

Investigation of Ion Exchange Resin Concentration, Particle Size and Process Temperature for Dextromethorphan HBr Complexation

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Purpose

Ion exchange resins are crosslinked water insoluble polymers with ionizable functional groups, they are commonly used for taste-masking and controlled drug release applications in liquid formulations. Exchange of counterions, between solutions of ionizable drugs and acidic or basic functional sites of the resin, allows reversible drug-resin complex formation and loading of drug onto resin sites.^{1,2} The drug-resin complex remains intact in the mouth leading to successful taste-masking, while the presence of ions and pH changes in the GI tract leads to release of drug from the resin complex. In this investigation, complexation of dextromethorphan HBr using a strong cationic sodium polystyrene sulfonate resin known as AMBERLITE™ Ion Exchange Resin (IER) (The Dow Chemical Company, USA) was explored. The influence of particle size and concentration of the resin as well as process temperature on drug loading rate and efficiency were evaluated.

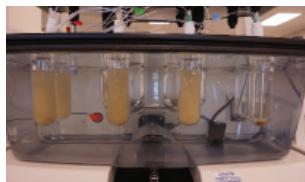
Methods

Preparation of Drug Loaded Resin

A dissolution apparatus (Hansen Research, USA) equipped with small volume (150 mL) dissolution vessels (Figure 1) was utilized to accomplish and continuously monitor the process of drug loading on the resin (resination) and to investigate the effect of temperature on the process. Dextromethorphan HBr was dissolved in DI water to prepare a 1% w/v drug solution. Two particle size grades of AMBERLITE™, IRP 69 ($d_{50}=60\ \mu\text{m}$), and IRP 476 ($d_{50}=125\ \mu\text{m}$) were dispersed into 150 mL of drug solution at 1:1, 1:2 and 1:3 w/w drug to resin ratios.

The drug-resin suspension was kept under constant stirring at 22°C or 37°C for 20 hrs, with samples withdrawn periodically to determine free drug concentration using a UV spectrophotometer at 278 nm. After 20 hrs of mixing, the suspension was filtered using a Buchner funnel and vacuum filtration assembly. The drug-loaded resins were dried in a vacuum oven at 60°C for 24 hrs.

Figure 1: (a) Small Volume Dissolution Bath Set Up



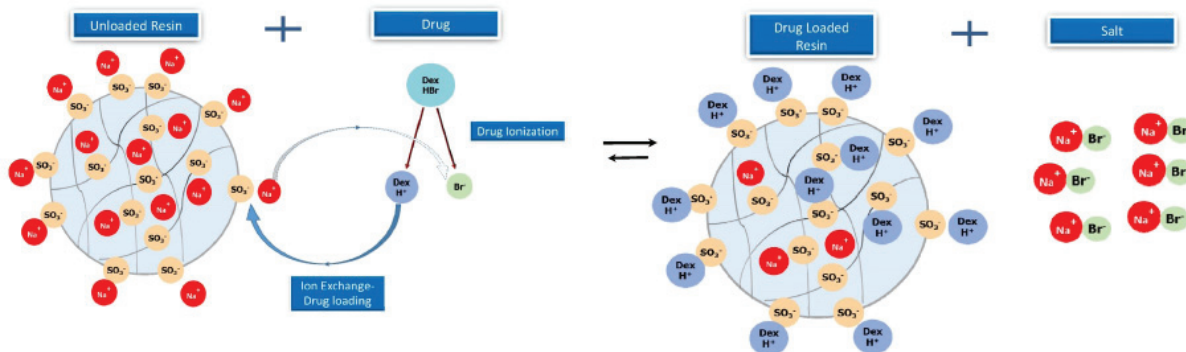
b) Small Vessel and Stirrer



Results

An illustration of the ion exchange drug loading process between dextromethorphan HBr and AMBERLITE™ IER is shown in Figure 2. In this process, the exchangeable sodium ions from the cationic resin structure are displaced by positively charged drug ions, initially at the resin surface and progressively from the resin core. Displaced sodium ions from the resin molecule associate with the negative charged bromide ions from the drug molecule to form a NaBr salt by-product.

Figure 2: Ion Exchange Process: Dextromethorphan HBr and AMBERLITE™ Resin



Effect of IER Particle Size and Concentration

Figure 3 shows the particle size distribution of the two grades of ion exchange resins, AMBERLITE™ IRP 69 and IRP 476 used in this study.

The finer particle size AMBERLITE™ IRP 69 resin provided a faster drug loading rate compared to the coarser AMBERLITE™ IRP 476 resin. For example, at 1:1 w/w drug to resin ratio, IRP 69 resulted in 78% of drug loading, compared to 53% with IRP 476 after 20 hrs (Figure 4). Finer particle size of the resin may provide more surface area and easier access to the exchangeable sites for the drug molecule, enabling faster drug loading rate.

