NOVEL POROUS RESINS WITH DUAL ION-EXCHANGE/REVERSED-PHASE RETENTION BEHAVIOR

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Introduction

In 1996, Waters designed and commercialized the Oasis® HLB sorbent, a water-wettable copolymer with hydrophilic-lipophilic balance (HLB) for SPE. Unique in its ability to retain both polar and non-polar compounds and their metabolites, with high reproducibility and recovery, Oasis® HLB sorbent has set the new standard for SPE. In order to meet the demand for extraction of basic or acidic drugs, Oasis® MCX, a new member of the Oasis® family has been developed. It has exhibited high selectivity and sensitivity for extracting basic drugs. Furthermore, Oasis® MAX for acidic drugs is also being developed.

Oasis® MCX and MAX are brand new porous resins having a hydrophobic fragment, a hydrophilic polar moiety, and an ion-exchange functional group. In this paper, we would like to discuss their synthesis, selectivity, reproducibility and recovery. In addition, an example of using Oasis® MCX as a universal sorbent for isolating acidic, basic, and neutral drugs will be reported.

Synthesis Strategy

Selecting a suitable matrix for surface derivation

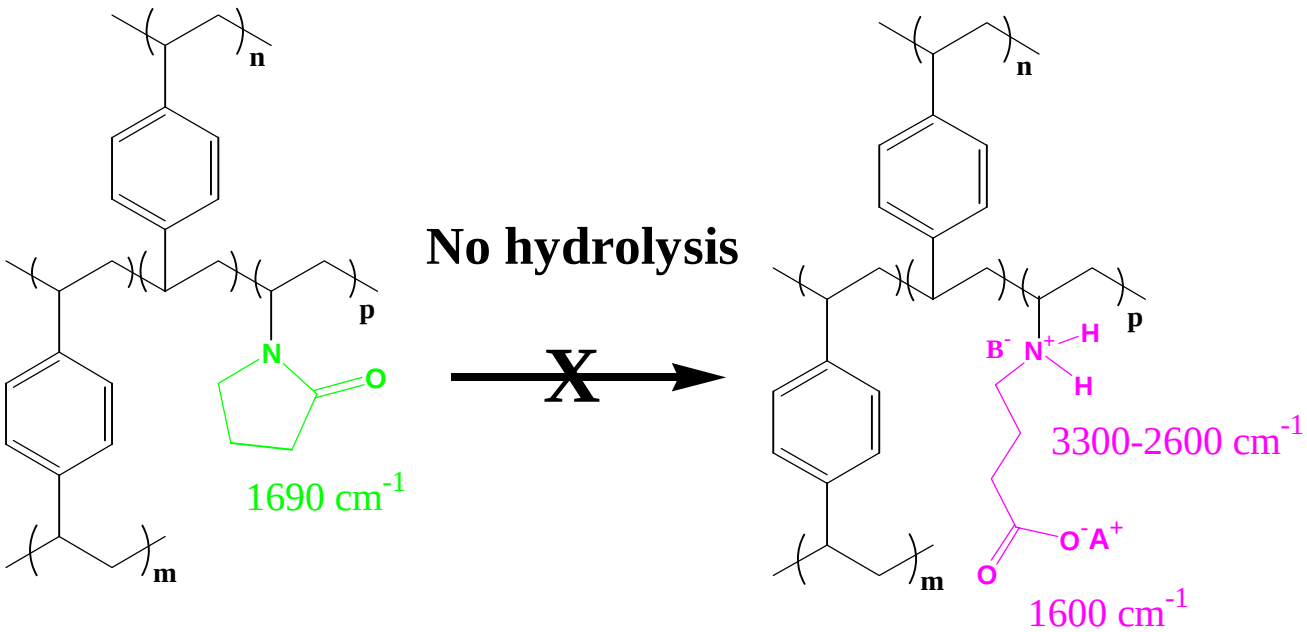
Disadvantage of silica matrix:

- Undesirable silanol activity
- pH limitations
- Low capacity
- Hydrophobic collapse

Advantage of Oasis® HLB sorbent:

- Porous poly(divinylbenzene-co-N-vinylpyrrolidone) resin with excellent chemical stability.
- Rigid porous resin with high surface area which provides better mechanical stability and binding capacity than that of conventional poly(styrene-co-divinylbenzene) resins.
- One of the cleanest sorbents available in the market.
- Hydrophilic-lipophilic balanced sorbent, surface modification by sulfonation, chloromethylation, and amination can be conducted without using halogenated or organic solvents.

