35Å Davisil® Chromatographic Media: A High Loading Adsorption Phase for Preparative and Process Scale

Oliver Genz
Thomas Pauly
Dr. Ian Chappell

Grace Davison Discovery Sciences
In der Hollerhecke 1
67545 Worms, Germany
T +49 (0) 6241 403 2013
Web site: www.discoverysciences.com

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Abstract

In traditional chromatographic purification and manufacturing processes of pharmacological small molecules, (active pharmaceutical ingredients = API) separation media with a 60Å pore size are very commonly used. A pore size of 60Å in the separation media particle allows small molecules (MW 150–300) to enter the pores easily and generally leads to good chromatographic separations.

35Å silica chromatography media, however, has an improved surface area compared to comparable 60Å silica separation media. This can lead to a significantly higher loading capacity in process scale purification. In addition to the solvent savings, this can reduce chromatographic manufacturing costs by more than 50% in total.

This poster demonstrates that with 35Å silica-based high-purity irregular chromatography media, solvent savings of up to 45% can be achieved. Switching to the 35Å media also reduces related solvent disposal costs, which can lead to an overall cost savings in process-scale chromatography costs, taking in to consideration that solvent costs are actually much higher than media costs in the production process.

Introduction

Previous studies[1] have established that high surface area silica, e.g. 700 m^2/g media, with small pores of 30-35Å can provide a substantial increase in loading capacity in chromatographic API separation, leading to significant reduction in process adsorption chromatography costs.

In addition, solvent consumption can be substantially reduced compared to traditional 60Å silica media with equivalent separation performance for small molecules. The theoretical improvement (approx. 50%) calculated from the relevant surface area/ml can be demonstrated both in small-scale laboratory trials using 0.46cm i.d. columns and also at a larger pilot plant scale using 15cm i.d. columns.

The main savings come from the 45% reduction in solvent required for a particular throughput. In process scale adsorption chromatography, solvent costs are comparatively much higher than media costs, so the potential savings can be substantial.

As the pharmaceutical industry continues to incorporate Green Chemistry and engineering practices and as solvents continue to play a significant role in pharmaceutical processes, the minimization of solvent use and waste generation has become a key focal point for reducing the overall environmental footprint of the industry.[2]

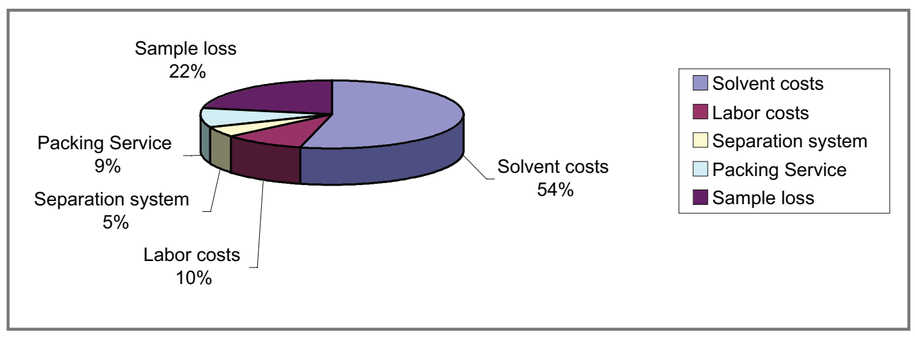
Switching to a small-pore 35Å high-surface area silica media can be a simple way to help comply with environmental, increased productivity, and cost-reduction initiatives as part of an overall “green” paradigm shift.

Figure 1

Davisil® Media		
Mean Pore Size:	35Å	60Å
Pore Volume (g/cc):	0.6	0.9
Surface Area (m^2/g):	725	550
Packing Density (g/mL):	0.63	0.55
Surface area (m^2/mL):	**457**	**300**

Typical parameters of 60Å silica media and the newly developed 35Å silica media. Note the 52% higher surface area in combination with the higher packing density of a 35Å silica based irregular media.

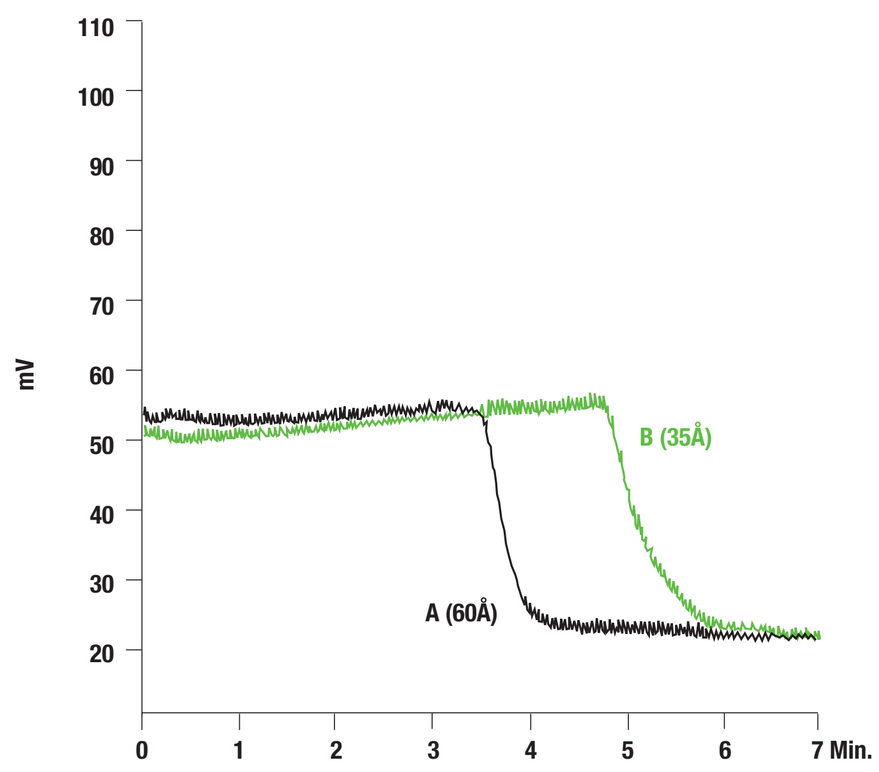
Solvent is a Significant Factor in the Overall Cost of Purification



Process scale cost split - Data gathered by Grace Davison Discovery Sciences at selected customers from top 20 Pharmaceutical companies.

Materials and Methods

Figure 2: The net relative capacity was 145% (633N = 100%) and a relative surface area/mL of 151%.



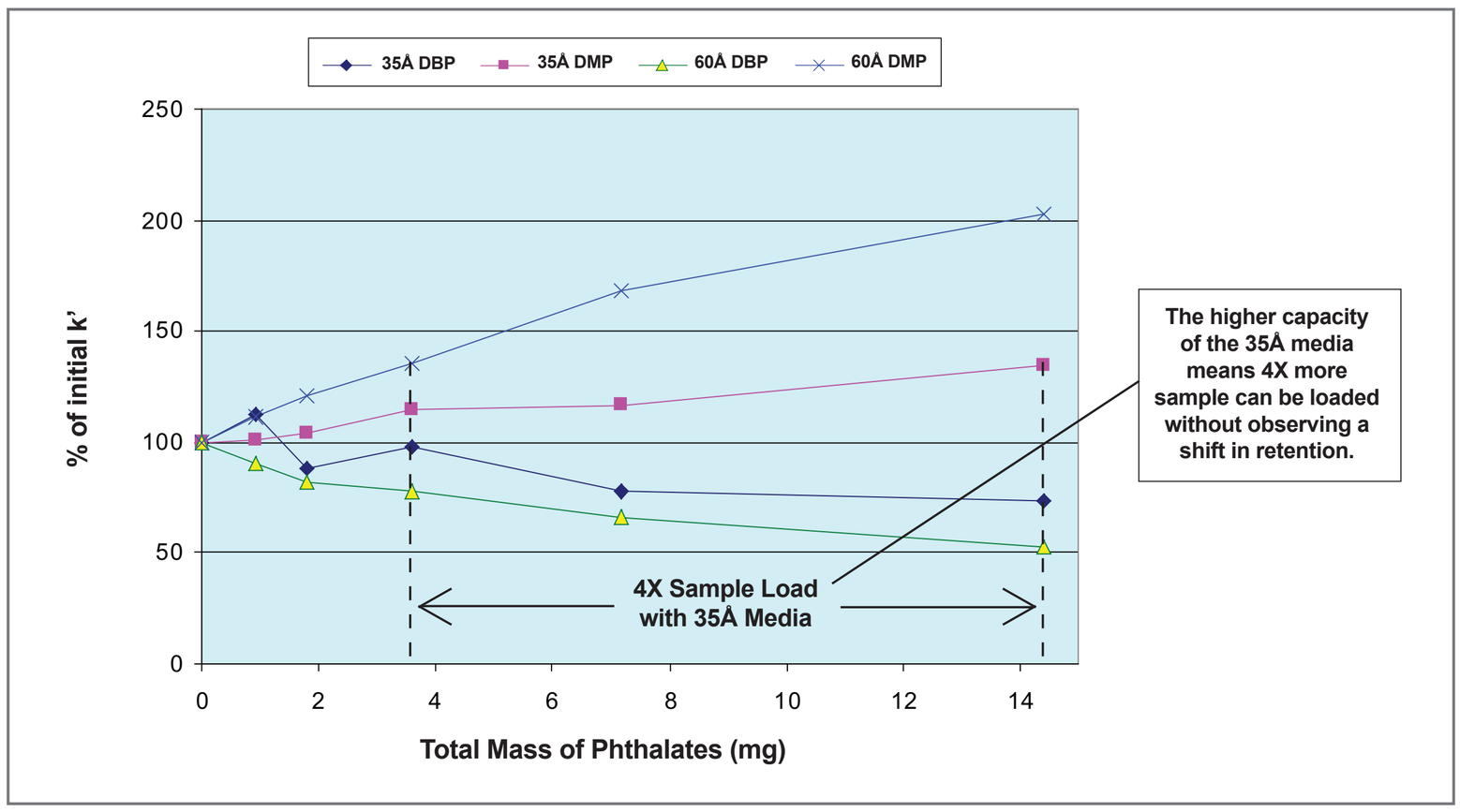
Column:	100 x 4.6mm columns dry packed
Packings:	60Å Davisil® 633N media and Davisil® 35Å media
Flow Rate:	1mL/min
Detector:	UV at 254nm
Conditions:	Columns were flushed with THF to remove water then purged with ethyl acetate. The solvent was changed to 1% MeOH in ethyl acetate and further purged until the methanol break through as seen by a reduction in the UV 250 signal.

