



New Uses of Ion Exchange Resins in Pharmaceutical Formulation

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SUMMARY

Novel ways of using ion exchange resins to modify drug release rate, increase the dissolution rate of poorly soluble drugs, and eliminate problems with deliquescence are presented. Current uses are discussed briefly.

INTRODUCTION

Ion exchange resins have been used for many years in pharmaceutical formulations. Their uses have ranged from simple excipients for tablet disintegration to the rate controlling function in extended release formulations. In this paper we report some novel uses that have recently been developed in the Research Laboratories of Rohm and Haas.

BACKGROUND

Typical properties of pharmaceutical grade ion exchange resins that are pertinent to their use in pharmaceutical formulations are shown in Table I. The fact that these materials are totally insoluble in all solvents and at all pH's, combined with their particle size means that they are not absorbed by the body, and so have proven to be non-toxic and very safe.

One of the most important properties of ion exchange resins is that they contain functional groups, attached to the backbone of the polymer, that can exchange ions with ions in solution. These exchangeable ions are not limited to the small, inorganic anions and cations typical of water treatment (eg Na^+ , Ca^{++} , Mg^{++} , SO_4^- , HCO_3^- , Cl^-), but can be organic ions of significant molecular weight, (e.g. typical drugs).

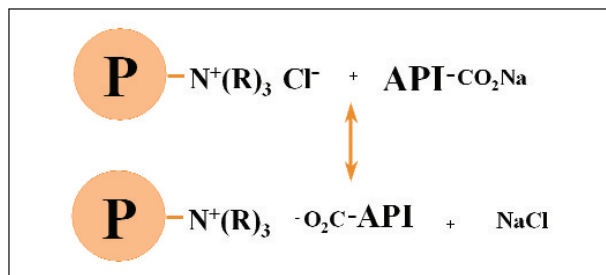


Figure 1

Fig. 1 shows the equilibrium reaction between an anion exchange resin and an Active Pharmaceutical Ingredient (API). It is important to recognize that this is a reversible reaction, the equilibrium position of which will depend on the environment in which the drug and ion exchange resin are found. Going in the direction down the page represents loading. The reverse direction represents release. Similar equations can be written for other types of ion exchange resins, both acidic and basic.

Table I – Properties of pharmaceutical grade ion exchange resins

- fine, free-flowing powders
- particle size of 25-150 microns
- contain functional groups capable of exchanging ions and/or ionic groups
- insoluble in all solvents, all pH's
- not adsorbed by the body
- do not have a defined molecular weight.

Factors controlling the equilibrium constant include the following:

- Molecular weight
- pKa of drug and resin
- Solvent
- Solubility
- Temperature
- Hydrophobicity/hydrophilicity
- Concentration of competing ions

The loaded resin is often referred to as a 'resinate'. The typical properties of resinates are shown in Table II. Note that the properties are very similar to those of the original ion exchange resin.

Table II. Physical Properties of Resinates
<ul style="list-style-type: none"> • fine, free-flowing powders • particle size similar to the starting polymer • can be ground to smaller size or agglomerated to larger size • contain the API in salt form • do not have a melting point

Over the last few decades, the ion exchange resins have been used in several different ways in pharmaceutical formulations. These include tablet disintegration, taste-masking, stabilization, and extended release.

Tablet disintegration is achieved through the swelling that occurs when the dried resin is put in an aqueous medium. An example of one of these products is polacrillin potassium¹.