Stability of Oasis® HLB Sorbent



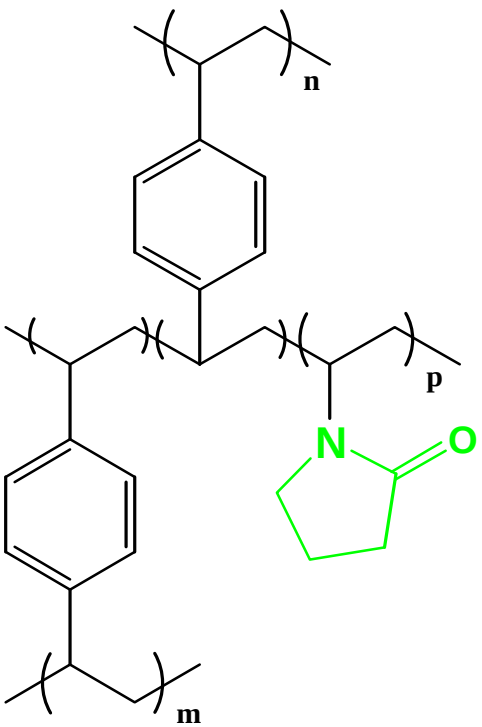
Oasis® HLB **zwitterion**

No indication of hydrolysis of Oasis® HLB

Oasis® HLB has a five member ring amide moiety. Surprisingly, no zwitterion was detected by FTIR after Oasis® HLB was treated under the following severe conditions:

- 140 °C in 20% KOH solution overnight
- 95 °C in 10% HCl solution overnight
- 120 °C in conc. Sulfuric acid for 23 hours

