processed combinations of excipients having been launched. New co-processed excipients continue to be announced. It seems likely that this trend will continue for the foreseeable future.

However, the current options for particle engineering do not overcome the issue of excipient chemical incompatibility. Since these 'new' excipients, whether co-processed or new grades of existing materials, will have the same reactive groups, they will have the same potential to react with and degrade a susceptible active pharmaceutical ingredient (API). Such chemical reactivity can only be overcome by using different excipients not containing the reactive group(s). This is not always easily achieved (see below).

Other factors influencing excipients

The other factors in the 1996 paper (2) were as follows:

- Just-in-Time (delivery of excipients to the user's site)
- Automation (of pharmaceutical product manufacturing)
- Materials science approach to excipient characterization
- Validation
- Developments in (pharmaceutical product) manufacturing technology
- The interface between (pharmaceutical product) development and production
- Globalization
- Harmonization

There have been developments in most of these areas which are discussed briefly below.

Just in time

This is a logistics strategy whereby materials (API and excipients) are delivered to the manufacturing site just in time to be tested, released and used. There are savings related to reduced quantities in inventory and storage. While this strategy works well for e.g. engineering supplies such as nuts and bolts where we have the technology to control manufacture to within very tight dimensional tolerances, it does not work so well for pharmaceutical materials such as APIs and excipients because we do not have the ability to control their manufacture to achieve the necessary consistency in physical characteristics. Today, there does not appear to be much emphasis on just-in-time.

Automation (of pharmaceutical manufacturing)

The original discussion focused on three aspects of automation: computer-integrated manufacture (CIM), lights out manufacture and robot workstations. It can be argued that the first two aspects have been achieved, at least for tablet manufacture, with the approval of marketing authorizations for products produced by continuous manufacturing in both the US and Europe. The robot workstation concept was related to the concept of form, fill and seal. However, in this case the concept was to compress and immediately package individual unit doses using work stations that could be installed in e.g. isolation cabinets to reduce operator exposure to hazardous drugs and/or assure product stability by excluding e.g. moisture or oxygen. As far as is known to the author, this concept has not been commercialized; however, the technology exists in other industries. The nearest approach to the concept in pharmaceutical product manufacture would be the packaging of effervescent tablets coming directly off the tablet press to reduce issues with the storage of the unpacked tablets in bulk.

The materials science approach to the characterization of pharmaceutical materials

Progress has been made in this area. In part this has been a consequence of the move to the use of Quality by Design (QbD) concepts in pharmaceutical development projects. With QbD there is a requirement on the part of the regulatory authorities that the marketing authorization applicant demonstrate enhanced understanding of their excipients (and API) and how they impact pharmaceutical finished product critical quality attributes (CQAs). The applicant is required to justify the use of each excipient, to justify their specifications, and to demonstrate that any critical material attributes (CMAs) are properly controlled. This requires that the applicant characterize their excipients beyond those tests listed in the pharmacopeia monograph. These aspects, and others, together form the Control Strategy for the release of batches of finished product. In addition, in the EU the applicant is expected to justify and assess that the excipient has been manufactured to an acceptable level of cGMP, and is fit for its intended purpose (see later).

The 1996 (2) paper also discussed the idea of standardized functionality tests which would be accepted by all. This has not happened, and probably will never happen, because excipient functionality (performance) is very much linked to its use, i.e. the particular product formulation in which it is being used, and each formulation and its processing are different, as are the likely CMAs and functionality tests. In addition, there can be many ways to assess a particular performance characteristic. For example, the Handbook of Pharmaceutical Excipients, 2nd Ed. (5)

lists seven different test conditions for the determination of compression characteristics with several different types of equipment being used in the different test procedures. While there may be a correlation between the different procedures with some materials, that may not be the case for all materials.