Table III. Taste-masking examples		
Spiramycin	Amberlite™ IRP64M	GB 118023
Dextromethorphan	Amberlite™ IRP64	J.Pharm.Sci. 60(10), 1523-7
Talampacillin-HCl	Amberlite™ IRP88	Res. Discl., 176 12-13
Beta-lactam Antibiotic	Amberlite™ IRP88	Res. Discl., 176 12-13
Ranitidine	Amberlite™ IRP64/69/88	DE3915347
Dimenhydrinate	Amberlite™ IRP64	KR9402943
Paroxetine	Amberlite™ IRP88	WO95/20964

Taste masking occurs because the resinate is insoluble and therefore has no taste. Some example of this application are shown in Table III. The use of ion exchange resins to stabilize molecules such as vitamin B12² was discovered early in their history (ca1958), but this B12 resinate is still made and sold commercially. Not only did resination improve the shelf-life of B12, it also provided some *in vivo* stability, as reported in the initial patent:

"...the products of the present invention have certain definite advantages when administered to patients or to animals requiring such treatment. The vitamin adsorbed on the resin is appreciably protected from the action of acid gastric juices and passes practically unchanged through the gastric system into the intestinal tract..."

Another use of the resins is to achieve extended release. Two commercial examples are an extended release solid formulation of diclofenac³ and an extended release liquid formulation of anti-tussives such as dextromethorphan⁴. In the case of the diclofenac product the release rate is totally controlled by the release from the resinate. With the antitussives the release from the resinate alone has been found to be too fast, so that a permeable coating is applied to provide further control of the release rate.

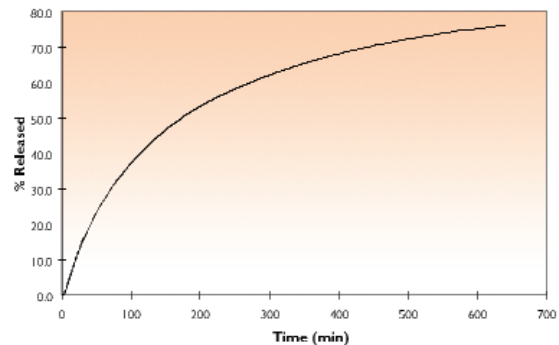


Figure II: Cumulative resin from Diclofenac resinate

NEW METHODS FOR MODIFIED RELEASE⁵

The first new use I am going to describe is the use of ion exchange resins in a novel way to achieve different types of modified release. Fig II shows the release curve for a standard resinate formulation, this specific example is diclofenac loaded onto a strongly basic ion exchange resin. As can be seen from the graph, very significant extended release is achieved, with about 70% of the drug released over an eight hour period. The curve is typified by rapid release at the start with logarithmic decay in the release rate.

This release rate profile has been a limitation to the use of ion exchange resins in controlled release applications because although the overall release rate may be changed by varying loading, coating, and resin type, the shape of the curve is always the same.

The release profile shown in Fig III was obtained using a new approach. It was achieved by co-administering a drug resinate (actually the same resinate as in Fig II) and an unloaded resin. In this particular example the ratio of resinate to unloaded resin was 1:1.5 w/w. This release rate is essentially constant over the period tested.

¹ USP25, page 2592

² US 2,830,933

³ US 4,221,778

⁴ US 4,510,128

⁵ Patent applications filed

By changing variables such as loading, particle size and ratio it is possible to achieve release rate curves between the two extremes represented by Figs II and III, and even go beyond Fig III into a curve that has gradually increasing release rate during the first part of the profile.

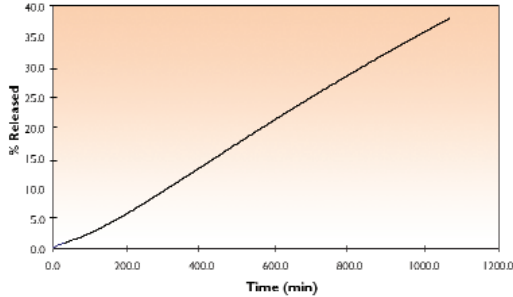


Figure III: Cumulative release from Diclofenac CRS

In this particular example, the unloaded resin was the same type as was used for the loaded resin, so no new excipients were needed.