Characteristics of Oasis® HLB Sorbent

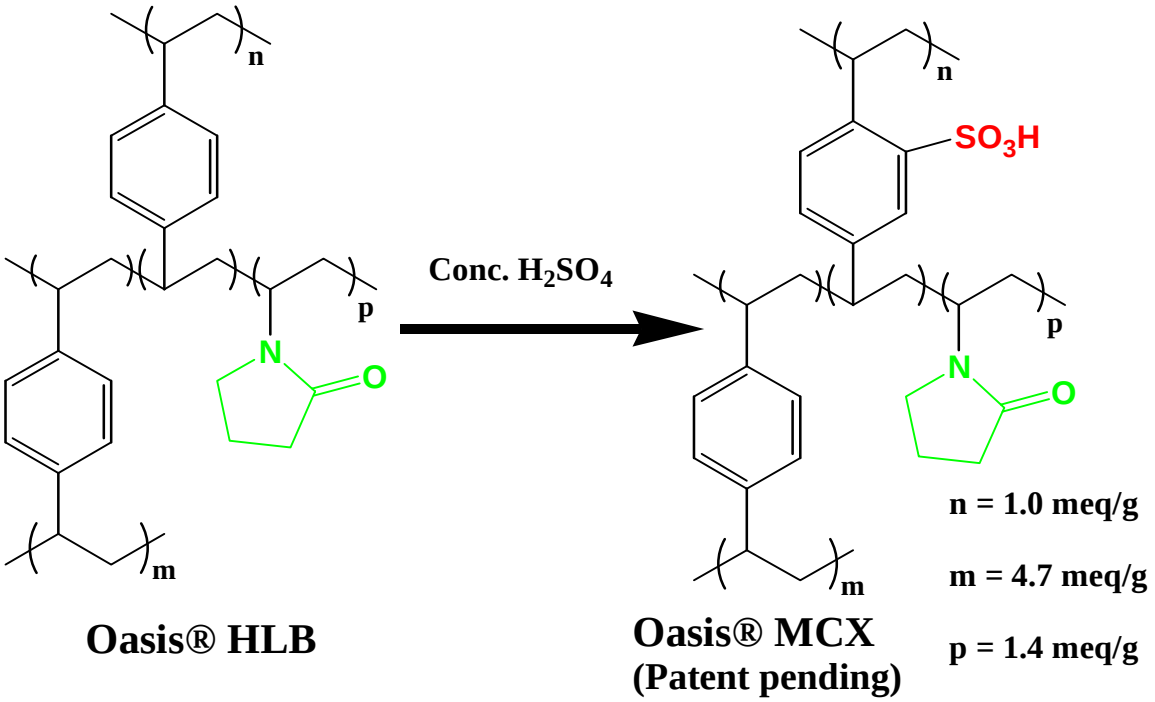


Oasis® HLB

Specific Surface Area:	**810 m^2/g**
Average Pore Diameter:	**80 Å**
Total Pore Volume:	**1.3 cm^3/g**
Mean Particle Diameter:	**30 µm**
Percent Fines < 10 µm:	**0.1%**
Pyrrolidone:	**20%**
Cross-linked:	**> 30%**

- Waters Oasis® HLB sorbent is patented (US 5,882,521).
- Having greater than 30% cross-linking, which is about 2 to 10 times higher than that of conventional poly(styrene-co-divinylbenzene) resins.
- A highly clean sorbent purified by Waters proprietary processes after suspension polymerization.

Synthesis of Oasis® MCX Sorbent



Oasis® HLB

Oasis® MCX
(Patent pending)

- Oasis® MCX is prepared by treating Oasis® HLB in conc. H_2SO_4 at 25°C for 1 hour, which is a very environmentally friendly process. Whereas, conventional poly(styrene-co-divinylbenzene) ion-exchange resins are prepared at high temperature with halogenated or organic solvents.
- Since Oasis® MCX is prepared at low temperature without using solvents, no contaminants are generated during the sulfonation.
- Cleanliness test of Oasis® MCX shows the extractable components less than 6 µg/g, which is as clean as Oasis® HLB.
- Oasis® MCX is a unique porous resin with a hydrophobic fragment, a hydrophilic polar moiety, and an ion-exchange functional group.[1]

Development of Synthesis Process

Ruggedness and robustness

Factorial experiment design was used to study the following synthesis variables:

- Components of sulfonation reactants
- Concentration of reagents
- Temperature of reaction (-30 °C to 120 °C)
- Reaction time (1 minute to 24 hour)

Summarizing from the above studies, a synthesis process with only two variables is developed and their relations are as follows:

Degree of sulfonation (ion-exchange capacity, meq/g of $-SO_3H$)

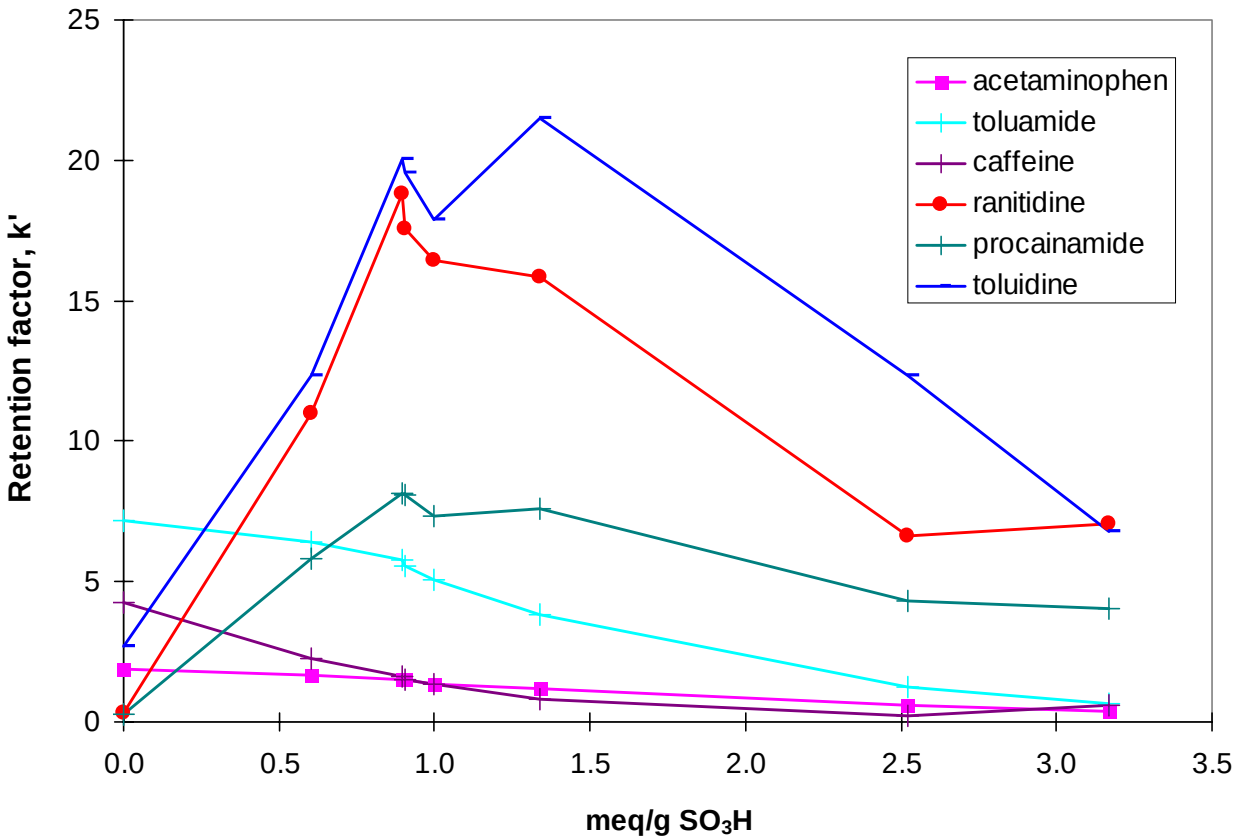
= 0.53 meq/g + 0.018 meq/g °C x (temp. °C) + 0.017 meq/g h x (time, h); R^2 =0.996

