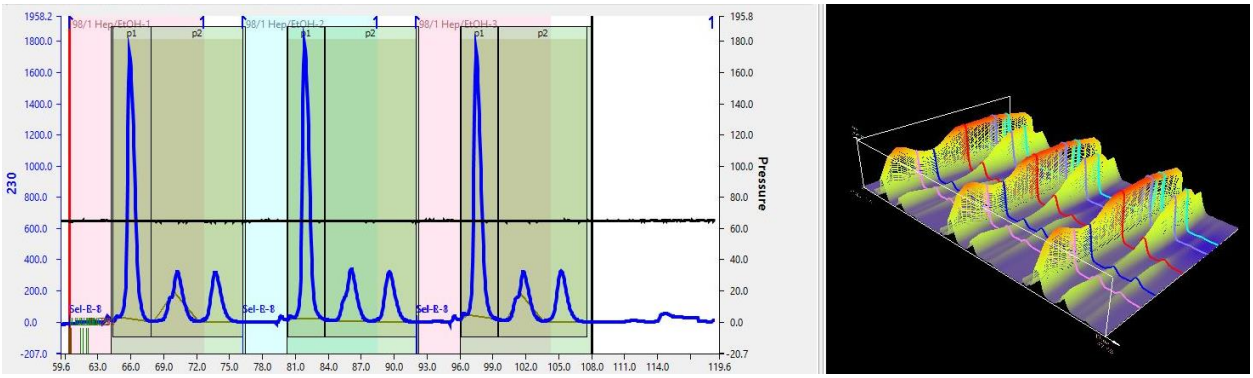
AutoMDS Systems (Automated Method Development)

PDR started developing AutoMDS and AutoPrep Software in 1998. PDR previously had developed the ALP (Advanced Laser Polarimeter), was operating a fast-pace contract purification service, and was unhappy with available software. PDR needed walk-away automation for method development and preparative purification to rapidly purify previously unknown compounds for big-pharma in the range of 1-1000 grams. PDR still continue aggressive development and improvement of AutoMDS and AutoPrep software. AutoMDS can run continuously without attention; assuming adequate solvent, waste, and sample solution. AutoMDS features include the following.

1. **Methods and sequences only contain chromatographic parameters** so all systems have same user interface whether analytical method development or larger-scale preparative purification. Our device drivers translate chromatographic parameters into device-specific commands. Methods, sequences, and user interface are independent of hardware idiosyncrasies. For example, HPLC and CCC/CPC applications have the same user interface, but much different methods.
2. **Each method can have multiple unique cycles** and each method and/or cycle can be repeated many times. For example, a CCC/CPC method usually contains 3 or 4 different cycles pumping different solutions at different flow rates and the method is repeated many times. Whereas an HPLC preparative purification method usually contains a single cycle repeated many times. Repeating a cycle is continuous, does not restart the method, and allows overlapping (stacking) of injections.
3. **Method Development and Preparative Purification software are identical**, except for configuration settings. User interface is consistent and software upgrades apply to all products. Software is modular so new features and improvements can be released often and upgrades are very easy to apply.
4. **Parameters can be changed during a run**. You can start a preparative purification run with conservative injection volume and injection spacing (stacking), then increase injection volume and reduce injection spacing to improve productivity as the system equilibrates and results are clear. This helps improve productivity in purification jobs requiring many injections and high purity. Stopping a run only to change parameters is never required.
5. **Peak collection decisions** can be made in real-time using derivative (slope) and +/- sign of DALP derivative, rather than time. Time works OK if elutions are stable, but peak derivative collections follow shifting or changing peaks accurately. This can be very important to purity and recovery during long-running purifications by compensating for minor changes in eluent and sample solution.
6. **Method and Sequence Editors** use a spreadsheet format that is very good for building, editing and monitoring methods and sequences.
7. **Repeats/Runtime** display clearly shows job progress and end times helping you schedule liquid management, other activities, and following jobs.

Repeats/Runtime			
Methods: waiting/done	9 /		2
Cycles: waiting/active/done	1 /	1 /	1
Minutes: done/remaining	12.02 /		9.48
Expected method end time:	Oct 11, 2022 3:16:24 PM		
Expected run end time:	Oct 11, 2022 6:30:41 PM		

8. **Realtime 2D and 3D Plots** show detector data in real time continuously.



