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Addressing Formulation Needs With a Different Technology: Say "Hello" to Ion Exchange Resins

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Introduction

In the 1930s, the original ion exchange patents were produced to address industrial applications, such as wastewater and water purification. In the 1950s, some of these resins were commercialized as fine, free-flowing powder for the pharmaceutical industry to use in formulation applications as an active pharmaceutical ingredient. Since then, the market has expanded into ion exchange excipients for formulations and addresses applications like controlled release, taste masking, abuse deterrence, solubility enhancement and stability.

Ion exchange resins help address delivery challenges in multitude types of dosage forms, with these forms exhibiting several characteristics, including:

- Better drug safety
- Therapeutic benefit
- Improved patient compliance
- Less tablets to take
- Easier to swallow
- Better tasting medicines

The brands of the pharmaceutically-approved ion exchange resins from The Dow Chemical Company are known as AMBERLITE™ and DUOLITE™ **Figure 1.** Their attributes are around formulation diversity, improving the safety of products, and improving patient compliance. Ion exchange resins can be used in a combination with controlled-release matrix formulations to prevent spiking of highly water soluble APIs.

They can also be used in most drug delivery systems, including orally disintegrating tablet lines. They can enable multiple attributes in one formulation as well: for example, a controlled-release tablet with taste masking components.

From a safety standpoint, ion exchange is also a good technology to use in abuse-deterrent formulations and they can help stabilize APIs that are unstable and hard to formulate, such as drugs that exhibit hydroscopic behavior and liquid drugs. Finally, solubility enhancement can be achieved by loading a poorly soluble drug onto an ion exchange resin and making it amorphous for a more consistent release.

Regarding patient compliance, ion exchange works well in suspension formulations to control the release and taste mask bitter drugs.

Drug Delivery Using Ion Exchange Resins

Ion exchange is a solution for many formulation challenges, like modified release, taste masking of bitter drugs, improving the solubility of poorly soluble materials, as an abuse deterrent, and

for poorly stable materials. The different drug delivery systems that ion exchange can be used in is fairly diverse, which is one of the main attributes of the material.

- Suspensions are a very good way to use ion exchange to get controlled release of actives, either by loading them onto the resin or employing a coating strategy to get a longer extended release.
- In matrix tablets, early drug spikes can be reduced. And because of good flow properties, capsules can be filled with the ion exchange either as is or by adding a binder and granulating it for different types of flow properties.
- The orally disintegrating area is very interesting, as ion exchange can be used in thin film strips, chewable tablets, fast-melt technologies, and lipid-based chewies and gummies. A higher dose drug can be formulated into a chewable dosage form, whereby a lipid-based formulation is implored with the ion exchange resin.
- Gums and gummies are an area where ion exchange has already been used for decades.

The ion exchange resins are made by suspension polymerization. They are round beads that are dried and ground into fine, free-flowing powders with a Gaussian-distributed particle size because they are impact-milled.

Resin Structures

Dow offers several ion exchange resins. They are:

- AMBERLITE™ IRP69 is a strong acid cation. It is a styrenic resin that is cross linked with divinylbenzene and sulfonated, so its functionality is the sulfate group. It is supplied in sodium form.
- DUOLITE™ AP143 is also a styrene-DVB resin, but it is functionalized with quaternary amine so acidic drugs can be loaded onto the material for delivery. It's supplied in the chloride form.
- AMBERLITE™ IRP88 and AMBERLITE™ IRP64 are both methacrylate resins. AMBERLITE™ IRP88 has been functionalized and converted to the partial potassium form, so it is an ionized material. AMBERLITE™ IRP64 is supplied in free acid form.

Loading these resins is done by making the drug solution and adding the resin. Over a specific period of time, a resinate is formed and a salt byproduct, which is rinsed away. The resinate would be further formulated by drying it, binding it to a granule, or coating it. When the formulation is done and in its final dosage form, it is taken *in vivo*. As the resinate comes in contact with the salt and acid in the body, it will unload in the GI fluids. Then, the active ingredient is available for therapeutic effect.

