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Tablet Excipients to the Year 2001: A Look into the Crystal Ball

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ABSTRACT

The future for tablet excipients is reviewed from a number of viewpoints: new materials, formulation development, quality, regulatory aspects, logistics, and production. The field of excipients is changing rapidly in response to economic, regulatory, and scientific pressures. As our understanding of drug delivery improves, so will the demands we place on excipients and on their quality, both chemical and functional. In order to fully optimize drug delivery systems, a better understanding of excipients and their properties and limitations is required. The materials science approach to the study of excipients will help to increase our understanding of excipients and how best to use them. But excipients are only one part of the very complex mechanism whereby new medicinal products are brought to the marketplace. It is important that the processes of formulation design and development are properly integrated to obtain optimized drug delivery systems as early as possible. Developments in related fields such as manufacturing technology, logistics, and analytical techniques will also influence the field of excipients.

INTRODUCTION

A bulk drug on its own is generally of little use to the patient. Patients require the drug in a form they can use effectively with as little inconvenience as possible.

The use of formulations can be traced back to the ancient Egyptians and ancient Greeks who formulated ointments and creams and compounded medicines. The reasons why we need to formulate drugs may be summarized as follows:

Convenience of the patient
Accuracy of dose/consistency of dosing
Improved bioavailability
Improved stability
Taste masking/improvement of palatability
Reduction of side effects
Controlled dissolution/release

Today drugs are administered as formulated medicines via many different routes:

Oral	Buccal
Inhalation	Sublingual
Parenteral	Rectal
Topical/dermal	Intranasal
Transdermal	Vaginal
Intraocular	

The oral route is by far the most important, and in particular solid-dosage forms (tablets, capsules, and powders) are the most common formulations. The tablet was introduced in the mid-19th century and has become the most widely used solid-dosage form. The development of the two-piece hard gelatin capsule is generally credited to Lehuby in France in 1846, but commercialization was somewhat later (1). Despite the disadvantages of the oral route, it is likely to remain the primary route of administration through the millennium.

The term *formulation* does not fully explain a medicinal product. The more modern terminology of drug delivery system better emphasizes the key role that the formulation plays in getting the drug to the patient. (The term *drug delivery system* has tended to be restricted to controlled drug delivery systems and devices. In fact, all formulations or dosage forms are intended to deliver a pharmacologically active substance [the drug] to the patient, and it is to emphasize this point that drug delivery system is used in the broader context in this report.)

Thus the objective of any drug delivery system is to deliver the drug to the target organ or receptor in the body in the appropriate manner. It is the responsibility of the formulator, in conjunction with other members of the development team, to design a drug delivery system capable of consistently achieving this desired delivery profile in routine manufacture. There are also other factors that must be taken into account when designing a drug delivery system such as patient compliance and convenience.

During the therapeutic revolution, the focus has been on new therapeutic agents. For a number of reasons the emphasis of the drug discovery pathway has changed. Today the pharmaceutical industry operates in an environment where therapeutic advantage over existing therapies, optimization of drug delivery, and cost containment must be considered along with the historical parameters of efficacy and safety before a new drug product will be accepted.

A medicinal product consists of more than just the active drug(s). There are other materials present that are necessary to allow the formulation to be processed or to achieve the desired pharmacological and/or pharmacokinetic effect. These other materials are generally referred to as excipients.

Excipients are therefore fundamental to the design of drug delivery systems whether the drug is intended for bolus administration or controlled release. It is the excipient that allows the formulation scientists to achieve their objective. Without excipients it is arguable whether the therapeutic revolution could have taken place. Yet excipients have received scant attention from the pharmaceutical industry. Excipients can thus be regarded as the "Cinderellas" of formulation science.

Traditionally, excipients have been defined as inert, i.e., exerting no pharmacological activity. However, recent developments, particularly the concept of controlled release, have shown this traditional definition to be inadequate. IPEC-America has produced the following definition of an excipient (2):

> Pharmaceutical excipients are any substance other than the active drug or prodrug which has been appropriately evaluated for safety and is included in a drug delivery system to either:
>
> 1. aid processing of the system during manufacture, or
> 2. protect, support or enhance stability, bioavailability or patient acceptability, or
> 3. assist in product identification, or
> 4. enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use."

This definition can be summarized according to Blecher (3) for most purposes as "Pharmaceutical excipients are the components of a formulation other than the active drug."

With the changes facing the pharmaceutical industry, it is becoming clear that formulation scientists, amongst others, require an ever deeper understanding of the uses and limitations of excipients in order to minimize the potential problems of scale-up and transfer of new products into production, and also to minimize the time required for formulation design, development, and stability. This is particularly important for controlled-release products requiring that the raw materials used in the delivery systems exhibit well-controlled physicochemical characteristics in order to provide reproducible in-vitro performance (4).

The existing list of excipients for oral use is limited and many of them have been around for many years. Shangraw (5) has reviewed the history of tablet excipients. It is surprising how many of the materials from the

turn of the century were still in use until quite recently. (For the most part it has been potential safety considerations, rather than ineffectiveness, that have caused demise of excipients such as the mineral oils and boric acid for oral use.)