- It will take more than 5 °C or 5 hours variation to have about 10% change in ion-exchange capacity (1.0 meq/g of $-SO_3H$) of Oasis® MCX sorbent.

- During the product development, twelve different batches were prepared with reactors ranging from 0.5 L to 80 L by several people in different locations. The $-SO_3H$ loading was 0.98 meq/g, σ = 0.05 meq/g.

Why Oasis® MCX Sorbent has 1.0 meq/g of Cation-Exchange Capacity?

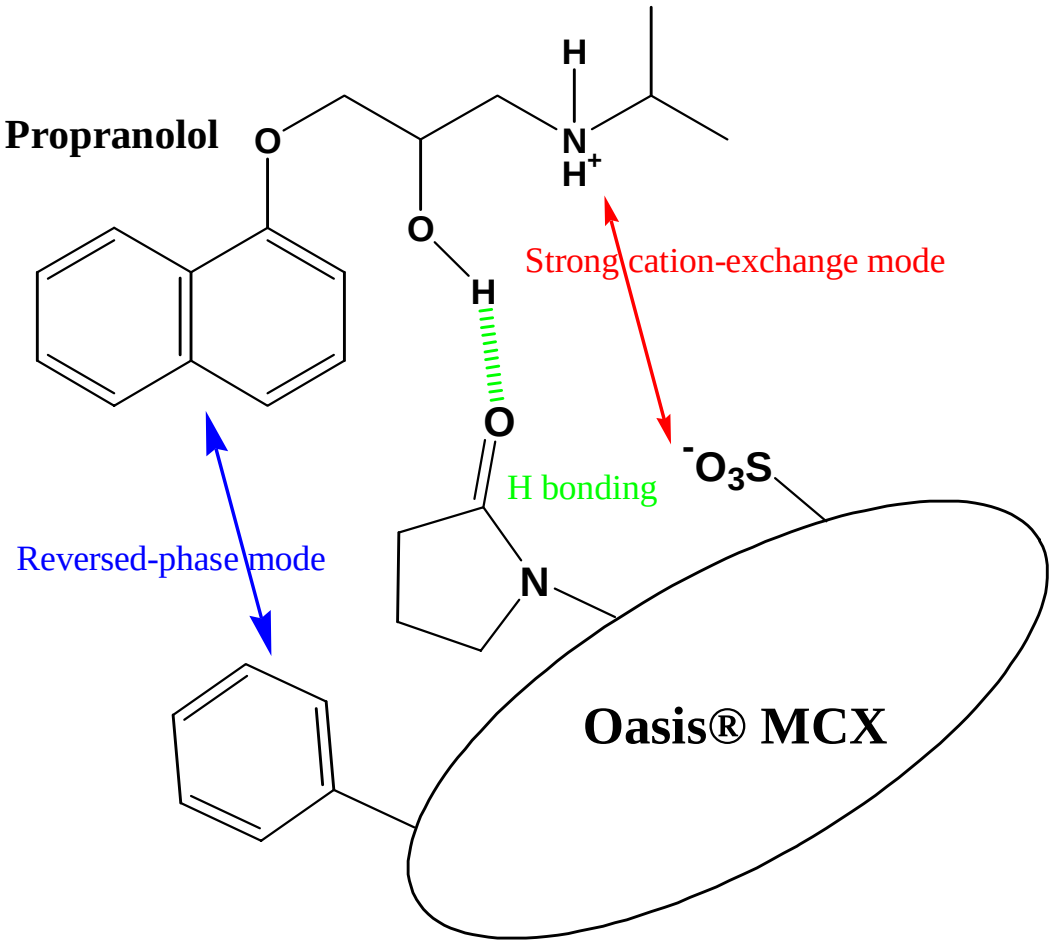
Effect of ion-exchange capacity on retention behavior



