



## BDG SYNTHESIS

### Certificate of Analysis

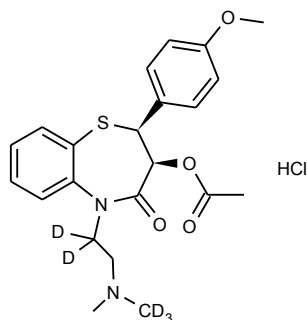
BDG Synthesis certifies that this reference material meets or exceeds the specifications stated herein.

*Barry Dent*

Barry R. Dent, PhD, Director  
29 June 2008

**Name:** Diltiazem-d<sub>5</sub> HCl  
**CAS Number:** 33286-22-5 (unlabelled)

**Structure:**



**Molecular Weight:** C<sub>22</sub>H<sub>21</sub>D<sub>5</sub>N<sub>2</sub>O<sub>4</sub>S.HCl = 456.01  
**Lot Number:** BDG 3733.1  
**Appearance:** White, crystalline solid  
**Corrected Purity:** 97.4 % (HPLC) - 0.5 % (ethanol) = 96.9 %  
**Isotopic Purity:** Under 0.5 % d<sub>0</sub>  
**Re-test Date:** 29 June 2013  
**Storage and Handling:** Temperature: ambient laboratory temperature; may be refrigerated.  
Humidity: not believed to be hygroscopic; may be handled in normal laboratory atmosphere.  
Light: protect from strong sunlight.  
Caution: only experienced laboratory personnel should handle the material.

## Identity and Purity

### Proton NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available. The complexity of the spectrum indicates two rotamers of the product are present in solution.

Isotopic Labelling: signals at the sites of deuteration are absent, compared with the spectrum of unlabelled material, indicating clean deuteration.

Residual Solvents: a small amount of ethanol (0.5 % w/w) is observed.

Impurities: no significant impurities are evident in the spectrum.

### Carbon-13 NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available. All signals are duplicated indicating that two rotamers of the product are present in solution.

Isotopic Labelling: signals at the sites of deuteration have collapsed to small multiplets compared with the spectrum of unlabelled material, indicating clean deuteration.

### High-resolution Mass Spectrum (ESI+)

Found  $m/z$  420.2008.  $C_{22}H_{22}D_5N_2O_4S$   $[M+H]^+$  requires  $m/z$  420.2005. The deviation of 1.9 ppm is within normally accepted limits for the establishment of identity by HRMS. No signal for  $d_0$  material was seen (detection limit about 0.5 %).

### HPLC

A broad, slightly tailing peak is observed (97.4 %). An impurity at 6.7 minutes (2.3 area %) is most likely to be desacetyldiltiazem- $d_5$ . This conclusion was supported by a spiking experiment. Note: in the absence of reference materials for preparing calibration curves, it is assumed that all peaks have the same detector response. Where possible, the conditions of analysis follow a pharmacopeial or literature method, or have been adapted from same.

### Elemental Analysis

	Found:	C 57.57, H 5.23, D 2.38, N 6.10 %
$C_{22}H_{21}D_5N_2O_4S.HCl$	Requires:	C 57.95, H 4.86, D 2.21, N 6.14 %

The elemental analyses fall within generally accepted limits for establishing the molecular formula given. The results may also be taken to imply the absence of significant quantities of water or inorganic salts (which have not been elsewhere tested for because of sample size limitations).