The ion exchange resins are made by suspension polymerization. They are round beads that are dried and ground into fine, free-flowing powders with a Gaussian-distributed particle size because they are impact-milled. They contain functional groups capable of exchanging ions. They are insoluble in all solvents and are not absorbed by the body. So, when taken *in vivo*, the drug unloads, and the resin passes through the

Figure 1: AMBERLITE™ and DUOLITE™ Excipients

Ion Exchange Attribute	Strengths for Formulating with Ion Exchange Resins
Formulation Diversity	• Can be combined with Matrix formulations to prevent spiking of highly water soluble APIs • Can be used in most drug delivery systems including ODT's • They can have multiple attributes for one formulation like modified release and taste masking
Increased Safety	• No immediate release due to tampering (Abuse Deterrence) • Helps to stabilize API's • Consistent release – amorphous form of API for solubility enhancement
Improved Patient Compliance	• Suspension formulations for controlled release and taste masking in the geriatric and pediatric populations

body unchanged.

Case Studies

AMBERLITE™ and DUOLITE™ offer solutions in modified-release formulations, taste masking, poorly soluble drugs, abuse deterrence, and stability. A variety of case studies exemplify their use in addressing these formulation challenges.

Modified-Release Case Studies—The data was collected

Figure 2: Modified Release – Case Study #1

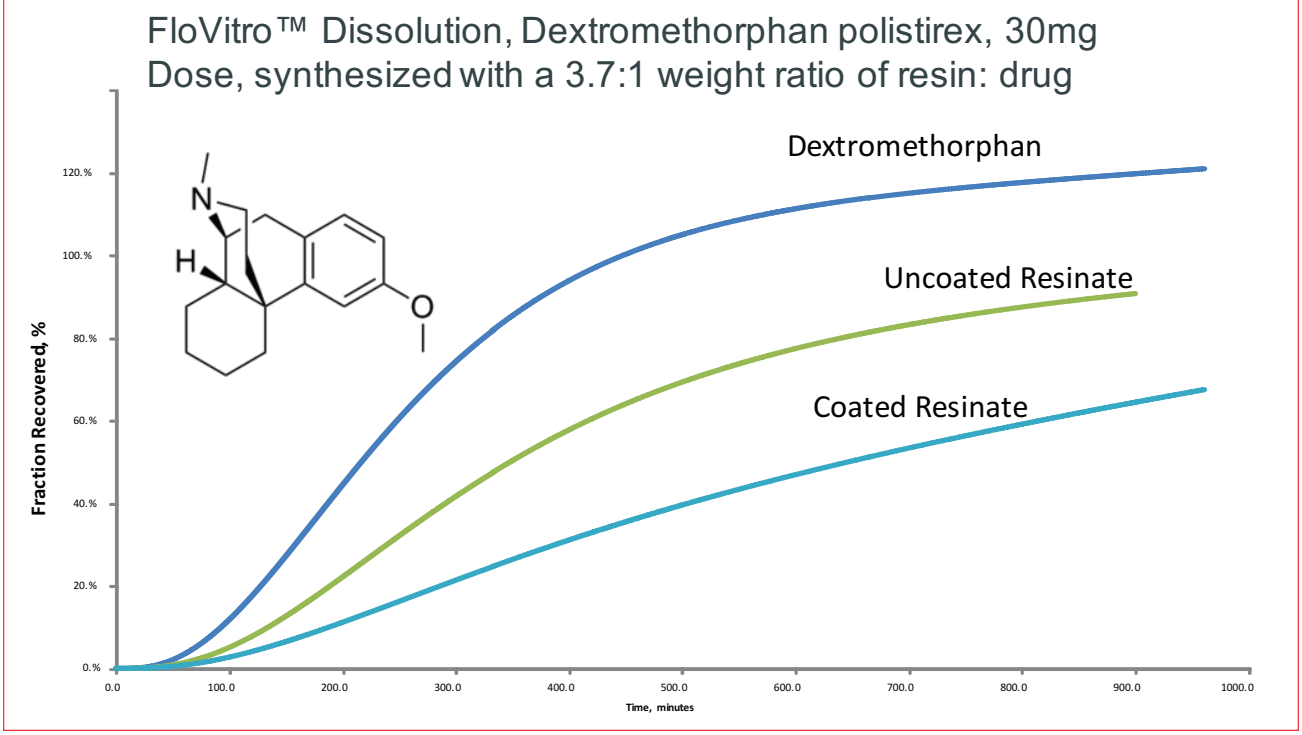
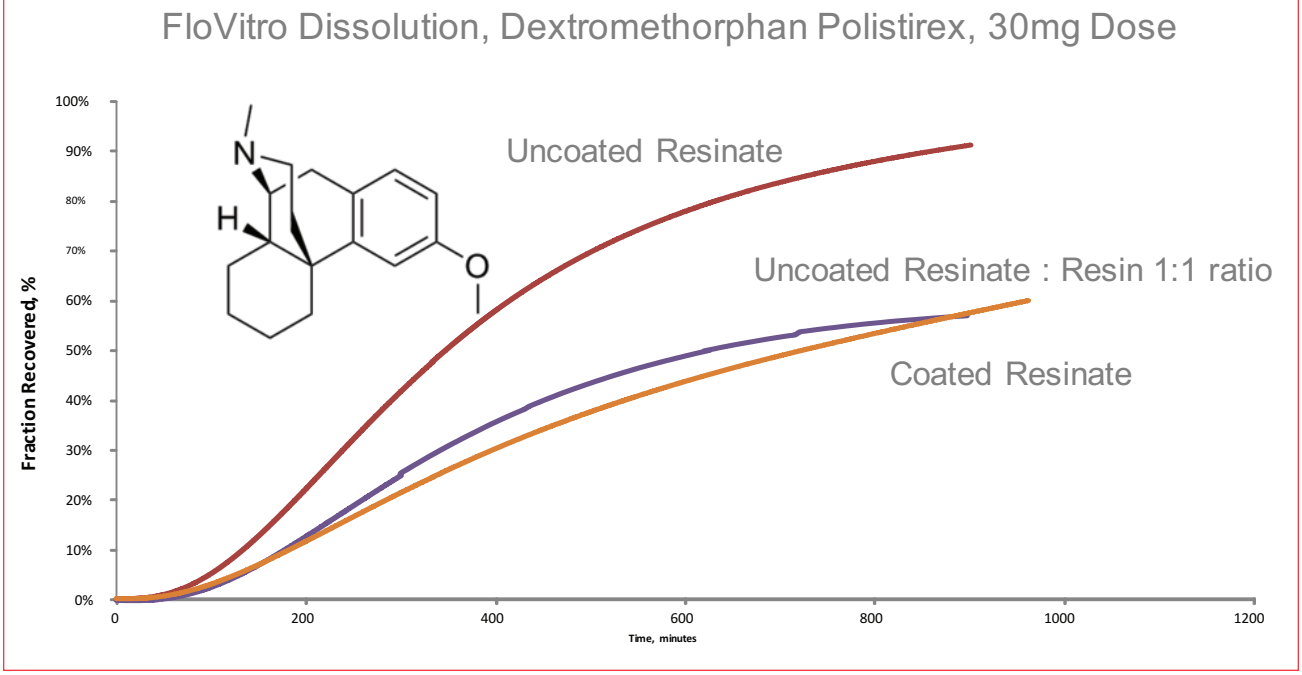


Figure 3: Modified Release – Case Study #2



using FloVitro™ Technology, a dynamic flow-through GI dissolution test, representing the gastric environment, the intestinal environment, and the blood plasma. Data was collected every 30 seconds. Fasted simulated gastric fluid and simulated intestinal fluid were used to show the results.

