(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2013 (19.12.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/188431 A1

(51) International Patent Classification:
C01B 33/24 (2006.01) *C02F 1/42* (2006.01)
B01J 19/18 (2006.01)

(21) International Application Number:
PCT/US2013/045219

(22) International Filing Date:
11 June 2013 (11.06.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/658,117 11 June 2012 (11.06.2012) US
13/829,415 14 March 2013 (14.03.2013) US

(71) Applicant: **ZS PHARMA, INC.** [US/US]; 1120 South Freeway, Fort Worth, Texas 76104 (US).

(72) Inventors: **KEYSER, Donald, Jeffrey**; 1216 Wyndham Hill Lane, Southlake, Texas 76092 (US). **GUILLEM, Alvaro, F.**; 727 Lathrop Street, Lantana, Texas 76226 (US).

(74) Agents: **TATE, Rodger, L.** et al.; Hunton & Williams, Intellectual Property Department, 2200 Pennsylvania Avenue, N.W., Washington, District of Columbia 20037 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

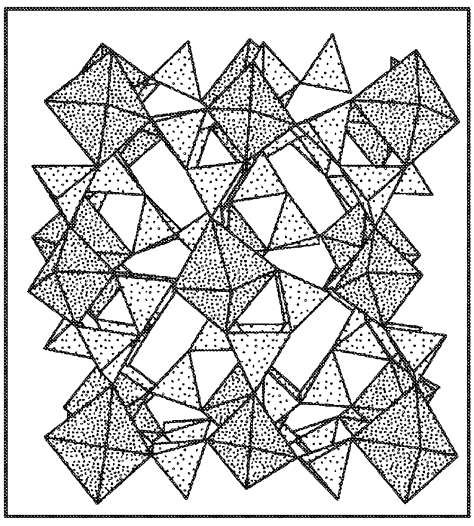
Published:

— *with international search report (Art. 21(3))*

[Continued on next page]

(54) Title: PRODUCTION OF IMPROVED MICROPOROUS ZIRCONIUM SILICATE

(57) Abstract: The present invention relates to novel microporous zirconium silicate compositions having a desired particle size distribution and methods of making those compositions. These compositions have an ideal particle size distribution for use *ex vivo*, for example in a dialysis exchange cartridge, yet retain many of the desirable properties of prior improved absorbers including high cation exchange capacity. Further, the new zirconium silicate molecular sieve absorbers can be manufactured using a technique that achieves the desired particle size distribution while eliminating the screening step that was previously necessary.



Dark = ZrO3 (oct), Light = SiO2 (tet), Cations not shown

Fig. 1

WO 2013/188431 A1

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

PRODUCING SOLIDS AND RELATED MOTHER LIQUORS

RELATED APPLICATIONS

The present application claims benefit from U.S. Provisional Patent Application Serial No. 61/658,117 filed June 11, 2012 and U.S. Utility Patent application Serial No. 13/829,415 filed March 15, 2013, the contents of which are incorporated herein by reference, in their entireties.

BACKGROUND OF THE INVENTION

(i) Field of the Invention

The present invention relates to novel microporous zirconium silicate compositions and processes for making such novel compositions. The novel compositions have a desirable particle size distribution. The invention also relates to novel techniques for manufacturing the microporous zirconium silicate compositions disclosed herein. These novel compositions are particularly useful for certain extracorporeal applications, including specifically within dialysis columns.

(ii) Description of the Related Art

Zirconium silicate or titanium silicate microporous ion exchangers are described in U.S. Patent Nos. 6,579,460, 6,099,737, and 6,332,985, each of which is incorporated herein in their entirety. Additional examples of microporous ion exchangers are found in U.S. Patent Nos. 6,814,871, 5,891,417, and 5,888,472, each of which is incorporated herein in their entirety. Improved zirconium silicate microporous ion exchangers were disclosed in U.S. Provisional Application No. 61/441,893 filed February 11, 2011 and U.S. Application No. 13/371,080 filed February 10, 2012, which are incorporated by reference herein in their entirety. These ion exchangers addressed several undesirable effects when utilized *in vivo* for

the removal of potassium in the treatment of hyperkalemia. For example, these applications disclose that screening can be used to remove particles having a diameter below 3 microns and that removal of such particles is beneficial for therapeutic zirconium silicate compositions.

As described in U.S. Provisional Application No. 61/441,893 filed February 11, 2011 and U.S. Application No. 13/371,080 filed February 10, 2012, earlier reactor designs, as shown in Fig. 2, did not include heat exchange baffles. It was discovered by adding heat exchange baffles to the reactor sidewall, as shown in Fig. 3, allowed for production of high ion exchange capacity mircoporous zirconium silicate and eliminated the need for seed crystals in the process. However, it was disclosed that the ZS-9 crystals had a broad particle size distribution. For example, Fig. 4 shows the particle size distribution of a sample prior to screening.

In order to manufacture a product having an adequately defined particle size distribution, it was necessary to screen the particles after they were removed from the reactor to physically eliminate particles having unwanted sizes. The disclosed methods of screening included

hand screening, air jet screening, sifting or filtering, floating or any other known means of particle classification. It was also disclosed that in addition to screening or sieving, the desired particle size distribution may be achieved using a granulation or other agglomeration technique for producing appropriately sized particles.

SUMMARY OF THE INVENTION

The inventors have discovered novel zirconium silicate molecular sieve absorbers that include an ideal particle size distribution for use *ex vivo*, for example in a dialysis exchange cartridge, yet retain many of the desirable properties of prior improved absorbers including

high cation exchange capacity. Further, the new zirconium silicate molecular sieve absorbers can be manufactured using a technique that achieves the desired particle size distribution while eliminating the screening step that was previously necessary.

In an aspect, the invention relates to a cation exchange composition comprising a zirconium silicate of formula: $A_pM_xZr_{1-x}Si_nGe_yO_m$ (I) where A is a potassium ion, sodium ion, rubidium ion, cesium ion, calcium ion, magnesium ion, hydronium ion or mixtures thereof, M is at least one framework metal, wherein the framework metal is hafnium (4+), tin (4+), niobium (5+), titanium (4+), cerium (4+), germanium (4+), praseodymium (4+), terbium (4+) or mixtures thereof, "p" has a value from about 1 to about 20, "x" has a value from 0 to less than 1, "n" has a value from about 0 to about 12, "y" has a value from 0 to about 12, "m" has a value from about 3 to about 36 and $1 \leq n + y \leq 12$, wherein the composition exhibits a volume weighted mean particle size between 5 and 20 microns wherein less than 10% of the particles have a size below 5 microns and less than 10% of the particles have a size above 25 microns, wherein the particle size distribution does not result from a screening or classification process. Preferably, the mean particle size is between 10 and 15 microns. Preferably the cation exchange capacity is greater than 4.0 meq/g, more preferably greater than 4.4 meq/g. The cation exchange composition may be incorporated into a number of devices, such as exchange columns, dialysis columns, etc.