The loading capacity test shows the methanol breakthrough curves of Davisil® 60Å (A) and 35Å (B) media. Line A shows the 60Å dropping earlier at 3.5 minutes, whereas 35Å drops at 4.75 minutes, indicating net relative capacity increase by 45% leading to a relative surface area increase of 151%. This experiment demonstrates the higher surface area and loading capacity of 35Å compared to a traditional 60Å silica media.

Thus depending on what criteria is chosen, the 35Å Davisil® silica can have up to 45% (MeOH breakthrough), 100% (DMP peak width), or 400% (DMP % change in k’) higher loading capacity than a traditional 60Å silica media. In the J. Chrom publication, the loading capacity for an exploratory herbicide increased from 200g to 560g by changing from a 60Å to a 35Å media; an increase of 260%.

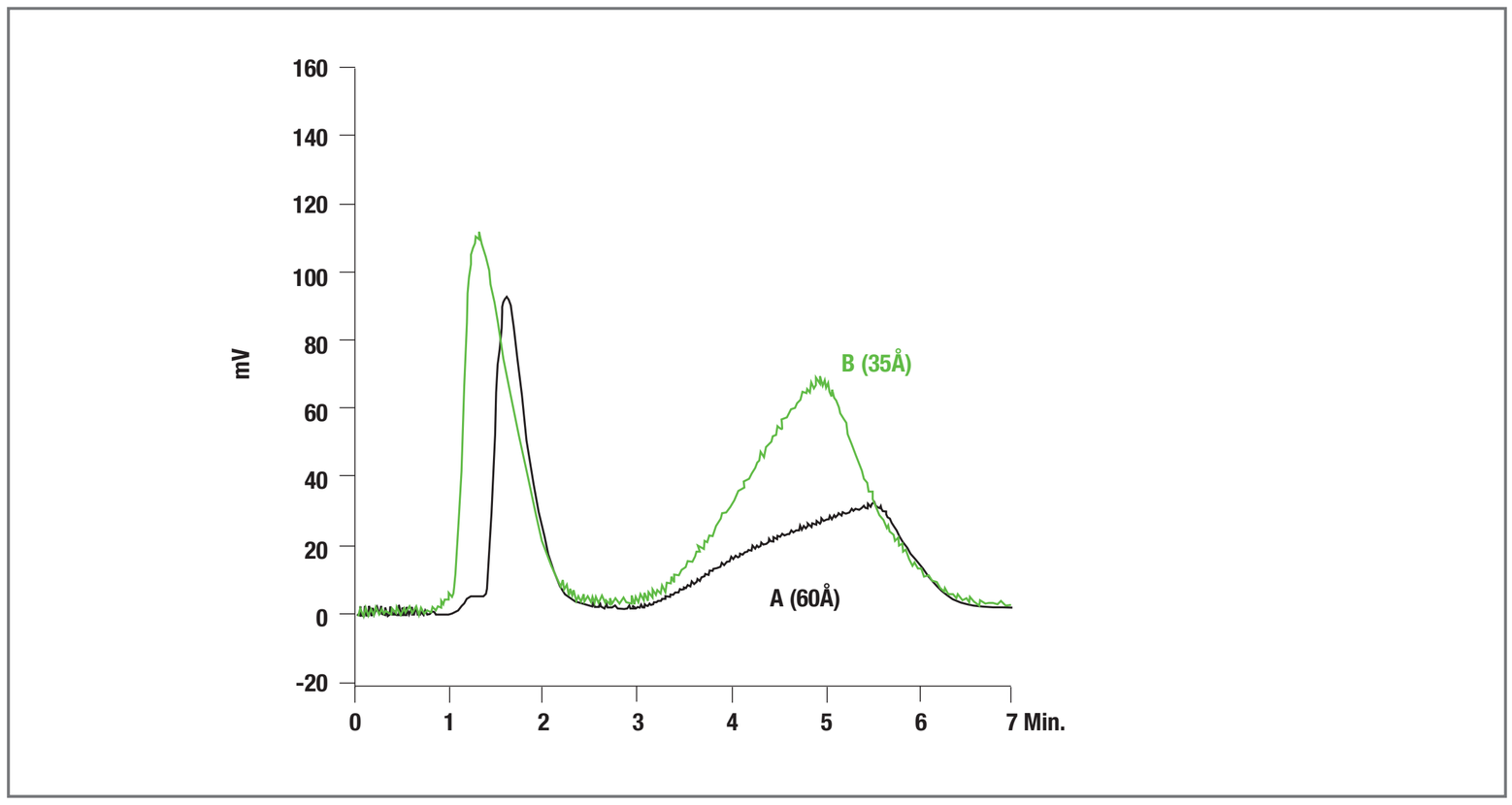
To demonstrate the higher loading capacity experimentally, the Phthalate loading study from the J.Chrom publication was replicated using a 1:1 mixture of Dibutyl (DPP) and Dimethyl Phthalates (DMP) and an eluent of IPA in Petroleum spirit (1% IPA for the 633N and 3% for the 35Å). The column performance was established with a low mass injection (16µg) followed by successively increasing amounts in the range 0.8 to 13µg (1 to 16µl) of the 1:1 mix.