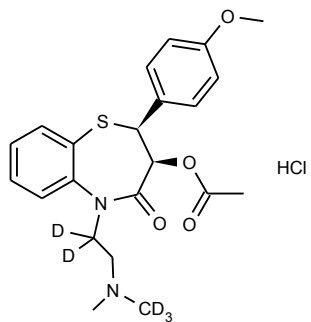
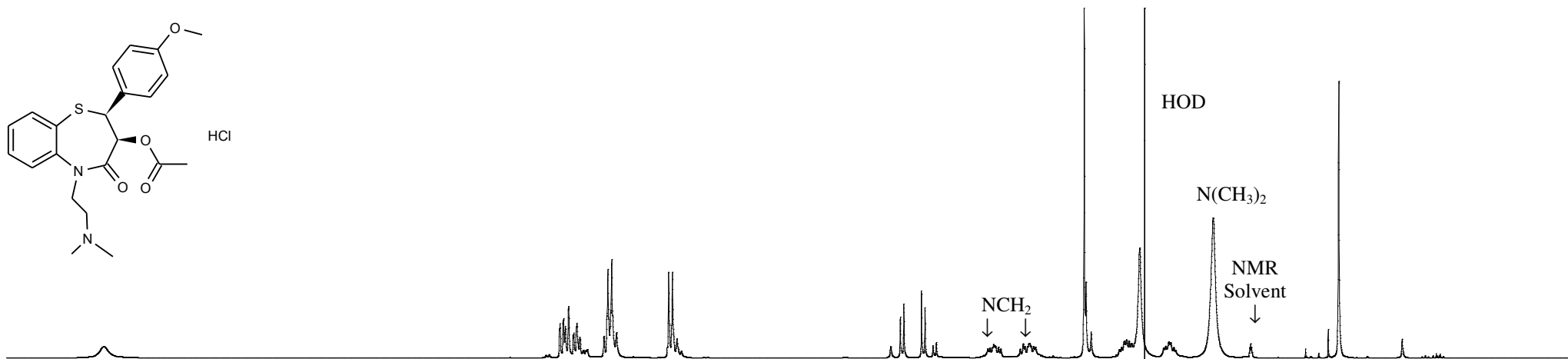
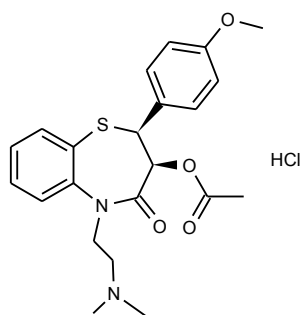
The available quantity of custom-synthesised material is always small, and this limits the extent and type of analytical data which can be obtained. This Certificate is presented in descriptive format for use by analytical chemists who are trained in the use of custom-synthesised materials. Custom materials often contain higher levels of residual solvents and/or water, and we urge you to use the corrected purity where needed rather than the raw HPLC purity. This compound is intended for use as an analytical reference material and it is not for human administration.

The re-test date is assigned from experience gained with the material in the laboratory and/or on storage. It is not possible to perform formal storage studies because of the small amount of material available.