In another aspect, the invention involves a method including steps of providing a reaction mixture comprising sodium silicate and zirconium acetate in a reactor; agitating the reaction mixture with an agitator in the presence of one or more baffle-like structures in a range of agitation speed ranging from 80 rpm to 350 rpm. It has been unexpectedly found that end-sized microporous zirconium silicate can be produced when operating the reaction within this range of agitation speed. The invention advantageously avoids the need to conduct any

screening or classification of the microporous zirconium silicate. Where desirable, different lots of the microporous zirconium silicate can be blended in order to produce a desired particle size distribution.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a polyhedral drawing showing the structure of microporous zirconium silicate $Na_{2.19}ZrSi_{3.01}O_{9.11}$.• 2.71H_2O (MW 420.71)

Fig. 2: Reaction vessel with baffles for production of enhanced ZS-9

Fig. 3: Detail of baffle design for 200-L reaction vessel for production of enhanced ZS-9

Fig. 4: Particle size distribution of UZSi-9 without screening.

Fig. 5: Particle size analysis for Example 1a.

Fig. 6: Particle size distribution for final product of Example 1a.

Fig. 7: Particle size distribution for solids from groove of Rosenmund for Example 1a.

Fig. 8: Particle size analysis for Example 2.

Fig. 9: Particle size distribution for Example 2.

Fig. 10: Particle XRD for Example 3.

Fig. 11: Particle size analysis for Example 3.

Fig. 12: Particle size distribution for Example 3.

DETAILED DESCRIPTION OF THE INVENTION

As described in U.S. Provisional Application No. 61/441,893 filed February 11, 2011 and U.S. Application No. 13/371,080 filed February 10, 2012, Zirconium silicate has a microporous framework structure composed of ZrO_2 octahedral units and SiO_2 tetrahedral units. Figure 1 is a polyhedral drawing showing the structure of microporous zirconium silicate $Na_{2.19}ZrSi_{3.01}O_{9.11}$.• 2.71H_2O (MW 420.71) The dark polygons depict the octahedral

zirconium oxide units while the light polygons depict the tetrahedral silicon dioxide units. Cations are not depicted in Fig. 1.

The microporous exchanger of the invention has a large capacity and strong affinity, *i.e.*, selectivity, for potassium or ammonium. Eleven types of zirconium silicate are available, UZSi-1 through UZSi-11, each having various affinities to ions have been developed. *See e.g.*, U.S. Patent No. 5,891,417. UZSi-9 (otherwise known as ZS-9) is a particularly effective zirconium silicate absorber for absorbing potassium and ammonium. These zirconium silicates have the empirical formula:

$$A_pM_xZr_{1-x}Si_nGe_yO_m \quad (I)$$

where A is an exchangeable cation selected from potassium ion, sodium ion, rubidium ion, cesium ion, calcium ion, magnesium ion, hydronium ion or mixtures thereof, M is at least one framework metal selected from the group consisting of hafnium (4+), tin (4+), niobium (5+), titanium (4+), cerium (4+), germanium (4+), praseodymium (4+), and terbium (4+), "p" has a value from about 1 to about 20, "x" has a value from 0 to less than 1, "n" has a value from about 0 to about 12, "y" has a value from 0 to about 12, "m" has a value from about 3 to about 36 and $1 \leq n + y \leq 12$. The germanium can substitute for the silicon, zirconium or combinations thereof. It is preferred that x and y are zero or both approaching zero, as germanium and other metals are often present in trace quantities. Since the compositions are essentially insoluble in bodily fluids (at neutral or basic pH), they can be orally ingested in order to remove toxins in the gastrointestinal system.

The zirconium metallates are prepared by a hydrothermal crystallization of a reaction mixture prepared by combining a reactive source of zirconium, silicon and/or germanium, optionally one or more M metal, at least one alkali metal and water. The alkali metal acts as a templating agent. Any zirconium compound, which can be hydrolyzed to zirconium oxide or

zirconium hydroxide, can be used. Specific examples of these compounds include zirconium alkoxide, *e.g.*, zirconium n-propoxide, zirconium hydroxide, zirconium acetate, zirconium oxychloride, zirconium chloride, zirconium phosphate and zirconium oxynitrate. The sources of silica include colloidal silica, fumed silica and sodium silicate. The sources of germanium include germanium oxide, germanium alkoxides and germanium tetrachloride. Alkali sources include potassium hydroxide, sodium hydroxide, rubidium hydroxide, cesium hydroxide, sodium carbonate, potassium carbonate, rubidium carbonate, cesium carbonate, sodium halide, potassium halide, rubidium halide, cesium halide, sodium ethylenediamine tetraacetic acid (EDTA), potassium EDTA, rubidium EDTA, and cesium EDTA. The M metals sources include the M metal oxides, alkoxides, halide salts, acetate salts, nitrate salts and sulfate salts. Specific examples of the M metal sources include, but are not limited to titanium alkoxides, titanium tetrachloride, titanium trichloride, titanium dioxide, tin tetrachloride, tin isopropoxide, niobium isopropoxide, hydrous niobium oxide, hafnium isopropoxide, hafnium chloride, hafnium oxychloride, cerium chloride, cerium oxide and cerium sulfate.

Generally, the hydrothermal process used to prepare the zirconium metallate or titanium metallate ion exchange compositions of this invention involves forming a reaction mixture which in terms of molar ratios of the oxides is expressed by the formulae:

$$aA_2O:bMO_{q/2}:1\text{-}bZrO_2:cSiO_2:dGeO_2:eH_2O$$

where "a" has a value from about 0.25 to about 40, "b" has a value from about 0 to about 1, "q" is the valence of M, "c" has a value from about 0.5 to about 30, "d" has a value from about 0 to about 30 and "e" has a value of 10 to about 3000. The reaction mixture is prepared by mixing the desired sources of zirconium, silicon and optionally germanium, alkali metal and optional M metal in any order to give the desired mixture. It is also necessary that the mixture have a basic pH and preferably a pH of at least 8. The basicity of the mixture is

controlled by adding excess alkali hydroxide and/or basic compounds of the other constituents of the mixture. Having formed the reaction mixture, it is next reacted at a temperature of about 100°C to about 250°C for a period of about 1 to about 30 days in a sealed reaction vessel under autogenous pressure. After the allotted time, the mixture is filtered to isolate the solid product which is washed with deionized water, acid or dilute acid and dried. Numerous drying techniques can be utilized including vacuum drying, tray drying, fluidized bed drying. For example, the filtered material may be oven dried in air under vacuum.