- Prototypes ranging from 0 to 3.2 meq/g of -SO_3H were packed in HPLC columns to study the retention of neutral and basic analytes. Neutral compounds' retention decreases greatly when sulfonation is above 1 meq/g. Basic compounds' retention increases when sulfonation is increased to about 1 meq/g. However, retention decreases at higher levels of sulfonation.[2]

- At 1.0 meq/g sulfonation, Oasis® MCX has both maximum ion-exchange and hydrophobic retention capabilities enabling the retention of acidic, neutral and basic drugs.

Drug- Sorbent Interactions



- The strong acid sulfonate (-SO_3H) groups on the polymer interact with basic and cationic solutes.
- The amide groups enable the resin to have polar interactions and hydrogen bonding capabilities with polar analytes.
- The hydrophobic fragments of divinylbenzene and vinylpyrrolidone enable the affinity towards nonpolar substances through hydrophobic interaction.

Extraction of Basic Drugs on Oasis® MCX Cartridges

Basic drugs[4]	Conc. (µg/mL)	% Recovery	% RSD
Methadone	**0.01**	**100**	**2.7**
Methadone metabolite	**0.04**	**98**	**1.0**
Estazolam	**0.2**	**97**	**1.5**
Propranolol	**0.08**	**100**	**2.7**
Oxprenolol	**0.08**	**92**	**3.2**
Metoprolol	**0.08**	**100**	**3.4**
Verapamil	**4.5**	**100**	**0.2**
Nor-Verapamil	**3.4**	**98**	**0.5**
Verapamil-Methoxy	**6.7**	**100**	**3.3**
Codeine	**0.12**	**99**	**1.2**
Codeine (metabolite)	**0.12**	**100**	**1.5**
Ranitidine	**0.24**	**93**	**2.6**

Generic Oasis® MCX method for extraction of basic drugs from human urine: [3]

- Load 3 ml spiked and acidified urine into a cartridge
- Wash with 2 mL of 0.1N HCl
- Wash 3 or 4 times with 2 mL of methanol
- Elute with 2 mL of 5% ammonium hydroxide in methanol
- Evaporate and reconstitute in 300 µL of 20% methanol

Without preconditioning Oasis® MCX cartridges, routine recoveries greater than 85% with RSDs less than 5% can be achieved across a broad range of basic drugs.[3]