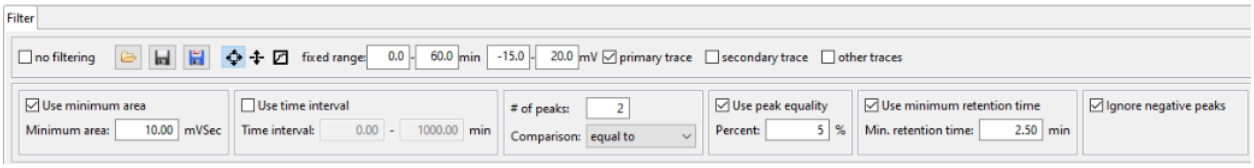
AutoPrep Example from 2019 job at PDR

AutoMDS:

AutoMDS is the ideal program for automated method development. Method and sequence editors use simple spread-sheet format making it easy to build, edit, and use large method screening sequences. An AutoMDS installation includes methods and sequences specifically built for your applications.

- Easily Write, Edit, and Run Methods and Large Sequences
- Single Keyboard Control of up to 88 Columns - including tandem configurations - and Random Gradient Mixing from up to 20 Solvent Bottles
- Supports 24/7 Continuous Unattended Operation
- Calculates Specific Rotation, Enantiomeric Excess, and a full-set of Achiral Chromatographic Parameters
- Sequences and Methods are Included for your applications

Data Processing Tool (DPT), see snip below, filters chromatograms based on area, time, number of peaks, peak equality (e.g., in chiral separations), etc. Thus, avoiding the necessity to review all chromatograms in a method screening sequence. Proper DPT searches usually return only a few methods for final consideration.



Data Processing Tool (DPT)

Methods should be selected for optimization based on intended application. Analytical applications are usually different from preparative purification applications. For example, additives are often used in analytical methods but are not desirable in preparative purification methods because the additive may be difficult to remove.

Method Optimization Considerations:

- Separation
- Elution Order (target peak should be first)
- Impurities
- Solubility in Eluent
- Stability in Eluent
- Recovery from Eluent (additives can be difficult to remove in preparative purification)
- Availability and/or cost of Solvents

Multi solvent bottle gradients (more than binary) can be used to maintain constant eluent additive concentration without requiring additive to be in every solvent bottle, see example in Gradient Mixer section below. For example, if all gradients are run against Hexane, then solvents could include 3 bottles with Hexane, one neutral, one with acid additive, and one with base additive. The 2 additive bottles would be mixed, for example, at 20 times the intended eluent concentration. As long as each method is run with a constant of 5% from the bottle containing Hexane + additive in the eluent, each eluent will maintain proper additive concentration without needing to put additive in all bottles. This technique allows us to screen a wide variety of normal, reverse, and polar organic phase eluents with neutral, acid, or base additives using only 20 bottles total. To avoid column + additive memory effects we often load column selectors with 3 sets of the same column, one for neutral, acid, and base eluents. This means we do not need to spend time equilibrating our columns because of eluent additive changes.

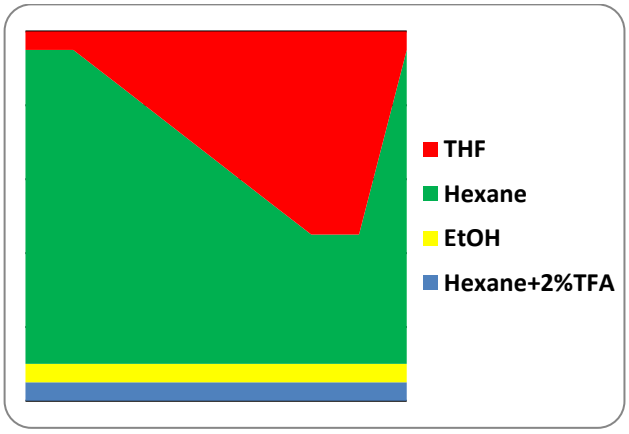
Gradient Mixer:

The PDR Gradient Mixer can proportion from 10 or 20 solvent bottles to create any requested mixture. Solenoid valves are microprocessor controlled and valves can be changed individually. We also have a valve control module that can control any type valve (electrical, pneumatic, etc.) for larger flows.

Multi solvent bottle gradients (more than binary) can be used to maintain constant eluent additive concentration without requiring additive to be in every solvent bottle. For example, to run gradients against Hexane mix 1 bottle of Hexane with additive at 20 times desired final additive concentration and run at constant 5%. Along with this 5% with additive, proportion Hexane and desired modifiers to make up the remaining 95%. Additive is only required in 1 bottle. See figure below on right. This technique permits screening a wide variety of normal, reverse, and polar organic phase eluents with neutral, acid, or base additives using 20 bottles total.

If using additives, it may be best to avoid column + additive memory effects by loading column selector with columns dedicated to a specific additive. Otherwise it takes time to wash additives from columns before next use. Larger labs with multiple systems usually dedicate different systems to different additives.

Gradient Mixer: 10w x 6h x 12d inches, 100-240 VAC, 50-60 Hz

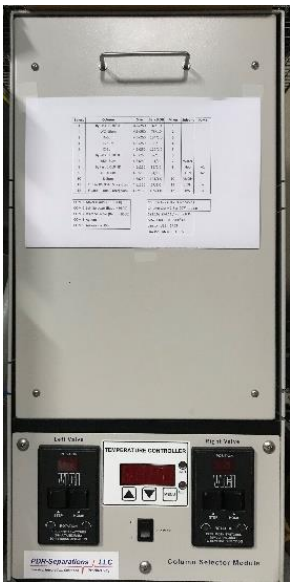


Gradient Profile using Additive in only 1 Bottle

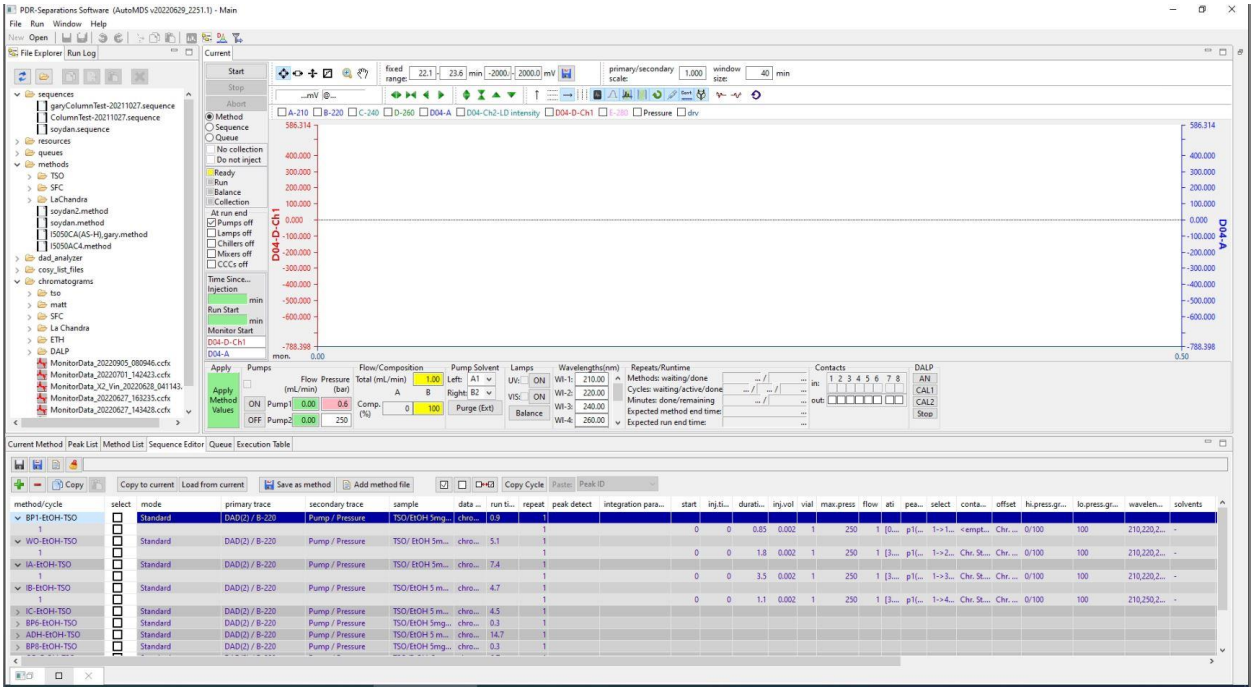
Column Selector:

Column Selector available with one or two valves, various port sizes, and with or without heat/cool. Pull door handle to release magnetic latches and set-aside door during column changes. Pull-out upper manifold for easy access to columns. Typically shipped with 0.010" ports and 2 valves each with 12 column positions for a total of 24 column positions. Other valves and port sizes are available. We usually plumb valve position 1 of each valve with bypass tubing for fast flushing during eluent composition changes, resulting in 22 useful column positions.

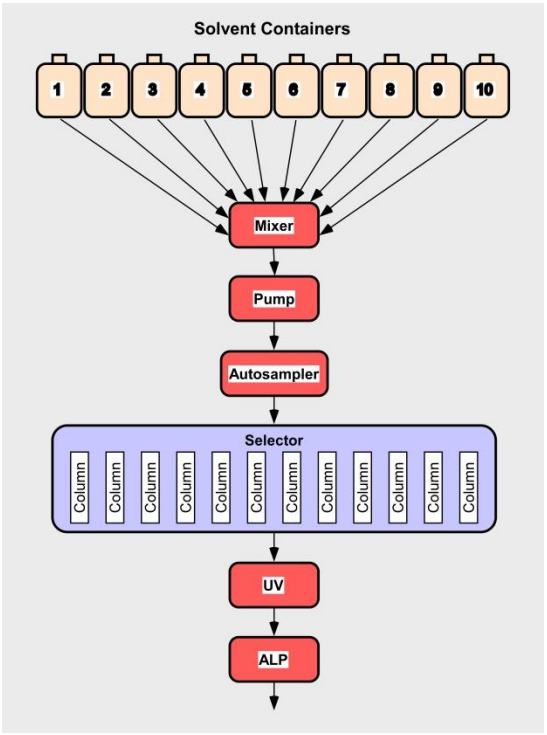
10w x 21h x 12d inches
100-240 VAC, 50-60 Hz



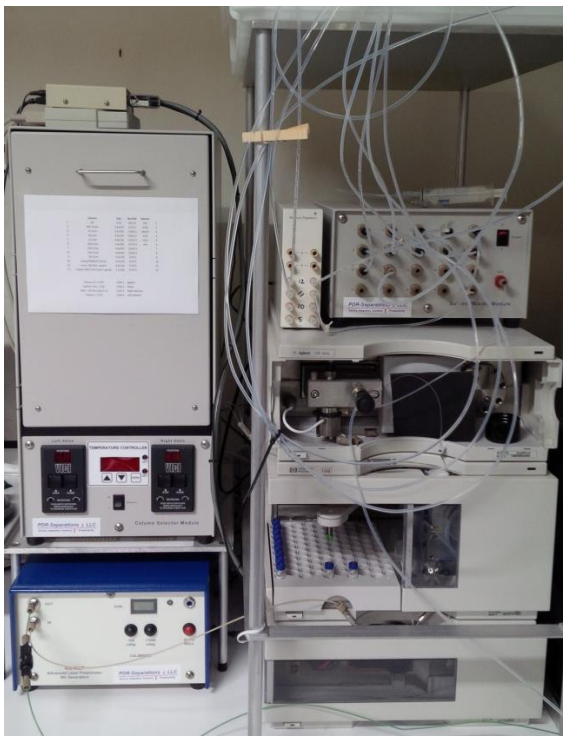
AutoMDS Examples:



7 – AutoMDS



Method Development Plumbing



AutoMDS on Agilent with ALP, 20 bottles/24 columns

AutoMDS on Agilent with old-style column selectors: 10 bottles/12 columns HILIC on left; and 10 bottles/24 columns Chiral on right with one column selector for neutral and the other for acid additives.

3 – AutoMDS & AutoPrep on Analytical/Semi-Prep CCC.