To allow for ready reference, the different structure types of the zirconium silicate molecular sieves and zirconium germanate molecular sieves have been given arbitrary designations of UZSi-1 where the "1" represents a framework of structure type "1". That is, one or more zirconium silicate and/or zirconium germanate molecular sieves with different empirical formulas can have the same structure type.

The X-ray patterns presented in the following examples were obtained using standard X-ray powder diffraction techniques and reported in U.S. Patent No. 5,891,417. The radiation source was a high-intensity X-ray tube operated at 45 Kv and 35 ma. The diffraction pattern from the copper K-alpha radiation was obtained by appropriate computer based techniques. Flat compressed powder samples were continuously scanned at 2° (2θ) per minute. Interplanar spacings (d) in Angstrom units were obtained from the position of the diffraction peaks expressed as 2 θ where θ is the Bragg angle as observed from digitized data. Intensities were determined from the integrated area of diffraction peaks after subtracting background, "I_o" being the intensity of the strongest line or peak, and "I" being the intensity of each of the other peaks.

As will be understood by those skilled in the art, the determination of the parameter

2θ is subject to both human and mechanical error, which in combination can impose an uncertainty of about ±0.4 on each reported value of 2θ. This uncertainty is, of course, also manifested in the reported values of the d-spacings, which are calculated from the θ values. This imprecision is general throughout the art and is not sufficient to preclude the differentiation of the present crystalline materials from each other and from the compositions of the prior art. In some of the X-ray patterns reported, the relative intensities of the d-spacings are indicated by the notations vs, s, m and w which represent very strong, strong, medium, and weak, respectively. In terms of $100xI/I_o$, the above designations are defined as w=0-15; m=15-60; s=60-80 and vs=80-100.

In certain instances the purity of a synthesized product may be assessed with reference to its X-ray powder diffraction pattern. Thus, for example, if a sample is stated to be pure, it is intended only that the X-ray pattern of the sample is free of lines attributable to crystalline impurities, not that there are no amorphous materials present.

The crystalline compositions of the instant invention may be characterized by their X-ray powder diffraction patterns and such may have one of the X-ray patterns containing the d-spacings and intensities set forth in the following Tables. The x-ray pattern for ZS-11 as reported in U.S. Patent No. 5,891,417, is as follows:

Table 1 - UZSi-11	
d(Å)	I
6.0-6.8	w-m
5.5-6.3	m
5.4-6.2	vs
5.2-6.0	m
2.7-3.5	s
2.5-3.3	m

The x-ray diffraction pattern for the high-purity, high KEC ZS-9 is reported in U.S. Patent Application No. 13/371,080 (Example 13, Fig. 13) as having the following characteristics d-spacing ranges and intensities:

Table 2 - UZSi-9	
d(Å)	I
5.9-6.7	m
5.3-6.1	m-s
2.7-3.5	vs
2.0-2.8	w-m
1.6-2.4	w

The formation of zirconium silicate involves the reaction of sodium silicate and zirconium acetate in the presence of sodium hydroxide and water. In order to obtain high potassium ion exchange capacity and crystalline purity (as shown by XRD and FTIR spectra) it is necessary to properly position a baffle-like structure in relation to the agitator within the crystallization vessel. When these conditions are met, significantly higher levels of potassium exchange capacity (KEC) are attainable. For example, UZSi-9 crystals will have a potassium exchange capacity of greater than 2.5 meq/g, more preferably greater than 3.5 meq/g, more preferably greater than 4.0 meq/g, more preferably between 4.3 and 4.8 meq/g, even more preferably between 4.4 and 4.7 meq/g, and most preferably approximately 4.5 meq/g. These techniques also allow one to dispense with using seed crystals. An elevated exchange

capacity for other ions such as ammonium (NH4+), alkali metal cations (K+, Na+, Rb+, Cs+), alkaline earth cations (Mg2+, Ca2+, Sr2+, Ba2+) and hydronium can be achieved. When used as an absorber for ammonium cations, UZSi-9 crystals will exhibit an exchange capacity of greater than 3.0 meq/g, more preferably greater than 5.0 meq/g, more preferably greater than 5.5 meq/g, more preferably between 5 and 6 meq/g.

It has been unexpectedly found that when producing high cation exchange capacity absorbers using these techniques that an end-sized product having a desired particle size distribution can be obtained through careful control of the reaction conditions. The production of an end-sized product is advantageous in that it elminates the need for any subsequent screening steps which were previously required. The following examples demonstrate that through careful control of the agitation rate in a reactor having baffles an end-sized absorber can be obtained without the use of screening steps. Specifically, when a lower rate of agitation is utilized, the product will tend to have a higher mean particle size. When a higher rate of agitation is used, the product will tend to have a lower mean particle size. In either case, the microporous zirconium silicate exhibited a particle size distribution that was adequate for use of the particles without further screening. These compositions differ structurally from screened compositions by exhibiting smoother size distributions which are not as sharp as those obtained when the PSD is obtained using screens or other classification techniques.

Although it is envisioned that the process of the present invention will completely eliminate the need for any particle screening or classification, the microporous zirconium silicate of the present invention may be subject to screening if desired. The term screening includes hand screening, air jet screening, sifting or filtering, floating or any other known means of particle classification. In the case where screening is utilized, the present invention

provides an initial product that is closer to the desired size thereby improving the screening efficiency. In addition, the product of the present invention may be subjected to other processes for producing appropriately size particles such as granulation or agglomeration if desired.

EXAMPLE 1a (Engineering Run #4) -- 150 RPM & 77h @ 210°C

In this example, reactants including zirconium acetate (11.5 kg), sodium silicate (27.81 kg), NaOH (3.68 kg), and deionized water (50.67 kg) were charged to the reactor and the temperature was directly heated to 210°C. This temperature was maintained for 77 hours. The temperature was then lowered to 76°C over 1.5 hours. This example utilized a stir speed of 150 rpm.

The Final product weighed 7.79 Kg. The product had a clean ATR and PXRD spectra. The potassium exchange value was 3.16 and the solids pH was 8.67. The protonation slurry was adjusted to pH=4.66 during this run.

Table 3 below summarizes the particle size analysis data.