Use of higher resin concentration increased the number of reaction sites and significantly improved the drug loading efficiency to 97% w/w (at 1:2 drug to resin ratio) and 98% w/w (at 1:3 drug to resin ratio). Additionally, faster drug loading rates and shorter process times were observed at higher resin concentrations (Figures 5 and 6).

Figure 3: IER AMBERLITE™ IRP 69 and 476 Particle Size Comparison

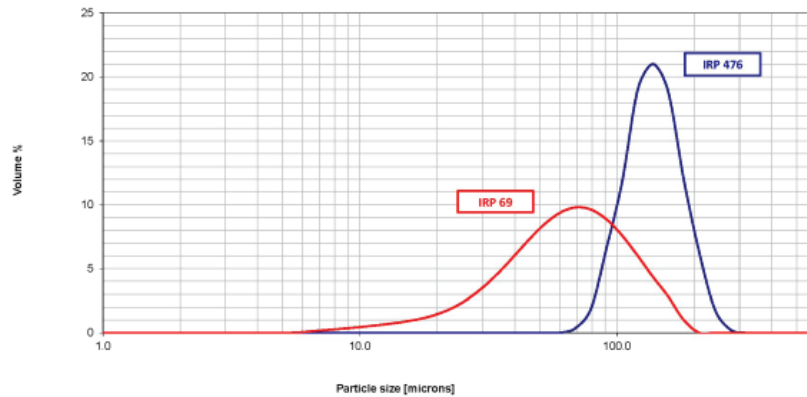


Figure 4: Dextromethorphan HBr Loading on AMBERLITE™ IRP 69 and IRP 476 at 1:1 w/w Ratio and Room Temperature (22°C)

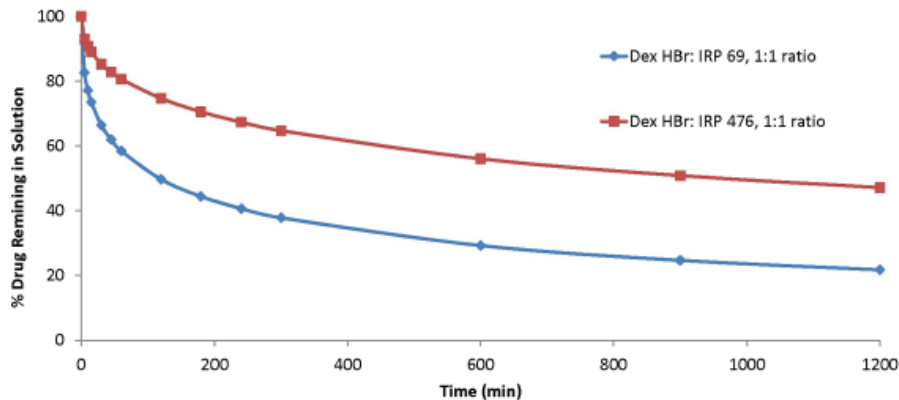


Figure 5: Dextromethorphan HBr Loading on AMBERLITE™ IRP 69 and IRP 476 at 1:2 w/w Ratio and Room Temperature (22°C)

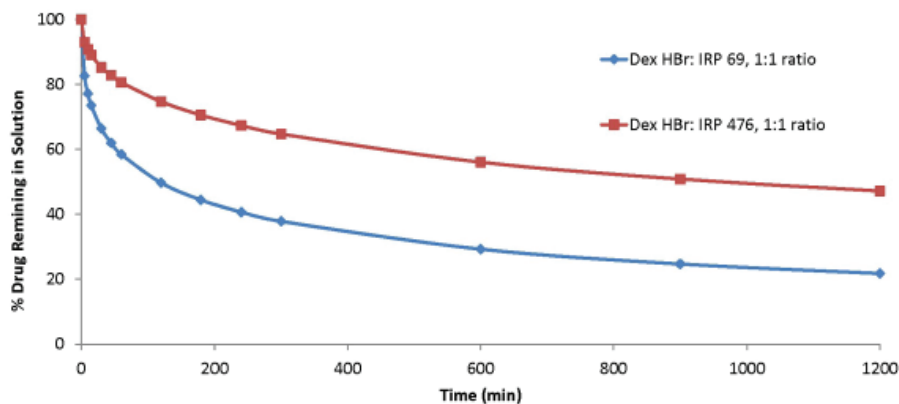
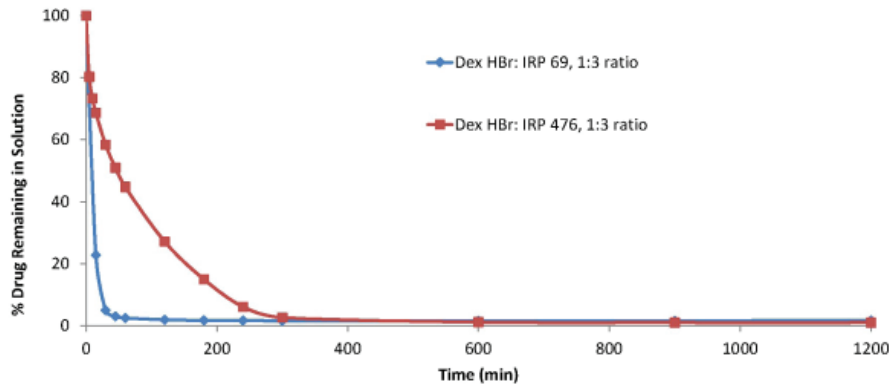