The rate controlling mechanism is shown in the cartoon in Fig IV. At the start, there is unloaded resin and loaded resin. When the loaded resin enters the GI tract, the drug starts to release by the mechanism of ion exchange as it tries to establish thermodynamic equilibrium, in the same way as conventional extended release from resins. However, the unloaded resin starts to absorb some of the drug because it is on other side of the equilibrium. In addition, some of the released drug gets absorbed by the body. This situation continues until the originally unloaded resin reaches equilibrium with the dissolved drug. Because drug is continually being removed from solution by absorption into the body, the equilibrium is continually shifting, so that the newly loaded resin now starts to release drug back into solution.

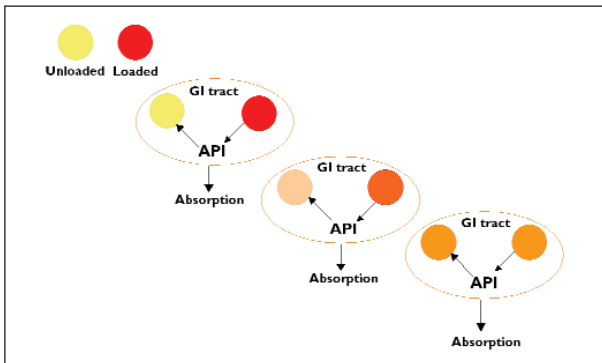


Figure IV

An extension of the use of resinate and unloaded resin is to use drug and unloaded resin. The unloaded resin absorbs the drug from the medium

in which the drug is dissolved, regardless of how the drug got into solution. In the case shown in Fig V, the result is a release curve almost identical to that obtained using the resinate.

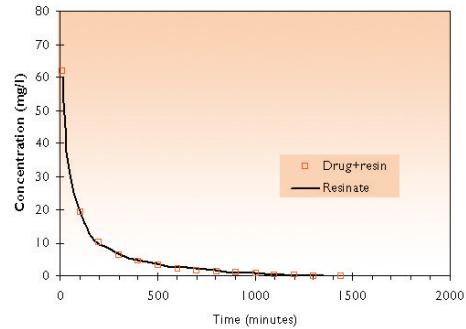


Figure V: Release from Diclofenac ERS

Not creating the resinate in the first place and simply co-administering the drug and unloaded resin has some advantages in that the resinate need not be manufactured prior to formulation. In this case, the drug and resin would simply be co-formulated. This is also likely to be easier in terms of regulatory requirements as the resinate may require some characterization whereas using this approach, the drug is used in its original form and the ion exchange resin is added as part of the formulation.

From a mechanistic approach (Fig VI), this system behaves very similarly to the previous example. The release curve is derived from the fact that the affinity of the drug for the unloaded resin is high so that the resinate quickly forms in the medium and is gradually released as the drug in solution is absorbed by the body.

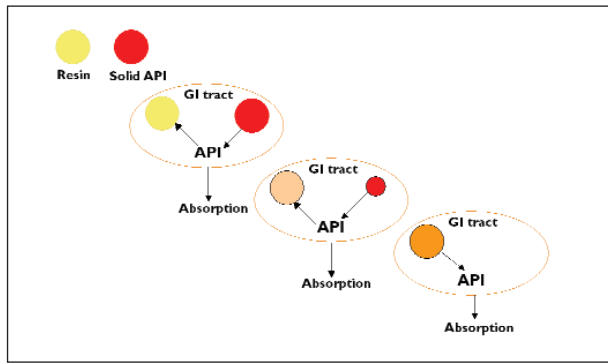


Figure VI

Simply using the drug substance by itself would have resulted in a concentration spike which would decay quickly (within 1 hour).

IMPROVED DISSOLUTION OF POORLY SOLUBLE DRUGS

The problem of dissolution of poorly soluble drugs is well known in the industry. We have found that, in the case of poorly soluble ionizable drugs, the release of drug from a resinate can be faster than the rate of dissolution of the solid form of the drug. Hence one can increase the rate at which poorly soluble drugs 'dissolve'. This is demonstrated by the data in Table IV. The data in the table shows the results of a USP constant volume dissolution test on an indomethacin resinate. The footnote refers to a formulation where micronization of the indomethacin has been used to enhance dissolution rate. Note that the resinate gives a dissolution rate very similar to this formulation. Note also that the test was done at ambient temperature, not the required 37°C. Increasing the temperature will increase the rate of release. Clearly, resination can be as effective as micronization in enhancing dissolution of poorly soluble drugs.

Time (mins)	% Released (22°C)
0	0
10	61
20	78
45	97
120	100
USP: not less than 80% in 20 minutes at 37°C	

We believe that this rapid dissolution occurs because of two factors:

Each individual drug molecule is bound to a functional site - there is no crystal lattice energy to overcome.

The ion exchange matrices are relatively hydrophilic and so allow water and aqueous solutions easy access into the 3-dimensional structure – eliminating problems with 'wetting-out' the drug

A dramatic demonstration of the effect was also seen during attempts to dissolve indomethacin directly into simulated gastric fluid. After 3 days the concentration in solution was only about 1 mg/l,

compared to a published solubility of about 6 mg/l. However, when an indomethacin resinate was put into the simulated gastric fluid a concentration of about 6 mg/l was achieved within 30 minutes.

Note that this technique, like micronization, increases the rate of dissolution. It does not increase the solubility of the drug.

ANTI-DELIQUESCENT⁶

A very recent discovery in our laboratories has been that using resinates can eliminate deliquescence during manufacturing and storage.

We have found that resinates of deliquescent and highly hygroscopic drugs retain the properties of the resin and are not deliquescent and remain free-flowing powders. Their water absorption characteristics are similar to those of unloaded resins, so that any formulation equipment that can handle the resins can handle the resinate of the deliquescent drug without need for special manufacturing conditions.

For example, sodium valproate is a drug which is well known to be highly deliquescent. However, we have found that valproate resinates remain free-flowing even after exposure to ambient air. Table V summarizes results from several resinates using different anion exchange resins to make the resinates. Sodium valproate became liquid within an hour. The implication of this discovery is that dosage forms of deliquescent or highly hygroscopic drugs could be manufactured with no special equipment or atmospheric controls, and deliquescence during storage is eliminated, simplifying the packaging requirements.

Resin used	30 mins	60 mins
Cholestyramine USP	Free flowing	Free flowing
Amberlite™ IRA458	Free flowing	Free flowing
Amberlite™ IRA67	Free flowing	Free flowing
Colestipol USP	Free flowing	Free flowing
Sodium valproate	Sticky	Liquid
Conditions: 24°C/55% RH		

⁶ Patent applications filed

In vitro release tests on these resins confirmed that the drug is released on exposure to GI Fluids

Even though the resins were not deliquescent, they did still absorb water. However, the amount of water they absorbed was less than for the starting resins. This was a very surprising result. In fact, the amount of water absorbed decreased with increasing amount of valproate in the resin. This seems to be counter-intuitive, but was confirmed in several experiments. Some supporting data is presented in Table VI.

Very similar results have also been obtained with another deliquescent drug, rivastigmine bitartrate using cation exchange resins to make the resin, showing that the technique is generally applicable.

Colestipol	59.6
11% valproate	54.3
18% valproate	48.6
26% valproate	41.8
Sodium valproate	112.7 (liquid)
Conditions: 24 hours @40°C/75% RH)	

CONCLUSION

Ion exchange resin technology is frequently considered to be old technology. While it is true that it has been in use for several decades, these new applications show that the technology is still alive and well and capable of solving some of the problems associated with modern drug formulation. Using ion exchange resins to control release rate, to improve dissolution, to taste-mask, or to handle deliquescent and hygroscopic drugs represent simple, very safe, low cost approaches to solving these difficult problems

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