Table 3

Exp. # 2724-	Description	Particle Size Analysis				
		D[v,0.10](μm)	D[v,0.50](μm)	D[v,0.90](μm)	D[4,3](μm)	Appendices
66J	Final	8.8	16.3	28.5	17.6	Figs. 5, 6
66A	24h aliquot	9.6	19.8	50.3	29.3	
66C	48h aliquot	11.8	20.0	32.8	21.3	
66E	72.5h aliquot	11.4	20.1	34.3	21.6	
66G	94h aliquot	16.2	24.8	37.7	26.1	
66K	Rosenmund solids	14.1	23.6	38.9	25.3	Fig. 7

EXAMPLE 1b (Engineering Run #3) -- 150 RPM & 60h @ 210°C

In this example, reactants including zirconium acetate (11.55 kg), sodium silicate (27.84 kg), NaOH (3.68 kg), and deionized water (50.57 kg) were charged to the reactor and

the temperature was directly heated to 210°C. This temperature was maintained for 60 hours. This example utilized a stir speed of 150 rpm.

The Final product weighed 7.87 Kg. The product had a clean ATR and PXRD spectra. The potassium exchange value was 3.07 and the solids pH was 8.77. The sodium (Na+) content was 9.38%. The protonation slurry was adjusted to pH=4.86 during this run. The preliminary mean particle size measurement was 17.6μm with no particles below 6.325 μm being present. The final mean particle size remained nearly twice as large as when faster stirring is used (see Examples 2-3 below) and no particles below 6.325μm were observed.

As observed in Example 1a, which also utilized a slower 150 rpm stirring speed, the particle size is larger than in faster, 307 rpm, experiments shown below in Examples 2-3.

EXAMPLE 2 (Engineering Run #2) -- 307 RPM & 60h @ 210°C

In this example, reactants including zirconium acetate (11.54 kg), sodium silicate (27.99 kg), NaOH (3.69 kg), and deionized water (50.59 kg) were charged to the reactor and the temperature was directly heated to 210°C. This temperature was maintained for 60 hours. This example utilized a stir speed of 307 rpm.

The Final product weighed 7.37 Kg The product had a clean ATR and PXRD spectra. The potassium exchange value was 3.21 and the solids pH was 8.75. The sodium (Na+) content was 8.43%. The protonation slurry was adjusted to pH=4.93 during this run.

Table 4 below summarizes all the PSA data for this run and lists the Appendices where the summary tables and the representative particle size distribution (PSD) graphs are located for the new data.

Table 4

Exp. # 2724-	Description	Particle Size Analysis				
		D[v,0.10](μm)	D[v,0.50](μm)	D[v,0.90](μm)	D[4,3](μm)	Appendices
60K	Final	5.5	9.8	16.9	10.6	

60A	21.5h aliquot	5.1	9.7	18.0	10.8	
60C	49h aliquot	4.7	9.0	16.4	9.9	
60E	62h aliquot	4.7	9.0	16.7	10.0	
60G	63.75h aliquot	7.0	11.9	20.1	12.9	Fig. 8, 9
60I	Re-filtered solids from filtrates	6.6	10.6	16.6	11.2	
60L	Rosenmund solids	6.3	10.9	18.3	11.7	

EXAMPLE 3 (Engineering Run #5) -- 307 RPM & 45h @ 210°C

In this example, reactants including zirconium acetate (11.49 kg), sodium silicate (27.86 kg), NaOH (3.68 kg), and deionized water (50.75 kg) were charged to the reactor and the temperature was directly heated to 210°C. This temperature was maintained for a shortened time of 48 hours. This example utilized a stir speed of 307 rpm.

The Final product weighed 7.79 Kg. The product had a clean ATR and PXRD spectra. The potassium exchange value was 3.23 and the solids pH was 8.80. The protonation slurry was adjusted to pH=4.89 during this run.

Table 5 below summarizes the PSA data and lists the Appendices where the summary tables and the representative PSD graphs are located.

Table 5						
Exp. # 2724-	Description	Particle Size Analysis				
		D[v,0.10](μm)	D[v,0.50](μm)	D[v,0.90](μm)	D[4,3](μm)	Appendices
69E	Final	4.6	8.5	14.8	9.2	Fig. 11
69A	25h aliquot	4.6	8.8	15.9	9.7	S, T
69C	48.5h aliquot	4.9	8.8	15.3	9.5	S, U

As can be seen from the PSA data above, the particle size is smaller in the faster stirred reaction.

Extracorporal Applications

The zirconium silicate absorber compositions of examples 2-3 are particularly useful in the case of extracorporal applications such as in ion exchange columns, absorption columns or dialysis cartridges. Also, since there is no need to screen the particles thus obtained, the manufacturing processes of Examples 2-3 are more efficient than prior processes which did not produce an end-sized product.

Dialysis cartridges in the past have been manufactured using absorbents such as zirconium phosphate for adsorbing ammonium ions produced from urea degradation. For example, U.S. Patent No. 7,566,432 to Raymond Wong, the contents which are incorporated by reference herein, discloses dialysis cartridges utilizing ZrP as the adsorbent material. One specific extracorporal application that this invention is particularly suitable for is in the manufacture of dialysis cartridges. This is because the inventive zirconium silicate absorbers can be made with a high exchange capacity for ammonium and a desirable particle size distribution. These desirable particles can be prepared without the use of a particle screening or classification step based on the end-sized particles obtained with processes of the present invention.

In one aspect, a dialysis cartridge is prepared and loaded with the absorbent particles of Example 1a. The dialysis cartridge will thus have a microporous zirconium silicate with a volume weighted mean particle size of 17.6 μm with less than 10% of the particles having a particle size below 8.8 μm and less than 10% of the particles having a particle size larger than 28.5 μm. By avoiding significant quantities of material having a particle size below 10 μm, the dialysis cartridge will exhibit an adequate flowrate at pressures used in dialysis systems. Further, the dialysis cartridge will benefit from enhanced cation exchange capacity and a process of production that avoids particle screening and/or classification.

In another aspect, a dialysis cartridge is prepared and loaded with the absorbent particles of Example 3. The dialysis cartridge will thus have a microporous zirconium silicate with a volume weighted mean particle size of 9.2 μm with less than 10% of the particles having a particle size below 4.6 μm and less than 10% of the particles having a particle size larger than 14.8 μm. The flowrate through this dialysis column would be lower than the cartridge utilizing the absorbents of Example 1a at a given working pressure of the dialysis machine.

