

1 Core-shell microspheres with porous nanostructured shells for liquid
2 chromatography

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9 **Running title:** Core-shell particles for liquid chromatography

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13
14 **Abbreviations:** CTAB, cetyltrimethylammonium bromide; CTAC, cetyltrimethylammonium
15 chloride; DRIFTS, diffuse reflectance infrared Fourier transform spectroscopy; HILIC, hydrophilic
16 interaction chromatography; HKUST-1, Hong Kong University of Science and Technology; LbL,
17 layer-by-layer; MIL-100, Materials of Institute Lavoisier; MPTMS, 3-
18 mercaptopropyltrimethoxysilane; MOFs, metal-organic frameworks; MW, molecular weight; OTMS,
19 octadecyl trimethoxysilane; PDDA, poly(diallyldimethylammonium chloride); PMT, pseudomorphic
20 transformation; PSD, particle size distribution; SOS, spheres-on-sphere; SPPs, superficially porous
21 particles; TEOS, tetraethyl orthosilicate; UHPLC, ultra-high pressure liquid chromatography; UiO-66,
22 Universitetet i Oslo; ZIF-8, zeolitic imidazolate framework.

23
24 **Keywords:** core-shell particles / superficially porous particles / spheres-on-sphere silica / hybrid
25 particles / fast liquid chromatography

27 **Abstract:** Development of new stationary phase has been the key aspect for fast and efficient HPLC
28 separation with relatively low backpressure. Core-shell particles, with solid core and porous shell,
29 have been extensively investigated and commercially manufactured in the last decade. The excellent
30 performance of core-shell particles columns has been recorded for a wide range of analytes, covering
31 small and large molecules, neutral & ionic (acidic and basic), biomolecules, and metabolites. In this
32 review, we firstly introduce the advance and advantages of core-shell particles (or more widely known
33 as superficially porous particles) against non-porous particles and fully porous particles. This is
34 followed by the detailed description of various methods used to fabricate core-shell particles. We then
35 discuss the applications of common silica core-shell particles (mostly commercially manufactured),
36 spheres-on-sphere particles, and core-shell particles with non-silica shell. This review concludes with
37 a summary and perspective on the development of stationary phase materials for HPLC applications.

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42 **1. Introduction**

43 LC has been widely used for separation, analysis, and detection. In addition to routine analysis of
44 small molecules in chemistry and chemical-related industry labs, the use of LC covers separation of
45 bio-related molecules (e.g., amino acid, peptide, proteins, lipids, glycans & saccharides,
46 oligonucleotides), metabolic phenotyping, food science & nutrition, forensic toxicology,
47 environmental analysis, and pharmaceutical analysis [1]. The development of modern LC has targeted
48 fast and efficient separations, with improvements being made in innovative stationary phase and
49 instrumentation [2]. The stationary phase materials in LC can be generally classified into two
50 categories: microspheres and monoliths [3,4]. Monolith columns can offer fast separation and may be
51 particularly useful for separation of large macromolecules. There are several products of monolithic
52 columns on the market. However, the spherical packing materials (indeed silica spheres) are still
53 dominating the market and widely investigated in research and development [3]. Because separation
54 in LC is based on the adsorption/retention and desorption between the target molecules in the mobile
55 phase and stationary phase, an increase in surface area of the stationary phase can increase the number
56 of adsorption/desorption sites and enhance the separation efficiency. Both porous and non-porous
57 spheres are used. While porous spheres exhibit high surface areas, non-porous spheres are
58 mechanically more stable, which can be very important when operational pressure is high. The
59 development and use of uniform and smaller silica microspheres has been the driving force for highly
60 efficient HPLC. However, the backpressure generated by the use of small particles is a big obstacle
61 for the HPLC systems.

62 To address the dilemma in high performance and high operational pressure for smaller particles,
63 instrumentation design of the HPLC system with short narrow-bore columns has been shown to
64 achieve fast separation with excellent sensitivity [2]. **For the narrow-bore columns**, the factors that
65 can significantly compromise the analysis performance or reproducibility include extra-column
66 volume (including injector system, connector tubing, detector cell), dwell volume, data acquisition
67 rate, and injection cycle time [2]. The instrumentation design may also include coupling of on-line
68 sample pre-treatment techniques with HPLC columns. This is to separate and enrich target

69 compounds in the complex samples with very low concentration. Typically, the sample pre-treatment
70 techniques are solid phase extraction or liquid phase extraction [5]. To simply enhance separation
71 efficiency and selectivity, column modulation via serial coupling of different columns under
72 compatible conditions can be employed [6]. This, however, may cause a huge increase of operational
73 pressure.

74 High operational pressure can give rise to detrimental effects of frictional heating generated by
75 percolation of the mobile phase flowing through the packed particles. The heat generated is
76 proportional to the pressure drop and flow rate [3]. This creates the temperature gradient along the
77 axial direction (the flowing direction of mobile phase) and the radial direction (due to the high
78 temperature in the central part and the heat loss through the wall), leading to serious band broadening
79 and poor reproducibility. This effect may be reduced by using narrow-bore columns and reducing
80 backpressure inside the column [2]. The high pressure can also lead to significant change in partial
81 molar volume, which is the change of molar volumes of solute molecules bound to the stationary
82 phase and solute molecules in the mobile phase. The changes are greater for large molecules such as
83 proteins, peptides and other biomacromolecules. This can in turn influence the retention and
84 separation of such molecules, as explained by the solvation parameter model [7].

85 Reducing operational pressure whilst maintaining high separation efficiency can generate multiple
86 benefits. The use of core-shell silica particles, with solid core and porous shell, as column packing
87 materials, has been regarded as a big step forward in HPLC column technology in the last decade or
88 so [8]. These core-shell silica particles are also known by some of other commonly used names, such
89 as fused-core, solid core or superficially porous particles (SPP) [4]. The main commercially available
90 core-shell columns include Poroshell (Agilent), Cortecs (Waters), Accucore (Thermo Fisher
91 Scientific), **Ascentis Express (Sigma-Aldrich)**, Halo (Advanced Materials Technologies), Kinetex
92 (Phenomenex), Ultracore (Advanced Chromatography Technologies) [4,9]. Core-shell columns with
93 particles of 2.6-2.7 μm have been found to show better or the same efficiency compared with fully
94 porous 1.7 μm column (BEH C₁₈), but with much lower back pressure [9]. The particle size
95 distribution could also have a big impact on the operational pressure [9]. The core-shell particles
96 columns have considerably enhanced the applications of HPLC in various areas [1,10]. There are, of

97 course, other exciting developments in the development of novel stationary phase materials, for
98 example, for hydrophilic interaction chromatography (HILIC) [11], mixed-mode HPLC [12], size
99 exclusion chromatography (SEC) [13], and metal-organic frameworks (MOFs) as new type of
100 stationary phase for HPLC [14]. These new development may be based on core-shell silica particles
101 or fully porous/non-porous silica particles.

102 In this review, we focus on the fabrication and use of core-shell particles for enhanced HPLC
103 applications. The fabrication methods are particularly covered in details. The fundamentals for HPLC
104 and core-shell particles and examples of the applications are also described.

105

106 **2. Core-shell particles as packing materials and the mechanism for high performance**

107

108 2.1 Columns packed with non-porous particles, totally porous, and core-shell particles

109 Separation of a complex mixture into individual species by LC requires the stationary phase to
110 selectively retain analytes based on their chemical composition and structure [15]. Usually a column
111 packed with porous micron-sized particles is employed in order to achieve the separation. **In LC, the
112 analytes are transported by a convective flow of the mobile phase through the packed column.**

113 Diffusion of solutes in a liquid phase is usually three orders of magnitude slower than in the gas phase
114 for small to medium sized molecules. In addition, diffusion into and out of tortuous pores (pore
115 diffusion) is reduced significantly as compared to diffusion in the liquid bulk phase. A central
116 problem in HPLC is therefore to overcome the limited mass transfer of solutes due to pore diffusion
117 by providing sufficient access to the interactive surface sites. One way is to reduce the average
118 particle size of the packing to minimize the diffusion path length by using smaller microspheres [15].

119

120 **2.1.1 Non-porous silica particles**

121 Works on the use of non-porous sub-2 μ m silica particles in ultra-high pressure liquid chromatography
122 (UHPLC) with columns id < 200 μ m were carried out since late 1990s. The particles used were 1.0
123 and 1.5 μ m. These particles were monodisperse and yielded very efficient chromatographic columns
124 [16-18]. Spherical organosilica particles of 670 nm (stable in 1 < pH < 11) containing C18 moieties

125 were prepared by Cintron and Colon using a simple one-step synthesis process [19]. When applied in
126 UHPLC for the separation of a mixture of ascorbic acid, hydroquinone, resorcinol, catechol and 4-
127 methylcatechol, a fast analysis time (< 4 min) and high theoretical plates (500,000 plates/m) were
128 achieved. Elevated-temperature UHPLC was performed using polybutadiene-coated 1 μm non-porous
129 zirconia particles in a study by Lee and co-workers [20]. Five herbicides were separated in 1 min at
130 26,000 psi and 90 °C with a column efficiency of 420,000 plates/m. It was shown that non-porous
131 particles with uniform size (below 1.5 μm) could form robust packed column and yield low plate
132 height at elevated column pressure [17,20]. However, non-porous materials have comparatively
133 lower surface area which results in low loading capacity.

134 For small non-porous particles, the challenge is the resulting high column pressure which
135 renders the instrument dangerous and impractical to operate [19]. Xiang et al. studied the safety
136 concerns of operating UHPLC with fused-silica capillary columns [21]. Liquid jets and high speed
137 projectiles of silica particles due to rupture of the capillary or failure of the ferrule in the capillary
138 connection might lead to injuries. To avoid the high pressure and potential danger, some studies using
139 sub-2 μm silica were carried out on capillary electro-chromatography (CEC). CEC utilizes electro-
140 osmotic driving force instead of pressure drop to achieve high separation efficiency [22-24].

