Characterising polymeric excipients

Excipients are an integral part of pharmaceutical products and a good analytical characterisation will help provide an assurance of safety, efficacy and quality.

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Excipients are the largest components of any pharmaceutical product, whether oral or topical. Thus, they play a role in the overall safety and performance – including efficacy, stability, release properties and aesthetic profile – of pharmaceutical products. The regulatory environment for pharmaceuticals continues to evolve, and closer scrutiny of excipients is on the agenda of several organisations including IPEC, WHO, ICH and the EU Commission (1, 2, 3, 4). These changes signal an increasing need to understand and efficiently monitor excipients.

It is evident that the chemical characterisation and appropriate quality control of excipients are elements that must be monitored to ensure safety and performance. Meeting this objective highlights the need for detailed knowledge of the composition and structure of excipients available on the market. In theory, this process applies to any excipient, but in practice it is more critical in the case of novel excipients, because regulatory authorities scrutinise them more carefully.

This paper focuses on the pertinence of various analytical techniques for the characterisation of polymeric excipients and discusses how a good characterisation can help quality testing. Silicone materials are used to illustrate this approach, but the general strategy is a priori applicable to any polymeric excipient – be it of synthetic, fermentation or natural origin.

Polymeric excipients: advantages and complexity

Polymeric excipients are numerous and very diverse. They encompass materials made up of polymers of natural origin (such as yellow wax, sodium alginate and cellulosic derivatives), synthetic origin (including polyethylene glycols, mineral oils, petrolatum and silicones) and fermentation origin (for example, xanthan gum). Some polymeric excipients have been used in pharmaceutical applications since ancient times, while innovative, high-performance polymeric excipients have been introduced only recently. These novel polymeric excipients are designed to bring additional benefits in terms of stability, sensory profile (for example, taste-masking and texture), efficacy or release properties.

In the simplest case, a polymeric excipient is composed of a single polymeric material, which can be defined by its average structure and molecular weight distribution. In the more common case, it would comprise several closely related polymeric materials, each defined by its own average molecular structure and molecular weight distribution.

Obviously, impurities are always present. If the excipient is of synthetic origin, one might expect catalyst, initiator by-products and residual solvents to be present, as well as residual raw materials. These residual raw materials are usually monomers but, in the case of copolymeric excipients, they could be polymers. With excipients of increased complexity, the raw materials can also be polymeric in nature (for example, the raw material of copolymeric surfactants). If the excipients are of natural origin, residual extraction solvents and natural “undesired” impurities are to be expected. Additives such as preservatives or stabilisers can also be present.

With such complex components, the composition of polymeric excipients must be carefully defined to encompass all the compounds (called intentional compounds) that give the excipient its unique properties and functionalities. Thus, in the case of silicone copolymers (for example, silicone emulsifiers or silicone waxes), residual raw materials play a role in the performance of the excipients – they are not considered as “undesired” impurities and may be present in significant amounts.

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Applications of silicones in pharmaceutical products

Because of their unique properties, silicone polymers are useful in pressure-sensitive adhesive (PSA) applications and as a matrix for transdermal drug delivery systems (TDDS) and wound care. They are also useful as additives in solid dosage forms, as a process aid or hydrophobisation agent for tablets. Dimethicone and cyclomethicone are described in the Pharmacopoeia (5). More recently, a new class of excipient based on silicone has been introduced to improve topical formulations (6).

The benefits associated with silicones are excellent biocompatibility, chemical inertness and an ability to provide lubrication and permeability to a wide range of therapeutic substances. As topical excipients, silicones can specifically provide a superior aesthetic profile, an improvement in active drug substantivity and the formation of long-lasting films on skin. When silicone PSAs are used, they provide optimal adhesive properties, minimal irritation potential and patient comfort. In topical formulations, the use of occlusive silicone waxes or non-occlusive silicone elastomers can provide the appropriate level of permeability.

Silicones meet the increasing demands of the pharmaceutical industry for novel synthetic excipients. The versatility of silicone chemistry means that high-performance copolymeric excipients can be developed. Although silicone excipients (including PSAs) do not contain preservatives, organic plasticisers, antioxidants, tackifiers or stabilisers (which make their composition “simpler” compared with other types of polymer), their polymeric structure must be fully characterised to support pharmaceutical use.

It is clear that, unlike copolymeric silicones, dimethicone does not present any major difficulty regarding characterisation because it has a relatively simple structure. On the other hand, copolymeric or elastomeric silicones have more complex structures and are therefore more difficult to characterise. However, they offer superior performance in many ways.

Analytical strategy for characterising polymeric excipients

An adequate strategy is required to save cost and time resources. Over-characterisation is not desirable, because excessive use of time and resources could actually hamper the launch of innovative excipients.

For excipient analysis, analytical techniques could be classified according to the type of information generated: (a) structural, (b) purity, (c) impurity profile and (d) physico-chemical properties. These are illustrated schematically in Figure 1.