Given the importance of the oral route of administration, and in particular tablets and capsules, which is likely to continue through the millennium, it is of great interest to consider the possibilities for the introduction of new excipients and other developments that in turn will influence the choice and application of new and existing excipients.

NEW EXCIPIENTS

Perhaps the first question to be answered is, "Why do we need new excipients for solid-dosage forms?" There are several reasons:

1. There are gaps in the current range of available excipients: e.g., a soluble universal lubricant having a balance of properties and an effectiveness similar to magnesium stearate.
2. There will certainly be new drugs that will inevitably be incompatible with many of our existing excipients, and new excipients will be necessary to overcome such problems. This is likely to be the case with drug products derived from the biotechnologies where conformational stabilizers may be required to allow solid-dosage forms to be developed when oral dosing of protein drugs becomes a reality.
3. There will be developments in processes and equipment, particularly increases in production rates, which will possibly exceed the practical limits of our existing fillers. Besides materials having better flowability, materials with better compressibility will be required as tablet machines operate with shorter and shorter dwell and contact times.
4. Some materials will become unacceptable for reasons of patient comfort or safety. Examples of excipients currently being discussed in this context are arachis oil and lactose for oral use. A balanced assessment of the risk-benefit ratio and availability of a suitable alternative should be the objective criteria for acceptance or rejection. However, it is possible that media outcry may prejudice such issues, leading to the abandonment of otherwise extremely useful materials.

   Golightly et al. (6,7) and Smith and Todd (8) have reviewed the incidences of adverse reactions due to excipients in drug products. The true prevalence of adverse reaction to excipients is impossible to predict because of the lack of controls and because of our inability to accurately test of the susceptibility of individuals to the large number of excipients available (6). But to put it into context, the likelihood of an adverse reaction to a drug is much greater than that for an excipient.
5. There may be further, as yet undiscovered, delivery systems that will require their own specialized excipients: examples of such delivery systems already in the marketplace are metered-dose inhalation devices and transdermal delivery patches.

There are three types of "new" excipients that could be considered: new chemical entities, new grades of existing materials, and new combinations of existing materials. The latter two types are examples of what is now called *particle engineering,* a term first introduced by Staniforth (9).

CHEMICAL EXCIPIENTS

This terminology refers to excipients that are new chemical compounds. Such materials require full safety testing in the same way that new chemical actives are tested for safety. In Europe this concept was established in the 1975 EEC Directive (75/318/EEC, June 1975). In the United States the picture is slightly different in that the safety of the excipient will be established via the NDA (new drug application) filing for the product; however, the net result is the same. There is as yet no formal approval system for an excipient per se.

In certain types of formulation, particularly where the toxicity formulation is very close to the final product formulation, it may well be possible, or even desirable, to "piggy-back" the excipient safety evaluation on the back of the drug safety evaluation. However, there have to be very strong arguments to persuade a pharmaceutical manufacturer to risk the fate of a potential blockbuster product on an unknown and untested excipient. "Piggy-back" testing is not necessarily feasible for new general-purpose excipients, such as those used in the formulation of tablets and capsules, where the formulation used in safety testing is often very different from the final marketed formulation.

A possible exception to this general rule is the cyclodextrins. It is believed that a formulation using one of this group of materials may have been submitted for regulatory approval. It is likely that the safety evaluation has been "piggy-backed" in this case. It should also be remembered that the cyclodextrins are not new molecules; β-cylodextrin was discovered in the 1890s.

For new chemical excipients the question of the cost of the safety testing and recovery of investment ("pay-back" time) is complex. The question of patent extension to cover extended development times, which is available for new drugs, may not be available for new excipients. In any case, excipients are relatively low-cost items, which, unlike drug products, are not launched for direct use by the ultimate consumer (the patient). The targeted customers for excipients are the pharmaceutical manufacturers.

The overall position is summed up in Figure 1. While it can be argued that Figure 1 is unduly pessimistic, the conclusion that the pay-back time for new chemical excipients will be much reduced is unavoidable. Given the costs of safety evaluation and the revenues generated by existing excipients, it appears that the development of new chemical excipients may not be economically sound.

The safety testing for new excipients is currently being reviewed and IPEC-America has recently proposed a rational approach to the safety testing of new chemical excipients that takes into account the intended route of administration and possible duration of therapy. A summary of the proposals is presented in Table 1. However, it must be stressed that these are only proposals and have not been accepted by regulatory authorities. Even if they were to be accepted, the testing necessary for new excipients for oral delivery would still require a considerable financial and time investment.