141

142 2.1.2 Totally porous silica particles

143 In 2005, robust porous sub-2 μm silica materials were brought into the limelight for fast and efficient
144 chromatographic separation [25]. Mesoporous sub-2 μm silica materials, being smaller in size
145 compared to conventional 5 and 3 μm packing materials, could generate enhanced separation
146 efficiency. The large surface area also significantly improves loading capacity. These factors allow for
147 the use of column with shorter length and smaller id to achieve the same or even higher resolution in a
148 very short analysis time compared to conventional HPLC [25].

149 Some researchers have focused on the development of chromatographic application using
150 sub-2 μm materials and relatively high-pressure instrumentation. Wu and Clausen discussed the
151 fundamental and practical aspects of UHPLC such as particle size, frictional heating, pressure drop,
152 column diameter, pump and injection systems, detection as well as packing materials [26]. Since then,

153 the development of sub-2 μm porous silica material continues to contribute significantly to the field of
154 liquid chromatography. These silica materials have demonstrated good performance in achiral
155 chromatographic separations and have shown great promise in fast enantioselective separation of
156 racemic compounds.

157 The advantages of smaller fully porous particles compared with the conventional larger
158 particles are clearly demonstrated by the kinetic plots as shown in Figure 1a [27]. The pressure limit
159 of the conventional columns (used on conventional equipment) is assumed to be 400 bar, whereas that
160 of the smaller particles with UHPLC equipment is assumed to be 1200 bar. For separations requiring
161 up to about 100,000 plates, the curve for the 1.8 μm column lies well below that of the 3.5 μm
162 column, indicating that a faster analysis can be achieved.

163

164 2.1.3 Core-shell silica particles

165 A big forward in column technology came in 2007 with the introduction of SPPs by Advanced
166 Material Technologies [28], following the concept of pellicular particles which were initially tested in
167 the 1970s, with the particle size of 50 μm and the shells made of aggregates of nanoparticles only a
168 few μm thick [29]. Progress was then made on the preparation and evaluation of particles with
169 controlled surface porosity [30] and the SPPs with 5 μm core and 1 μm shell [31]. While the particle
170 size of the majority of SPP columns was of the order of 2.6 μm , columns packed with sub 2 μm SPPs
171 are now widely available and can give further improvements in performance, if appropriate
172 instrumentation is available [10, 32-34]. This improvement can be seen in the kinetic plots in Figure
173 1b where separations requiring around 20,000 plates can be achieved in around 1 minute on a 1.6 μm
174 SPP column, but require significantly longer on the totally porous column of about the same particle
175 size (1.8 μm) [27].

176 The advantages of smaller core-shell particles (1.0-1.3 μm) have been investigated, including
177 commercially available 1.3 μm particles with 0.9 μm non-porous core and porous shell < 0.2 μm thick
178 [3, 35-37]. Minimum plate heights of 2.2 μm were observed, corresponding to a plate count of
179 450,000 plates/m. However, only short columns of 3-7.5 cm length operated at modest flow rates
180 could be used. Clearly, practical column dimensions and operation are severely limited by the

181 maximum pressure of current instruments, and their band spreading effects [3]. Only the instruments
182 with the lowest extra-column bandspreading could be used to obtain these results [2]. Nevertheless, it
183 was observed that the extra-column bandspreading could have a major impact on the apparent kinetic
184 performance; significant plate count loss was noticed for retention factors <5 , even with the best
185 system used for the experiments, which had σ^2 (extra-column) = $2 \mu\text{L}^2$ at the flow rates used [3]. It
186 was also demonstrated that the loss in performance caused by frictional heating effects remained
187 negligible, but the short column lengths and flow rates used should be taken into account when
188 considering this observation. The performance of $1.3 \mu\text{m}$ particles was further studied in the gradient
189 elution mode with both small molecules and peptides (which have different diffusion characteristics)
190 [38,39]. The material appeared to be particularly well suited for fast separations, but the advantages
191 were much more obvious for peptides than small molecules. This was due to the possibility of
192 working closer to the optimum flow velocity for peptides, as they have smaller mobile phase diffusion
193 coefficients.

194 Kirkland and co-authors debated whether sub- $2 \mu\text{m}$ SPPs were really necessary in many
195 practical applications [40]. While the introduction of SPPs in the sub- $2 \mu\text{m}$ range as opposed to the
196 original $2.5 - 2.7 \mu\text{m}$ particles allowed very fast separation, the efficiency advantage of these very
197 small particles is not often realised nor sufficient to overcome some of the practical limitations and
198 associated disadvantages. A $2.0 \mu\text{m}$ SPP was suggested to retain many of the advantages, while
199 minimising some of the disadvantages [40].

200

201 2.1.4 High performance of core-shell particle columns

202 The advantages of SPP columns can be extended to their substitution for conventional larger $5 \mu\text{m}$
203 totally porous particles [41]. The core-shell particle columns show a clear improvement in separation
204 power over their fully porous counterparts by allowing faster separations (at the same efficiency) or a
205 higher separation resolution (at the same analysis time). Van Deemter and kinetic plots showed that 5
206 μm SPPs provide a superior kinetic performance compared with the fully porous particles over the
207 entire range of separation conditions, when both types of particles were evaluated at the same
208 operating pressure. The same observations were recorded both for isocratic and gradient analysis [42].

209 It was demonstrated that the SPPs do not compromise sensitivity due to loadability issues, and
210 that the columns could be used on conventional equipment without modification to obtain significant
211 improvement in analysis time, especially if the columns of 4.6 mm id packed with larger particles
212 (~2.6 μm) are utilised, which reduce the need for instrumentation giving a low extra column
213 bandspreading contribution [43-45]. Gritti and Guichon found values of the minimum reduced plate
214 height of 1.3-1.5 for a 4.6 x 150 mm column packed with 4.6 μm SPPs [46]. The separation speed and
215 resolution of these columns was claimed to be equivalent to that of 2.5 μm totally porous particles for
216 hold up times larger than only 10s, and virtually equivalent to that of 2nd generation silica monoliths.
217 Care must be taken when comparing the performance of the packed columns with different physical
218 dimensions, because the internal diameter of the column can influence the performance [43,46].

219

220 2.2 Theoretic aspects of high performance core-shell particles

221 Daneyko et al. undertook a comprehensive computational investigation of longitudinal diffusion, eddy
222 dispersion and trans-particle mass-transfer in random packing of core-shell particles with varied shell
223 thickness and shell diffusion coefficient [47]. An excellent summary of current knowledge of the
224 various band spreading processes within a column was given. The van Deemter equation [48] written
225 in modern terminology (equation 1) gives a simple description of these processes:

226

$$227 \quad H = A + \frac{B}{u} + Cu \quad (1)$$

$$228 \quad h = av^{0.33} + \frac{b}{v} + cv \quad (2)$$

$$229 \quad \Delta P = \phi \frac{\eta Lu}{d_p^2} \quad (3)$$

230

231 Equation (2) is the Knox equation and uses h and v , the reduced forms of H (Height of equivalent
232 theoretical plate, HETP) and u (velocity) in equation (1). The Knox equation is often employed for
233 physicochemical comparison purposes [49]. For equation (3) (the Darcy's law), ΔP is the
234 backpressure generated, ϕ is the flow resistance, u is the average velocity, η is the viscosity of the
235 mobile phase, L is the column length, and d_p is the diameter of the particles.

236 In the van Deemter equation, the A term includes contributions to flow biases taking place
237 over different characteristic lengths in the column that can be divided into:
238 (i) transchannel (associated with the dimensions of the interparticle channels between
239 neighbouring particles);
240 (ii) short-range interchannel (associated with the scale of a few particle diameters);
241 (iii) long range interchannel (associated with the distances between local defects in a packing);
242 (iv) transcolum effects (associated with heterogeneities at the scale of the column dimensions).
243 The B term is related to an apparent, complex diffusion coefficient accounting for the sample
244 diffusivity in the interparticle bulk eluent and in the pore network of the stationary phase. The C term
245 (mass transfer term) accounts for all mechanisms resulting in a finite response time for transfer
246 between solid and the bulk liquid mobile phase. It should be pointed out that the coefficients in the
247 equation are semi-empirical and as a consequence cannot be directly related to a physical description
248 of the individual mechanisms.

249 The A and C terms directly depend on the particle diameter, so the reduction in particle size
250 enhances the performance of the separation. Nevertheless, this leads to an immediate drawback:
251 columns packed with smaller particles have lower permeability and this causes higher backpressures,
252 according to Darcy's law [Equation (3)]. This means that optimal flow rates for fully-porous particles
253 will generate backpressures several times higher in columns packed with sub-3 μm or sub-2- μm
254 particles than in the case of the 5- μm particles.

255 Gritti and Guiochon had previously outlined these processes, and proposed that the good
256 performance of SPP columns resulted from a smaller B term (due to the non-porosity of the core
257 giving a reduced packed bed volume accessible for diffusion) and a much reduced A term [50,51].
258 Other work indicated that the smaller A term in SPP columns was mainly due to a higher transcolum
259 homogeneity rather than an improved bed morphology on smaller length scales [52,53]. It was shown
260 that when analysis of small molecules was performed at (for isocratic) or somewhat above (for
261 gradients) the optimum flow, the eddy diffusion term contributed to the majority of the band
262 broadening. The greatest contribution to eddy dispersion is from wall and/or border layer trans-

263 column effects. As the bed aspect ratio (the ratio of the column to particle diameter) increases, the
264 column performance tends towards the infinite diameter column [54].

265 Due to their complex preparation procedures, the reproducibility of the manufacturing SPP
266 columns might be questioned especially with regard to the reproducibility of the eddy diffusion and its
267 effect on the total efficiency. However, studies have indicated that for several different commercially
268 available products, reproducibility was good. Differences in column efficiency between columns were
269 attributed merely to the random nature of the packing process and the resulting lack of homogeneity
270 of the column bed [55]. For 2.6 μm SPPs in 2.1 x 100 mm column formats, the relative standard
271 deviation (RSD) of the eddy diffusion contribution was less than 10% [56]. Similar results were found
272 for SPPs with larger pore size designed for the separation of peptides [57]. The question of the
273 monodispersivity of the particles and its influence on column performance has long been a subject of
274 debate amongst researchers in this area. SPPs have a very narrow particle size distribution (PSD) and
275 a considerably lower proportion of “fine” particulates left behind from the manufacturing process
276 compared to preparation methods for totally porous particles. It seems possible that this could indeed
277 influence the A term in some way. Horvath et al developed a theoretical framework for calculation of
278 the effect of PSD on efficiency, demonstrating that a wider PSD was detrimental to performance [58].
279 A constant packing density was assumed in that work. The PSD mostly affects intraparticle diffusion;
280 therefore, its effect is negligible in the case of small molecules. However, its influence increases as
281 the size of solute molecules increases, because intraparticle diffusion becomes increasingly
282 significant. Thus SPPs with a narrow PSD should be advantageous. It was shown that bimodal phases
283 (which consist of deliberate mixtures of particles of different size) had no advantage over
284 monodispersed particles - manufacturers are known to sometimes add small quantities of larger
285 particles to a UHPLC packing in order to reduce the operating pressure [3].

286 Recently, fully porous particles with narrow PSD have become available, and their properties
287 have been briefly reviewed [59]. By comparison of their performance with SPP columns, some
288 elucidation of the factors leading to high efficiency might be possible. Guiochon and co-workers
289 studied 2.1 and 3.0 mm id columns packed with 1.9 μm porous particles [60,61]. These materials had
290 particle size distribution of 10 % RSD, intermediate between that of classical porous particles (~20 %)

291 and SPPs (~5 %). The Titan material exhibited low reduced plate height (h) values of 1.7-1.9, which
292 is low for totally porous particle columns although does not reach the even lower values exhibited by
293 some SPP columns. The authors pointed out that it was tempting to therefore assume a correlation
294 between narrow PSD and high efficiency. However, they attributed the performance instead to the
295 unusually small diffusivity of analytes across the porous particles (about a factor of 3 lower than for
296 typical porous C18 particles), leading to the lowest h values being obtained at low reduced velocities
297 (around 5 instead of 10). Therefore the performance is attributable to a reduction in the B term. An
298 undesirable consequence however, is a larger C term, which leads to poorer performance at high
299 mobile phase velocity. Increasing the pore size of the material from 80-120 Å produced improvements
300 in the efficiency of the columns when applied to the analysis of peptides and small proteins [62,63].

301

302 2.3 Suitability of core-shell silica particles for separation of large molecules

303 The effect of shell thickness has been studied particularly with regard to the separation of large
304 molecules. In general, studies have suggested a compromise between a short diffusion path (which
305 leads to high efficiency) and adequate retention / mass load tolerance. SPPs with thinner porous shells
306 show marginal improvement in column efficiency for small molecules, but improved performance for
307 larger molecules which have much smaller diffusion coefficients and thus give higher mass transfer
308 contributions to band broadening [64]. This particular study indicated the best compromise for large
309 molecules was a 0.2 µm shell thickness. This value represents a rather thinner shell than used in the
310 original materials, which reflect the slower diffusion of large molecules and its consequent negative
311 influence on mass transfer [64].

312 For the separation of larger molecules such as peptides and proteins [65], the pore size must
313 be large enough to accommodate the solutes. SPPs with larger pores are now commercially available
314 [66]. Wagner et al. estimated that solutes with MW >5000 could show restricted diffusion and poor
315 performance in 2.7 µm shell packings with a conventional pore size (e.g. 90 Å) while the SPPs with
316 pore size 160 Å were limited to solutes of MW <15000 [67]. SPPs with pore size of 400 Å were
317 suitable for separation of proteins with MW 400 kDa or higher [67]. Further work explored in more
318 detail the added effect of shell thickness on performance using particles of diameter 3.4 µm with

319 different pore sizes in the range of 90-400 Å and shell thickness 0.15 - 0.5 µm for the separation of
320 proteins [68]. It has confirmed that large molecules (even up to 500 kDa) have unrestricted access to
321 the bonded phase of the material.

322

323 2.4 Important characteristics of core-shell silica particles

324 Langsi and co-workers studied the preparation of SPPs of overall diameter 1.5, 1.7 and 1.9
325 µm coated with a thin 50 nm shell [69]. These particles were manufactured via micelle templating
326 using short chain alkylammonium halide surfactants followed by hydrolysis/condensation of a pure
327 silica precursor. The materials were comprehensively characterised using scanning and transmission
328 electron microscopy (SEM, TEM), dynamic light scattering, gas adsorption, elemental and
329 thermogravimetric analysis, DRIFTS, and inverse size exclusion chromatography. The minimum
330 reduced plate heights were around 4; this value was larger than that for a 1.7 µm packing with a
331 thicker 150 nm shell [69].

332 While much work has centred on the question of the pore size of SPPs, it seems that the pore
333 size distribution of these materials is considerably wider than that of totally porous particles, as
334 demonstrated using inverse size exclusion chromatography [70]. This observation is perhaps
335 unsurprising in view of the completely different methods used to produce these different kinds of
336 particles, and must arise from the method of shell synthesis.

337 The loading capacity of SPPs is sometimes questioned in that only a proportion of the particle
338 is porous and therefore accessible to solutes. The capacity of SPPs was found to be not greatly
339 reduced compared with totally porous particles yielding similar efficiency [71,72]. The original small
340 particle SPP columns had a value of ρ of 0.63 [73], indicating that about 75 % of the particle is porous
341 compared with a totally porous particle of the same particle diameter. Other popular commercial
342 varieties of SPP column have a solid core of diameter 1.9 µm and an overall diameter 2.6 µm,
343 implying a value of $\rho = 0.73$ and around 61 % of porous volume. The ρ value of close to 1 for the
344 original pellicular particles indicates a very much smaller porous volume. In view of these values,
345 there is no particular reason to suspect that for these small “thick” SPPs the loading capacity should
346 be drastically compromised, although clearly their capacity might be expected to be somewhat

347 reduced. However, this favourable assessment may not be true for more recently developed SPPs with
348 different shell thickness. In addition, other factors may be involved in loading capacity; it is possible
349 that solutes do not penetrate completely to the centre of totally porous particles, indicating that some
350 of their potential capacity could be redundant. Furthermore, the specific surface area of the porous
351 shell (in m^2/g of shell material) may be different from that in totally porous particles [3].

352

353 **3. Fabrication of core-shell particles for separations**

354 Core-shell particles are usually fabricated by a two-step or multiple step method; the core is usually
355 formed first and the shell is generated on the core subsequently. **The shell may be formed from**
356 **aggregated nanoparticles, nanofibers, or nanorods. The interstitial spaces between the nanostructures**
357 **generate the porosity, which is the platform for HPLC separation.** Different methods have been used
358 to prepare such core-shell particles [74]. Among them, some methods are frequently used to produce
359 core-shell microspheres for HPLC.

360

361 3.1 Silica core-shell particles by layer-by-layer deposition

362 The layer-by-layer (LbL) method is mostly used for the preparation of core-shell packing materials,
363 particularly for those commercially available ones. The fabrication by the LbL technique starts with a
364 non-porous solid sphere (as the core), followed by alternate deposition of the charged polymer and
365 oppositely charged nanospheres (Figure 2). This method utilizes the electrostatic interaction and other
366 forces such as hydrogen bonding, covalent bonding, van der Waals interaction between the positively
367 charged and negatively charged molecules/particles [4]. For commercial core-shell particles used in
368 chromatography, the whole particle is usually made of the same material silica.

369 This concept was first introduced 50 years ago using glass beads or polymer particles as the
370 cores coated with the shell of a few micrometers thick [29]. These particles were intended for the
371 analysis of macromolecules and were expected to provide high loading capacity and a low solid-liquid
372 mass transfer [29, 75]. The development of core-shell particles was slow over the years and it took
373 time before reliable procedures had been developed. This led to the introduction of second generation
374 of core-shell particles appearing in 1992 [31]. Poroshell columns were introduced later. The core was

375 made from totally porous particles which were densified at 1050 °C. The core-shell particles were
376 made by spray-drying a suspension of silica core and silica sol. A subsequent elutriation was required
377 to produce the desired size and distribution [31]. The particles met with limited success in spite of
378 improved separation of proteins compared fully porous particles [76, 77]. The limitations were
379 addressed with the introduction of modern 2.7 µm Halo core-shell particles (third generation)
380 developed by Kirland et al. [28, 73]. The technology gained considerable attention with the
381 achievement of a minimum reduced plate height of 1.5 for small molecules separations [28,78]. With
382 this achievement, smaller particles such as Phenomenex 2.6µm and then Kinetex 1.7 µm were later
383 introduced, exhibiting exceptional performance [79,80].

384 These core-shell particles show very narrow PSD of $d_{90}/d_{10} \leq 1.25$. This is achieved by the
385 use of monodisperse non-porous solid microsphere cores, which are prepared via a Stöber method
386 [81]. The Stöber method can be modified to obtain sub-2 µm and sub-3 µm non-porous silica particle
387 to be used as core for core-shell particles [82]. The second step is building a stable and homogeneously
388 thick layer of porous silica shell around the non-porous core [83,84]. A large percentage of core-shell
389 silica particles used for chromatography are prepared via the LbL approach. Several successive steps
390 are needed to build a homogeneously thick layer of sol shell [85]. The thickness of the shell and the
391 size of the silica sol can be tuned to suit different types of chromatographic applications as it strongly
392 affects the mass transfer for different analytes [32, 33]. But it is also important to achieve a sufficient
393 shell thickness to improve retention factor and sample capacity. The formation of the shell is driven
394 by electrostatic interaction of silica sol onto the core, which is firstly coated with cationic polymers
395 [33].

396 Manufacturing core-shell silica particles with the LbL method is time-consuming, resulting in
397 low productivity as it requires extensive dilutions of reagents below 0.5 w/w% to reduce
398 agglomeration and repetitive washes of excess reagents in order to main the narrow particle
399 distribution [33,86]. Several studies were carried out to optimise the method by examining various
400 factors such as the effect of polymer chain, pH and temperature on improving the deposition of sol
401 onto the surface [33, 86]. Thicker shell can be obtained depending on the molecular weight of the
402 polymer as it can absorb several layers of sol particles at one time as the charge density of the

403 electrolyte is increased allowing more extended conformation. Thus, rather than forming monolayer
404 deposition per coating cycle, altering the polymer chain results in change in the polymer behaviour in
405 solution, which allows longer segments to protrude into the suspension and hence maximize the
406 amount of nanoparticles adsorbed. This approach has considerably improved the productivity of the
407 synthesis and higher level of porosity of the silica shell. The behaviour of the polymer in solution is
408 influenced by suspension ionic strength and pH.

409 Colloidal silica sol is regarded as an important part in controlling shell roughness and
410 physical properties (Figure 3). A number of sol layers are needed to produce a sufficient surface area,
411 which is commonly around 50-100 m²/g. This is generated from the inter-particle voids of the sol
412 particles during shell growth, with the pore size usually in the range of 8-10 nm (the size of silica sol
413 control the final pore size) [33, 86]. Thus, to obtain the desired surface area for separation of small
414 molecules it is recommended that porous layer thickness should be between 24-41% of the total
415 particle diameter [32, 64, 87]. For the separation of large molecules, the shell thickness less than 13%
416 was recommended by Horvath and co-workers for increased efficiency and mass transfer [87]. It
417 should be noted that these values refer to the whole mass of the particles that includes non-porous
418 cores. Taking into account the volume fraction of the porous shell only, specific surface area would be
419 equivalent to fully porous particles. Synthesis parameters such as drying and sintering temperatures
420 can lead to shell deformity and loss in surface area and pore volume [88]. Drying a wet-shell by
421 lyophilisation can better preserve the structure of the porous shell and contribute to a higher surface
422 area. Sintering temperature was also investigated ranging from 550 – 1050 °C to improve the stability
423 of shell without significant shrinkage or melting of the shell [89]. The stability of the shell increased
424 with increasing sintering temperature, accompanied by a decrease in shell thickness. With
425 temperatures above 1000 °C, shell melting and deformity occurred with a significant loss in surface
426 area < 40 m²/g. The data obtained indicated an approximately 5% drop in surface area with 100 °C
427 increase in sintering temperature [89]. Nonetheless, it was determined that 950 °C gave the optimum
428 mechanical strength without substantial loss in specific surface area, pore volume and pore size.

429

430 3.2 One-pot synthesis of spheres-on-sphere silica particles

431 The current core-shell particles preparation method does have its limitation, e.g., poor quality control
432 in multiple-step synthesis, time consuming, and a large amount of waste, particularly when
433 constructing the particles with thick shell. Recently, a unique type of core-shell particle with large
434 macropores was reported by Ahmed et al. [90]. The particles were prepared by one-pot synthesis at
435 room temperature from a single precursor 3-mercaptopropyltrimethoxysilane (MPTMS). The obtained
436 particles showed a unique spheres-on-sphere (SOS) structure (Figure 4). Monodisperse SOS particles
437 can be prepared from the one-pot synthesis, without the need to elutriate and classify the particles as
438 normally employed by the commercial manufacturing process [91]. Both the core and the shell are
439 formed within a single vessel in the synthesis. A time study was carried out to track the formation of
440 particles throughout the reaction using SEM. The data suggested two stage nucleation process
441 occurred at different intervals which was induced by use of appropriate silica source and reagents.
442 The first stage was the formation of the core microsphere. Within a short time after the core
443 formation, the second stage of nucleation led to shell formation which was made up of nanoparticles
444 $\leq 100\text{nm}$ in diameter on the surface of these microspheres [90]. The shell thickness and porosity can
445 be controlled by fine-tuning preparation conditions such as pH and solvent ratios. The interstices from
446 the assembly of the nanospheres on solid microspheres generate the interconnected macroporosity
447 which serves as the foundation for HPLC separation. These SOS particles are highly efficient as
448 stationary phase for separation of small molecules and particularly peptides and large biomolecules
449 [91-93]. This method is an alternative to the mainstream approach of producing solid core-shell silica
450 particles which use the time-consuming LbL approach and could potentially offer easier quality
451 control and lower manufacturing cost.

452 For the SOS particles, both the nanospheres and microspheres are nearly free of mesopores,
453 although a type I nitrogen isotherm was generated implying the presence of microporosity less than 1
454 nm in size after low temperature sintering [90]. Surfactants have minimal contribution in microporosity
455 formation and the microporosity is believed to be mainly from the decomposition of MPTMS during
456 sintering. Further studies were carried out to co-condense other silanes, such as the commonly used
457 tetraethyl orthosilicate (TEOS) and octadecyltrimethoxysilane (OTMS), into the SOS framework,
458 promoting the formation of surfactant-templated mesopores [94]. The resulting particles exhibited

459 higher surface area reaching up to 680 m²/g and bimodal micropore (<1nm) and mesopore (2-3nm)
460 distribution (Figure 5). However, these mesopores are too small for efficient HPLC separation which
461 usually requires minimum pore size of 7 nm. The mesopores in these SOS particles could be further
462 expanded to about 8 nm by a solvothermal swelling approach with pore expanding reagents N,N-
463 dimethyldecylamine and 1,3,5-trimethylbenzene [94]. The type of pores within the particles is
464 critically important for certain applications and entrapment of other materials. There is great interest
465 in utilisation of SOS particle macroporosity rather than mesopores as it can offer higher mass transfer
466 for biomolecules [91-93]. The surface structure of the assembled nanoparticles of SOS particles also
467 allows the growth of interesting materials such as metal-organic framework (MOF) nanoparticles
468 [95,96].

469 The one-pot synthesis strategy has also been adopted by other researchers. For example, the
470 rods-on-sphere silica particles were prepared from solutions containing cetyltrimethylammonium
471 chloride (CTAC), Na₂SiO₃, and formamide in water with magnetic stirring at 35 °C. The prepared
472 particles were calcined in air at 550 °C to remove the surfactant templates [97]. Like the SOS
473 particles, the column packed with the rods-on-sphere particles showed good HPLC separation with
474 low backpressure [97].

475

476 3.3 Core-shell particles with silica-core and MOF-shell.

477 MOFs are crystalline microporous materials which are formed by metal ions or clusters linked with
478 organic ligands. MOFs are usually synthesized via one-pot reactions between ligands and metal ions
479 in solutions between room temperature and 250 °C. This results in crystalline pore structures with
480 uniform pore size and pore shape with better interconnectivity. Its porosity can be systematically
481 adjusted due to the enormous variety of metal ions and organic ligands available [98-100]. MOFs
482 have been widely investigated for applications such as gas storage, drug delivery, catalysis, medical
483 sensors and separation [98 and the references in the issue]. For chromatographic separation, having
484 well-defined interconnected pores with minimal dead volume can offer better efficiency [101]. MOF
485 materials have been used as stationary phase for HPLC [14]. This includes direct packing of MOF
486 particles [101-104] and incorporation of MOF into porous silica [105]. The issues with MOFs as

487 stationary phase are: (i) The micropores are not suitable for separation of smaller molecules in liquid
488 phase; (ii) MOF particles are not spherical and are difficult to pack into column, leading to low
489 efficiency; (iii) Poor mechanical stability of MOF particles leads to crush of the particles under
490 operational pressure; (iv) Most of the MOFs are not stable in the presence of water, particularly under
491 acidic and basic conditions.

492 The core-shell particles with silica core and MOF shell have emerged as promising stationary
493 phase, combining the advantages of MOFs and easy packing/mechanical stability of silica spheres.
494 However, only water-stable MOFs are usually employed to produce silica-MOF core-shell particles or
495 other MOFs if the mobile phase contains no water. The MOFs mostly investigated in this regard
496 include ZIF-8 [96, 106-109], UiO-66 [110-112], and HKUST-1 [95]. This is likely because these
497 MOFs can be readily formed on the silica surface with reasonable coverage and not too harsh
498 conditions. MIL-100 (Fe) and some other MIL-typed MOFs have good stability and are used as
499 stationary phase directly [104, 113-115]. However, the reports on core-shell particles with MIL-100
500 (Fe) are not as much as the other MOFs, which may be attributed to the difficulty in forming MIL-100
501 (Fe) coating on silica.

502 A number of strategies have been attempted to prepare the microspheres with MOF coating.
503 This involves either a single or multiple depositions using metal source and organic ligand to achieve
504 a uniform growth of MOF crystals. This can be achieved by simple synthesis of MOFs in the presence
505 of microspheres or pre-modifying the surface of the microspheres with the functional group that can
506 form linkage with the organic ligand. Figure 6 shows the scheme of the latter method in synthesizing
507 silica spheres with UiO-66 coating [111]. This is expected to promote the formation of stable
508 coatings.

509 Han et al. reported the synthesis of MIL-68(Al) onto silica at 403 K by introducing both
510 $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ and terephthalic acid [116]. This resulted in MIL-68(Al) coated onto silica but particle
511 fusion and random growth of MOF crystals was observed. A similar attempt was carried out by
512 hydrothermal synthesis of UiO-66 (Zr) onto silica particles at 120 °C [110]. The particles were
513 collected by centrifugation with successive washes, but silica@UiO-66 (Zr) microsphere could not be
514 isolated from the UiO-66 (Zr) nanocrystals. The resulting composite material was applied in LC

515 separation of small aromatic molecule demonstrating the unique selectivity of MOF. A control growth
516 of these crystals on the surface seems to be an issue with further reported studies by Tanaka et al. who
517 prepared chiral (R)-CuMOF-1 on silica [117]. Nonetheless, this does not seem to diminish the column
518 performance but does affect mass transfer kinetic resulting in broader peaks.

519 In recent years, methods have been developed to simplify the separation of core-shell MOF
520 particles from liquid suspension by combining magnetic particles with MOFs. For example, Fe₃O₄
521 nanoparticles was used as a scaffold for the growth of HKUST-1 [118] and MIL-100(Fe) [119] shell.
522 Step-by-step assembly growth strategy using ethanolic solutions of metal source and ligand was used
523 and desired shell thickness was achieved by repetitive deposition process. Qin et al. used the
524 composite magnetic silica particles as scaffold for the synthesis of UiO-67 (Zr) coating [120]. The
525 step-by-step coating was again utilised to achieve the desired coating. The composite core-shell
526 particles were packed into HPLC column for the separation of polar aromatic molecules. The
527 selectivity of the MOF molecules was illustrated, but peak shape was poor [120].

528 The surface functionalities of silica may provide strong interaction with metal ions, hence to
529 drive more controlled growth of MOF crystals and better isolation from liquid suspension. Ahmed et
530 al. showed the surface functionality could be a critical factor in improving interaction, adherence and
531 coverage on the microspheres [95, 96]. The SOS particles were functionalized with –COOH groups
532 and –NH₂ groups which promoted the formation of HKUST-1 [95] and ZIF -8 [96] nanoparticles.
533 This methodology has also been demonstrated with different supports such as polymer [100], alumina
534 [121] and silica [107, 108]. Sorribas et al. [108] and Naik et al. [122] manipulated the growth kinetics
535 of ZIF-8 using a seeded growth technique followed by secondary and repetitive crystal growth cycles,
536 achieving a sufficient thickness. Figure 7 shows the morphology of mesoporous silica spheres, seeded
537 microspheres, and the change in thickness of ZIF-8 coatings under 1 and 2 growing cycles [108]. The
538 seeded growth and carboxylic acid functionality are believed to be the key factors in obtaining
539 uniform and homogenous coverage of ZIF-8 shell.

540 The surface morphology of the microspheres may play a significant part in crystal nucleation
541 and growth. This has been evidenced by the use of SOS particles for the controlled growth of
542 HKUST-1 [95] and ZIF-8 [96] MOF crystals. Surface roughness, functionality and type of solvent

543 were found to significantly influence the crystal morphology, attributing to interaction with metal ions
544 and crystal growth kinetics [96].

545

546 3.4 Core-shell particles with silica-core and other inorganic shell

547 Although core-shell particles are mainly prepared from silica for LC, other types of shell materials
548 have also been used in chromatographic applications. The coating shell using different materials on
549 silica core could increase functionality, selectivity and stability. The synthesis of such materials is
550 achieved through a one-pot method or a multiple-step process on a pre-synthesised core via different
551 approaches such as LbL coating, polymerisation of the shell on solid core [74, 123].

552 Continuous flow synthesis was used to coat colloidal silica with Ag nanoparticles [124]. A
553 solution of silver nitrate, colloidal silica, formaldehyde were mixed with ammonia solution at the T-
554 junction of the flow system. The result showed a consistent and reproducible formation of patchy
555 silica@Ag particle at high yields. The distribution of Ag nanoparticles was affected by the flow rate
556 of mixing. Faster mixing led to accelerated nucleation and random growth in between the colloidal
557 silica. Hanisch et al. reported the synthesis of Ag nanoparticles necklaces coating on silica particles
558 without addition of reducing or templating agents [125]. It was found that ammoniacal silver complex
559 was essential for necklace formation, at a high pH typically around pH 11. The silica surface
560 dissolution at this pH interacted with the ammoniacal silver complex and promoted the formation of
561 Ag nanosized necklaces [125].

562 Dun et. al. applied the LbL method for the deposition of ZrO₂ nanoparticles on silica core
563 [126]. Stable and homogenous layers of ZrO₂ were formed in the present of SDS by alternate
564 adsorption steps, reaching up to 326 nm shell thickness on the silica core particles. Zirconyl chloride
565 octahydrate was used to synthesize the ZrO₂ nanoparticles. The particle size increased from 3.5 μm to
566 3.8 μm, and the removal of SDS resulted in surface area ranging from 131 to 326 m²/g with 84 Å
567 pores depending on the number of layers [126]. SiO₂@ZrO₂ particles were used in chromatographic
568 separation of inorganic and organic ions. Both pH and the strength of Lewis base of the mobile phase
569 played an important role in retention behaviours. The particles exhibited excellent pH stability at pH
570 12 after 5000 column volumes [127]. A follow-up study was reported without the use of surfactant

571 during the synthesis [128]. Electrostatic attachment of positivity charged zirconia nanoparticles onto
572 negatively charged silica particle was achieved by adjusting the pH around 6. This also led to further
573 condensation reaction between the Si-OH and Zr-OH groups on the surface resulting in the formation
574 of Zr-O-Si linkages. Sub-2 μm silica particles were used for the formation of $\text{SiO}_2@\text{ZrO}_2$ particles. A
575 dense coverage of nanoparticles on the surface was formed. The reported surface area ($42 \text{ m}^2/\text{g}$) after
576 calcination was much lower than the LbL method, with smaller pores around 32\AA . However, this did
577 not reduce the chromatographic performance of the composite particles [128].

578 Ge et al. prepared silica core-shell particles with porous titania shell by alternate adsorption of
579 SDS and titania nanoparticles on $6 \mu\text{m}$ silica core particles [129]. The titania sol was prepared using
580 tetrabutyl titanate acetic acid in ethanol, which resulted in nanoparticles around 12 nm in diameter.
581 The shell thickness reached about 300 nm after 6 layers coating with surface area almost doubled
582 from 110 to $200 \text{ m}^2/\text{g}$ and an increase in particle density [129]. The surface areas decreased
583 significantly when the treatment temperature increased to above $500 \text{ }^\circ\text{C}$. The silica@titania particles
584 were found to offer good stability under extreme chromatographic conditions for basic compounds
585 separation [130]. In another report, liquid phase deposition was utilised for the coating of titania
586 nanoparticles onto silica surface [131]. Ammonium hexafluorotitanate ($(\text{NH}_4)_2\text{TiF}_6$) was incubated at
587 $35 \text{ }^\circ\text{C}$ in boric acid/silica solution for 16 hours. The boric acid acted to stabilize the fluoro complex
588 and facilitate oxide precipitation onto the silica surface. The deposition was repeated to obtain
589 different levels of titania coating and more surface roughness with an estimated 3 nm shell thickness.
590 The material was successfully applied for the separation of Adenosine phosphate compounds due to
591 the Lewis-acid-base interaction with the phosphate groups [131].

592 Cationic polymer poly(diallyldimethylammonium chloride) (PDDA, $M_w = 100 - 200 \text{ kDa}$)
593 was used in the LbL assembly of iron oxide nanoparticles on silica core [132]. The PDDA-coated
594 silica was added into the Fe_2O_3 nanoparticle suspension and the process was carried out under
595 sonication to reduce aggregation. No pH control was performed, similar to the silica LbL method. The
596 homogeneity of the shell coating and thickness was somewhat random. These core-shell particles
597 showed superior performance in removing methylene blue and methyl orange, attributing to the
598 electrostatic interactions between the dyes and iron oxide coating [132].

599

600 3.5 Surfactant-templated shell in core-shell particles

601 Sol-gel synthesis can be combined with surfactant templating to fabricate mesoporous silica materials
602 [133]. By using amphiphilic triblock copolymers as the structure-directing agents, silica materials
603 with well-ordered uniform pore sizes up to 300 Å, thicker wall, and greater hydrothermal stability can
604 be formed [134, 135]. However, most of these materials are irregularly shaped porous powders,
605 limiting their use in areas such as HPLC. Yang and others developed the methods to fabricate
606 mesoporous spheres [136-138]. They focused on optimizing the one-pot reactions through adjustment
607 of pH, stirring rate, adding co-solvent, using spray drying, etc., to control the particle size, particle
608 size distribution, pore size, and pore size distribution simultaneously. However, the synthesized
609 materials usually have either broad particle size distributions or small pore sizes.

610 The surfactant-templating approach has been used to synthesize SPPs. One method is similar
611 to the LbL method, where a thin porous silica shell was grown on non-porous particles for multiple
612 times in the presence of a surfactant. At least seven layers were required to form final particles with a
613 surface area of 100 m²/g [32]. Recently, Min et al. reported the preparation of dandelion like
614 core-shell silica microspheres with hierarchical pores [139]. Although it has the potential to be used
615 as the stationary phase in HPLC separation, an etching process was involved to create the porosity in
616 the shell, which significantly reduced the mechanical stability of the structure. Furthermore, the pore
617 sizes were still too small (<7 nm).

618 Different from bottom-up methods, such as coacervation and LbL, a top-down method called
619 “pseudomorphic transformation” (PMT) was used to form mesoporous microspheres as stationary
620 phase for HPLC. The process was firstly used to transform amorphous porous spheres to micelle-
621 templated totally porous particles with the same particle morphology [140-143]. By starting the
622 transformation process with non-porous spheres (either silica or metal oxide spheres) and controlling
623 the reaction time, it is possible to fabricate solid-core porous-shell particles [65, 144-145]. In this
624 process, non-porous silica particles are dispersed in an alkaline solution with the presence of
625 surfactant. When the temperature increases, the silica on the particle surface first dissolves and the
626 resulting silicic acid subsequently precipitates around ordered, positively charged micelles on the

627 silica particles without changing the overall particle morphology. The advantages of this process are
628 that the properties of the particles and the properties of the pore structure can be independently
629 optimized. The particle size and size distribution are determined by the starting materials and the
630 intra-particle pore structure is controlled by the PMT variables such as surfactant, swelling agent, pH,
631 and reaction time.

632 Wei et al. explored the process of PMT and developed an improved process for the SPPs with
633 a unique shell pore structure [146]. The thin porous shell contained elongated pore channels normal
634 to the particle surface (Figure 8). The impact of the novel pore structure on the performance of these
635 particles was evaluated by measuring van Deemter curves and constructing kinetic plots. Reduced
636 plate heights as low as 1.0 was achieved on conventional LC instruments, suggesting greater
637 efficiency of such particles compared to conventional totally porous and superficially porous particles.
638 It is interesting to note that these preparations provide radially ordered pore systems within a single
639 shell whilst the pore structure in the common SPPs is rather random (Figure 8).

640 Qu et al. produced monodisperse silica spheres with solid core and fibrous shell synthesized
641 using a bi-phase reaction using cyclohexane to slow down the rate of silane hydrolysis and
642 condensation [147]. Both the thickness and the pore size of the fibrous shell could be finely tuned by
643 changing the stirring rate during synthesis. When the stirring rate was adjusted from 0 to 800 rpm, the
644 thickness of the shell could be tuned from 13 to 67 nm and the pore size from 5 to 16 nm. By
645 continuously adjusting the stirring rate, fibrous shells with hierarchical pore structure ranged from 10
646 to 28 nm and thickness up to 200 nm could be obtained in one pot (Figure 9). The particles were
647 functionalised with a C18 bonding and packed in to a column showing separation performance as high
648 as 2.25×10^5 plates m^{-1} for naphthalene and back pressure as low as 5.8 MPa. The columns were not
649 evaluated for reduced parameters or kinetic performance.

650

651 3.6. Core-shell particles with non-silica core

652

653 Materials other than silica have also been used as the core to construct core-shell particles. Deng et al.
654 developed a method to coat polystyrene particles with an organo-silica shell, although these materials

655 were intended for applications outside HPLC such as in medicine or catalysis, where core-shell
656 materials have also attracted considerable attention [148]. Carbon particles, derived from oxidised and
657 carbonised polystyrene-divinylbenzene particles, were used as the core to fabricate core-shell particles
658 [149]. The LbL deposition of amine containing polymer and nanodiamonds onto these carbon cores
659 was performed. The particles showed good mechanical, thermal and pH stability, and good
660 separations of essential oils [149]. A commercially available variant of this material with pore size
661 180 \AA was evaluated for the separation of proteins [150]. As the stationary phase contained some
662 protonated amine groups within the structure, the retention mechanism was expected to be a mixture
663 of hydrophobic interaction and anion exchange, although it appeared the former was the dominant
664 mechanism [150]. The robustness of the material allowed the effect of temperature variation over the
665 range of 30-80 °C to be studied even with the use of larger amounts of trifluoroacetic acid (TFA) in
666 the mobile phase than usual (0.2-0.5 % compared with the usual 0.05-0.1 %), which was necessary to
667 improve efficiency. Changing the temperature over this range hardly affected the peak capacity of the
668 gradient separations, but did give interesting selectivity changes.

669 Wide pore materials (120, 180 and 250 \AA) with carbon core and nanodiamond-polymer shell
670 were evaluated for the separation of proteins [151]. The largest pore size gave the best performance
671 for large molecules. The particles were shown to be smooth (Figure 10) and therefore do not benefit
672 from the proposed packing advantages of rough silica SPPs, a property which may improve the radial
673 homogeneity of the packing and reduce eddy dispersion. However, it was considered that eddy
674 diffusion may not be a significant contributor to band broadening for large molecules. The smooth
675 surface morphology of these particles in this case could be an advantage for separation of large
676 molecules [151].

677

678 **4. Applications of silica Core-Shell particles**

679 The need for stationary phases with improved kinetic performance has increased in demand. Among
680 them, increasing sample analysis throughput has become a target in many applications. Core-shell
681 silica columns offer faster analysis without compromising separation efficiency. The short path
682 diffusion in the porous shell improves mass transfer and minimises peak broadening, which in turn

683 increases resolution and efficiency for complex mixtures. This was demonstrated by comparing
684 Kinetex and Zorbax columns for the separation of three alkylphenones [41]. There was a clear
685 improvement in peak width and 30% in plate height. With increasing flow rate this difference in plate
686 height was more than 75%. Fekete et al. evaluated Ascentis Express C18 (2.7 μm) for the separation
687 of a mixture of steroids against sub-2 μm particles stationary phase [152]. The separation was
688 completed in less than 2 min with lower backpressure due to its higher column permeability. Column
689 permeability is significantly influenced by core-shell particle size. Bobály et al. showed that Kinetex
690 1.3 μm particles suffered from low permeability compared to Kinetex 1.7 μm particles under optimal
691 linear velocity [39]. The best comparison to Kinetex 1.7 μm particles was Cortecs 1.6 μm particles
692 with similar permeability, but the Cortecs 1.6 μm particles possessed excellent kinetic performance
693 with reduced plate height (H_{min}) of 2.66 μm (Kinetex 1.7 μm H_{min} of 3.17 μm).

694

695 4.1 Applications in food and drinks

696 The core-shell technology is still evolving and the number of commercially available core-shell
697 particles is rapidly growing to cover a wider range of applications. Core-shell particles have been used
698 in determining several classes of antioxidant and natural contaminants in food or drinks.
699 Comprehensive characterisation of a variety of complex flavones and phenolic acids matrices in wine
700 were successful explored and resolved within 30 min at elevated temperature 60 °C [153]. A study
701 was carried out to compare fully porous sub-2 μm BEH particles to Halo 2.7 μm C18 particles for the
702 separation of 10 phenolic compounds in canned artichoke [154]. The obtained results for core-shell
703 column in term of efficiency, speed, resolution and pressure, demonstrated the potential of SPPs over
704 totally porous particles (Figure 11).

705 Manns and Mansfield explored complex antioxidant compounds from red and white juices
706 and wines produced from *Vitis vinifera* and hybrid cultivars [155]. The resolving power of Kinetex
707 2.6 μm C18 column successfully resolved the first two classes of antioxidant nonanthocyanin and
708 phlogucinolysis. Anthocyanins antioxidant was better separated using Kinetex 2.6 μm PFP particles,
709 which offered different selectivity due to π - π and H-F interaction. The unique selectivity of PFP phase
710 (Kinetex 2.6 μm) was also demonstrated in the separation of positional isomers chlorogenic acids and

711 sesquiterpene lactones in chicory root without additional purification step [156,157]. Simonovska et
712 al. developed a rapid separation method to determine lutein in spinach pigments extract (xanthophylls,
713 all-trans-violaxanthin, all-trans-zeaxanthin and all-trans-lutein, chlorophylls and all-trans- β -carotene)
714 on a Kinetex 2.6 μm C18 column in less than 13 min [158]. The column did show some limitation,
715 with poor resolution observed for targeted compounds lutein and structural isomer zeaxanthin.
716 Fontana et al. developed an approach for rapid determination of multiclass polyphenols in grape
717 pomaces using Kinetex 2.6 μm C18 column under 12 min [159]. Considering the complexity of the
718 grape pomaces extract, which includes high quantity of target analytes of different chemical nature,
719 classes and concentrations, high sensitivity and rapid analysis were demonstrated for the core-shell
720 particles column. The method was suitable for quantification and determination of 20 polyphenols
721 from different grape varieties.

722 Natural contaminants mycotoxins are low molecular compounds and can be very toxic at low
723 concentrations closer to 1 $\mu\text{g}/\text{kg}$. In routine control of red wines, quantification of Ochratoxin A levels
724 below 2 $\mu\text{g}/\text{L}$ levels is mandatory [160]. The low operation pressure of core-shell column, e.g.,
725 Kinetex 2.6 μm C18 particles, facilitated the use of conventional HPLC for these analysis, detecting
726 Ochratoxin A at the concentrations as low as 0.0028 $\mu\text{g}/\text{L}$ with high efficiency.

727 Core-shell columns were also applied into agricultural products such as determination of five
728 *Alternaria* toxins and citrinin in tomato juice [161], microstins in drinking water [162], and
729 deoxynivalenol in cereal products [163]. The analysis of bisphenol compounds contamination caused
730 by the coating inside the soft-drink (such as cola, orange soda, energy drinks, etc) containers was
731 reported by Gallart-Ayala et al. [164]. Supelco Ascentis Express 2.7 μm C18 column was used to
732 carry out a gradient elution of bisphenol compounds coupled to MS. Fast elution was achieved in less
733 than 3 min with higher resolution of five bisphenolic compounds in beverages [164].

734

735 4.2 Applications in separation of large biomolecules

736 Macromolecules are highly complex and chromatographic analysis is still challenging. The
737 importance of analysing biomacromolecules is increasing due to its substantial development in life
738 science and biomedical applications. Wide pores in the porous shell are required to allow free

739 diffusion of such molecules. It has been claimed that the pore should be at least four to ten times the
740 hydrodynamic diameter of the biomolecule, which would allow less restriction on mass transfer and
741 better separation efficiency [165]. Close et al. investigated the influence of pore size 80, 150 and
742 400 Å on nucleic acids chromatographic resolution [166]. Triethylammonium acetate and
743 tetrabutylammonium bromide were used as the ion pair reagent in conjunction with Accucore 2.6 µm
744 C18 column. The results for the separation of oligonucleotides, a 2'-deoxythymine ladder (dT 19 –
745 24) and large dsDNA/RNA fragments showed that the increase in pore size resulted in increased
746 resolution, rapid and high throughput analysis. The effect of having wider pore size for the diffusion
747 of large proteins up to at least 400 kDa such as ribonuclease A and insulin was investigated by
748 Wagner et al. [67]. In this study, Halo 2.7 µm C18 columns with pore size of 90, 160 and 400 Å were
749 used and the results showed significant improvement in peak shape, resolution and selectivity (Figure
750 12).

751 Due to significant advances in biopharma sector, there are still needs for larger pores to
752 sustain biomolecules greater than 350 kDa. The preparation of core-shell prototype particles with pore
753 size of 1000 Å was recently reported and the packed column was evaluated against the columns
754 packed with core-shell particles of smaller pores around 400 Å [167]. The results suggested that both
755 400 and 1000 Å pores were well suited for biomolecules up to 350 kDa. The advantage of large pores
756 showed better efficiency for the separation of base pair DNA (~660 kDa) with minimal peak
757 broadening.

758

759 4.3 Core-shell particle columns for HILIC

760 Some hydrophilic molecules are poorly retained by conventional reversed stationary phase. As an
761 alternative, HILIC has been used to offer higher efficiency for the separation of small polar
762 compounds using the solvents with lower viscosity [168]. Heaton et al. demonstrated that the kinetic
763 performance of bare silica core-shell (Cortecs) was superior compared with hybrid and conventional
764 bare silica phases and exhibited higher diffusion of hydrophilic base cytosine [169]. In another study,
765 the Halo silica 2.7 µm columns were used in HILIC mode to separate a mixture of acidic and basic
766 compounds, with acetonitrile (85%): ammonium formate as the mobile phase. When three columns

767 were coupled together with a length of 45 cm, over 100,000 theoretic plates were achieved, with the
768 total backpressures generated only 280 bar [170]. Kirkland et al. used the modified Halo silica (2.7
769 μm , pore size 90 Å) with ligands for HILIC to provide efficient separation of compounds that are
770 difficult to separate by reversed-phase HPLC [171]. This modified column with a highly polar poly-
771 hydroxylic phase, Halo Penta-HILIC (100 mm x 2.1 mm), could efficiently separate a mixture of
772 drugs of abuse and selected metabolites, using a mobile phase of acetonitrile (95%)/5 mM ammonium
773 formate aqueous solution (5%). This column can be used for separation of highly polar solutes such as
774 sugars, peptides, and nucleic acids, as demonstrated by the separation of 15 compounds containing
775 nucleosides and bases within 8 minutes with a gradient mobile phase [171].

776

777 4.4 Core-shell particle columns for SEC

778 Separation based on the size difference of molecules has been developed as an effective technique
779 known as SEC. Given the complexity of protein and peptides-based parenteral therapies, a set of
780 complementary separation techniques, including SEC, are required to monitor the critical quality
781 [172, 173]. SEC are predominantly favoured for routine and validated analysis to monitor protein
782 aggregation. Totally porous silica particles have been employed in SEC separation, provided that a
783 significant reduction in silanol activity is achieved. In recent years, SPPs have been used in SEC
784 separation. Pirok et al. investigated the feasibility of using core-shell particles in SEC [13]. The
785 results showed good resolution and performance, depending on pore size of the core-shell particles.
786 The core-shell particles with large pores of 1000 Å were used for the separation of polystyrene
787 standard (17.5 kDa to 1.8 mDa) [167].

788 The total pore volume is reduced for the core-shell particles, and hence a lower loading
789 capacity, when compared to the standard SEC porous particles. But this is usually compensated for by
790 an increase in efficiency. Schure and Moran compared the SEC performance between fully porous
791 SEC particles and core-shell particles with different pore sizes of 160 and 1000 Å (Figure 13) [174].
792 Having large pore volume is thermodynamically advantageous for better separation, but the porous
793 shell faster diffusional kinetic compensate for the loss of pore volume and thermodynamic limitations.

794 Thus, diffusion length is much shorter, offering narrower peaks which tend to preserve the peak
795 capacity of the separation and higher efficiency.

796

797 **5. Applications of SOS particles**

798 The large interstitial space between the nanospheres of the SOS shell provide high porosity and good
799 performance in HPLC separation. The studies published have covered a range of HPLC applications
800 from small to large molecules [91-94] and polycyclic aromatic hydrocarbons [92, 95-96]. The focus
801 has been on separation of large molecules, because of the large pores and high surface area.
802 Nevertheless, modifications of SOS particles offer the option of tuning the particles properties to
803 optimise the separation of small molecules by creating mesopores across the shell [94].

804 The reduced intra-particle mass resistance allows the use of high flow rates, which
805 particularly helps the fast separation of large molecules [93]. The good performance of C4 bonded
806 SOS particles was shown in gradient mode analysing large molecules such as insulin, myoglobin,
807 BSA, mbA and reduced ADC (antibody drug conjugate) in comparison to commercial fully porous
808 and core-shell materials usually used for proteins separation such as Aeris C18, Halo Protein C4 and
809 BEH300 C18 (Figure 14) [93]. The findings highlighted the SOS capabilities in fast separation
810 showing lower retention at high flow rate (0.4 mL/min) compared to the other materials, with good
811 peak shapes and high peak capacities [93]. In the same study, the efficiency of SOS columns was
812 examined by obtaining h-v plots with butylparaben, decapeptide and glucagon in isocratic mode,
813 resulting in minimum reduced plate height $h_{\min} = 2.6, 3.3$ and 3.3 respectively [93]. The analysis
814 resulted in the average column permeability at different batches as $K_v = 1.09 \times 10^{-10} \text{ cm}^2$, and the lowest
815 separation impedance as $E_{\min} \sim 48000$, categorising the SOS particle at the performance level of the
816 best state-of-the art commercial columns [93].

817 The large pores of SOS particles and the lack of mesoporosity limit their application for small
818 molecules separation. The separation of small molecules was explored through modifying SOS
819 particles using CTAB templates [94]. The modified synthesis process resulted in 6.9 nm mesopores
820 on the particles shell that allowed improved column efficiency (up to 68000 plates/m), but it also
821 resulted in higher retention time due to the increased surface area [94]. The separation of toluene,

822 nitrobenzene and nitroaniline isomers in normal phase HPLC resulted in 39 bar backpressure and 6
823 min retention time, while a different normal phase mixture using toluene, 2,4-di-tert-butylphenol, o-
824 nitroaniline and cinnamyl alcohol showed separation within 5 min [94]. Furthermore, the modified
825 SOS particles did not have significant loss of performance in the separation of large molecules
826 because the separation occurred in the shell interstitial space. This was demonstrated by the separation
827 of ribonuclease A, cytochrome c, lysozyme, trypsin and BSA under reverse phase mode [94]. The
828 separation completed in 2.5 minutes showing comparable column efficiency to the un-modified SOS
829 particles based on similar peak capacities (17 and 19 respectively). The addition of carbonic
830 anhydrase to the mixture expanded the analysis to 3 minutes showing a backpressure of 355 bar [94].

831 The performance of SOS particles in separating compounds with a wide range of molecule
832 sizes has been further demonstrated. The normal phase HPLC analysis of toluene and nitroaniline
833 isomers using 6.5 μm calcined SOS particles showed fast separation in 2 min, a very low back
834 pressure of 18 bar, and a higher permeability ($K_v = 2.79 \times 10^{-13} \text{ cm}^2$), compared to the commercial
835 Hypersil silica columns ($K_v = 1.24 \times 10^{-13} \text{ cm}^2$) [92]. A modification of the SOS with diol groups
836 improved the efficiency further to 65,380 plates/metre and reduced the backpressure to 14 bar. The
837 HILIC separation for sugars mixtures for the same column showed column efficiency of 43,900
838 plates/m and a backpressure of 17 bar. The separation of a large proteins mixture containing
839 ribonuclease A, cytochrome C, lysozyme, trypsin, and BSA was achieved using the C8-modified SOS
840 particles [92]. The results of this reverse phase testing under gradient mode showed fast separation
841 within 2.5 min, a backpressure of 222 bar, and efficiency of 91,705 plates/m [92].

842 The applications on separation of small molecules was also reported by Hayes et al. [91]
843 using C4 bonded 2.9 μm SOS particle columns in order to examine a selection of peptides comprised
844 of 5 small molecules and a selection of proteins. The separation data for the small molecules revealed
845 fast separation within 3 min and 259 bar backpressure. The good performance of the column was also
846 highlighted by reverse phase HPLC analysis for the proteins mixture showing retention time within 6
847 min and a maximum backpressure of 400 bar. However, the use of CTAC instead of CTAB for the
848 preparation of the SOS particles produced smaller pores ($< 100 \text{ \AA}$) that limited the efficient separation

849 of the larger proteins such as BSA, thyroglobulin and myoglobin resulting in peak tailing and poor
850 defined peaks [91].

851 In order to further explore the separation of small molecules, other modifications of SOS
852 particles were performed, for example, by coating with MOF nanocrystals [95]. Two types of MOFs,
853 HKUST-1 [95] and ZIF-8 [96], were formed on SOS particles. The columns packed with
854 SOS@HKUST-1 particles showed the separation of xylene isomers although with relatively poor
855 resolution and low efficiency. The original SOS column itself could not separate the xylene isomers
856 [95]. For the SOS@ZIF-8 particles, the packed column exhibited fast separation of aromatic
857 compounds with column efficiency up to 19,000 plates/m [96]. The good chromatographic analysis
858 obtained by these two materials highlights the potential and possibilities for further development of
859 the SOS particles to tune their composition for more efficient separations.

860

861 **6. Applications of core-shell particles with non-silica shell**

862 Although not many, there are applications of core-shell particles with non-silica shell for HPLC. The
863 limited chemical stability of silica in the pH range of 2-8 is the drive for the use of different metal
864 oxides forming the shell around the silica solid cores. Such metal oxides include titania [129, 175] and
865 zirconium [126-128] nanoparticles coated on silica microspheres. The titania-coated silica particles
866 showed a strong ability to separate adenosine phosphate compounds and good column reproducibility
867 [175]. The column efficiency was reported to be up to 30000 plates/m when separating basic
868 compounds using 35% acetonitrile as the mobile phase [175]. This study also reported low
869 permeability of $K_v = 1.56 \times 10^{-14} \text{ m}^2$ and good column stability under extreme pH condition (pH 7-12)
870 [175]. In another study, the octadecyl-bonded $\text{TiO}_2/\text{SiO}_2$ showed good stability at high pH (pH 9-10)
871 using phosphate buffer [129]. In addition, aromatic isomeric compounds were well separated under
872 normal phase conditions using n-hexane as the mobile phase (0.7 mL/min) and also the separation of
873 nitroaniline using hexane-ethanol (70/30 at 1 mL/min) [129]. However, the column efficiency (~4000
874 plates/m) was relatively low compared to those of the SOS particles [129]. Nevertheless, the
875 separation of 15 basic compounds under the reverse phase showed high symmetrical peaks and good
876 separation of pyridine and aniline derivatives [129].

877 Zirconia-coated silica particles produce a similar performance in HPLC applications,
878 demonstrating the high stability over a wide pH range. One study using such particles showed the
879 separation of hydroxybenzenes, basic compounds, organic and inorganic anions [127]. The inorganic
880 anions were examined by modulating the pH from 3 to 5 using 20 mM of potassium chloride,
881 showing increased retention with $\text{pH} > 4$ due to the weaker anion exchange [127]. The organic anions
882 tested at pH 4.6 and 5.5 showed longer retention time and weakness to elute all the components. On
883 the other hand, good separation of basic compounds using different contents of ethanol as mobile
884 phase confirmed the advantage of these hybrid particles over silica particles. Efficient separation and
885 symmetrical peaks were also observed at the other end of pH range when three acidic compounds
886 were analysed (hydroxybenzenes) using ethanol/hexane (25:75) as mobile phase, highlighting the
887 excellent stability across a wide range of pH [127]. Another study reported a column efficiency of
888 5000 plates/m, short retention time, and symmetrical peaks during the separations of neutral
889 compounds, isomers and aromatic compounds using hexane-isopropanol (85:15) as the mobile phase
890 [128]. The column stability was demonstrated at pH10 using a sodium phosphate solution and a 70:30
891 methanol-water mobile phase. The results showed that the stationary phase was stable at pH 10
892 without noticeable changes on the retention factor or peak width of the solutes [128]. The stability of
893 C18 bonded $\text{ZrO}_2/\text{SiO}_2$ phase was also examined at pH 12 [126]. The tests were performed via the
894 separation of a mixture of aromatic hydrocarbons using methanol-water (80:20) as the mobile phase at
895 ambient temperature. After the columns were conditioned for 30 min with the mobile phase, the data
896 showed good stability at pH 12 without noticeable changes on the capacity factor or peak width. The
897 explanation was the creation of a hydrophobic shield consisting of a cross-linked alkylpolysiloxane
898 layer that protected the Zr-O-Si bonds from hydrolysis [126].

899 It can be concluded that the hybrid core-shell particles present good stability over a wide
900 range of pH for HPLC applications. This advantage is highly appealing for all types of particles used
901 for HPLC separations, and quite possibly indicating the need of creating hybrid core-shell particles for
902 even wider range of applications.

903

904 **7. Summary and perspectives**

905 It has been demonstrated by various reports that core-shell particles (e.g., 2.6 μm particles) show at
906 least the same or better column efficiency in HPLC separation, compared to sub-2 μm fully porous
907 silica particles. But the backpressure is much lower, which makes the traditional HPLC systems
908 usable. The LbL technique is most widely used for the production of core-shell silica particles,
909 particularly the commercial ones. The one-pot synthesis of SOS particles has provided an effective
910 route to novel columns offering fast separation with low backpressure, particular for large
911 biomolecules. Other developments, e.g., hybrid particles with silica core and metal oxide shell/MOF
912 shell, are also covered in this review. These non-silica shell particles offer high stability under basic
913 and acidic conditions or new functionality that separates mixtures (e.g., isomers) that would otherwise
914 not be separated using silica as stationary phase. Although not intended to be exhaustive, we provide
915 examples to show how different types of core-shell particles have been used for HPLC separation
916 over a range of test mixtures, usually with high efficiency/sensitivity, fast separation, and low back
917 pressure.

918 For future development, new methods/procedures should be continuously developed and
919 optimized to produce uniform core-shell particles with controlled thickness and tuneable pores
920 (particularly wide pores) in the shell. Although hybrid particles with metal oxide shells have been
921 fabricated and evaluated and their high stability has been demonstrated, the column efficiency is still
922 rather low. This may be improved by controlling the thickness and pore size of the shell. MOF@silica
923 particles have been intensively investigated but the controls on the shell thickness and the porosity
924 between the assembled MOF nanoparticles are very limited. Another development, which has been
925 rarely reported, is the shell formed of porous graphitic carbon or nanodiamonds. Their chemical
926 stability will be highly attractive for chromatographic separations under extreme conditions.
927 Similarly, the challenge will be the control of the shell thickness and the formation of wide pores. In
928 addition, finding parameters/conditions to fabricate monodispersed particles will be highly beneficial
929 because that will exhibit sharp peaks, high selectivity, and high separation efficiency.

930 Another important aspect will be applying newly developed core-shell particles for separation
931 of complex mixtures. When selecting suitable core-shell particles, the important characteristics
932 include shell thickness, pore size, particle size, chemical stability, and surface functional groups. This

933 will inform the best ways to utilize the columns, e.g., in reverse phase mode, normal phase mode,
934 HILIC, ion exchange chromatography, or SEC. Different analytes, i.e., small molecules, large
935 molecules, peptides, proteins, oligonucleotides, ionic compounds, or drug metabolites, will require the
936 columns with corresponding characteristics. Instrumentation of the HPLC system will be required in
937 order to achieve the best selectivity, sensitivity, and efficiency for complex mixtures.

938

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1392

1393 **Figure Captions**

1394

1395 **Figure 1.** Kinetic plots showing the progress (vertical and horizontal arrows) made recently for (A)
1396 sub-2 μm fully porous (FP) particles (red data) vs FP particles before the introduction of sub-2 μm
1397 particles. (B) Inclusion of core-shell (CS) particles. Plots are for small MW compounds, measured on
1398 C18 columns in reverse phase mode. Reprinted with permission from ref [27].

1399

1400 **Figure 2.** The schematic representation for the preparation of core-shell microspheres by the layer-by-
1401 layer deposition method. Reprinted with permission from ref [4].

1402

1403 **Figure 3.** Comparison of colloidal silica size on the preparation of core-shell silica particles from 0.9
1404 μm non-porous silica spheres, 0.5 wt % poly(diallyldimethylammonium chloride) ($M_w = 100 - 200$
1405 kDa, cationic polymer), and 10 % colloidal silica dispersion ($\text{pH} = 3.5$) by one coating process. (A)
1406 Nyacol Nexsil125 (125 nm); (B) Nyacol NexSil85 (85 nm); (C) Nalco 1060 (60 nm); (D) Nalco 1030
1407 (13 nm); (E) Ludox, AS-30 (12 nm); and (F) Nyacol NexSil8 (8 nm). Reprinted with permission from
1408 ref [33].

1409

1410 **Figure 4.** Monodisperse SOS particles prepared under modified reaction conditions with
1411 polyvinylpyrrolidone and cetyltrimethylammonium chloride. The inset image shows a close-up look of a
1412 SOS particle. Reprinted with permission from ref [91].

1413

1414 **Figure 5.** Effect of organic templates on surface morphology and pore size distribution of modified
1415 SOS particles. (A, B) cetyltrimethylammonium bromide (CTAB) + TEOS; (C, D) OTMS + TEOS,
1416 both added at $t = 30$ min. Reprinted with permission from ref [94].

1417

1418 **Figure 6.** The scheme shows the preparation of silica-UiO-66 core-shell particles by modifying the
1419 silica sphere first. Reprinted with permission from ref [111].

1420

1421 **Figure 7.** SEM images showing the morphology (A) mesoporous silica microspheres; (B) the seeded
1422 microsphere; (C) one cycle growth of ZIF-8; (D) two cycle growth of ZIF-8. And the TEM images
1423 showing the thickness of ZIF-8 coating: (E) the core-shell sphere with one ZIF-8 coating; (F) the
1424 core-shell sphere with two ZIF-8 coatings, where the particles were embedded in epoxy resin and cut
1425 with ultramicrotomy. Reprinted with permission from ref [108].

1426

1427 **Figure 8.** High-resolution SEM comparison between (A) PMT-SPPs and (B) SPPs made from the
1428 multilayer method. Cross-section view of pore channels on (C) PMT-SPPs and (D) SPPs made from
1429 the multilayer method. The sol-aggregated pore structure made by the multilayer process shows a
1430 more tortuous diffusion pathway than the ordered elongated channel made by pseudomorphic
1431 transformation. The red line/curve illustrate the differences in pore structures and diffusion pathways.
1432 Reprinted with permission from ref [146].

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1434 **Figure 9.** The structure of core-shell silica particles with solid core and nanofibrous shell. Reprinted
1435 with permission from ref [147].

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1437 **Figure 10.** SEM images of the carbon core (A) and the finished material (B) of carbon-based nano-
1438 diamond wide-pore particle. Reprinted with permission from ref [151].

1439

1440 **Figure 11.** Chromatograms of artichoke extract obtained with the BEH-C18 column (A) and Halo-
1441 C18 column (B) at different linear velocities. Mobile phase: MeOH/water (88:12); injection volume: 2
1442 μ L; UV detection: 320 nm. Reprinted with permission from ref [154].

1443

1444 **Figure 12.** Effect of pore size in core-shell particles on the separation of the mixture containing 7
1445 compounds. Columns: 4.6 mm \times 100 mm; particles: 2.7 μ m; mobile phase – A: 10%
1446 acetonitrile/aqueous 0.1% trifluoroacetic acid; B: 70% acetonitrile/aqueous 0.1% trifluoroacetic acid;
1447 gradient: 0–50% B in 15 min.; flow rate: 1.5 mL/min; temperature; 30 $^{\circ}$ C; injection: 5 μ L; instrument:

1448 Agilent 1100; detection: 220 nm; peak identities: (1) Gly-Tyr – 238 g/mol, (2) Val-Tyr-Val – 380
1449 g/mol, (3) methionine enkephalin – 574 g/mol, (4) angiotensin II – 1046 g/mol, (5) leucine enkephalin
1450 – 556 g/mol, (6) ribonuclease A – 13,700 g/mol, (7) insulin – 5800 g/mol; peak widths in minutes
1451 measured at 50% height for ribonuclease A and insulin. Reprinted with permission from ref [67].

1452

1453 **Figure 13.** Chromatographic elution data of polystyrene solutes and toluene superimposed on the time
1454 axis. (A) SPPs with pore size of 160 Å; (B) SPPs with pore size of 1000 Å; (C) Fully porous particles
1455 with pore size of 200 Å; (D) Fully porous particles with pore size of 1000 Å. All data shown here are
1456 from the flow rate of 0.25 mL/min. Reprinted with permission from ref [174].

1457

1458 **Figure 14.** Representative chromatogram of reduced ADC (brentuximab-vedotin). Columns:
1459 Prototype SOS (sphere-on-sphere) C4 (100 mm × 2.1 mm, ~2.5 m), Halo Protein C4 (150×2.1mm,
1460 3.4 m), BEH300C18 (150×2.1mm, 1.7 m) and Aeris Widepore C18 (150 × 2.1 mm, 3.6 m). Mobile
1461 phase A: 0.1% TFA, mobile phase B: 0.1% TFA in acetonitrile. Flow-rate of 0.4 mL/min, gradient:
1462 27–42%B in 12 min on the SOS column and 30–45% B on the other columns, temperature: 80 °C, UV
1463 detection was carried out at 280 nm. Reprinted with permission from ref [93].

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