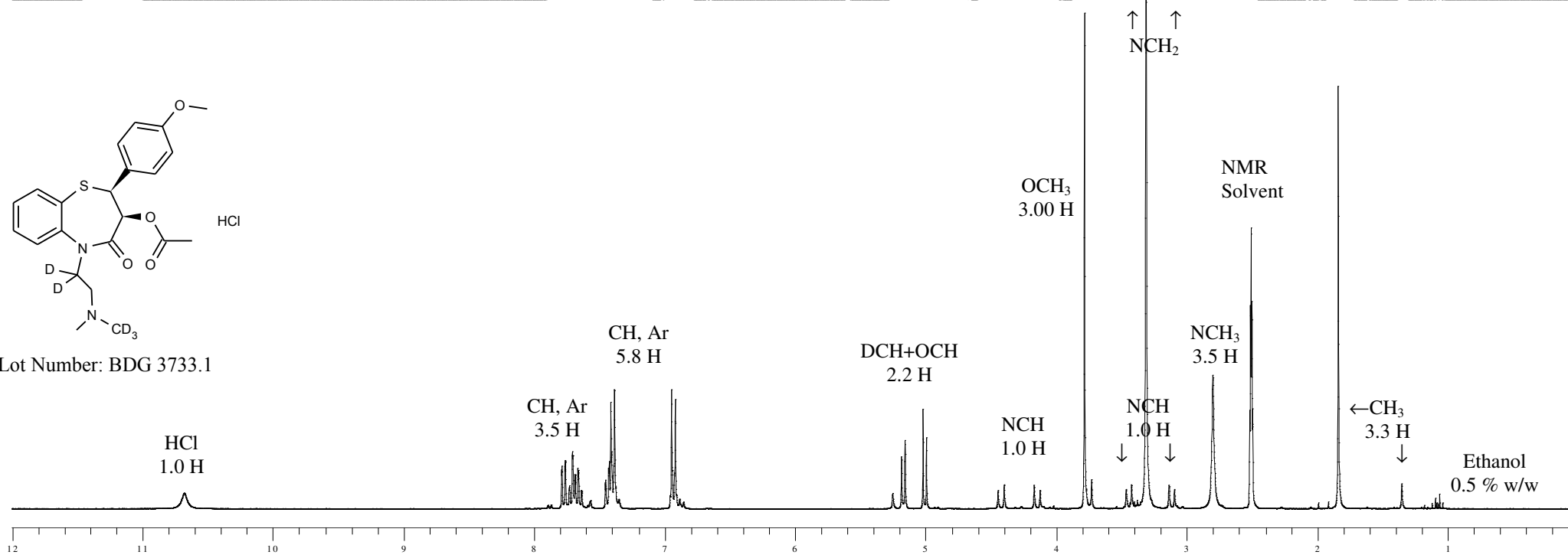


Proton NMR Spectrum of Diltiazem HCl (top) and Diltiazem-d<sub>5</sub> HCl (bottom) in DMSO-d<sub>6</sub>

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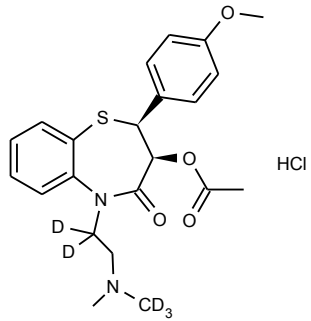
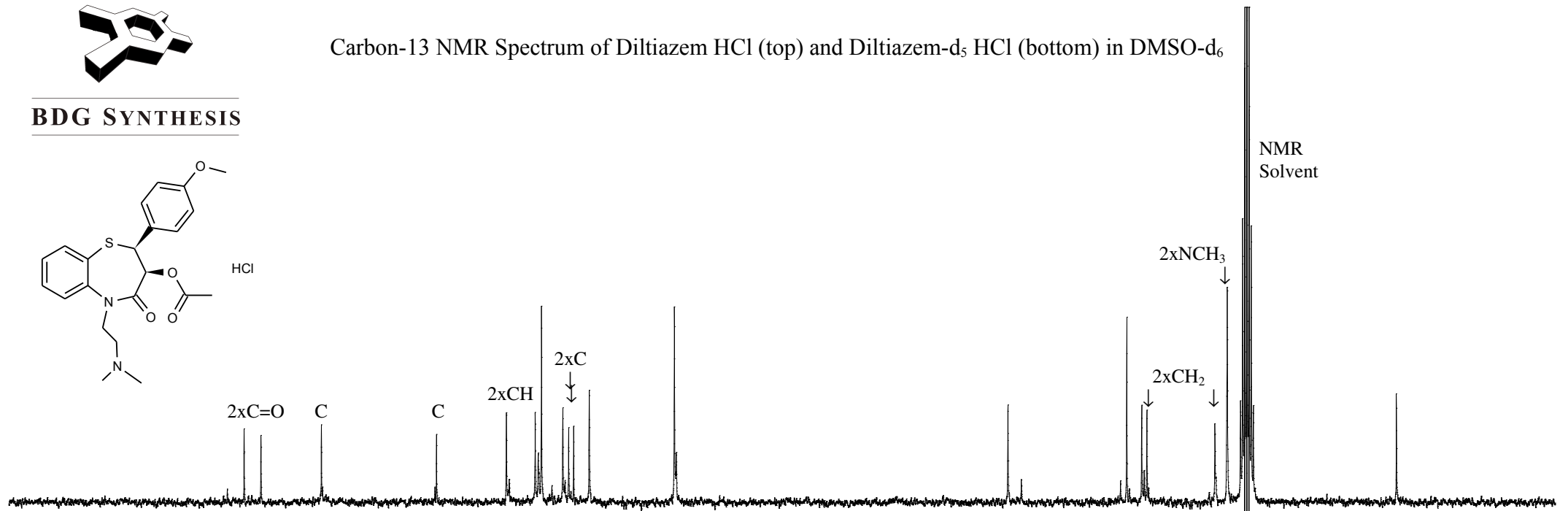
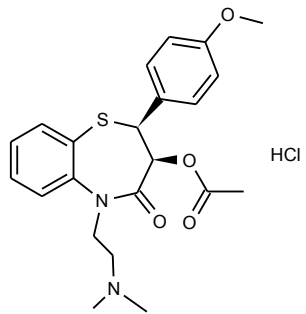
Lot Number: BDG 3733.1