The dissolution test of dextromethorphan polistirex is seen in **Figure 2**. This shows that whether coated or not, a modified release using ion exchange is achieved. Cmax decreased as

Figure 4: Modified Release – Case Study #3

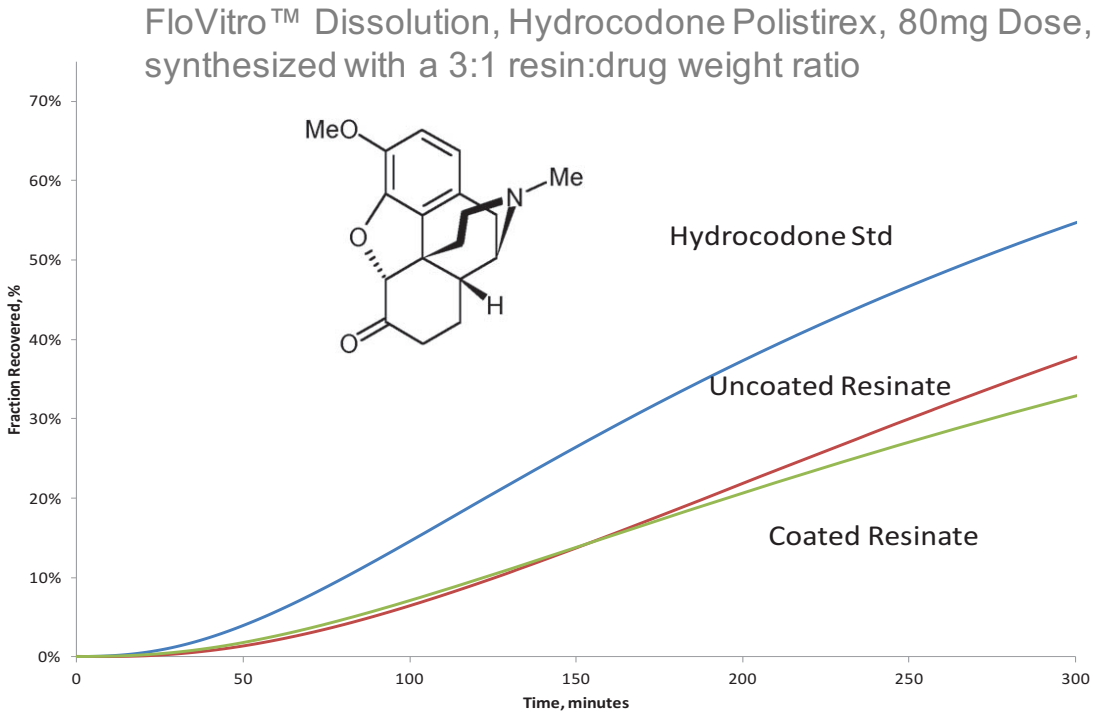
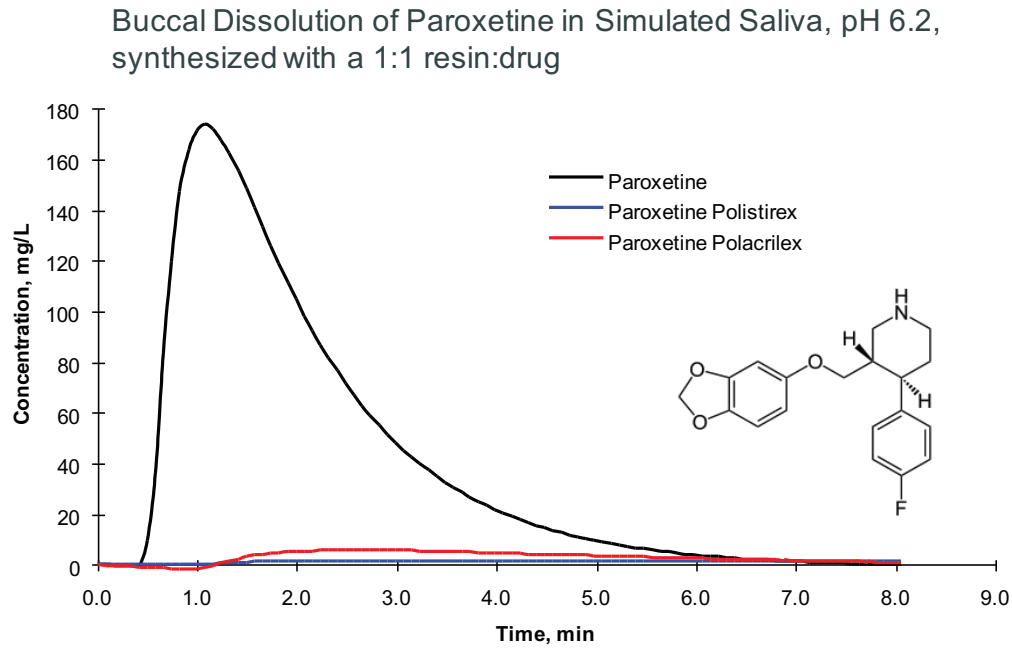