PARTICLE ENGINEERING

Particle engineering is a broad term that covers a wide range of modifications to particle structure. These modifications are intended to change or improve the performance of the bulk excipient. There are several methods by which particle structure and properties can be modified:

Particle size changes by physical methods
Granulation to give modified crystal agglomerates, but without polymorphic or polytypic changes
Crystallization control to give
- Increased crystallinity
- Changes in polymorphic form or the ratios of different polymorphic forms
- Changes in polytype
- Co-crystallization or co-precipitation

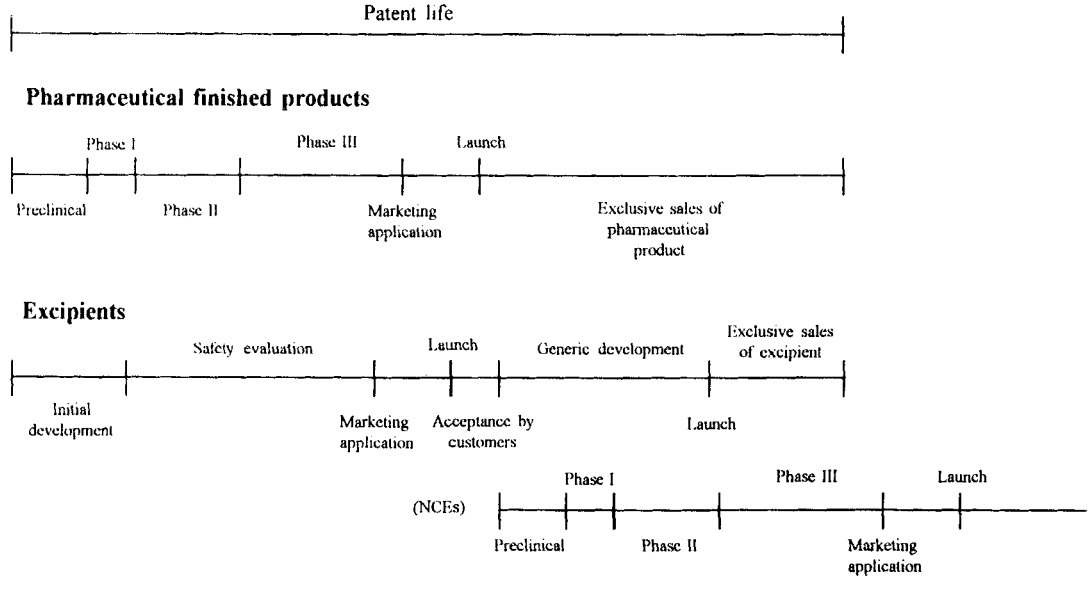

Figure 1. Economic return on investment for excipients.

Table 1

Summary of Proposed Excipient Guidelines: Routes of Exposure for Humans

Tests	Oral	Mucosal	Trans dermal	Dermal/ Topical	Parental	Inhalation/ Intranasal	Ocular
Appendix 1—Base Set							
Acute oral toxicity	R	R	R	R	R	R	R
Acute dermal toxicity	R	R	R	R	R	R	R
Acute inhalation toxicity	C	C	C	C	C	R	C
Eye irritation	R	R	R	R	R	R	R
Skin irritation	R	R	R	R	R	R	R
Skin sensitization	R	R	R	R	R	R	R
Acute parenteral toxicity	—	—	—	—	R	—	—
Application site evaluation	—	—	R	R	R	—	—
Pulmonary sensitization	—	—	—	—	—	R	—
Phototoxicity/photoallergy	—	—	R	R	—	—	—
Ames test	R	R	R	R	R	R	R
Micronucleus test	R	R	R	R	R	R	R
ADME—intended route	R	R	R	R	R	R	R
28-Day toxicity (2 species)—intended route	R	R	R	R	R	R	R
Appendix 2							
90-Day toxicity (most appropriate species)	R	R	R	R	R	R	R
Teratology (rat and rabbit)	R	R	R	R	R	R	R
Additional assays	C	C	C	C	C	C	C
Genotoxicity assays	R	R	R	R	R	R	R
Appendix 3							
Chronic toxicity (rodent, nonrodent)	C	C	C	C	C	C	C
One-generation reproduction	R	R	R	R	R	R	R
Photocarcinogenicity	—	—	C	C	—	—	—

R: Required; C: Conditional.

New Grades of Existing Materials

New grades of existing excipients are one way of overcoming some of the shortcomings of the current excipient grades. Often the development of newer grades may be at the request of one particular customer or group of customers. However, economic factors will also have an important influence on what can be achieved; there is a certain scale that must be achieved to be economic. The current programme of mergers and consolidation, particularly within Europe, may have a beneficial influence on the development of more optimal grades. Larger customers will mean that economies of scale can more readily be achieved and the manufacture of special grades becomes more realistic. Examples of the kind of approaches that might be considered here are different particle size distributions, different densities, different surface areas, or different moisture contents. The essential point is that the chemical nature of the grade still corresponds to the original grade.

New Combinations of Existing Excipients (Co-processed Excipients)

In general there has been some resistance within the pharmaceutical industry toward fixed combinations of excipients. In some cases there is a perception that the combination shows no advantages over simple admixtures or granulations that can be prepared using well-established technologies. In other cases the fixed combination may not be considered optimal for a particular formulation or group of formulations. The key to acceptance will be the synergy derived from the particular combination and processing: the synergy must be greater than can be achieved using simple blends or granulates.