Fractionation with Oasis® MCX Cartridges

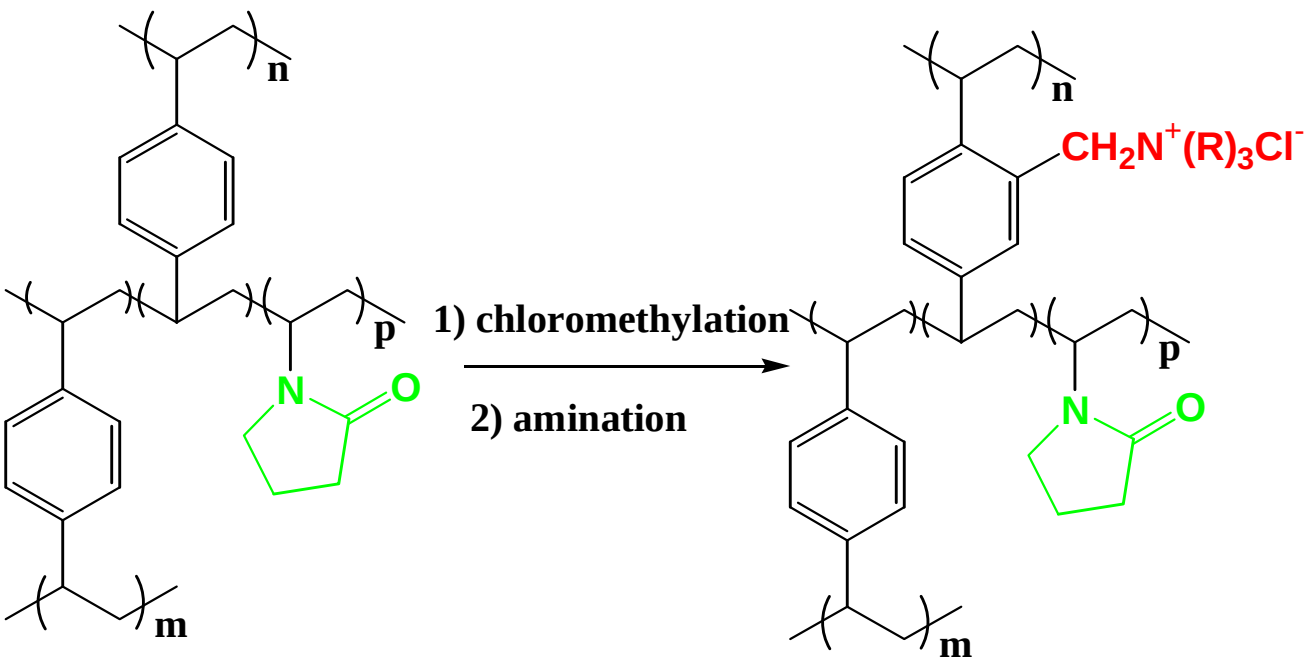
Drugs[4]	Conc. (µg/mL)	Fraction	% Recovery	% RSD
Acetaminophen (neutral drug)	2	Elute A	100	0.6
Barbital (weak acid drug)	2	Elute A	98	1
Amphetamine (basic drug)	4	Elute B	96	1
Methamphetamine (basic drug)	4	Elute B	90	4

Generic Oasis® MCX method for extractions of neutral, acidic, and basic drugs from plasma: [3]

- Equilibrate cartridges with 1 mL methanol/1 mL water
- Load 1 ml spiked and acidified plasma into a cartridge
- Wash with 1 mL of 0.1N HCl
- Elute A: with 1 mL methanol
- Elute B: with 1 mL of 5% ammonium hydroxide in methanol
- Evaporate and reconstitute

Oasis® MCX fractionated samples into the combined acidic and neutral drug fraction (Elute A) and a basic drug fraction (Elute B) with high recovery.

Synthesis of Oasis® MAX Sorbent



Oasis® HLB

Oasis® MAX
(Patent pending)

- Designed to be a mixed-mode anion exchange/reversed-phase sorbent capable of retention of acidic, neutral and basic compounds and with high selectivity to cleanup acidic drugs.
- Prepared through an environmentally friendly process without halogenated or organic solvents.
- Currently in the ruggedness and robustness testing stage at Waters' ISO 9002-certified plant under cGMP standard and available soon.

References

1. Jeng-Jong Lee, John O'Gara, "*Novel Sulfonated Porous Resins for Solid Phase Extraction and Chromatography*" U. S. Patent Application filed on June 12, 1998.

2. James S. Fritz reported similar effect on sulfonated polystyrene-divinylbenzene resins; Chambers, T. K.; Fritz, J. S.; *Journal of Chromatography A*, 797 (**1998**) 139-147.

3. *Oasis® Sample Extraction Products Applications Notebook*, ©1999 Waters Corporation, Literature WN047.

4. Structure of analytes: