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Shedding New Light on an Old Problem

Dr Lyn Hughes at Rohm and Haas demonstrates a unique approach to dealing with polymorphism

Dr Lyn Hughes is a graduate of King's College, University of London. He joined Rohm and Haas in 1977, working in technical support for acrylic monomer manufacturing, and then joined the research division of the ion exchange resins business in 1989. Since that time, he has focused on the pharmaceutical applications of the resins, in particular their use in pharmaceutical formulations. In his current role, he is responsible for providing technical support globally for the ion exchange resin healthcare products and technologies. He is a member of the AAPS.

Polymorphs are solid forms of the same compound in which the molecules are arranged in different ways. These arrangements can lead to varying physical properties such as melting point, solubility, dissolution rate and crystal shape. Polymorphs have become a major issue for the industry since the now famous incident with ritonavir, in which lots of Abbott's Norvir® failed dissolution tests due to the formation of a less bioavailable form of the drug. The product was eventually withdrawn from the market. This example demonstrated the importance of polymorphism. The major issue in the Norvir® case was that the drug changed form spontaneously during storage, that is it was physically unstable, even though its chemical stability was excellent.

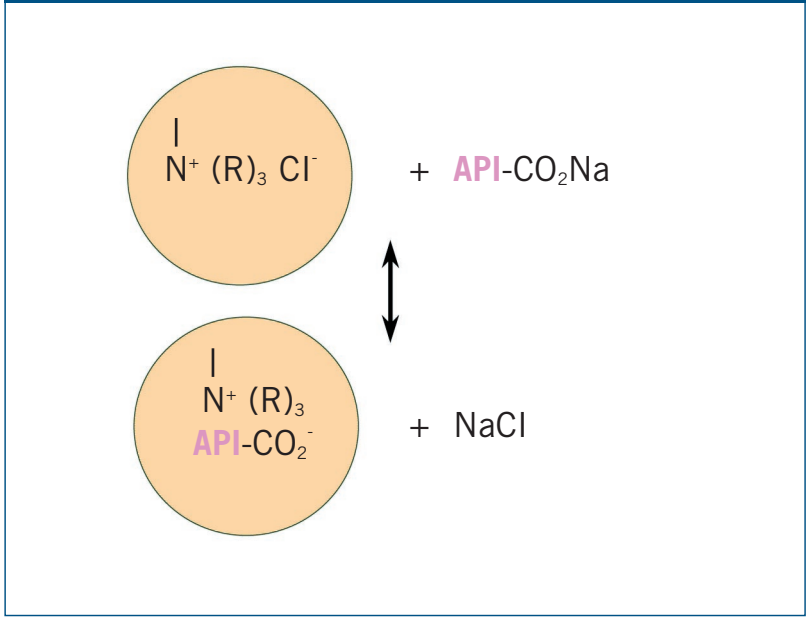
The general approach of the pharmaceutical industry to this issue has been to try to identify all the forms of a particular API and characterise them in the hope of finding a form with acceptable solubility and physical stability, before developing a robust manufacturing process to ensure that the desired form is consistently produced. Unfortunately stability and solubility tend to work against one another. From a thermodynamic viewpoint, it is almost inevitable that the most physically stable form will also be the least soluble and *vice versa*. For example, amorphous forms (that is, no crystallinity) are the most easily soluble of all the forms but also the least physically stable. This has led to many attempts to stabilise the amorphous forms. Trying to identify all forms can also be extremely time consuming and labour-intensive, although there have been recent attempts to automate polymorph screening. However, if one considers all the possible salt forms that can be made, the existence of various hydrates or solvates, and that all of these can be polymorphic, one quickly realises that complete coverage of all possibilities is well nigh impossible. Even if one uses this approach, it is not possible to be certain that the most stable form has been identified and there is always a risk that the chosen form could undergo change after formulation.

One way to overcome polymorphism problems that has received very little attention is the formation of ion exchange resinates. Most reviews on polymorphism fail even to mention this approach, though a couple of examples are provided in the bibliography (1,2). Ion exchange resinates are complexes formed by loading a drug onto an ion exchange resin (3,4). Ion exchange resins are non-toxic, non-absorbed, insoluble, cross-linked polymers that contain acidic or basic groups attached to the backbone, and can be thought of as insoluble polyelectrolytes. Resins with acidic groups are called cation exchange resins and those with basic groups are called anion exchange resins. They are able to form complexes with acidic or basic molecules in which the molecule forms a salt pair with one of the functional groups of the polymer. This is not just a surface effect but rather the molecule diffuses into the polymer matrix. It is unusual for all the ion exchange functional groups to be complexed with drug, but loadings of 1:1w/w are commonly achieved. The formation of the complex is almost

always reversible, so that when it is exposed to salt solutions, such as biological fluids, the complexation is reversed and the drug is released into solution. These materials have a long history of safe use in pharmaceutical formulations as excipients to control release, improve stability, disintegrate tablets and to taste mask bitter or unpleasant drugs (5).