Validation

In 1995/6 the pharmaceutical industry was operating according to the three-batch validation paradigm whereby three batches were manufactured at commercial scale and if all three batches met specification, the product and process were considered validated. However, it was recognized that this did not always ensure that subsequent routine product manufacture met specification. The United States Food and Drug Administration (FDA) has stated publicly that there were products on the market that had been validated according the three-batch validation paradigm, but that as many as one in two batches failed. The FDA now encourages continuous verification of product manufacture to demonstrate that each batch manufactured is fit for purpose and that the Control Strategy is still satisfactory to assure the suitability of the released finished pharmaceutical product (6).
Second sourcing of excipients as a part of a risk mitigation strategy was also discussed in the 1996 paper (2). This remains an option. However, if this is contemplated from the outset, it should be included in the QbD Design of Experiments (DoE) (see below).

Developments in (pharmaceutical product) manufacturing technology

The 1996 paper (2) discussed the increases in manufacturing output that might be contemplated, such as increased speed of compression on a rotary tablets machine, and made the point that there was a limit, beyond which even the most compactible material will fail to compact properly. The reality is that the improvements in equipment design have focused on adding better sensors to allow more and better data capture linked to better control of manufacturing output. While manufacturing equipment is more sophisticated today than ca. 25 years ago, the manufacturing or filling speeds have not dramatically increased for either oral solid dosage forms or liquid dosage forms.

There have been other developments in pharmaceutical manufacturing technology since 1996. The first 3D-printed tablet product has been approved in the US (see below). In addition, hot-melt extrusion (HME) has emerged as an alternative to spray drying for the manufacture of e.g. amorphous polymer dispersions of poorly water-soluble drugs. There are now drugs approved for sale in the US market that are manufactured using HME. Another major development in pharmaceutical manufacturing technology has been the adoption of continuous manufacturing for pharmaceutical products (see below). These newer manufacturing technologies will place extra demands on our excipients in terms of designed functionality and consistency of performance.

The interface between (pharmaceutical product) development and production

As a consequence of the introduction of the FDA's SUPAC (Scale-Up and Post-Approval Changes) Guidance documents and the introduction of QbD, there has been considerable progress in smoothing the transition from pharmaceutical product development to routine commercial manufacture. Although the SUPAC documents strictly relate to products which have been launched and are thus in commercial production, these documents do indicate the FDA's thinking on scale-up and equipment changes in general. The transition to the use of QbD concepts in the development of pharmaceutical products and the introduction of the concepts of risk assessment and risk mitigation have required us to better understand our pharmaceutical formulations and their manufacturing processes, and the effects of scale changes.

Globalization

The pharmaceutical industry and the excipient manufacturers have continued to consolidate. For example, since 1995 Pfizer has taken over Warner Lambert-Parke Davis, Pharmacia and Wyeth, Novartis

was formed from the merger of Ciba-Geigy and Sandoz, Roche took over Genentech, Sanofi acquired Genzyme, and there have been others. Among the excipient companies Rettenmaier took over the Mendell division of Penwest Pharmaceuticals to form JRS Pharma and Dow Chemicals and Dupont are in the process of merging and splitting. At the same time Dow Dupont took over FMC Biopolymer. Many companies in both the pharmaceutical products and excipients areas have expanded into India and China. Both the pharmaceutical and excipient sectors are global and will continue to be so.

Harmonization

There has been considerable progress in the area of pharmacopeial harmonization of excipient monographs and general chapters. However, it must also be stated that progress has not always been smooth. Of the approximately 60 excipients on the harmonization list, approximately 40 have been harmonized, but none have been harmonized completely. There was little to no progress during the first10 years of the harmonization effort under the Pharmacopeial Discussion Group (PDG). On review, it was found that there was typically one test, sometimes two, that the pharmacopeias could not agree on. The PDG then introduced the concept of 'harmonization by attribute' to overcome this. In effect, the pharmacopeias indicate in the monograph what they have agreed on and what they could not agree on. It may not be perfect, but it is much better than nothing. There has been better progress in the area of general chapter harmonization with some general chapters being completely harmonized.