Figure 6: Dextromethorphan HBr Loading on AMBERLITE™ IRP 69 and IRP 476 at 1:3 w/w Ratio and Room Temperature (22°C)



Effect of Elevated Process Temperature

AMBERLITE™ IRP 69 (Fine Particle Size Grade)

At elevated temperature (37°C), faster drug loading process was observed, enabling shorter equilibrium time for drug-resin complexation at 1:1 w/w drug to resin ratio (Figure 7). However, use of high process temperature did not significantly reduce the drug loading time at 1:2 and 1:3 w/w drug to resin ratio (Figure 8).

AMBERLITE™ IRP 476 (Coarse Particle Size Grade)

Faster drug loading rate at elevated process temperature was observed for the coarse particle size grade Amberlite™ IRP 476 (Figure 9). Unlike IRP 69, use of elevated process temperature provided significant drug loading time reduction at higher drug to resin ratios (Figure 10).

Use of elevated process temperatures resulted in higher kinetic energy of drug molecules, allowing faster diffusion of the molecules from drug solution to the resin sites for the ion exchange process. Additionally, higher kinetic energy of the drug molecules at elevated temperature may increase the collision frequency of counterions to favor a faster loading rate.

Figure 7: Effect of Process Temperature on Dextromethorphan HBr Loading on AMBERLITE™ IRP 69 at 1:1 w/w Drug to Resin Ratio

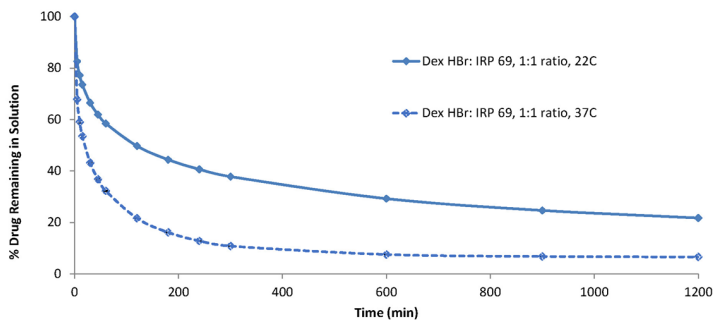


Figure 8: Effect of Process Temperature on Dextromethorphan HBr Loading on AMBERLITE™ IRP 69 at 1:2 and 1:3 w/w Drug to Resin Ratio

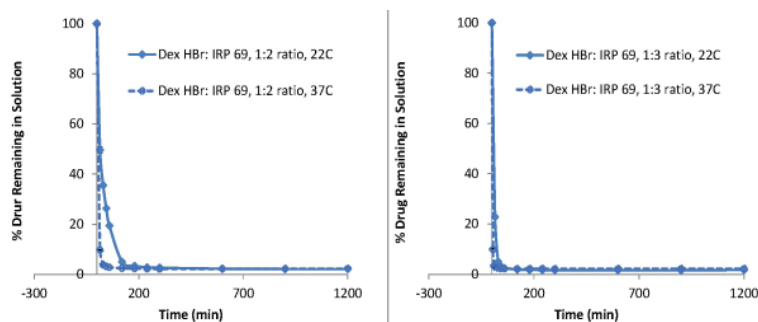


Figure 9: Effect of Process Temperature on Dextromethorphan HBr Loading on AMBERLITE™ IRP 476 at 1:1 w/w Drug to Resin Ratio