Figure 3



The plot of retention change with mass loading clearly show that the 35Å Davisil® media resists overloading far better than the 60Å 633N. In the case of the DMP, four times the mass of sample (14.1mg/g on 35Å vs 3.8mg/g on 60Å) is required to see a similar 35% shift in capacity factor.

Figure 4: Up to 50% Capacity Increase with Davisil® 35Å Media



This overlay shows that twice the mass of DMP (13.6mg 35Å vs. 6.8mg 60Å) can be chromatographed with the same peak width using a 35Å Davisil® media. Therefore, for the same purification capacity as a 60Å media, only half the column size, significantly less solvent, and much less time is required on a 35Å media for the same amount of target molecule. In addition to the increased capacity, the concentration of the collected fraction is twice as high leading to a 50% reduction of the impurities coming from the solvent after evaporation which can also lead to a significant reduction in the size of the process chromatography system required.

Conclusion

The experiments performed show that with a 35Å silica chromatography media you can purify up to 50% more pharmaceutical small molecule (MW <300) compared to commonly used 60Å media. Up to 50% less solvent is used for the purification. Reduced contamination and solvent impurities in post-purification treatments of the target compound can be additional benefits.

In summary, the higher surface area of a 35Å media can provide multiple benefits in large scale chromatography purification of small molecules. The higher loading capacity, reduced solvent consumption, and decreased risk of contamination from solvent impurities can lead to an overall significant increase in productivity in the production process. Additionally, the use of 35Å silica chromatography media in large scale manufacturing can help reduce environmental impacts and supports the effort of the pharmaceutical industry to improve production processes and make chemical production more “green”.

The waste generated by pharmaceutical companies has increased concerns about environmental and human safety. Direct releases of treated solvent wastes, hazardous work conditions, and accidental releases of toxic chemicals into the environment have led to the implementation of many laws and regulations including the Clean Air Act, the Clean Water Act, and the Occupational Safety, and Health Act. These governmental regulations in addition to many others have created a widespread interest in Green Chemistry and technology[3].

To meet these interests and needs, the new 35Å chromatography separation media was developed and is now commercially available on the market.

References

[1] I.Chappell, P.E.Baines and P.K.Carpenter, J.Chromatography, 603 (1992) 49-61

[2] Green Chemistry in the Pharmaceutical Industry Peter Dunn, Andrew Wells, Michael T. Williams (2010) 73

[3] Green Chemistry in the Pharmaceutical Industry Peter Dunn, Andrew Wells, Michael T. Williams (2010) 50