Figure 5: Taste Masking – Case Study #1



drug was loaded onto the resin, and the Tmax is extended, indicating modified release.

Figure 3 shows dextromethorphan, but with a little tricky edge to it: the uncoated resinate and plain resin. Release is similarly controlled with the coated material. Again, the Cmax decreased and the Tmax has increased as the resinate is coated or by using a resinate/resin combination.

Figure 4 shows hydrocodone polistirex. Whether the res-

Figure 6: Taste Masking – Case Study #2

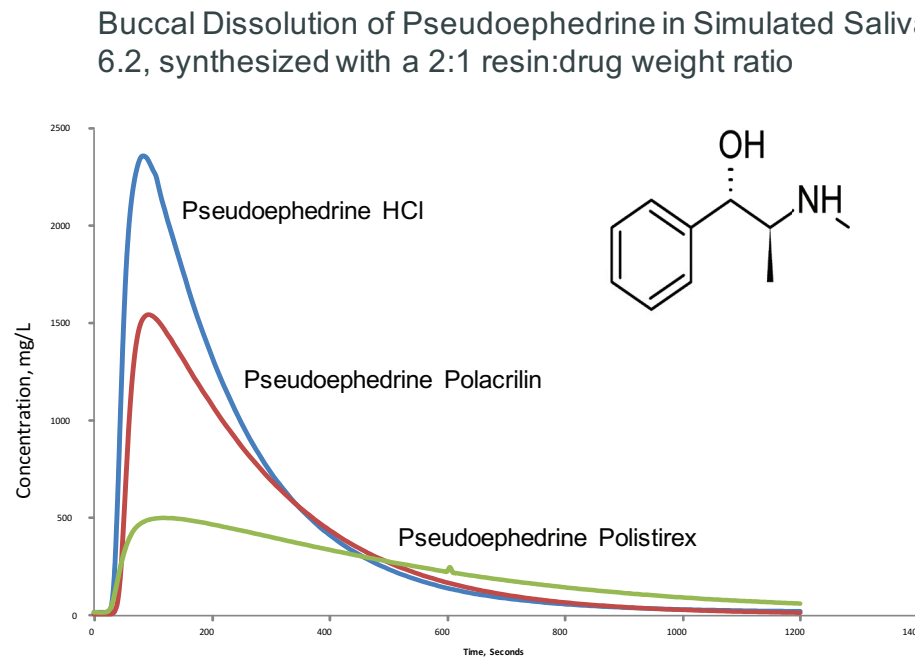
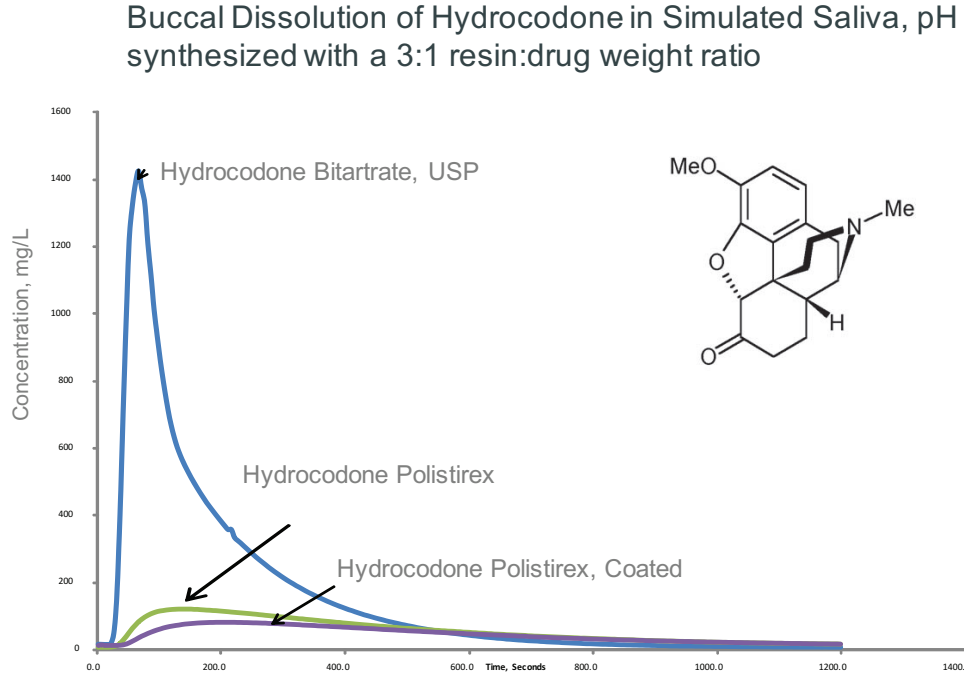


Figure 7: Taste Masking – Case Study #3



inate is coated or uncoated, modified release is achieved, which can improve the safety of the product and prevent dose dumping.

Taste Masking Case Studies—Data was collected with a patented buccal dissolution test. This is also a dynamic flow-through test, using a single cell. Saliva was simulated pH 6.2. Data was collected every 30 seconds. In one test, paroxetine in simulated saliva was synthesized on the resin at 1:1 resin-to-

Figure 8: Solubility Enhancement with Ion Exchange Resin

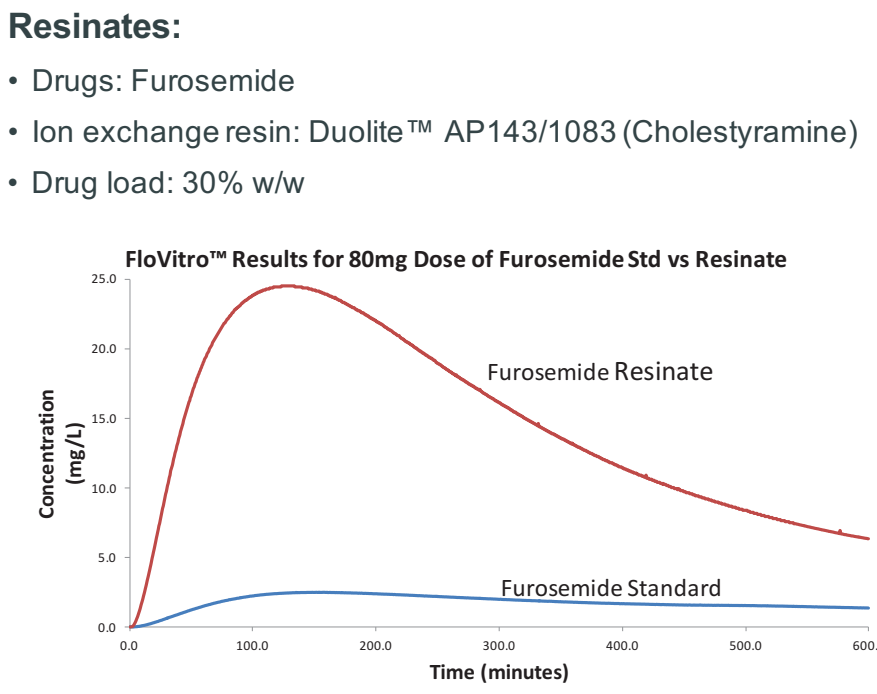


Figure 9: Abuse Deterrence Case Study – Oxycodone

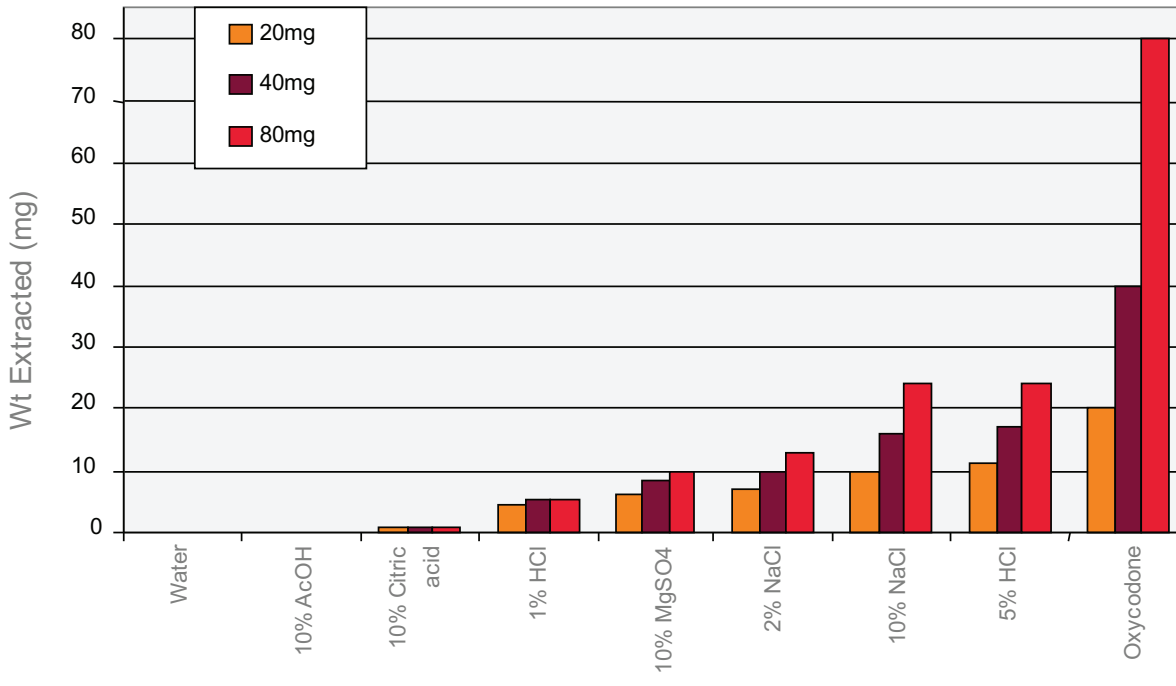
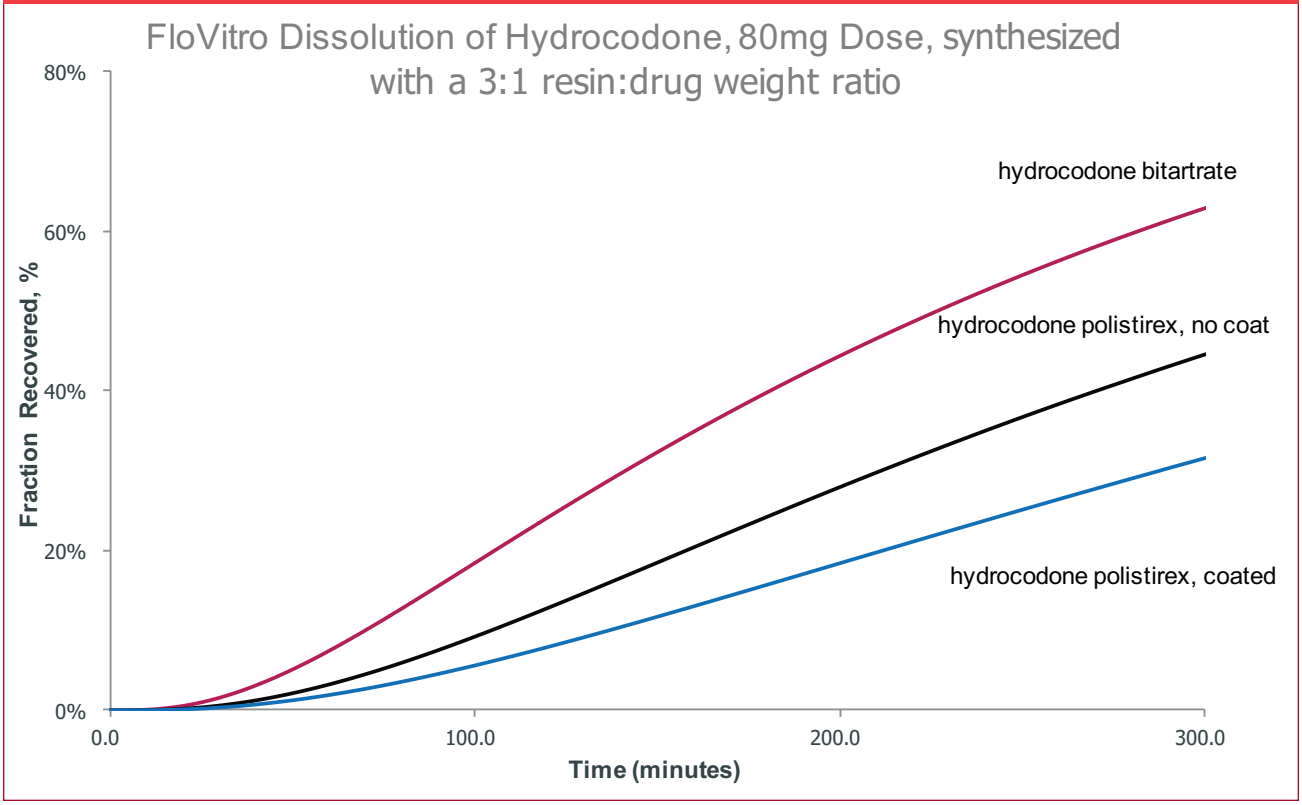