In yet another aspect, a dialysis column may be prepared by blending two or more batches of microporous zirconium silicate prepared in accordance with the present invention. By blending different batches a microporous zirconium silicate, the cartridge can be prepared with an optimal particle size distribution without the need for screening or classification steps.

While the present invention has been shown to avoid the necessity of additional screening or classification steps for particular applications, it still may be desirable to screen batches of blends of batches of microporous zirconium silicate for a particular application. In this case, the particle size distribution of the present invention is still beneficial as the number

of screening steps may be reduced significantly. For example, it may be desirable to screen out particles having a size above a predetermined cutoff without also screening out particles having a size below a certain amount, or vice-versa.

Other embodiments and uses of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. All references cited herein, including all U.S. and foreign patents and patent applications, are specifically and entirely hereby incorporated herein by reference. It is intended that the specification and examples be considered exemplary only, with the true scope and spirit of the invention indicated by the following claims.

1. A cation exchange composition comprising a zirconium silicate of formula (I):

$$A_pM_xZr_{1-x}Si_nGe_yO_m \quad (I)$$

where

A is a potassium ion, sodium ion, rubidium ion, cesium ion, calcium ion, magnesium ion, hydronium ion or mixtures thereof,

M is at least one framework metal, wherein the framework metal is hafnium (4+), tin (4+), niobium (5+), titanium (4+), cerium (4+), germanium (4+), praseodymium (4+), terbium (4+) or mixtures thereof,

"p" has a value from about 1 to about 20,

"x" has a value from 0 to less than 1,

"n" has a value from about 0 to about 12,

"y" has a value from 0 to about 12,

"m" has a value from about 3 to about 36 and $1 \leq n + y \leq 12$,

wherein the composition exhibits a volume weighted mean particle size between 5 and 20 microns wherein less than 10% of the particles have a size below 5 microns and less than 10% of the particles have a size above 25 microns, wherein the particle size distribution does not result from a screening or classification process.

2. The cation exchange composition of claim 1, wherein the mean particle size is between 10 and 15 microns.

3. An ion exchange column loaded with exchange media, wherein the exchange media comprises the cation exchange composition of claim 1.

4. The composition of claim 1, wherein the potassium exchange capacity is greater than 3.0 meq/g.

5. The composition of claim 1, wherein the potassium exchange capacity is greater than 4.4 meq/g.

6. The composition of claim 1, wherein the potassium exchange capacity is between 3.7 and 4.7 meq/g.

7. A method for making the composition of claim 1 comprising:

providing a reaction mixture comprising sodium silicate and zirconium acetate in a reactor;

agitating the reaction mixture with an agitator in the presence of one or more baffle-like structures with an agitation speed within a range of 80 rpm to 350 rpm; and

obtaining the cation exchange composition from the reactor.

8. The method of claim 7, further comprising a step of contacting the zirconium silicate with a dilute solution of strong acid and/or water.

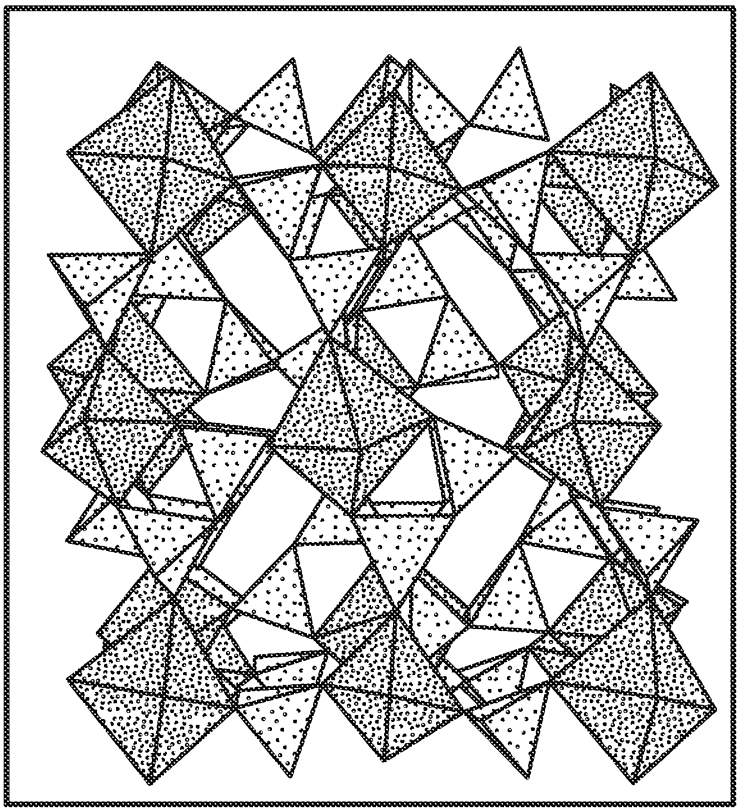
9. The method of claim 7, further comprising a step of blending different lots of the cation exchange composition to produce a desired particle size distribution.