Newer developments in the excipient field will probably include coprocessed materials where the added material is used to improve the properties of the main component rather than for its own properties, and any beneficial properties from the added material that carry over into the final excipient will be additional advantages. This is analogous to the crystal poison approach, or cryogenic stabilizers, rather than traditional coprocessing. An example of this type of excipient already on the market is Emdex (Hydrous Dextrates NF), which is a minimum of 93% dextrose with the remainder being maltodextrin. The special structure of the Emdex particles is achieved by means of co-crystallization. This special structure is not possible using dextrose alone. The benefits of the structure include very good compressibility and a large, rough surface that allows for good interactive mixing, particularly of fine particles (10). As an added benefit, the good mouth-feel of the maltodextrin component is also carried through to Emdex, and to the final product.

OTHER FACTORS INFLUENCING EXCIPIENTS

Besides developments with new grades and combinations of excipients, there are developments in related areas that will influence excipients, and thus have an important influence on our attitudes to excipients in general, our understanding of how excipients work, and the critical features required of a particular material. Some of these developments will be in the field of manufacturing/processing technology, some in the field of materials science, and some in the areas of quality, specifications, etc.

Just-In-Time

Just-in-time is a very simple concept: components and raw materials arrive at the site of manufacture just in time to be used. The idea is to reduce costly buffer stocks and pipelines. This saves inventory costs and reduces the ancillary costs associated with warehousing (labor, building costs, etc.). In today's cost-conscious environment there is a resurgence of interest in this concept. However, the just-in-time concept assumes that certain other objectives have also been achieved:

1. Consistent raw material or component quality such that the product made can achieve a consistent performance with every batch. This implies a confidence in the quality of raw material or component delivered by the supplier.
2. Reliable delivery. With just-in-time there is little or no allowance for disruptions to the supply chain for whatever reason. However, if a manufacturer wants to gain the most from just-in-time, then it makes sense to have reliable production scheduling. Most suppliers will make every effort to comply with urgent requests from time to time, but when every order becomes an emergency supply there is something wrong. It may be that just-in-time is not flexible enough for some operations and it may be necessary to negotiate with the supplier to have stocks of certain items held locally for immediate delivery.

Both these considerations imply that there is a certain confidence between the supplier and the pharmaceutical manufacturer, and also a degree of openness that could not be found when buying on the open market (possibly from a different supplier for each delivery). Some companies are investing in vendor certification programs, but it must be emphasized that they are an investment, both for the supplier and the purchaser, in terms of time and effort—scarce commodities in most organizations.

It must also be remembered that in many cases just-in-time simply shifts the buffer stock back up the supply chain, i.e., from the user to the supplier or agent. There is a cost associated with any buffer stock so that some of the potential cost savings may not be realized.

Automation

With our increasing knowledge of microelectronics, and the parallel software developments in "fuzzy logic" and neural networks, many more manufacturing processes are becoming automated at smaller and smaller scales and with greater and greater flexibility. In principle it should be possible to automate most processes involved in the manufacture of pharmaceutical solid-dosage forms. In the short to medium term the effective limitation is more likely to be our understanding of the process and the means of end-point identification than the complexity of the electronics or the software.

A modern pharmaceutical manufacturing unit is an expensive sophisticated operation and all ways of maximizing return on investment must be considered as one aspect of cost containment or reduction. Besides raw materials, other major costs are energy, labor, and investments. Raw materials and energy costs are unavoidable and the areas with most potential for savings are labor and investment. A typical pharmaceutical produc-

tion unit operates for 8 to 12 hours per day; at night and on weekends it is often shut down. Adding extra shifts is often not the best way to extend the working time of equipment because of the extra labor costs associated with shift working. Automation, if properly implemented, can lead to cost savings in several ways (11):

Better use made of invested capital
Reduced labor costs
Improved inventory control
Reduced lead times
Reproducible quality
Full documentation

There are disadvantages in that new facilities are necessary that require new investment. According to Körblein (11), there is a common misunderstanding that an automated factory requires more investment, whereas, in reality, the money is used in different ways because generally automated facilities need fewer work centers with higher automation, less overall space, and fewer high-class GMP (good manufacturing practice) areas. However, there is also a balance to be found between the cost savings due to automation and the costs associated with reduced flexibility.

One thing that is necessary for the implementation of any automated system is consistency: consistent quality of raw materials and components (confidence in the suppliers), consistent (robust) manufacturing processes, consistent (reliable) performance of the finished product, and consistent (reliable) performance of the automation system. In addition, the degree of control afforded by the automation system must be sufficient to control the product output to ensure it meets the accepted standards and tolerances of performance.

Automation can take various forms. For this presentation automation will be considered in terms of CIM (computer-integrated manufacture), "lights-out" manufacture, and robot workstations.

Computer-Integrated Manufacture

What is meant by CIM? Körblein (11) has defined CIM operations as follows:

> CIM-factories provide computerised interconnections between semi- or fully-automated work centres, including related storage and transportation facilities.

Computer-integrated manufacture is, in its simplest form, a means of optimizing manufacturing output from a production unit by eliminating bottlenecks, with the flow of materials and product being monitored by computer. This involves monitoring raw material and component usage to ensure that there is sufficient material and components in the pipeline so that manufacture can continue uninterrupted, while monitoring the buildup of finished product to ensure that overproduction is avoided. More sophisticated implementations can include the use of AGVs (automatic guided vehicles) and other materials handling systems, leading to reduced manning with consequent reductions in labor costs.

The reduction in bottlenecks and the consequent avoidance of in-process buffer stocks, together with reductions in raw material and component buffer stocks and associated storage areas, and finished product storage leads to cost savings (reduced inventory at the different stages of production, reduced space, etc.).

Lights-Out Manufacture

Lights-out manufacture refers to manufacturing operations that continue with the normal production operator absent for extended periods and only minimal checking by personnel. It is really a logical extension of CIM. With lights-out operations the objective is a reduction in manning levels compared with two or three shifts working and the consequent reduction in labor costs per unit volume. There is again a need for a thorough understanding and validation of raw materials sources and processes, and the overall "robustness" of the manufacture. The necessary investments will require financing.

Robot Workstations

In this context robot workstations can be considered simplistically as an adaptation of the form-fill-seal concept as used in the preparation of sterile plastic ampoules and in the filling of soft gelatin capsules using the rotary die method.

The objective is to prepare ready-packaged-unit solid-dose forms, normally tablets. This approach does away with the traditional demarcation between compression and packaging. All raw materials and components are fed directly to the workstation and unit doses are prepared already packed, e.g., blisters, and without transfer to other equipment.

The reasons for adopting such an approach are less concerned with increasing throughput; the present technology is relatively slow. The reasons are largely to do with protection: either protection of the active material, or protection of the operator, or possibly both. Such systems could be of value in the manufacture of solid-dosage forms of drugs that are incompatible with water or oxygen, or to protect operators from potentially toxic

materials (e.g., anticancer drugs). Instead of having to protect or condition a complete operating suite, the individual workstations can be maintained under slight positive or negative pressure, as necessary, thus saving on air treatment cost and potentially damaging future worker compensation claims.

The Materials Science Approach to the Characterization of Pharmaceutical Materials

Traditionally, the characterization of pharmaceutical materials (actives or excipients) has focused on the biopharmaceutical and quality control aspects of the material with limited regard for the properties of the materials themselves, either as individual particles or in bulk. This traditional approach, sometimes called physical pharmacy, is now being superceded by a materials science approach. The main difference is that the properties of the materials themselves are studied with regard to function, either as single particles or in bulk. (The precision that can be applied to any measurement is also recognized.) If a tablet is the chosen dosage form, then the compression properties of the materials themselves are studied as well as in combination with other potential components or ingredients. Other properties of the material that are studied include flowability, particle, bulk and tapped densities, and interaction with moisture. If differences between lots or sources of materials are found, instead of just asking "How are they different?" the question "Why are they different?" must also be asked. In the traditional approach the differences were simply stated, whereas in the materials science approach the key is to understand both the materials and the differences.

The traditional studies are still carried out; their importance has not diminished, but it is recognized that understanding the functional properties of the materials themselves is also important to the overall task of getting a validated, robust, consistent formulation to the marketplace. It is a recognition of the fact that the excipients bring the necessary properties to the formulation to allow the medicinal product to be produced. This fact has always been understood but generally not given much consideration. There seems to have been a general assumption that the formulation scientist will always cope with whatever the discovery team comes up with. But as we understand more about the whole process of drug delivery, it becomes more and more apparent that pharmaceutical preparations have not always delivered the drug efficiently. Whereas this was not so much a consideration in the past, it is no longer acceptable today. With the pressures from many sides to contain health care costs, it is now clear that the delivery of a new drug needs to be optimized at an early stage in its development pathway.

Developments in Analytical Methodology

One of the consequences of the materials science approach is that methods of characterization from other fields, e.g., polymer chemistry or engineering, are being used in the evaluation of pharmaceutical materials. Some of the techniques have been used in pharmaceutical formulation science for several years, but on an ad hoc basis. The difference today is that these methods are being more routinely applied. Some new methods are also appearing.

Just as important, detectors are becoming more sensitive, and the general availability of microcomputers allows more and more data to be analyzed.

Functionality Testing

Functionality testing is the name given to tests on raw materials that seek to predict some aspect of the final performance of the material, usually an excipient, in the finished product. It has long been recognized that pharmacopoeia monographs are biased in favor of chemical quality with some acknowledgment of physical testing, e.g., rudimentary particle size control. There are very few monosource excipients, and compliance with the monograph does not always mean that materials from different sources function in the same way. There are many examples published in the literature, but important examples are magnesium stearate (12) and the work by Shah et al. (13) on controlled-release matrix systems using hydroxypropylmethyl cellulose from different sources.

The concept of functionality testing, and the acknowledgment of a need to standardize testing as well as the inadequacy of pharmacopoeia monographs, was formally recognized with the production of *Katalog der pharmazeutischer Hilfstoffe* (14), which was a cooperative project within the Swiss pharmaceutical industry. This was the inspiration behind the publication of the *Handbook of Pharmaceutical Excipients,* which is now in its 2nd edition (15).

There has been considerable debate in recent months concerning the inclusion of functionality testing in pharmacopoeias, even to the extent of including functionality in excipient monographs. There seems to be a

general consensus that a list of standard tests is needed, which could remove the confusion that sometimes exists, particularly between different pharmacopoeia regions, with certain physical testing.

The question of which tests and where to list them is not straightforward. There is a certain logic suggesting that perhaps they could be listed as an appendix to the pharmacopoeias. However, there is a reluctance on the part of some to follow this route because of the legal status of the pharmacopoeias. Perhaps a listing as an appendix to a future edition of the *Handbook of Pharmaceutical Excipients* might be an acceptable compromise.

Whether or not to include functionality testing in individual excipient monographs has generated considerable debate. Considering the number of pharmaceutical manufacturing units, the number of different actives, formulation preferences, and processing preferences, it is unlikely that a general functionality could be established for a general-purpose excipient. Functionality must be decided by the user, and the functionality demanded by different users will differ considerably. The functionality of microcrystalline cellulose used in wet granulation and direct compression, or for the manufacture of tablets or capsules, may be very different. Functionality should properly be included in the contract been the excipient manufacturer and the customer.

There is also a need to decide on which test for a particular functionality. Many excipient manufacturers and users have their own functionality tests and a considerable database built around them. Often the differences, as has been mentioned above, are based to an extent on the pharmacopoeia region, e.g., particle size and tapped density, where there are differences in equipment and methodology between the U.S. and Europe, and even within Europe. For compressibility there are several tests in common usage. The *Handbook of Pharmaceutical Excipients,* 2nd edition (15), lists six different tests for compressibility using four different compression devices, and there are others.

What is the best equipment and methodology? Is it relevant to manufacture on a high-speed rotary press? Is the equipment readily available to all excipient manufacturers and users? These are questions that need to be addressed. Progress has been made, and is being made, but there is still a long way to go. There is a logic suggesting that the harmonization of functionality test methods could be part of the scientific work of the IPECs (America and Europe) and JPEC.

Validation

It is important that patients have confidence in the medication they receive. The regulatory authorities are the guardians of patients' expectations. Validation is simply the demonstration that all reasonable care has been taken in the development of a medicinal product. Validation also implies understanding of the limits of the raw materials and the processing, which will allow the routine manufacture of a product that will consistently achieve the desired delivery profile. The regulatory authorities take the simple view that in order to demonstrate that something was done, it must be properly documented. Validation in practice reduces to good scientific method and the proper preparation and maintenance of records of the development and scale-up process.

The justification of the choice of a particular excipient is now being requested by some regulatory authorities. Second sourcing of materials, particularly excipients, is also of interest to some authorities, although this is a comparatively recent change.

Some companies take the view that they will apply the general principles of duplicating the scale-up development work to validating second sources of major excipients. Other companies appear to be less stringent. Some companies will not countenance second sourcing.

Developments in Manufacturing Technology

There has been a continual evolution of tablet and capsule manufacturing technology over the past 30–40 years with the introduction of high-speed rotary tablet presses and capsule machines, high-shear mixer granulators, alternative drying methods (e.g., microwave drying), more efficient dry blenders, etc. All these developments have helped to improve throughput and increase output and quality. There is still pressure to continue this evolution.

However, if we increase the speed of the rotary tablet press, i.e., reduce the contact time and dwell time, will our formulations be robust enough to allow manufacturers to take advantage of the increased speed? Microcrystalline cellulose (mcc) is probably the most compactible pharmaceutical excipient, but even mcc on its own will cap at very high speeds, as has been observed using a compaction simulator (16). When the effects of the other components of the formulation are also considered, capping could be a very real problem if tablet machine speeds are increased significantly. In wet granulation, Staniforth et al. (17) found that mcc can lose

compressibility depending on the drying method used; moisture content of the mcc also affects compressibility (18).

Hopefully the new understanding coming from the materials science approach to excipient evaluation will lead to newer grades of existing materials that can cope with the coming changes in processing technology.

With the increasing use of microcomputers to control manufacturing processes there is the possibility that the formulation–machine interface will be radically changed. Traditionally the formulation scientist has fitted the formulation to the machine. This is especially so in the preparation of solid-dosage forms. With microcomputer-controlled hydraulic cams on a rotary tablet machine, it may be possible to get closer to the concept of fitting the machine to the formulation (18).

The Interface Between Development and Production

One aspect of formulation development that has sometimes been neglected is the anticipation of properties required of the formulation and process in routine production at the formulation design stage. This may have been a consequence of the adoption of what might be called minimal formulation, i.e., the simplest possible formulation consistent with excipient compatibility, company policy, etc. Perhaps also it is a consequence of the ever increasing specialization that inevitably occurs as organizations get larger, where scientists are channeled into formulation design or scale-up. There seems to be a tendency to see the development process as a series of discrete phases with poor understanding of the other parts of the process. In reality, development is a continuous process and scale-up and production personnel can make important contributions at the formulation design phase.

A good example is the development of a tablet formulation from the formulation design stage to routine production. As compression speeds increase, the demands placed on the formulation will increase, as can be seen by the problems associated with the move from a single-punch machine at the formulation design stage to a high-speed rotary in the production unit. This is particularly the case with lubrication where the glidant characteristics of a lubricant such as magnesium stearate may not be sufficient for routine production using a high-speed roatary tablet press. It would be better to include a supplementary glidant at the formulation design stage and thus avoid the necessity of a formulation amendment during phase II/III studies (or later) with all the added complications.

Globalization

Successful new medicinal products have been introduced throughout the world for many years, although each market region has been run semi-independently. There has been a trend over a number of years to try to market the same formulation(s) of a new drug worldwide, although often, in the past, there was little or no control over local formulation modifications, and sometimes there are local variations concerning the regulatory status of certain materials, occasionally a prohibition on using imported materials in the manufacture of drug delivery systems. It was recognized that the world market for pharmaceuticals was international, but there was little or no integration of the different markets to achieve a truly global market. This is changing. There are several factors that have driven these changes:

1. Local subsidiaries purchased by some foreign-owned multinationals continued to trade under their old name for a variety of reasons. This is changing and many local subsidiaries are now trading under the parent's corporate banner.
2. The days of allowing foreign subsidiaries to adopt independent strategies are being abandoned in favor of a consistent approach, so that the parent company cannot be accused of allowing lower standards to be adopted in some countries.
3. Many of the major pharmaceutical manufacturing corporations are truly multinational. In order to avoid unnecessary duplication of development effort and resources, they have created centralized (corporate) R&D organizations that develop the new products. These are then transferred to the different manufacturing locations under a formal technology transfer procedure, with the parallel registration applications being administered centrally also. As part of this centralization, there is often a centralized equipment and process policy, and any new equipment must be approved centrally. This is, in part, a recognition of the fact that a consistent product can only be achieved worldwide by using a consistent formulation, consistent raw materials, and consistent equipment and processes.
4. In terms of travel and communications, the world is shrinking. There is far more direct contact between the regulatory agencies in different countries. This does not necessarily mean full acceptance of foreign data or inspections, but problems or concerns are discussed. The details of such exchanges remain confidential.

5. The changes in Europe, which are a consequence of the establishment of the "single market" within the European Union (EU), have been another influence in the globalization of the industry. Before the establishment of the single market, manufacturers had many smaller manufacturing and research units in many different countries to take advantage of the reimbursement schedules in those countries. We are now seeing a consolidation of the manufacturing operations in Europe, with many companies consolidating production of different types of product in one factory, e.g., one factory for tablets, another for sterile products, and another for creams and semisolids. These different factories may be at different sites, but one factory will produce, for example, all the tablets for the whole of the European market. This has forced the issue of local modifications to formulations.

All these different factors are having an influence on the globalization of the world pharmaceutical market, and the increasing interest in excipients now means that excipient supply is beginning to be viewed in a global context.

Harmonization

As a consequence of the First Open Meeting on Harmonization, and in response to the increasing awareness of the importance of excipients to the development and production of pharmaceutical dosage forms, and the recognition of the global nature of the pharmaceutical market, the International Pharmaceutical Excipient Councils (IPECs) were established in the U.S. (IPEC-America) and Europe (IPEC-Europe) together with their Japanese equivalent: JPEC (Japanese Pharmaceutical Excipient Council). The choice of the U.S., Europe, and Japan reflects the major world pharmacopoeia areas. The IPECs are nonprofit organizations open to both excipient producers *and* users, with the objectives of promoting a better understanding of excipients and accumulating expertise in the field of excipients.

The aims of IPEC-Europe are as follows:

1. To assist the pharmacopoeia authorities in the excipient harmonization process
2. To investigate more effective ways for the introduction of safe, new excipients into pharmaceutical use
3. To become the authoritative organization for questions on pharmaceutical excipients

The scientific work of the councils is carried out in three committees: Monograph Harmonization, GMP, and Safety. The work of the safety committee was discussed in the section New Chemical Excipients and will not be discussed further.

Monograph Harmonization

It has long been recognized that there are differences in the monographs for certain excipients between the pharmacopoeias. This causes an unnecessary amount of extra testing, both by the excipient manufacturers and also sometimes by the users. There was a desire among the pharmacopoeias and regulatory agencies to harmonize monographs to simplify international registrations. The IPECs and JPEC are now working closely with the pharmacopoeias to achieve monograph harmonization for the first tranche of excipients selected (based on the frequency of inclusion in registration applications). The list is presented in Table 2.

Progress has been made in most cases and the first excipient to complete the harmonization process was lactose. The harmonized monograph has now been published, although the complete monograph has not been adopted by the European pharmacopoeia.

ISO 9000 and GMP for Excipient Manufacture

The current GMP (good manufacturing practice) rules are directed toward medicinal products and devices. However, the manufacture of bulk chemicals (actives or excipients) is carried out under very different circumstances from the manufacture of finished products or devices. The FDA has recognized this with the supplementary *Guidelines for the Inspection of Bulk Pharmaceutical Chemicals*. Bulk active pharmaceutical chemicals are usually produced with the specific aim of incorporation into medicinal products. This is not necessarily the case for excipients. Very few, if any, excipients were originally developed as pharmaceutical excipients. Many excipients are available in a wide range of grades and qualities, and many are of natural origin with implications for potential contamination. Consequently it was considered appropriate to establish a more realistic set of GMPs for excipients that take into account the reality of excipient manufacture.

