



Ion Exchange Resins

Unique Solutions to Formulation Problems

Dr. L. Hughes, Global Technical Service Manager, Healthcare
Rohm and Haas Research Laboratories - Spring House

INTRODUCTION

Ion exchange resins have been used to help formulate pharmaceuticals since the late 1950's. During that time they have proved to be safe and effective excipients and are now used in many commercial formulations throughout the world. In this article we 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 with aqueous solutions surrounding them.

The equation in Figure I 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 including salt concentration in the aqueous phase. This property allows drugs to be loaded onto resins (forming drug resinates) and then released in vivo by the salts present in GI fluids. The resinates possess physical properties similar to the resin. These two properties - drug release and physical properties - can be manipulated to create many variations of use to the formulator.

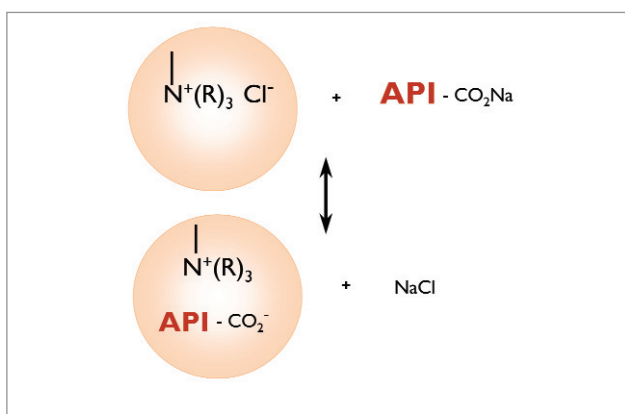


Figure I

STABILITY

The drug resinate is frequently more stable than the original drug. This 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 > 2 years. This technology is still used commercially today, more than 40 years after it was first introduced. Another example is nicotine. Nicotine discolors quickly on exposure 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 due to slow dissolution and/or low solubility. The rate of release of a poorly soluble, ionizable drug 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 ca 6ppm in simulated gastric fluid, but is released very quickly from a resinate. Figure II shows a graph of concentration vs time demonstrating this. Stirring an excess of indomethacin in simulated gastric fluid for 3 days achieved a concentration of only 1 ppm, whereas exposing a resinate of indomethacin to the same fluid gave a saturated solution within 30 minutes.

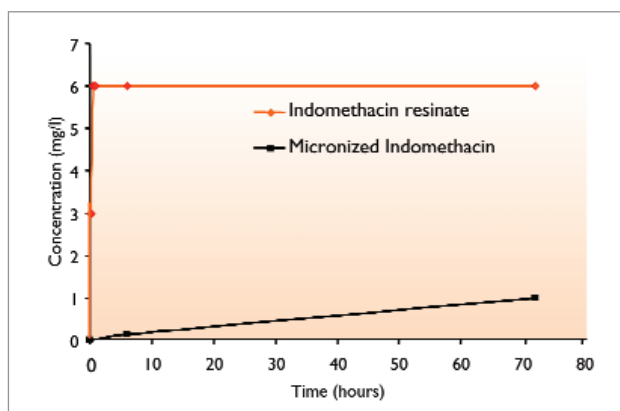


Figure II: Dissolution/Release of Indomethacin in Simulated Gastric Fluid

Using micronization to increase the rate of dissolution can be problematic, frequently requiring specialized equipment, and often having problem with agglomeration of the fine particles after grinding. The grinding can also result in melting and conversion to other crystal forms (see below). These problem are completely eliminated by using the ion exchange resin approach.

DELIQUESCENT

Deliquescence is the property of a solid whereby it absorbs so much water that it dissolves in the water it absorbs. While this is not a common problem it has been a very difficult one to solve, and requires the use of specialized equipment or careful scheduling of production in dry seasons. However, the resinate of a deliquescent drug is not deliquescent, permitting its formulation into typical dosage forms in standard equipment. Figure III show the results of testing 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 with increased amount of valproate in the resin. Under typical ambient conditions the resin remains free-flowing even if water is absorbed.