10. The method of claim 7, wherein the agitation speed is within the range of 120 and 170 rpm.

11. The method of claim 10, wherein the agitation speed is approximately 150 rpm.

12. The method of claim 7, wherein the agitation speed is within the range of 190 and 320 rpm.

13. The method of claim 12, wherein the agitation speed is approximately 307 rpm.



Dark = ZrO3 (oct), Light = SiO2 (tet), Cations not shown

Fig. 1

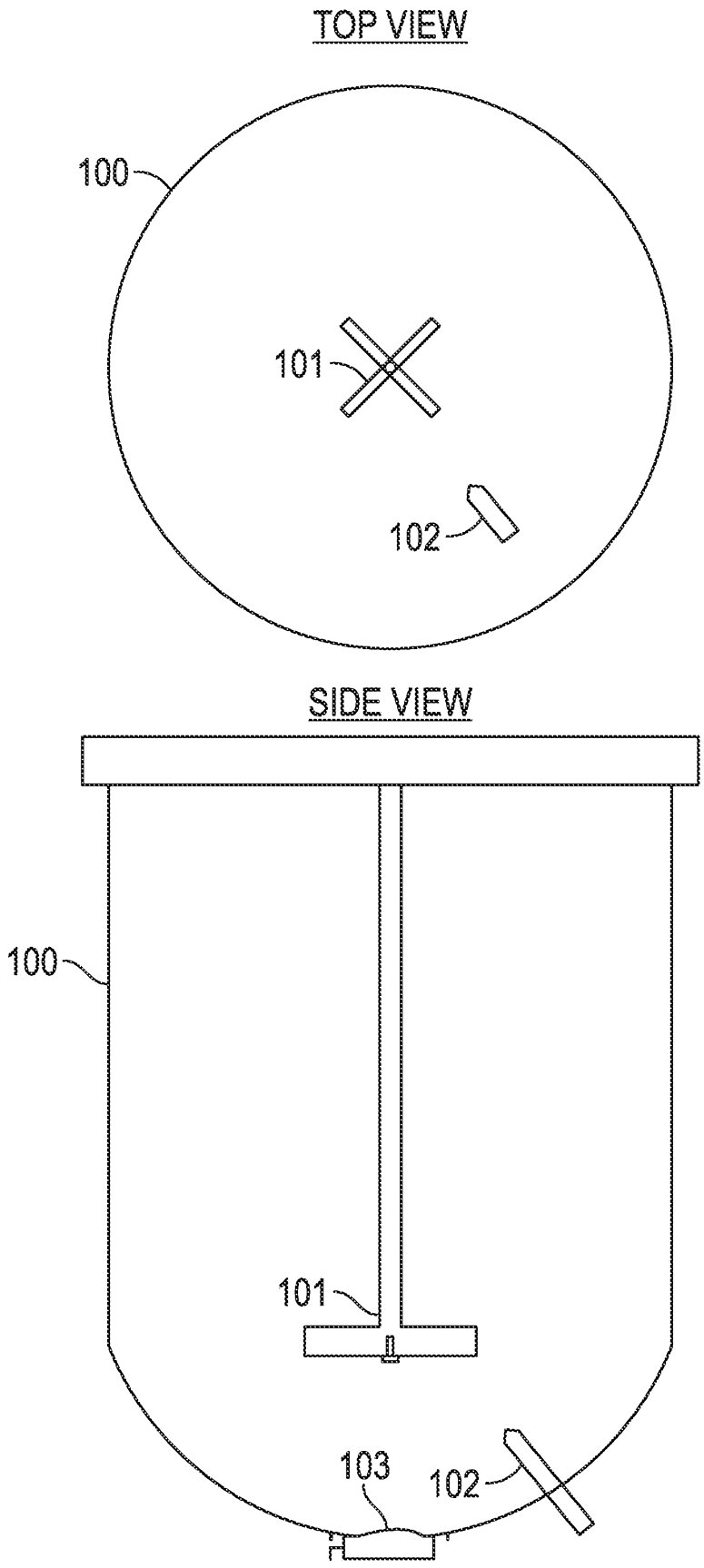


Fig. 2: 200-L reaction vessel with standard agitator arrangement.