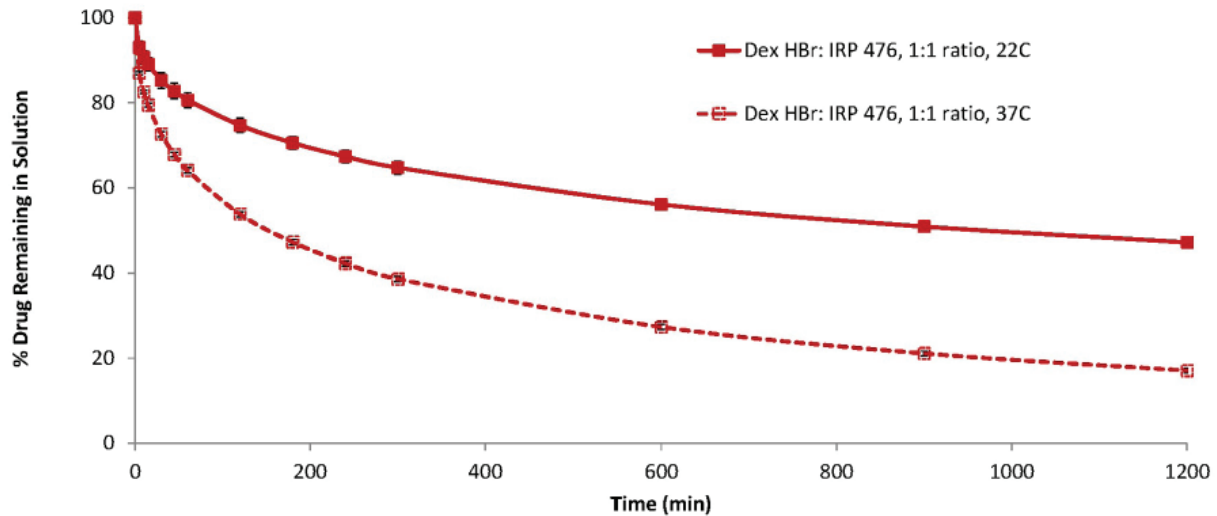
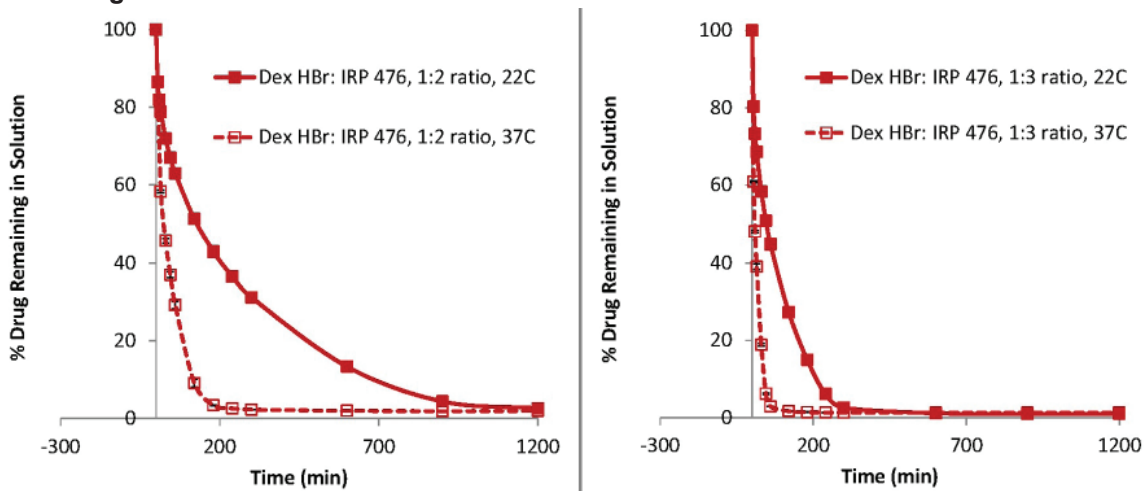


Figure 10: Effect of Process Temperature on Dextromethorphan HBr Loading on AMBERLITE™ IRP 476 at 1:2 and 1:3 w/w Drug to Resin Ratio



Conclusions

A streamlined, fast and efficient method for screening of ion exchange resins (AMBERLITE™) type and concentration for dextromethorphan HBr was developed, and their resinates successfully produced. Higher concentration of resin and selection of finer particle size of ion exchange resin provided a significant reduction of the drug loading time and better drug loading efficiency. Conducting the resination process at 37°C further reduced drug loading times which may be attributed to faster diffusion and ion exchange reaction rate.

References

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2. Kumar S, Jain S, "History, Introduction and Kinetics of Ion Exchange Materials," *Journal of Chemistry*, vol. 2013, Article ID 957647, 13 pages, 2013.

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