Why are these resinates of interest in dealing with polymorphism? The answer lies in the unique structure of the resins. The method of manufacture of the resins (free radical polymerisation) leads to an amorphous, three-dimensional polymer and the high degree of cross-linking prevents any re-organisation of the polymer so that it is permanently amorphous. Crystallisation of the polymer is impossible. Obviously, if the polymer is amorphous then the arrangement of the functional groups on the polymer must be disordered and fixed in space. The polymer can swell in water, but only the distance between groups changes, not their arrangement.

Figure 1: Chemical Equilibrium for an Acidic Drug and Anion Exchange Resin



Given this unique structure, what happens when a drug molecule is loaded onto the polymer? The molecule that loads is the ionic form of the drug and so carries a charge. This charge interacts with the functional group on the polymer and forms the salt pair. Because the polymer is amorphous, the resinate must therefore also be amorphous, but unlike traditional amorphous forms, it cannot crystallise because the functional groups are fixed in space. Even though the drug ions can diffuse through the polymer, they cannot organise into crystalline regions because the counterion (the polymer functional groups) cannot organise. This very simple chemical equilibrium is shown schematically in Figure 1 for an acidic drug and an anion exchange resin which has quaternary ammonium chloride functionality.

There is very clear evidence that this rationale is correct. Several groups have performed X-ray diffraction studies on resinates and have concluded that there is no crystallinity in the resinate. These include Pisa *et al* (6) who studied ciprofloxacin loaded onto a methacrylic polymer and performed IR, XRD and DSC studies on the resinate. They concluded that the resinate was amorphous. A similar conclusion was made by Akkaramongkolporn using propranolol (7), and chlorpheniramine (8). The author has studied lansoprazole resinates (9) and demonstrated that the release rate of the lansoprazole was independent of the crystal form that was used to make the resinate.

These resins are not used in the same way as more typical polymeric excipients. With ion exchange resins, it is necessary to load the drug onto the resin. Fortunately, this is usually quite simple. The drug is dissolved in a suitable solvent (for example water) and mixed with the resin for some time, usually a few hours. Filtration then produces the resinate. There are many examples in the literature on ways to do this and the reader is directed to some of the articles cited elsewhere in this article and others (10, 11). Making experimental samples of resinates does not need much drug. Drug loading can be characterised using only milligrams of material.

The price to pay for using resinates is that the release characteristics can be more difficult to characterise than simple salts. For some drugs, particularly hydrophobic ones, the release from some resinates can be slow. If one is trying to make an extended release formulation then this can be an advantage, but for immediate release it is not acceptable. The solution is to try different resins, different particle sizes and different amounts loaded. For example,

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a drug such as paroxetine (12) can form resinates quite easily, but using a sulfonic acid resin gives a resinate with slow release rate. Using a resin with carboxylic acid functionality gives rapid release. Another complication is the equilibrium nature of the loading/release. For some drugs, the equilibrium favours the drug loaded onto the resin. This can lead to erroneous conclusions of incomplete release when using some of the USP dissolution methods. *In vivo*, the equilibrium is continuously displaced toward release because of the absorption of the drug from the GI tract.

Using resinates can also bring some incidental advantages:

- Once dried, the resinate will be always be a flowable powder, thus avoiding the manufacturing issues that can occur with some crystal forms
- The resinate will have a taste masking effect
- If the drug is hygroscopic the resinate may be less hygroscopic
- The characteristics of the resin will be independent of the crystal form used to make it; it can even be a mixture. This could simplify the manufacturing process by avoiding some recrystallisation steps, or allowing the use of cheaper or safer solvent systems
- When loaded onto the resin the drug may be more stable chemically than it is by itself

A further advantage to using resinates is the possibility of obtaining patent protection for the formulation. It is about 50 years since the first use of resinates for an oral formulation, so there is no possibility of getting broad patent coverage, but patents are still being granted for specific formulation containing ion exchange resinates.

There are several suppliers of ion exchange resins. These include Rohm and Haas, Purolite, Dow, Ion Exchange India and Lanxess. All these suppliers have websites where information on the resins is available. Samples for development can be obtained either from these suppliers or from chemical supply houses such as Sigma-Aldrich.

In summary, making resinates to avoid polymorphism problems is an alternative that should be considered along with the more traditional methods. Not only can it be very effective, but it can also bring other advantages and even patent protection in some cases. Like the traditional methods, it is not a panacea. It may not give the optimal formulation in every case but, unlike the traditional methods, the amorphous resinate will always be physically stable. Why not give it a try? ◆

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