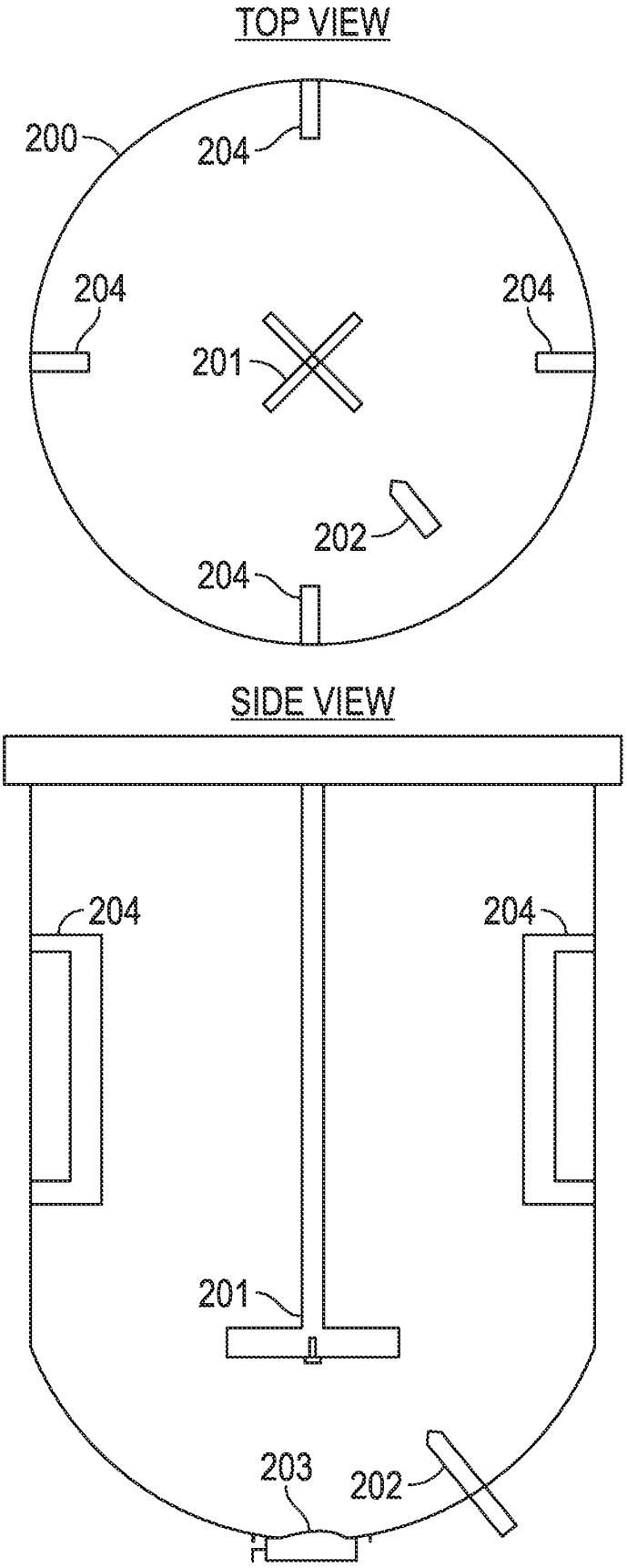


Fig. 3: 200-L reaction vessel with baffles for production of enhanced ZS-9

Serial Number: S3238
Range: 0.687 -995.6 um

MICROTRAC - S3000

Ver: 9.0h
Meas : Original

ZS9

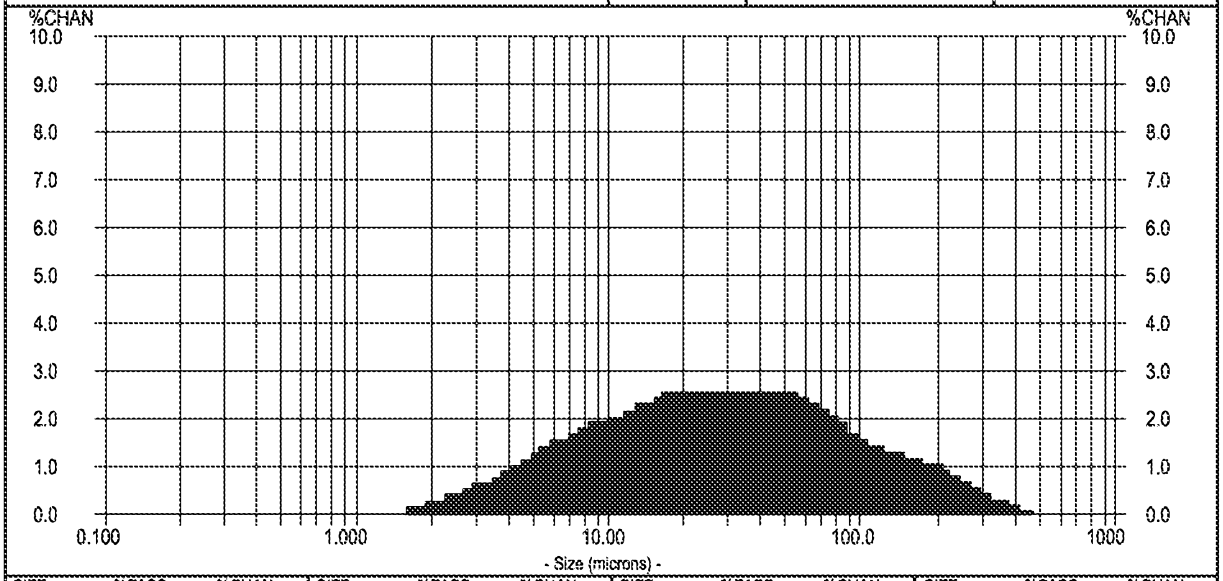
R/M
LOT: 5332-04310A

Date: 02/04/11 Meas #: 205
Time: 10:39 Pres #: 1

POWDERSIZE, INC.
20 PACIFIC DRIVE
QUAKERTOWN, PA 18951
TEL: 215-536-5605

OPERATOR: HM
PSI: S0072

Summary	Percentiles	Dia	Vol%	Width
mv = 52.85	10% = 5.808 60% = 39.45	28.24	100%	87.87
mn = 3.428	20% = 9.597 70% = 54.83			
ma = 14.62	30% = 14.36 80% = 79.46			
cs = 0.410	40% = 20.25 90% = 136.7			
sd = 43.93	50% = 28.24 95% = 197.5			



SIZE	%PASS	%CHAN	SIZE	%PASS	%CHAN	SIZE	%PASS	%CHAN	SIZE	%PASS	%CHAN
995.6	100.00	0.00	114.1	87.15	1.51	13.08	27.53	2.21	1.499	0.00	0.00
913.0	100.00	0.00	104.6	85.64	1.62	12.00	25.32	2.13	1.375	0.00	0.00
837.2	100.00	0.00	95.96	84.02	1.75	11.00	23.19	2.05	1.261	0.00	0.00
767.7	100.00	0.00	88.00	82.27	1.90	10.09	21.14	1.97	1.156	0.00	0.00
704.0	100.00	0.00	80.70	80.37	2.07	9.250	19.17	1.90	1.060	0.00	0.00
645.6	100.00	0.00	74.00	78.30	2.23	8.482	17.27	1.83	0.972	0.00	0.00
592.0	100.00	0.00	67.86	76.07	2.38	7.778	15.44	1.74	0.892	0.00	0.00
542.9	100.00	0.00	62.23	73.69	2.50	7.133	13.70	1.64	0.818	0.00	0.00
497.8	100.00	0.00	57.06	71.19	2.59	6.541	12.06	1.53	0.750	0.00	0.00
456.5	100.00	0.00	52.32	68.60	2.63	5.998	10.53	1.40			
418.6	100.00	0.18	47.98	65.97	2.64	5.500	9.13	1.28			
383.9	99.82	0.29	44.00	63.33	2.64	5.043	7.85	1.15			
352.0	99.53	0.36	40.35	60.69	2.62	4.625	6.70	1.04			
322.8	99.17	0.45	37.00	58.07	2.60	4.241	5.66	0.93			
296.0	98.72	0.59	33.93	55.47	2.58	3.889	4.73	0.83			
271.4	98.14	0.70	31.11	52.89	2.58	3.566	3.90	0.74			
248.9	97.44	0.83	28.53	50.31	2.59	3.270	3.16	0.65			
228.2	96.61	0.93	26.16	47.72	2.60	2.999	2.51	0.57			
209.3	95.68	1.03	23.99	45.12	2.62	2.750	1.94	0.49			
191.9	94.65	1.10	22.00	42.50	2.62	2.522	1.45	0.41			
176.0	93.55	1.16	20.17	39.88	2.60	2.312	1.04	0.34			
161.4	92.39	1.22	18.50	37.28	2.55	2.121	0.70	0.29			
148.0	91.17	1.27	16.96	34.73	2.49	1.945	0.41	0.25			
135.7	89.90	1.34	15.56	32.24	2.40	1.783	0.16	0.16			
124.5	88.56	1.41	14.27	29.84	2.31	1.635	0.00	0.00			

Distribution: Volume
Progression: Geometric Root8
Upper Edge: 995.6
Lower Edge: 0.687
Residuals: Disabled
Number Of Channels: 84

Filter: On

Run Time: 10 seconds
Run Number 1 of 1 runs
Particle: DefaultParticle
Particle Transparency: Trans
Particle Refractive Index: 1.51
Particle Shape: Irregular

Database Path: C:\MTWIN90\MT2_2011.DB

Fluid: ISOPAR G
Fluid Refractive Index: 1.42
Loading Factor: 0.1198
Transmission: 0.96
Above Residual: 0.00
Below Residual: 0.00

Fig. 4 (lot 5332-04310A w/o screening)

Fig. 5

PSA Summary Table 2724-66J & K, Engineering Run #4, Final Product and Rosenmund Solids

