DuPont Water Solutions
Life Sciences and Specialties

DuPont™ Amberlite™ and DuPont™ Duolite™ Ion Exchange Resin Excipients

Handling and Use Guidelines

Introduction

Excipients are considered as ingredients which make up a formulation with an active pharmaceutical ingredient (API). They ensure the conservation of the drug but also can have an impact on the availability of the API itself. Generally excipients are inert, and examples include starch, sugar and cellulose. Functional excipients have a direct impact on the availability of the API. Ion exchange resins can be considered as functional excipients. They can modify release of a drug in vivo, taste mask bitter drugs, and stabilize drugs for improved bioavailability and/or manufacturing.

Ion Exchange Principles

The use of ion exchange resins to deliver drugs from a formulation is based on the principle that positively or negatively charged APIs combine with the appropriate resins and yield resinates (resin bound API's). The API is bound to the resin through ionic interactions (and/or hydrophobic interactions in some cases) with the resulting resinate becoming a new salt form of the drug. Binding of drug to strong and weak cation and anion exchange resins is controlled primarily by an equilibrium phenomena, as shown below in Figure 1.

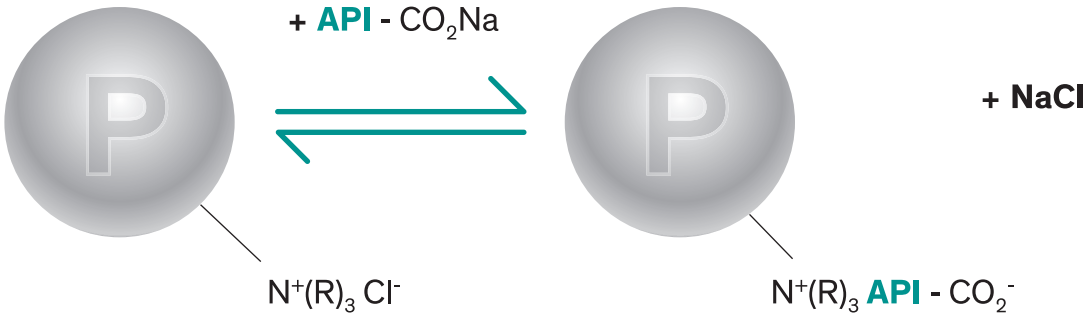

Figure 1 – Ion Exchange Mechanism

DuPont™ Amberlite™/ DuPont™ Duolite™ Pharmaceutical Resins

DuPont ion exchange resins are well known and globally recognized excipients with a long history of safe use. All of these resins are manufactured in Dow Chemical's cGMP and ISO 9001-certified facilities and Drug Master Files (DMF) are available for each resin.

Amberlite™ IRP69 (Sodium Polystyrene Sulfonate USP)

Amberlite™ IRP69 resin is an insoluble, strongly acidic, sodium form cation exchange resin supplied as a dry powder. It is suitable for use in pharmaceutical applications, both as an active ingredient and as a carrier for basic (cationic) drugs. It can be used for sustained release applications with compatible coating technologies. The structure for Amberlite™ IRP69 is shown below in Figure 2.

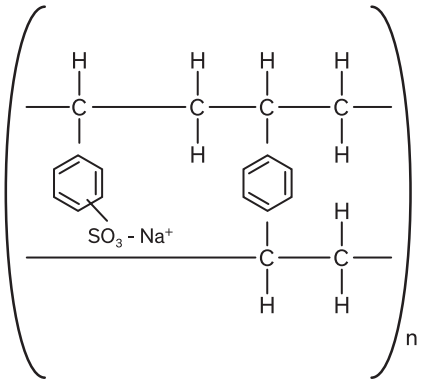

Figure 2 – Structure of Amberlite™ IRP69

Amberlite™ IRP64 (Polacrilex Resin)

Amberlite™ IRP64 resin is an insoluble, weakly acidic, free acid form cation exchange resin supplied as a dry powder. It is suitable for use in pharmaceutical applications such as stabilization of active pharmaceutical ingredients or masking objectionable tastes associated with certain basic drugs. The structure for Amberlite™ IRP64 is shown below in Figure 3 (H+ would replace the K+).