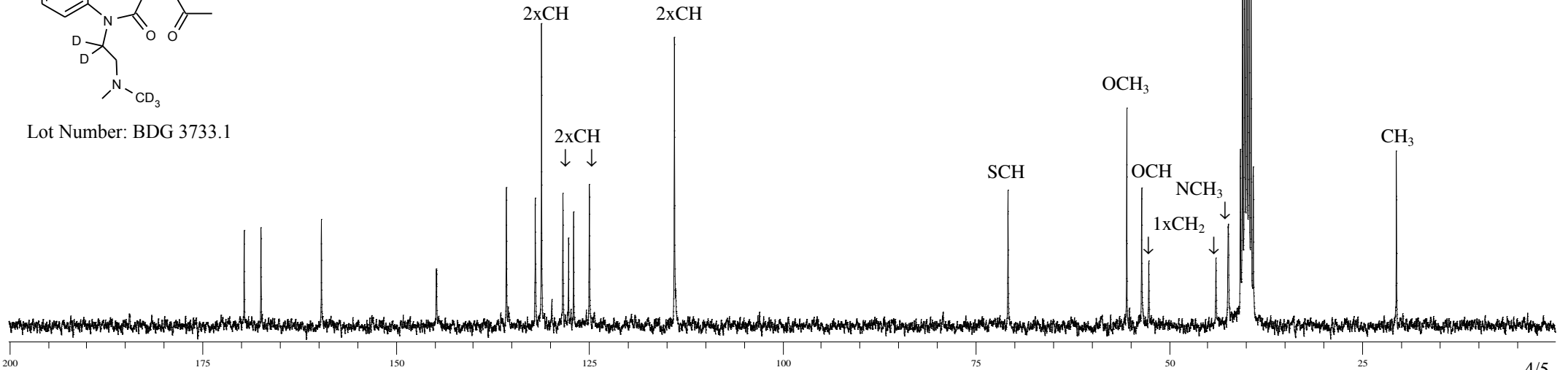


Carbon-13 NMR Spectrum of Diltiazem HCl (top) and Diltiazem-d<sub>5</sub> HCl (bottom) in DMSO-d<sub>6</sub>

