Ion Exchange Resins
Unique Solutions to Formulation Problems

Lyn Hughes

Ion exchange resins have been used to help formulate pharmaceuticals since the late 1950s. During that time, they have proven to be safe and effective excipients and are now used in many commercial formulations throughout the world. This article will look at some of the common problems faced by formulators and how using ion exchange resins may be able to solve them.

Ion exchange resins are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. The equation in Figure 1 shows a representative reaction when drugs are loaded onto or released from the resins. A drug ion and an inorganic ion are exchanged. The reaction is an equilibrium, the position of which will depend on many factors such as salt concentration in the aqueous phase. This property enables drugs to be loaded onto resins (forming drug resinates) and then released in vivo by the salts present in gastro-intestinal

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fluids. The resinates possess physical properties similar to those of the resin. These two properties—drug release and physical properties—can be manipulated to create many variations of use to the formulator.

**Stability.** The drug resinate is frequently more stable than the original drug. This tendency is exemplified by the stabilization of vitamin B₁₂ in the oldest pharmaceutical resinate application. Vitamin B₁₂ has a shelf life of only a few months, but the resinate is stable for more than two years. This technology is still used commercially today, more than 40 years after it was first introduced. Another example is nicotine. Nicotine discolors quickly when exposed to air and light but the resinate (used in nicotine chewing gums and lozenges) is much more stable.

**Poor dissolution.** Many of today’s drugs are poorly soluble because of slow dissolution and/or low solubility. The rate of release of poorly soluble, ionizable drugs from a resinate can be much quicker than the rate of dissolution of the pure drug. An excellent example is that of indomethacin, which is only soluble up to ~6 ppm in simulated gastric fluid but is released very quickly from a resinate (see Figure 2). Stirring an excess of indomethacin in simulated gastric fluid for three days achieved a concentration of only 1 ppm, whereas exposing a resinate of indomethacin to the same fluid yielded a saturated solution within 30 minutes. Using micronization to increase the rate of dissolution can be problematic because the technique frequently requires specialized equipment and often involves a problem with agglomeration of the fine particles after grinding. The grinding process also can lead to melting and conversion to other crystal forms. These problems can be eliminated by the use of ion exchange resins.

**Deliquescence.** Deliquescence is the property of a solid such that it absorbs so much water that it dissolves in the water it absorbs. Although this is not a common problem, it has been very difficult to solve and requires the use of specialized equipment or careful scheduling of production during dry seasons. However, the resinate of a deliquescent drug is not deliquescent, permitting its formulation into typical dosage forms in standard equipment. Figure 3 shows the results of tests conducted on resinates of sodium valproate, a well-known highly deliquescent drug. Even under such severe conditions, the resinates remain solid. In
fact, the amount of water absorbed decreases as the amount of valproate in the resin increases. Under typical ambient conditions, the resin remains free-flowing even if water is absorbed.

**Polymorphism.** Unlike deliquescence, polymorphism is a very common problem in the pharmaceutical industry, and huge sums of money are spent trying to identify polymorphs and making stable, suitably soluble forms. Failure to resolve such problems can result in significant stability problems for the final dosage form. Ion exchange resins present a unique way to solve the problem. A drug resinate is an amorphous solid that cannot crystallize or even form hydrates. In addition, the release of the drug from the resinate is independent of the crystal form that was used to make it. Consequently, the use of resirates can eliminate any problems with polymorphism. Figure 4 shows release--dissolution test data on lansoprazole and its resirates. These data clearly demonstrate that although the original crystal forms of the drug had very different dissolution rates, the release rates from the resirates were all the same.

**Physical state.** Some drug substances are liquids or difficult-to-handle solids. Because the physical properties of the resirates are similar to those of the resin and not the drug, the resirates of these trouble-some drugs are free-flowing solids. A very well established example of this is the nicotine resinate used in nicotine chewing gums and lozenges. Nicotine is a liquid, but the resinate is a stable, free-flowing solid.

**Tablet disintegration.** Some ion exchange resins will swell significantly when immersed in water. This property has led to their use as very effective tablet disintegrants. It is usually necessary to use only a few percent of the tablet weight to get complete disintegration within several minutes.

**Taste.** Because resirates are insoluble in water, they have no taste. This makes them excellent candidates for masking foul-tasting drugs. As long as the rate of release of the drug on contact with saliva is sufficiently slow (and it frequently is), this technology can work extremely well. It is equally applicable to liquid formulations (suspensions) and mouth-dissolving
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tablets. It is particularly effective in liquid formulations because the resinate will represent the thermodynamically stable form so that leaching of the drug into the aqueous phase will not occur. There are several examples of the use of this technology in the marketplace, including a liquid form of paroxetine.

**Extended release.** One of the early applications of ion exchange resins in drug formulation is their use in extended-release. The first commercial example of this is the “Penn-Kinetic” system in which dextromethorphan is loaded onto a resin and the resin is then coated. This combination provides an extended-release liquid formulation that is still sold commercially (e.g., Delsym). The technique has also been used for many years for extended-release diclofenac, but without the coating.

Until recently, this technology was limited by the release profile. Although the overall release rate could be changed, the shape of the release profile was always the same—a typical first-order release. However recent innovations have identified ways to change this shape significantly, even to the point of achieving an almost constant release rate.

**Abuse liability.** During the past few years, there has been much publicity about the abuse of prescription drugs (e.g., OxyContin). Ion exchange resins can be used to make it more difficult or less desirable to abuse such formulations. The technology can be manipulated to reduce the “high” associated with intentional abuse, reduce the likelihood of overdose by inadvertent abuse, and make illicit extraction more difficult and less efficient.

**Multiple benefits**

The benefits described are not necessarily mutually exclusive to one another. One example is the nicotine chewing gum. In this case, the main reason for making the nicotine resinate (nicotine polacrilex USP) is to extend the release of the nicotine from the chewing gum so that it lasts 10–20 min. However, the resinate also increases the stability of nicotine and makes it into an easily formulated, less-toxic solid. Another example is Delsym, in which the main reason for the resinate coating is to create an extended-release suspension. However, it also provides excellent taste masking. Finally, the use of a resin to...
stabilize vitamin B₁₂ also improves bioavailability.

Getting more information

Unfortunately for the formulator, ion exchange resin technology related to pharmaceutical formulation is taught in few, if any, schools and cannot be found in many textbooks. Even conducting literature searches through various scientific journals gives only a fragmented description of the technology. The number of manufacturers of pharmaceutical grade resins is also very limited and include Rohm and Haas, Dow Chemical, Purolite, and Ion Exchange India. Listed below are some useful resources to help the formulator find out more about this technology.

Textbooks

Journal articles/patents
- Y. Raghunathan, US patent 4,221,778
- S. Khanna, US patent 4,510,128

Web site
- www.rohmhaas.com/markets/pharmaceutical.html

Conclusion

Ion exchange resin excipients should be a part of every formulator’s basic toolkit. Although they are not as well-known in the industry as one might expect, ion exchange resin excipients can bring unique benefits and solve some very difficult problems.