For each of these categories, the analytical method used for the chemical characterisation of a given polymeric excipient could be screened according to the five factors listed below:

1. The polymer family Thus, for example, silicone waxes need techniques that can probe the organic part as well as the silicone part (for example, FTIR and Raman spectroscopies are particularly suitable), silicone volatiles require GC-MS analysis, silicone copolysiloxans benefit from SEC-MALDI-TOF or TGA analysis, and elastomeric silicones from the combination of 29Si-NMR, 13C-NMR and 1H-NMR spectroscopies.

2. Surrogate data If data are already available on similar polymeric excipients (for example, of the same but of different molecular weights), a less complicated analytical method could be used simply to check the data for this given excipient.

3. The critical components of the excipients These should be identified in terms of safety, quality and performance. This drives the choice of the analytical techniques to probe these components more specifically. For example, the performance of alkylmethyl silicone surfactants is related to the presence of the intended silicone copolyol as well as alkyl polymer and polyol that need to be fully characterised.

4. The synthesis scheme This enables one to look more specifically for residual reactive groups (for example, SiH and SiVi in silicone made by hydrosilylation), residual monomers, volatiles or traces of catalysts or solvents.

5. Performance This enables analysis of the parameters that are critical for the functionality of the excipient (for example, DSC analysis for silicone waxes).

The first guideline for polymer analysis is that only a multiple-technique approach will enable appropriate characterisation. The second is that, in difficult cases, hyphenated techniques (for example, GC-MS, HPLC-IR and TGA-MS) or preparative chromatography (for example, SEC followed by MALDI-TOF-MS) are necessary (see Figure 1). For copolymeric silicones, structure determination is usually the most challenging element. A difficulty in characterising copolymeric silicone excipients is how to reconcile differing results from various techniques. Each has its own uncertainty or grey area, and data sometimes appear to be incompatible if one does not carefully consider the uncertainty of each technique.

Once analysis is complete, determination of the structure, composition and impurity profile enables the writing of a scientific dossier describing the excipient. This information is of value for the regulatory dossier of the final pharmaceutical product that would contain the given excipient.

Impact on quality control testing

A scientific dossier of a (novel) excipient with a good analytical characterisation should facilitate the selection of stability indicators to guarantee to the regulator and customer the polymer structure, impurity profile and performance properties. Besides, a knowledgeable selection of the appropriate test methods is more easily done when the composition of the excipient is well-defined.

QC analytical methods could be classified according to the information provided under (i) identification (ii) purity/impurity profile and (iii) physico-chemical properties. Figure 1 illustrates this for silicone excipients, and the relationship between analytical techniques of...
Figure 1. Schematic chart of the analytical strategy for characterising polymeric excipients. Correlation between chemical characterisation techniques and QC analytical techniques is highlighted. The specific analytical techniques mentioned in this chart are given for silicone excipients.
characterisation and QC analytical techniques. In view of the constraints of the QC environment, there are fewer QC techniques available than for chemical characterisation. Fortunately, progress in automation continues to make more analytical techniques acceptable for a QC/QA environment, which makes the transition from characterisation analytical activities to QC testing much easier.

**Impact on market development**

It is worth noting that the need for structural characterisation techniques affects excipients in different ways. Monographed excipients can rely on the implementation of the requirements of the monograph, usually with simple, well-defined methods. By contrast, novel, innovative excipients (which by definition do not yet have a monograph) will have to build an appropriate dossier or information package to allow their review and acceptance by pharmaceutical manufacturers and regulatory authorities. The generation of data for this technical dossier relies on detailed chemical determination of the structure of the polymeric excipient, and might require the use of elaborate analytical techniques – such as those illustrated in this paper for silicones.

In view of the complexity and importance of such an information package, it is advisable that the characterisation task be considered in the launch-plan of a new excipient. This approach helps provide sufficient time and resources for the generation of analytical data, and considers the impact on price and market position. In addition, the sequential tasks performed as part of the QC testing can be arranged.

The complexity of characterisation of polymeric excipients will lead some companies to subcontract all or part of the process. Only companies with analytical expertise will be capable of completing it internally. With this perspective and strategic foresight, contract analytical laboratories might be poised to capitalise on the potential opportunity offered by excipient characterisation.

The chemical characterisation of polymeric excipients, and especially novel ones, should be driven by the use of good judgment, a polymer family approach and the checking of surrogate data together with a general understanding of the critical components of the polymer that affect safety, quality and efficacy. The formidable development of analytical tools over recent decades makes the characterisation of polymers achievable. The development of a good scientific dossier, including chemical characterisation, should make it possible to set up cost-efficient QC testing. Excipients can improve the performance of pharmaceutical products, and developers must consider analytical expertise as one of the contributing factors in making high-performance polymers available for the benefit of patients.

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More information about Dow Corning services and products can be obtained from the company website (www.dowcorning.com).

**References**

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