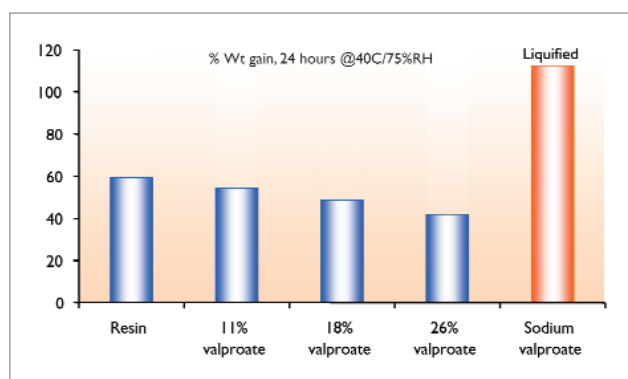


Figure III

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 trying to make 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 deal with 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, using resinates completely eliminates any problems with polymorphism.

Figure IV shows some release/dissolution test data on lansoprazole and its resinates. This data clearly demonstrates that although the original crystal forms of the drug had very different dissolution rates, the release rates from the resinates were all the same.

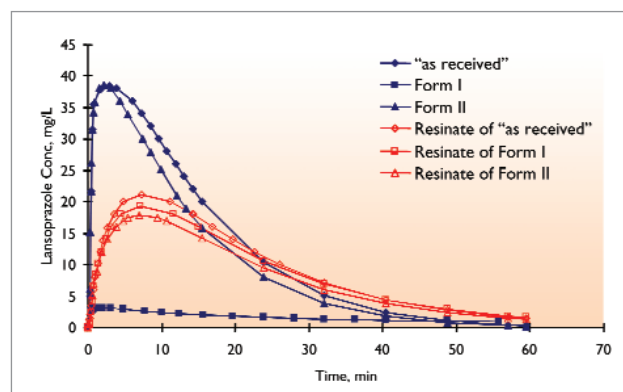


Figure IV: Dynamic in Vitro Dissolution Profiles

PHYSICAL STATE

While most drug substances are solids there are some that are liquids or difficult-to-handle solids. Because the physical properties of the resinates are similar to the resin not the drug, the resinates of these troublesome drugs will be 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

Certain of the ion exchange resins swell significantly on exposure to water. This 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 resinates are insoluble in water they have no taste. This makes them excellent candidates for taste-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 works extremely well. It is equally applicable to liquid formulations (suspensions) and dissolve-in-the-mouth 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 market place 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 was known as the PennKinetic system where dextromethorphan was loaded onto a resin and the resin was then coated. This combination gave an extended release liquid formulation that is still sold commercially (Delsym®). The technique, but without the coating, has also been used for many years for extended release diclofenac. Until recently this technology was limited by the release profile. While 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 almost constant release rate.

ABUSE LIABILITY

During the last few years there has been much publicity about the abuse of prescription drugs, eg 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. Here 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 last 10-20 minutes. However the resinate also increases the stability of nicotine and makes it into an easily formulated, less toxic solid. Another example is in Delsym® where 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 bio-availability.

USING ION EXCHANGE RESINS

In most cases making the resinates is very simple. The drug is dissolved in a suitable solvent, eg water or aqueous ethanol, and the resin is added. The loading takes place at ambient temperature and usually takes a few hours to complete. The resinate is then isolated either by filtration or by spray-drying. In some cases such as suspensions it may not even be necessary to isolate the resinate.

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 doing literature searches through the scientific journals gives only a fragmented description of the technology. Below are listed some useful resources to help the formulator find out more about this unique technology.

Textbooks

- **Ion Exchange**
Freidrich Helfferich, Dover publications, 1995.
- **Ion Exchange Resins**
Robert Kunin. Robert E. Krieger Publishing Co, 1990.
- **Remington** - The Science and Practice of Pharmacy. 20th Ed. Chapter 47. University of the Sciences, Philadelphia, 2000.

Journal Articles & Patents

- Y. Raghunathan. US 4,221,778.
- D.P Elder, A Park, P. Patel and N. Marzolini
Proceedings of IEX 2000. Ion Exchange at the Millennium. J.A.Greig (ed), 2000. 306 - 315.
- S. Khanna. US 4,510,128.
- W. J. Irwin, R. McHale, and P. J. Watts
Drug Development and Industrial Pharmacy, 16(6), 883-898 (1990).

Website

www.rohmhaas.com/markets/pharmaceutical.html

CONCLUSION

Ion exchange resin excipients should be a part of the formulators' basic toolkit. Although not as well known in the industry as one might expect from their wide utility they can bring unique benefits and solve some very difficult problems.

For more information, please contact :
Dr. L. Hughes, Rohm and Haas Research Laboratories,
Spring House, PA, USA
Tel: 215 641 7329 - e-mail: lhughes@rohmmaas.com