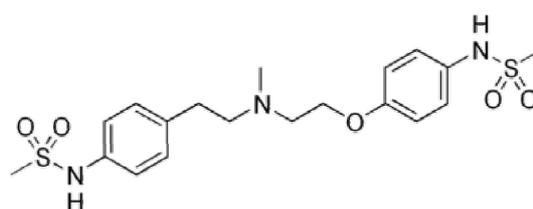


Dofetilide and Related Substances (USP)



Dofetilide

Dofetilide is a class III antiarrhythmic agent. It is marketed under the trade name Tikosyn. Due to the pro-arrhythmic potential, it is only available by prescription by physicians who have undergone specific training in the risks of treatment with dofetilide.

The current USP monograph method for Dofetilide and related substances specifies the use of a 150x3.9 mm column with L1 (ODS or RP-18) packing having 5 μ m particle size. System suitability requirements; a resolution of NLT 5.0 between dofetilide and dofetilide related compound A; a column efficiency of NLT 35,000 theoretical plates for the dofetilide peak; and with a tailing factor of NMT 1.5 for the dofetilide peak (using the system suitability solution).

We have redeveloped this monograph method using a monolithic Chromolith® HighResolution RP-18 endcapped column and the following pages illustrate that the all acceptance criteria are being met and the new method provide excellent performance at very low system pressure.

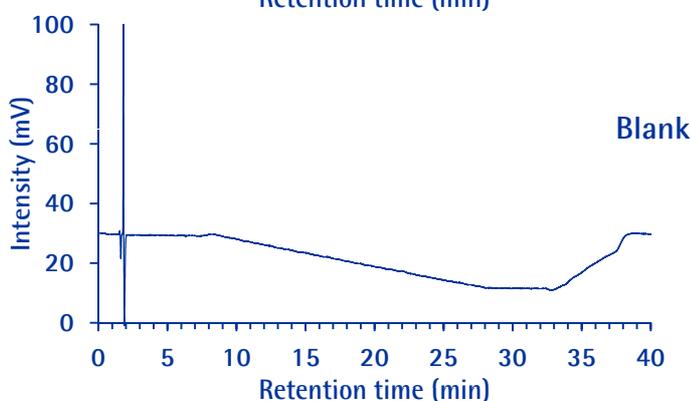
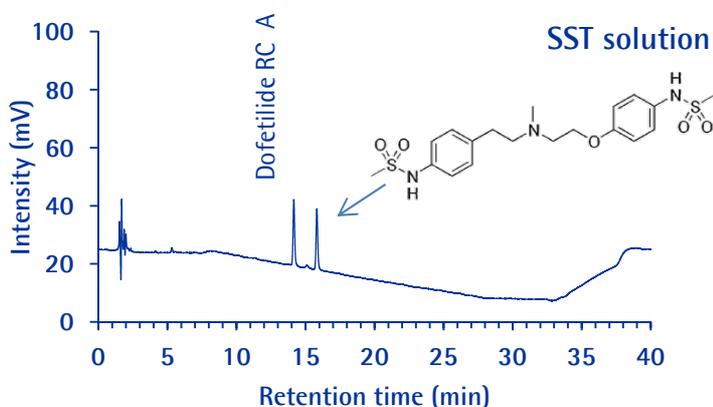
Using a monolithic column over a particulate counterpart, additional column life-time can be expected due to the more robust stationary phase backbone. In addition, a monolithic column exhibit lower backpressure and thus less wear on HPLC system (extra safety and lower maintenance cost). In summary, this means an overall lower cost per analysis.

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Chromolith® HighResolution RP-18 endcapped

Chromatographic Conditions

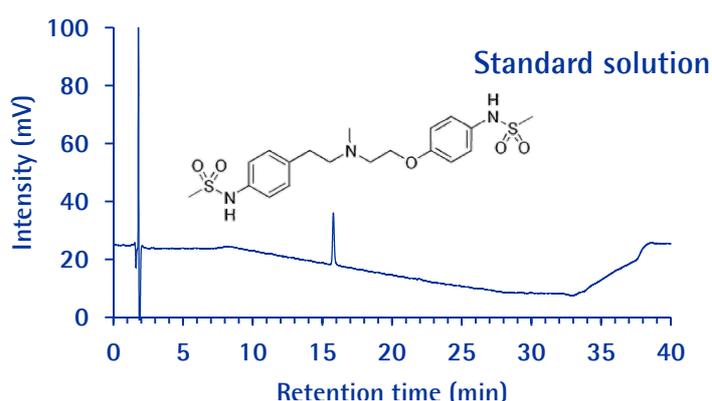
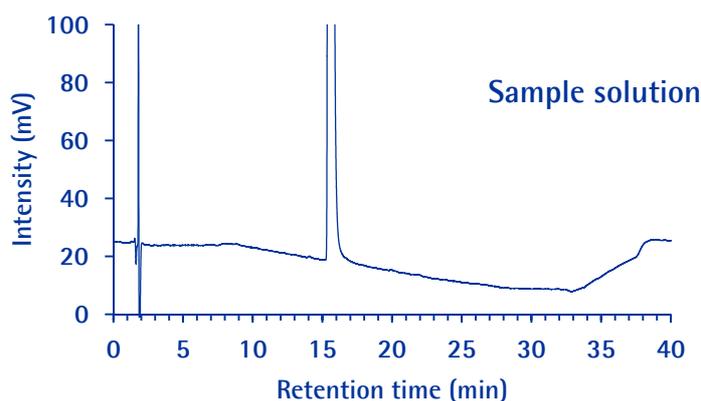
Column:	Chromolith® HighResolution RP-18 endcapped, 100x4.6 mm	1.52022.0001
Injection:	20 µL	
Detection:	UV 230 nm	
Cell:	10 µL	
Flow Rate:	1.0 mL/min	
Mobile Phase:	A: 0.78 g/L of ammonium acetate. Adjust with glacial acetic acid to a pH of 5.0 ± 0.1 B: Methanol	
Gradient:	See table	
Temperature:	30°C	
Diluent:	Acetonitrile and Buffer; 3:22 (v/v)	
SST Solution:	1.25 µg/mL each of Dofetilide and Dofetilide Related Compound A in diluent	
Standard Solution:	1.25 µg/mL of USP Dofetilide in Diluent	
Sample solution	0.25 mg/mL of Dofetilide in Diluent	
Pressure Drop:	52-65 Bar (754 - 943 psi)	



Time (min)	A (%)	B (%)
0.0	88	12
5.0	88	12
25.0	70	30
30.0	70	30
35.0	88	12
40.0	88	12

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With the use of a Chromolith® HighResolution column you can meet the system suitability without changing any parameter besides a reduction in injection volume from 50 to 20 µL.

New method would require revalidation though because of specification in monograph of column with particle size.

Chromatographic Data :

No.	Compound	Retention Time (min)	Resolution	Theoretical Plate
1	Dofetilide Related compound A	14.2		69968
2	Dofetilide	15.8	7.7	83075

Parameter	USP requirement	Observed value
Resolution	5.0	7.7
Theoretical plate for Dofetilide peak	35000	83075
Tailing factor for Dofetilide peak	NMT 1.5	1.1