Figure 10: Abuse Deterrence Case Study – Hydrocodone



drug ratio. As seen in **Figure 5** , paroxetine has a high taste in the simulated saliva. When loaded onto either a polistirex (IRP69) or a polacrilin resin (IRP88), excellent taste masking occurs.

In another example **Figure 6**, pseudoephedrine is used. Polistirex, a strong acid cation resinate, does an excellent job of taste masking pseudoephedrine.

Figure 7 presents hydrocodone. Using IRP69 as the polistirex resin, coated or not, does an excellent job of taste masking. However, adding the ETHOCEL™ coating gives an extra layer of taste masking.

Poorly Soluble Drug Case Study—A resinate was created using Duolite AP143, which is cholestyramine. The furosemide drug was loaded onto the resin at a 30% weight. When looking at the release characteristics of the standard alone, it has very poor solubility, so no bioavailability of this material is seen **Figure 8**. But when loaded onto a resinate, there is a higher payload of amorphous drug from the formulation. So this is a good way to improve solubility by using ion exchange resins.

Abuse-Deterrent Case Studies—**Figure 9** shows oxycodone in a kitchen chemistry study. Three different levels of oxycodone were studied: 20mg, 40mg and 80mg. The other parts of the bar graph represent all the resinates that were run. Some of the drug was extracted into 5ml of these materials within 30 minutes, but nowhere near the amount of drug that an abuser would be looking for.

The second study **Figure 10** looked at hydrocodone at the 80mg pain dose. This is synthesized with a 3:1 resin-to-drug ratio. Some modified release was achieved with the resinates and even more so with a coated resinate, showing that an abuse-deterrent formulation for an opiate drug is possible.

Stability Case Studies—Vitamin B12, probably the oldest example of a formulation using ion exchange resin, has a shelf life of about two to three months but extendes shelf life to greater than two years when formulated with an ion exchange resin. Another example is with nicotine. Nicotine colors readily upon exposure to air and light. This is also a liquid drug and hard to formulate. When added onto an ion exchange resin, a fine, free-flowing white powder is created. Now, content uniformity can be controlled, whether as a chewable or a lozenge.

Summary

Seventy percent of the APIs in the market today are ionizable and ion exchange resins address these drugs. These resins are capable of addressing several challenges in pharmaceutical development, including taste masking, stability, abuse deterrence, modified release, and poor solubility. The result is improved drug safety and enhanced patient compliance.