Pharmaceutical excipients for use in medicines for human or veterinary use are required to be manufactured to an acceptable standard of current Good Manufacturing Practice (cGMP). In 1995/6 there were no universally accepted GMP rules for excipients, and this is still the case today. However, it can be argued that some progress has been made. The International Pharmaceutical Excipients Council (IPEC), in particular IPEC-Americas and IPEC Europe, issued the first version of their Good Manufacturing Guide for Bulk Pharmaceutical Excipients in 1996. Subsequently, IPEC worked with the Product Quality Group (PQG) on revisions to the guide. The layout of the Guide is based on the structure of ISO 9001. The ISO 9001 Standard was revised and reissued in 2017. The IPEC-PQG Guide was revised in 2017, but is currently being further updated.

Third-party certification of excipient manufacturers is a current topic of discussion, and has been for some years. Quite simply, with the number of customers for a particular excipient manufacturing site (likely in the hundreds), there is simply not enough time available to accommodate all the site audit requests. Even if your company is the largest pharmaceutical company in the world, its business may only be a small fraction of output of the manufacturing plant since many pharmaceutical excipients are used in far greater quantities in other industries such as food, construction and oil and gas. Third-party certification has been proposed as a possible means to overcome this 'audit crunch'. Currently, there are two very similar schemes available, both based on ISO 9001; The EXCiPACT scheme (7) and the ANSI/NSF/IPEC 363 standard (8). The EXCiPACT scheme is an add-on to ISO 9001 and requires that the manufacturing site be certified to ISO 9001. The ANSI standard is stand-alone, and does not require ISO certification. Both schemes are intended to be identical to all intents and purposes. The Rx-360 consortium has a joint audit scheme whereby one audit is performed on behalf of a group of companies. However, this is not a certification scheme of EXCiPACT or ANSI type.

Developments since 1995/6 which have impacted excipients

Risk mitigation strategies

In the mid- to late- 1990s, risk mitigation on the part of excipient users in the supply of their excipients was a hot topic. One aspect which was investigated was the option for alternate sourcing. There may have been some successes; however, there were also some failures. The failures highlighted the fact that, in many instances, we did not, and still do not, know enough about our APIs, excipients and their variability to be

able to predict, with certainty, that the same grade of an excipient from a different manufacturer, or different manufacturing site from the same manufacturer, can be successfully substituted in a particular formulation. It must also be remembered that inclusion in the DoE, in and of itself, is not sufficient to allow a change to the alternate source to be made at some later date, e.g. due to interruption of supply of the excipient due to a manufacturing plant shutdown. In order to be able to switch in a timely manner to the alternate sourced excipient, regulatory authorities expect the alternate source to be used on a regular basis during routine commercial manufacture, e.g. 10 – 20% of batches be made on a continuing basis using the alternative source excipient. This acknowledges that excipients have some inherent variability and that their manufacturing processes can drift in ways that may not be obvious to the excipient manufacturer or user. Continued use of the alternate source excipient during routine manufacture will allow the excipient user to have an understanding of any changes in the variability of the alternate source excipient over time.

Scale-up and post-approval changes (SUPAC)

The first SUPAC Guidance for immediate release oral products (SUPAC-IR), was issued in November 1995 (9). This Guidance was developed from the work undertaken by Prof. Augsburger's group at the University of Maryland at Baltimore (UMAB). This was followed by Guidance for modified release oral drug products (SUPAC-MR) (10), again based on work undertaken at UMAB, and Guidance for nonsterile semisolid dosage forms (SUPAC-SS) (11). The SUPAC-IR Guide also introduced the concepts of 'the same design and operating principles' for manufacturing equipment. The FDA issued their first SUPAC-IR/MR Manufacturing Equipment Addendum giving details of equipment types and categorizing same design and operating principles in 1999 (12). The equivalent document for SUPAC-SS was issued in 1998 (13). These Manufacturing Equipment Addenda have since been combined and up-dated in 2013 (14) and again in 2014 (15). The SUPAC documents created a more uniform approach to scale-up and post-approval changes and helped ease the regulatory burden on pharmaceutical companies. Changes to the level of incorporation of excipients in drug products are addressed in all the SUPAC guidances.