Amberlite™ IRP88 (Polacrilin Potassium, NF)

Amberlite™ IRP88 resin is an insoluble, weakly acidic, potassium form cation exchange resin supplied as a dry powder. It is suitable for use in pharmaceutical applications as a super disintegrant or taste masking agent for masking objectionable tastes associated with certain basic drugs. The structure for Amberlite™ IRP88 is shown below in Figure 3.

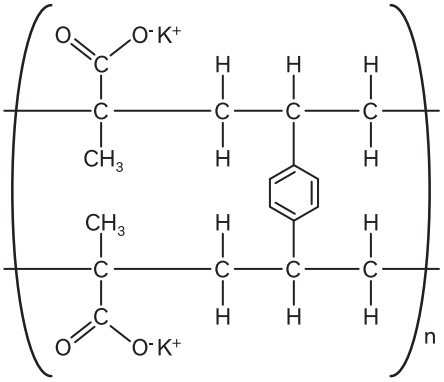

Figure 3 – Structure of Amberlite™ IRP64 and Amberlite™ IRP88

Duolite™ AP143 (Cholestyramine Resin USP)

Duolite™ AP143 resin is an insoluble, strongly basic, anion exchange resin supplied as a dry powder. It is suitable for use in pharmaceutical applications, both as an active ingredient and as a carrier for acidic (anionic) drugs. The structure for Duolite™ AP143 is shown below in Figure 4.

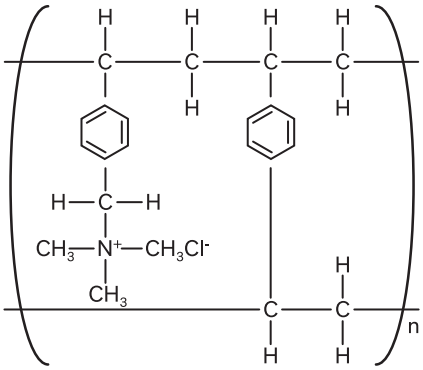

Figure 4 – Structure of Duolite™ AP143

Resin Selection

In general any ionizable API with a molecular weight <3,000 daltons can be loaded onto an ion exchange resin. The API functionality and intended application will determine which ion exchange resin is best suited for making a resinate. A resin selection chart is shown in Table 1, and this chart can be used as a starting point for choosing the appropriate resin.

Table 1: Resin Selection Chart

Drug Functionality	Taste Masking	Stability	Modified Release
Base	Amberlite™ IRP64	Amberlite™ IRP64	Amberlite™ IRP69
	Amberlite™ IRP69	Amberlite™ IRP69	
Base, Ionized	Amberlite™ IRP88	Amberlite™ IRP88	Amberlite™ IRP69
	Amberlite™ IRP69	Amberlite™ IRP69	
Acid	Duolite™ AP143	Duolite™ AP143	Duolite™ AP143
Acid, Ionized	Duolite™ AP143	Duolite™ AP143	Duolite™ AP143
Zwitterionic	Amberlite™ IRP64	Amberlite™ IRP64	Amberlite™ IRP69
	Amberlite™ IRP88	Amberlite™ IRP88	Duolite™ AP143
	Amberlite™ IRP69	Amberlite™ IRP69	
	Duolite™ AP143	Duolite™ AP143	
Neutral	Amberlite™ IRP64		

Resination Process

Resination is a process whereby an active pharmaceutical ingredient (API) is loaded onto an ion exchange resin. The resulting product is known as a resinate. The pre-formulated resinate can then be further formulated into tablets and capsules, or orally disintegration tables (ODT's). A description of how loading is expressed and calculated is given in the section "Resin Loading Determination". The procedure for resination is as follows.

1. Accurately weigh out the desired amount of drug.

2. Dissolve the API in a known amount of the solvent of choice, preferably deionized water. Aqueous/organic mixtures are acceptable for poorly soluble APIs. The use of buffers is discouraged as this will inhibit the loading of the API onto the resin.

   A typical example of API solution is dextromethorphan in water, prepared at a 2mg/mL concentration.