At the same time, there is currently much interest from excipient manufacturers, users, and regulatory agencies in the ISO 9000 Quality Systems Management standards. ISO 9000 is not GMP, but the two are related. Figure 2 is a schematic diagram that gives an indication of how the two systems are related. In reality the two can be considered complementary.

Table 2

Excipients for Harmonization

Excipient		Lead Pharm
1	Magnesium stearate	USP
2	Microcrystalline cellulose	USP
3	Lactose	USP
4	Starch:	
	Corn (maize) and tapioca	USP
	Wheat and potato	Ph Eur
	Rice	JP
5	Cellulose derivatives:	
	Carboxymethyl cellulose calcium	USP
	Carboxymethyl cellulose sodium	USP
	Microcrystalline cellulose	USP
	Powdered cellulose	USP
	Cellulose acetate	USP
	Cellulose acetate butyrate	USP
	Cellulose acetate phthalate	USP
	Hydroxypropyl cellulose (HPC)	USP
	Low substituted HPC	USP
	Hydroxypropyl methylcellulose	JP
	Hydroxypropyl methylcellulose phthalate	USP
	Ethyl cellulose	Ph Eur
	Hydroxyethyl cellulose	Ph Eur
	Methyl cellulose	JP
6	Sucrose	Ph Eur
7	Povidone	JP
8	Stearic acid	Ph Eur
9	Dibasic calcium phosphate	JP
10	Polyethylene glycol	USP
11	Hydrochloric acid	USP
12	Alcohol	Ph Eur
13	Benzyl alcohol	Ph Eur
14	Talc	Ph Eur
15	Sodium chloride	Ph Eur
16	Sodium starch glycolate	USP (Ph Eur)
17	Sodium hydroxide	Unassigned
18	Polysorbate 80	JP
19	Calcium disodium edetate	JP
20	Petrolatum	USP
21	Colloidal silicon dioxide	JP
22	Citric acid	Ph Eur
23	Methylparaben	Ph Eur
24	Sodium saccharin	USP
25	Titanium dioxide	USP (JP)

In seeking to establish proposals for excipient GMPs, it was intended from the outset to try to integrate GMP and ISO 9000, and the draft documents have adopted the layout and numbering system of ISO 9000. Currently in Europe the 2nd draft has been circulated.

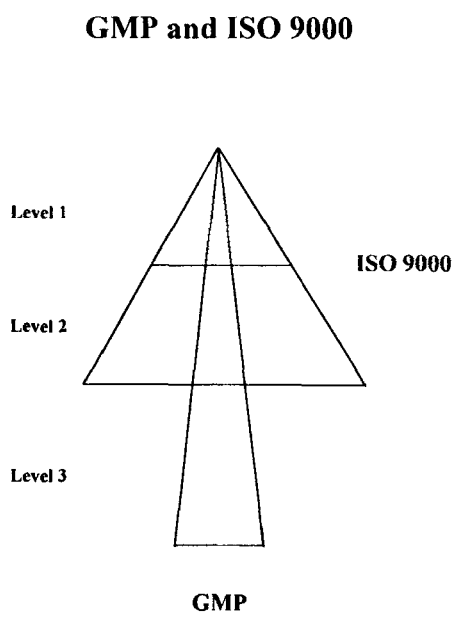

Figure 2. Schematic representation of the relationship between GMP and ISO 9000.

Harmonization of Excipient Registration Requirements

This could be a possible goal for the harmonization process. There is currently much duplication of effort in assembling regulatory submissions and assessing them in different countries.

The move to global registration may in effect have started for medicinal finished products with the establishment of the European Medicines Agency, where one registration will cover all member states of the European Union.

It is theoretically possible under the European arrangements to have a European Excipient Master File. But in reality, due to problems with what is confidential and nonconfidential in an application under German law (the German equivalent of the Freedom of Information Act), the arrangements have yet to be established.

CONCLUSIONS

The importance of excipients to the pharmaceutical industry is now recognized. The excipients bring the necessary characteristics to the formulation, which allow the production of a drug delivery system that delivers the active drug to the patient in the desired manner.

The likelihood of a new chemical general-purpose tablet excipient being introduced in the immediate future is still remote due to the cost of the necessary safety testing and the likely return on investment during the remaining patent life.

There is still hope for the introduction of new grades of existing materials and new co-processed materials. In the latter case the advantages of the co-processed material must be greater than can be achieved using simple mixtures or granulations.

The field of excipients will be considerably influenced by developments in the science and understanding of excipients, logistics and processing methodologies, regulatory and quality issues, and the harmonization of pharmacopoeia monographs. All these various influences will help to produce excipients with ever more consistent quality.

As drug delivery systems become more sophisticated they will require more consistent (less variable) excipients. An understanding of the strengths and weaknesses of the excipients will lead to more reliable (less variable) drug delivery systems. Perhaps ultimately such understanding may lead to delivery systems based on bio-interactive combinations of excipients to control drug release.

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