It should be noted that even with the introduction of Quality by Design (QbD), the SUPAC guidelines are still relevant and can provide useful information to support QbD-based product development projects.

Quality by Design

QbD is probably the most significant change in the pharmaceutical formulation development chemistry, manufacturing and controls (CMC) regulatory landscape in the past 25 years. In very simple terms, using all available information and risk assessments, potential excipient critical material attributes are identified which could impact the pharmaceutical finished product critical quality attributes. A Design of Experiments (DoE) is then set up to investigate these potential critical material attributes (and any critical process parameters) and executed. Following analysis of the results from the DoE, a Design Space is established, together with the Control Strategy, which should allow the drug product to be successfully manufactured on a routine basis.

QbD fits very well with the US FDA's concept of comparability protocols (16) and the Post Approval Change Management Protocol (PACMP) as proposed in the International Conference on Harmonization Q12 Step 2 document (17). For example, from our QbD formulation DoE, we will know what changes can be made within the Design Space, and which will be outside the Design Space and require further work. The concept of QbD is not new; Juran introduced the concept in the mid-1980s as part of the larger concept of Quality Planning. (18) However, it was new to the pharmaceutical industry when it was introduced by the Food and Drug Administration (FDA). The FDA's Critical Path Initiative (19) was the trigger for new quality initiatives including QbD (20). Although QbD is not obligatory, it is clear that the major regulatory authorities do require enhanced understanding and demonstration of formulation and process robustness in new applications. Since its adoption by the International Conference on Harmonization

(ICH) in ICH Q8: Pharmaceutical Development (21), QbD has caused formulation scientists to seek better understanding of all aspects of their formulations, including excipients. In addition, with the advent of combinatorial chemistry and high-throughput screening, small molecule drug candidates emanating from discovery have become, in general, much less water-soluble and thus more difficult to formulate. This has placed more emphasis on understanding the uses and limitations of our excipients. The rise in biotechnology drugs with their particular needs has added to the pressure for better understanding of our excipients in terms of composition and their minor concomitant components.

Falsified medicines directive (22)

The Falsified Medicines Directive (FMD) has regularized the status of pharmaceutical excipients under European Union (EU) law. (Previously, it was not clear how excipients were regulated under EU law.) Specifically, the Directive introduces the requirement that the appropriateness of the good manufacturing practice (GMP) applied to excipients be assessed in the context of the finished product intended use. Subsequently Guidelines were published regarding the formal risk assessment to be undertaken regarding the GMP for each excipient (23). In effect, The EU requires that the user of an excipient assess whether the GMP standards applied to the manufacture of the excipients they are using are sufficient to render the excipients fit for their intended use. This assessment is not a one-time assessment but is required to be on-going i.e. there should be periodic review and reassessment to ensure that the excipient remains fit for the intended use.

Continuous manufacturing of pharmaceutical finished products

Traditionally, pharmaceutical product manufacture was focused on batch processing where preselected quantities of APIs and excipients are processed together at the same time, and the material passes sequentially through all the required unit operations. In continuous processing, API and excipients are continuously fed into a process or equipment train and product is continually removed. When the equipment train is operating at constant input and outpour, all unit processes are operating at the same time. Theoretically, any pharmaceutical product could be manufactured in a continuous (as opposed to batch) mode. However; the focus has been on the manufacture of oral solid dosage forms since tablets and capsules are the most common types of pharmaceutical finished products.
Continuous manufacturing uses the same types of unit processes and excipients as are used with batch manufacture; however, continuous manufacture places more constraints on our excipients. There is likely to be less tolerance for excipient variability because there may be no way to compensate for it, such as mixing to an endpoint to compensate for API and/or excipient variability. (It may be possible to use a 'hybrid' manufacturing approach – continuous manufacture for most unit operations but with a critical unit operation operated in batch mode using several small units operating in a staggered fashion, e.g. the wet granulation step during tablet manufacture.). In addition, in this author's opinion, it is unlikely that the development of a continuous manufacturing process for a pharmaceutical formulation would be successful without a proper scientifically justified and executed Design of Experiments (DoE) which addresses all the necessary critical material attributes (CMAs) and critical process parameters (CPPs), and an appropriate, scientifically justified Design Space and Control Strategy. This must include the excipients used in the formulation.

The rise of biologic drugs

The modern era of biologic drug products started before 1995. (e.g. Humulin®, human insulin manufactured using recombinant DNA technology was introduced in 1982.) However, the majority of the biotechnology drugs, including human and chimeric monoclonal antibodies, hormones, cytokines, therapeutic enzymes, recombinant vaccines and fusion proteins, have been introduced since 1995. These types of molecules have high molecular weights and must be administered by injection. There can be issues with dose and viscosity of the injection, stabilization of the molecules and

aggregation. Of these issues, the two where excipients likely play a significant role are viscosity and aggregation. Excipients can be used to reduce the viscosity of high-concentration protein drug solutions. Aggregation is linked to immunogenicity. (24) In some instances, the aggregates seen in such formulations have been found to be excipient derived, e.g. higher molecular weigh free fatty acids present in polysorbates. In future, it is likely that there will be increasing requirements for excipients having a more controlled composition profile for use in the formulation and manufacture of biotechnology drugs. The motivation for the development of the FM1000 surfactant by Dow (3,4) appears to have been to avoid the hydrolysis of the ester linkages which can occur with polysorbates. The chemical linkage in this new surfactant is via amide bonds which are more resistant to hydrolysis.

Combinatorial chemistry and high-throughput screening

The application of combinatorial chemistry and high-throughput screening to drug discovery has revolutionized drug discovery. It is now possible to design drug molecules with enhanced specificity and receptor binding. However, this has led to both an increase in drug molecule molecular weight and the addition of more hydrophobic moieties to the molecule. Both these trends can impact drug solubility. From numerous different surveys, it appears that between 70% and 80% of the new drug molecules identified as drug development candidates today are considered poorly water-soluble ('very slightly soluble' or 'practically insoluble' according to the USP definitions of solubilities (25)). Such drug molecules require more sophisticated formulation and drug delivery methods such as self-nanoemulsifying drug delivery systems (SNEDDS), self-microemulsifying drug delivery systems (SMEDDS), amorphous drug dispersions prepared by either spray-drying or hot melt extrusion, solid solutions, drug-complex formation, or nanoparticulate formulations formed by either size reduction or precipitation. The use of these types of delivery systems, in turn, will require better understanding of our excipients in order to be able to design and develop robust pharmaceutical products and manufacturing processes.

3D printing of devices and dosage forms

Spritam® tablets (levetiracetam; Aprecia Pharmaceuticals) is the first drug product manufactured using 3D printing to be approved by the US FDA. In 3D printing, the dosage form is built up layer by layer. This can allow for very sophisticated combination products with multiple drugs releasing at different rates. Again, this will place more emphasis on excipients and excipient variability in ways that we have not had to consider previously.

So, what of the future for pharmaceutical excipients?

Having reviewed the progress and developments that have occurred since 1995, it is logical that we should look to see what developments in the field of excipients could be anticipated in the next five or six years, and beyond. In addition, it is also worth looking at the types of changes that will be necessary if excipients are going to be available to allow the formulation of increasingly sophisticated drug molecules and delivery systems. The developments may also require the development of new processing options; however, these are outside the scope of this review.

Can the existing range of excipients continue to satisfy the needs of the pharmaceutical industry?

From this author's perspective, the answer has to be no! We have already seen the recent approval of an inhaled insulin powder product (Afrezza® from Mannkind) containing fumaryl diketopiperazine where it has been stated that this excipient was essential for the proper performance of the product.

When we think about the oral delivery of oligopeptides, can we be certain that the existing range of excipients will be sufficient? Eligen® technology from Emisphere Technologies has been investigated for the oral delivery of peptides, including insulin and calcitonin. At the time of writing this report there were no commercial products using the Eligen® technology for peptide or protein delivery. However, there is an oral cyanocobalamin product (vitamin B_{12}, mol. wt. 1355.38

Da) using the Eligen® technology (Eligen B12™).

What other trends can we anticipate?

As a consequence of the introduction of QbD, it seems logical to suggest that there is going to be continued interest in assessing excipient variability. This most likely will go beyond conventional excipient characterization methods such as bulk and tapped densities, flowability, compactibility, thermal behavior, etc. Many of these traditional characterization methods are not quick, require large samples, and do not lend themselves to in-line, on-line or rapid testing. It seems likely that there will be need for more rapid methods using e.g. spectroscopic approaches which can give insights into excipient variability that cannot be seen by traditional methods. For example, Delaney *et al.*, (26) used solid-state NMR spectroscopy to characterize commercial samples of magnesium stearate and were able to show that there were at least three types of magnesium stearate in the market place. It seems logical to suggest that other excipients could be investigated using less traditional characterization methods in future.

Pharmaceutical excipients, for many years, were regarded simply as inert carriers. The last almost 25 years should have dispelled that thinking. Excipients may not be intended to have a pharmacological effect, but they can have effects on the human physiology. For example, polyols such as sorbitol can increase gut motility at moderate doses and can act as laxatives at higher doses. Indeed, lactitol (another polyol) is prescribed as a laxative. We also know that certain non-ionic surfactants can inhibit P-glycoprotein (P-gp) (27) and increase the oral bioavailability of drugs subject to efflux mediated via P-gp. It is also known that some excipients are contra-indicated in certain patient groups, e.g. the use of benzyl alcohol as an antimicrobial preservative in neonates and young children (28). It thus seems logical to suggest that information on how excipients impact the human body via different routes of administration could be collected in databases. These databases could be similar in concept to the EuPFI STEP database (29) on excipients for pediatric use, but not necessarily restricted to a particular age group or patient population.

Traditionally, excipient quality has been considered simply in the context of the pharmacopeia monograph and manufacture to an acceptable standard of cGMP. Very often the composition profile of the excipient has not been well characterized. However, it is also known that not all minor components of excipients should be classified as impurities; some minor components are necessary for the proper performance of the excipient in the formulation. Nevertheless, with the increasing use of excipients in the formulation of biological drug products, and the increasing use of e.g. amorphous polymer dispersions of small molecule drug products, better characterization of the composition of some excipients will be necessary in order to minimize the risk of product instability.

It would be very helpful if the PDG harmonization effort could be continued and expanded to include more excipient monographs, and to include more pharmacopeias. We may never achieve complete harmonization across all pharmacopeias, but e.g. 90% harmonization of a particular monograph is very much better than none.

What new pharmaceutical excipients might be required in the next several years?

In the small molecule space, and assuming oral solid dosage forms will continue to predominate, a soluble lubricant which is as effective as magnesium stearate and sodium stearyl fumarate is still desirable. However, it should also be easy to handle, i.e. non-irritant, and that is probably going to be very difficult to achieve. In addition, there is still a need for excipients that can enhance the solubility of poorly water-soluble drug substances. There has been progress in this area, but as the hydrophobicity and molecular weight of small molecule drugs increase, it is likely that we will need new and better excipients to achieve adequate dissolution and bioavailability.

In the biological molecule space, there is a need for more stabilizing agents of various types. However, this is only likely to be achieved on a case by case basis, given the complexity and diversity of biological drugs.