**BDG SYNTHESIS**



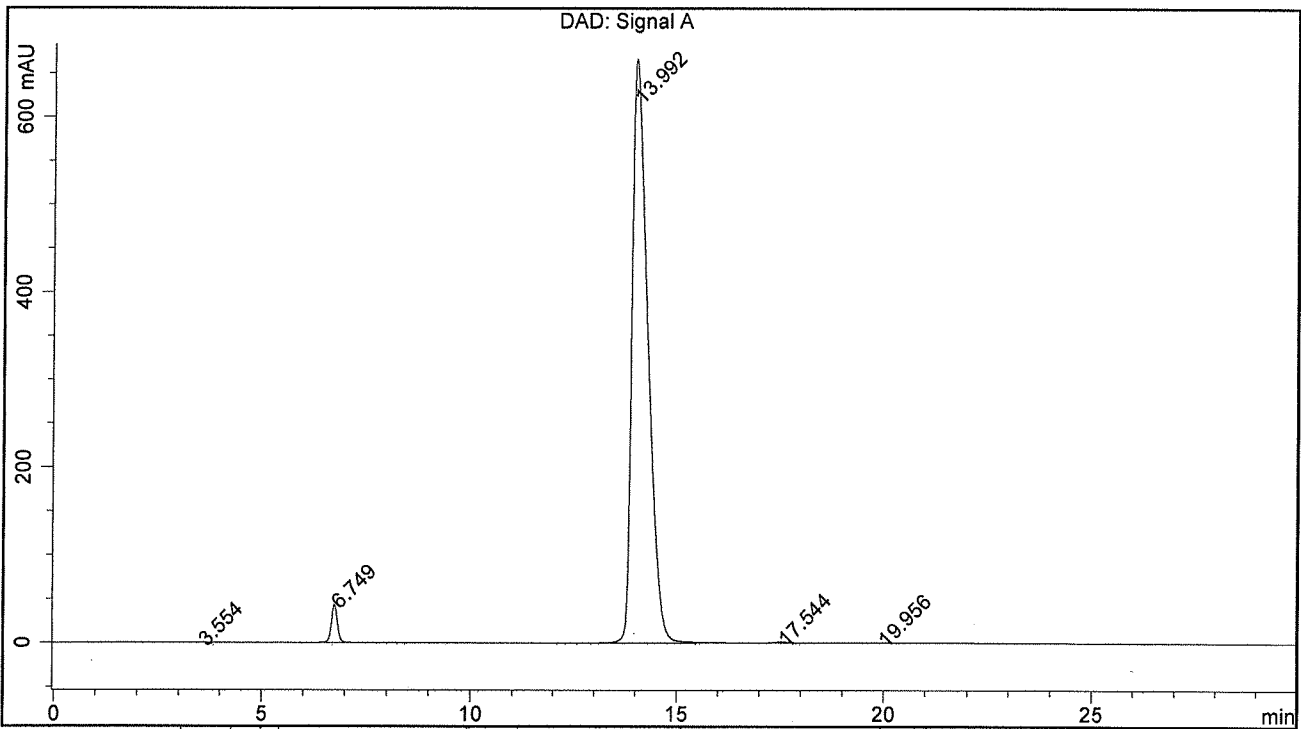
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BDG - Analysis of Diltiazem-d5 HCl

Column : Phenomenex Luna C18(2) 5um 250 x 4.6 mm  
 Guard : Phenomenex Security Guard C18 RP 4 x 3 mm  
 Mobile Phase : 70:25:5 50mM KH2PO4 + 0.01% N,N-Dimethyloctylamine pH=4.5 ( H3PO4 ) : Acetonitrile : Ethanol  
 Flow Rate : 1.5 mL/min  
 Sample Solvent : Mobile Phase  
 Column Temperature : 20C  
 Injection Volume : 10 uL  
 Detection : UV at 240 nm

<b>Sample Name</b>	BDG 3733.1	<b>Instrument</b>	AnalyticalLC01
<b>Acquisition</b>	29/06/2008, 11:29:51	<b>Method (rev.)</b>	LC10272a ( 4)
<b>Sequence</b>	BDG_29Jun2008c - Reprocessed	<b>Vial Position</b>	1
<b>Operator</b>	solvation010\cerityadmin	<b>Injection</b>	1 of 1



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	3.55 min	0.4395	4.0133	0.1365 min	0.022 %
2	6.75 min	43.0029	429.4878	0.1525 min	2.349 %
3	13.99 min	665.9746	17813.0829	0.4021 min	97.438 %
4	17.54 min	1.1524	30.4277	0.3361 min	0.166 %
5	19.96 min	0.1656	4.4428	0.3251 min	0.024 %