port material is silica based, chosen for its ability to reproducibly and durably bond a variety of stationary phases. The most typical stationary phase is C-18; alternative stationary phases include C-8, C-4, cyano and phenol.

One concern with silica stationary phases is that they often do not perform acceptably at extremes of pH and temperature, which has prompted the use of polymeric materials in numerous niche applications. Another alternative is 3 µm zirconia beads, offered by ZirChrom Separations, an Anoka, MN, company that just began marketing its products in 1997. "Our reverse-phase material, in particular, offers demonstrably better mechanical, chemical and thermal stability than silica," says Vice President Steven Rupp. "It allows scientists to perform analyses at very high pH which is useful for basic drugs and other amines, where silica has shown problems with tailing."

The company's ZirChrom® PBD columns for reversed-phase chromatography can be used across pH 1-14 and at temperatures up to 200°C. "We're going to be exploring high-temperature work, which is exciting," Rupp says, "and we've collaborated with pharmaceutical scientists in several areas, such as in devising microbore columns [1 mm internal diameter] for use with LC-MS work."

Zirconia, or zirconium dioxide (ZrO_2), is a metal oxide that can exist in a number of crystal and amorphous forms. The company uses a patented process called polymer induced collodial aggregation, or PICA, to make the 3µm porous beads. These spheres are then sintered at temperatures reaching 900°C to produce a monoclinic crystal form of zirconia. "The PICA process allows us to get very monodispersed particles, meaning the size distribution is very narrow, so the back-pressure on the columns is very reasonable," Rupp says. "We've been able to alleviate some concerns for people who are worried about the back-pressure with 3 µm particles when using long columns."

Another significant advancement in support materials has come in the form of non-porous silica spheres. Non-porous silica has been shown to offer superior stability, mass transfer and efficiency in the 1-3 µm sizes, but commercial products have only recently been possible, as all aspects of column manufacture-support synthesis, bonding and packing-are extremely difficult.

While porous supports have been improved, some say that porosity itself has limited the rapid advancement of small support columns. The variety of morphologies and surface areas inherent in porous supports lead to lower and less predictable mass transfer rates, meaning that analytes are held up differently from particle to particle and throughout the column. In a longer column, the average result might look acceptable, but if one were to speed. up the event by shortening the column, or by increasing the organic modifier concentration, resolution would quickly be lost.

The Aquasil® HPLC column from Keystone Scientific is now offered in a 3 µm particle size. Designed for highly aqueous mobile phases, the column is deactivated yet will not lose retention, even in 100% H_20. The Aquasil C18 is appropriate for catecholamines, nucleotides and water-soluble vitamins, and can be used with common reversed-phase eluents.

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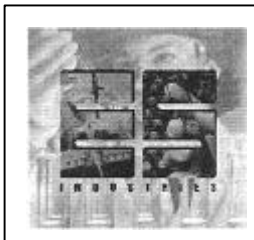

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IS SMALLER BETTER?

Dolan says more efficient and sensitive column formats present both advantages and disadvantages in method development and validation. "The touted advantages of smaller column formats are improved speed and sensitivity, lower detection limits and reduced solvent consumption," he says. "These are all very helpful, particularly when one is using expensive detectors, such as mass spectrometers." He notes that while it may sound appealing to talk about solvent savings in most cases solvent costs are a very small portion, usually a few percent, of the overall cost of an analysis.

Despite the promise of enhanced analytical performance and productivity, the reductions in column length, internal diameter and size of particles presents some challenges to chromatograpliers. Artifacts and column effects become much more significant, where with conventional columns, "they are important but of no practical consequence in most types of work," Dolan says. "Plumbing, injection volumes, flow rates and pump pressures all become very critical at smaller volumes, so instrument design and user practice have to take these things into account."

Columns with 3 µm and smaller particles get blocked rather easily, so samples need to be filtered thoroughly to ensure no particulate matter gets into the column. "You need to have a very low-porosity frit," which is the metal filter on the end of a column that holds the particles in the column, Dolan says. "Frits come in standard sizes, and the screen necessary to hold in 3 µm and smaller beads is obviously very fine and prone to blockage. Some manufacturers move up to 3.5 µm beads, so they can use a conventional frit."

Miniature columns also require smaller mixing volumes, so where pump heads conventionally deliver 80 µl per stroke, now analysts are using pumps delivering 10 µl per stroke. Delay volumes have dropped dramatically, as well, from 3-6 ml to .5 ml, which is particularly important for gradient elution analyses. Another concern with very short columns is that they tend not to provide a lot of separation power. Even with triple quad mass spec, which can provide adequate discrimination, coeluting compounds can suppress the ionization of compounds. "Though detection limits are better, due to narrower and taller peaks, this can