In addition, while not being 'new' excipients, there is a need for excipients with much improved composition profiles; e.g. giving lower levels of other components which can induce agglomeration in proteins, and thus reducing the chances of an immunogenic response in patients.

Continuous manufacturing imposes further constraints on our excipients. New excipients designed to address some of the issues in continuous manufacturing will likely also be required. However, co-processed excipients may offer a more attractive way forward than a new chemical excipient.

In the pediatric formulation field, there is a need for a non-cariogenic excipient which can be used in the formulation of pediatric medicines, but which does not have the laxative effects of e.g. mannitol, sorbitol or xylitol. Whether or not this can be achieved is a good question.

What other changes are required?

Excipient approval

One major point of debate which has not changed since 1995 is that there is no independent regulatory assessment (by the US FDA or any other major regulatory agency) for new chemical excipients. In order to be able to continue to develop effective drug products for each and every new drug molecule, that has to change. As implied above, we cannot expect our current excipients to always provide the properties and formulations necessary to ensure the effective delivery to the patient of every future new drug molecule. We will need new excipients and co-processing can only take us so far.

As discussed in the 1996 paper (2), it is very difficult to get a new chemical excipient accepted by pharmaceutical companies because they are concerned that the safety/toxicology package would not be accepted by the regulatory agency. At present, the regulatory agency will only assess the excipient safety/toxicology package during the review of the marketing application. In addition, the time taken for the excipient safety/toxicology testing combined with the clinical development times for new drugs mean that much of the patent life for the excipient will have expired by the time the drug product is launched. Together, these make such projects less financially attractive.

It is generally accepted by industry that any excipient assessment scheme would have to be self-funding and that any assessment would thus incur a cost. It is further believed that this would be acceptable to the excipient manufacturer since the 'official' assessment would facilitate faster acceptance by the drug product development and manufacturing companies.

It is understood (at least by this author) that a regulatory agency could not give a *carte blanche* approval for all possible uses of a new excipient; however, the agency could assess the safety/toxicology data package and indicate in a formal letter whether or not they consider the excipient safety/toxicology report and supporting data to be sufficient to support the administration of the excipients via a particular route of administration and up to a specified maximum dose. This would be a tremendous encouragement for the development of new chemical excipients.

Excipient safety testing

Assuming the excipient is intended to be used in the formulation of drugs for chronic therapy, the FDA Guidance on safety testing of new excipients (30) requires a battery of safety/toxicology studies to be undertaken, including and assuming eventual long-term use of the excipient:

- Up to 12 months chronic toxicology in rodent and non-rodent species
- Two-year carcinogenicity studies in rodent and non-rodent species

If it can be shown that the excipient is not absorbed via a particular route of administration, are long term safety studies related to that route of administration necessary? Do they enhance patient safety? Obviously, this would not apply to excipients intended for parenteral administration; however, it could be an approach for

e.g. oral or topical use. This would not mean no safety testing would be carried out; tolerability/irritancy assessments would still be required. However, the need for long term safety studies could be assessed based on the risk of the excipient (e.g. a novel polymer) being absorbed via the intended route of administration.

CONCLUSIONS

In the past almost 25 years, there has been significant progress in drug therapy and treatment of disease. There has also been some progress in the area of excipients, but perhaps not always as much as we would like. In the next few years it seems logical to suggest that there will continue to be considerable interest in excipients, including enhanced understanding of excipient composition, prediction of variability in performance and understanding of their physiological effects. There are still gaps in the range of excipients available. This is particularly the case for excipients for pediatric use and for use with biotechnology drug molecules. It is hoped that a regulatory pathway for the introduction of new chemical excipients can be achieved to allow the formulation of all future drugs for the benefit of future patients. It is also hoped that the excipient monograph harmonization efforts can be continued and expanded to recognize the global nature of the pharmaceutical industry and excipients.

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