3. For the initial screening study, accurately add the resin (recording the resin weight) in a 1:1 by weight ratio with the API. This amount can be very low (i.e. 20-40mg) depending on drug availability. The ratio of API to resin can be adjusted during the optimization studies.

4. Shake or stir the mixture overnight. If using mixing, DO NOT use a magnetic stir bar, as this will grind the resin and decrease the particle size. Process optimization will allow reduction of the cycle time down to 1-4 hours for most APIs.

5. Centrifuge the mixture or let the resinate settle out on the bench and remove ~2mL of supernatant using a syringe and then filter this supernatant with a 0.45µ filter.

6. Analyze the filtered supernatant for API using a calibration curve prepared by using a standard solution of API. Dilute the filtered sample as necessary to achieve a concentration within the linear range.

7. Refer to the "Resin Loading Determination" section to calculate the resin loading.

   If the API needs to be recovered from the resin or if the resinate will be used for further formulation, continue to the next step.

Figure 5 – Buchner Funnel Set-Up

8. Set up a small filtration apparatus using a Buchner funnel, house vacuum, with #4 Whatman paper or equivalent. An example of this set-up is shown below in Figures 5 and 6. Gently re-suspend the resinate slurry with a pipette as shown in Figure 6.

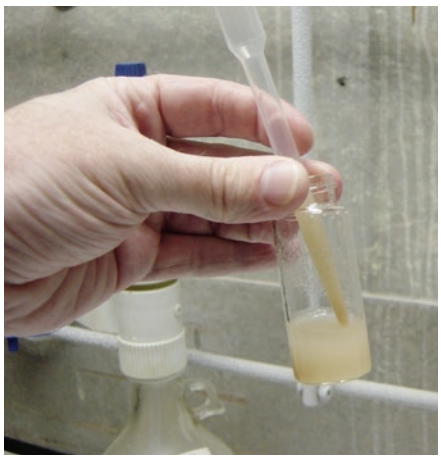

Figure 6 – Sample Resin Suspension

10. Transfer the suspension drop-wise into the center of the filter paper. It is important to mound the resin in the center, as shown in Figures 7 and 8. This will help prevent clogging of the filter.

Figure 7 – Begin Transfer of Resin to Filter Paper

Resination Process

Figure 8 – Continuation of Resin Transfer

11. Rinse the wet cake with DI water as shown in Figure 9, gently, allowing the washes to mix with the main filtrate. Rinse the vial used for the shake test with the DI water and pipette the rinse water onto the wet cake as shown below.

Figure 9 – Rinsing Vial and Wet Cake

12. Allow the wet cake to partially dry being careful not to allow it to dry completely. The wet cake should appear as in Figure 10 below.

Figure 10 – Rinsed Wet Cake

13. Remove the wet cake from the filter paper, as shown below in Figure 11, and measure the volume of the combined filtrate/wash. Record the volume.

Figure 11 – Removal of Wet Cake from Filter Paper

14. Transfer the wet cake to a suitable container (shown in Figure 12) and dry in a vacuum oven at a temperature that is acceptable to the API typically 40-70°C overnight.

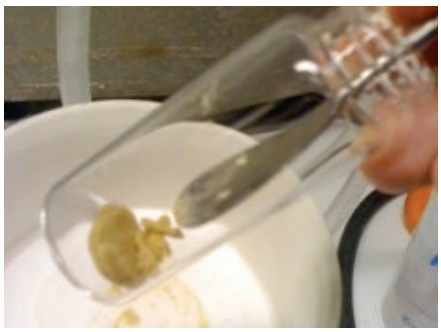

Figure 12 - Removal of the wet cake from the filter paper

15. Measure absorbance of the filtrate (combined supernatant and de-ionized water washings) at the desired wave-length of the API, and calculate the concentration of API in the solution. This is the 'unloaded' drug. The concentration of the API is equal to the absorbance of the filtrate divided by the standard curve slope (which should be determined from a prepared set of standards which are in the linear range of the detector).

16. Calculate the initial concentration of drug by the same method and units using a retained sample of the starting solution.

17. Drug Loading efficiency (%): 1-(conc of unloaded drug/conc of initial drug solution*100). The definitions and calculations for loading are shown in Table 2 and the appropriate reference data is presented in Table 3.

Resin Loading Determination

Table 2: Resin Loading Determination

Manual Calculation
Concentration of drug = UV dilution x UV absorbance / UV calibration slope
Wt not loaded = Conc unloaded x Volume of filtrates
Wt of pure drug = Wt of drug x Drug purity
Wt loaded = Wt of pure drug - Wt unloaded
Mol Loaded = Wt loaded/Drug MW
Loading efficiency = Wt loaded/Wt of pure drug
Wt of pure resin = Wt of resin x Resin % solids
Equiv of resin = Wt of pure resin x resin wt capacity x Conversion factor
% of capacity = Mol loaded/Equivs of resin
Wt gain = Mol loaded x (MW of drug ion — Atomic Weight (AW) of resin counterion)
Wt of resinate = Wt of pure resin + Wt gain
Loading = Wt loaded/Wt of resinate x100
% Recovery = Wt of dry resinate x (1- resinate LOD)/Wt of resinate)

Table 3: Reference Data

Resin	Amberlite™ IRP69	Amberlite™ IRP69H	Amberlite™ IRP88	Amberlite™ IRP88 H form	Amberlite™ IRP64	Duolite™ AP143
Resin Wt. Capacity	4.6	5.1	8.7	8.7	10.6	4.2
Atomic Weight of Counterion	23	1	39	1	1	35.5
Conversion Factor	100%	100%	69%	31%	100%	100%

Drug Assay Methods

Static Assay

Static assays will vary depending on each specific protocol for API analysis. Typically, as long as the procedure is conducted in a sufficiently large enough quantity of medium to allow for the API to unload from the resinate, it will be an acceptable assay technique. Common media for this is 0.1N HCl, 0.5N HCl: 0.5N NaCl (1:1 ratio), or USP phosphate buffer at pH 6.8. The addition of 20% organic solvent can improve the assay results.

Dynamic Assay

A dynamic assay is a technique used to evaluate and confirm drug loading calculations. It is a more representative to evaluate drug loading is since this procedure allows for all of the API to be removed from the resinate and prevents an equilibrium state that might be seen with the static assay.

Table 4: Assay Media for Basic Drugs

Resin	Drug Release	Assay Media	Flow Rate (mL/min)	Volume (mL)
Amberlite™ IRP64	Immediate	0.1N HCl	1.0	75
Amberlite™ IRP88	Immediate	0.1N HCl	1.0	75
Amberlite™ IRP69	Modified	0.5N HCl/ 0.5N NaCl	0.5	150

Procedure

A flow through system can be easily set up using a small column that allows for a liquid to flow through a small bed of resin. A small sample of resinate can be placed in the column (50-100mg). A solution from Table 4 below can be chosen to pump through the column to allow for the drug to be removed in a continuous mode at a flow rate of 0.5-1.0mL/min for a total of 75-150mLs to be collected for analysis. Fractions can be taken during development to determine the volume needed to complete the testing. Results should be compared to the calculated figures and good agreement should be observed. The requirements for complete release are as follows:

a. The majority of the API is contained in the first few fractions.

b. The last fraction contains essentially no API.

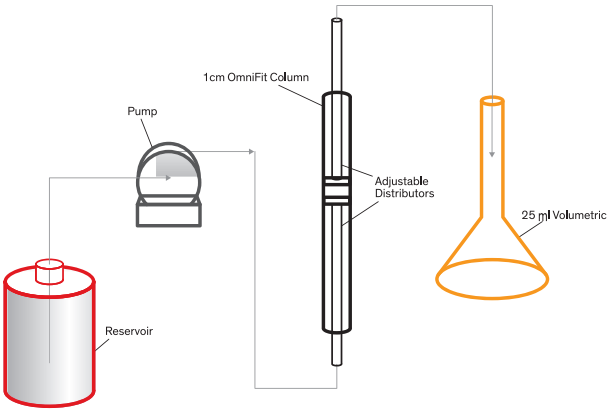

Figure 13 – Dynamic Assay Equipment Schematic

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