SAMPLE ID	CUMULATIVE VOLUME % LESS			MEAN
	D[v,0.10]	D[v,0.50]	D[v,0.90]	
2724 - 66J				
Measurement 1	8.8	16.3	28.5	17.6
Measurement 2	8.8	16.3	28.5	17.6
Measurement 3	8.8	16.2	28.4	17.6
Measurement 4	8.8	16.3	28.5	17.6
Calculated	8.8	16.3	28.5	17.6
Standard	0.0	0.1	0.1	0.0
% RSD	0.0	0.3	0.2	0.0
2724 - 60J				
Measurement 1	8.8	16.1	28.3	17.5
Measurement 2	8.8	16.1	28.2	17.5
Measurement 3	8.8	16.1	28.3	17.5
Measurement 4	8.8	16.1	28.3	17.5
Calculated	8.8	16.1	28.3	17.5
Standard	0.0	0.0	0.1	0.0
% RSD	0.0	0.0	0.2	0.0
2724 - 66K				
Measurement 1	14.2	23.6	38.6	25.2
Measurement 2	14.2	23.6	38.6	25.2
Measurement 3	13.7	23.6	39.8	25.4
Measurement 4	14.2	23.6	38.6	25.2
Calculated	14.1	23.6	38.9	25.3
Standard	0.3	0.0	0.6	0.1
% RSD	1.8	0.0	1.5	0.4
2724 - 66K				
Measurement 1	13.9	22.2	34.7	23.4
Measurement 2	13.9	22.2	34.7	23.4
Measurement 3	13.9	22.2	34.7	23.4
Measurement 4	13.9	22.1	34.7	23.4
Calculated	13.9	22.2	34.7	23.4
Standard	0.0	0.0	0.0	0.0
% RSD	0.0	0.2	0.0	0.0

Fig. 6

Representative PSD Graph 2724-66J, Engineering Run #4, Final Product

PTL Particle Technology Labs

MASTERSIZER 2000

Result Analysis Report

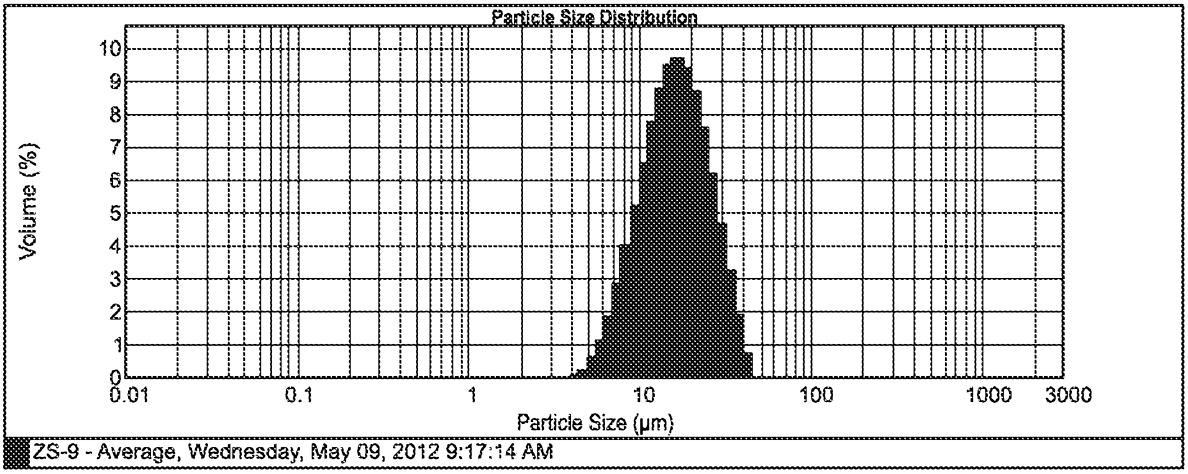
Operator notes:
CEDARBURG HAUSER ZS - 9
TM: MM755.03 2724 - 66J
Analyst: CZ Aliquot 1
Particle Technology Labs *PTL ID#: 90264*

SOP Name: ZS Pharma - ZS-9
Result Source: Averaged
Number of this Measurement: 1
Measured: Wednesday, May 09, 2012 9:17:14 AM
Analyzed: Wednesday, May 09, 2012 9:17:15 AM
Number of Measurements: 4

Particle Name:	Accessory Name:	Pump Speed:	Analysis model:	Sensitivity:
ZS-9(0.001)	Hydro 2000S (A)	2000 RPM	General purpose	Normal
Particle RI:	**Absorption:**		**Size range:**	**Obscuration:**
1.550	0.001		0.020 to 2000.000 um	15.76 %
Dispersant Name:	**Dispersant RI:**	**Average Result Records:**	**Weighted Residual:**	**Result Emulation:**
Water	1.330	"41,42,43,44"	0.647 %	Off

Concentration:	Span:	Uniformity:	Result units:
0.0334 %Vol	1.207	0.373	Volume
Specific Surface Area:	**Surface Weighted Mean D[3,2]:**	**Vol. Weighted Mean D[4,3]:**	
0.414 m^2/g	14.495 um	17.608 um	

d(0.1): 8.839 um **d(0.5):** 16.254 um **d(0.9):** 28.462 um



Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	3.72	50.238	100.00	355.656	100.00
0.022	0.00	0.159	0.00	1.125	0.00	7.962	6.49	56.356	100.00	399.052	100.00
0.025	0.00	0.178	0.00	1.262	0.00	8.934	10.42	63.248	100.00	447.744	100.00
0.028	0.00	0.200	0.00	1.416	0.00	10.024	15.62	70.963	100.00	502.377	100.00
0.032	0.00	0.224	0.00	1.589	0.00	11.247	22.13	79.621	100.00	589.577	100.00
0.035	0.00	0.252	0.00	1.783	0.00	12.619	29.87	89.337	100.00	632.458	100.00
0.040	0.00	0.283	0.00	2.000	0.00	14.159	38.64	100.237	100.00	709.627	100.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	48.08	112.458	100.00	796.214	100.00
0.050	0.00	0.356	0.00	2.518	0.00	17.825	57.77	126.191	100.00	893.367	100.00
0.058	0.00	0.399	0.00	2.825	0.00	20.000	67.20	141.589	100.00	1002.374	100.00
0.063	0.00	0.448	0.00	3.170	0.00	22.440	75.92	158.866	100.00	1124.683	100.00
0.071	0.00	0.502	0.00	3.557	0.00	25.179	83.48	174.250	100.00	1261.915	100.00
0.080	0.00	0.564	0.00	3.991	0.00	28.251	89.68	200.000	100.00	1415.892	100.00
0.089	0.00	0.632	0.00	4.477	0.00	31.698	94.30	224.404	100.00	1588.656	100.00
0.100	0.00	0.710	0.00	5.024	0.24	35.566	97.49	251.785	100.00	1782.502	100.00
0.112	0.00	0.796	0.00	5.637	0.81	39.905	99.33	282.508	100.00	2000.000	100.00
0.126	0.00	0.893	0.00	6.325	1.89	44.774	99.98	316.979	100.00		

Fig. 7

Representative PSD Graph 2724-66K, Engineering Run #4, Solids from groove of Rosenmund

PTL Particle Technology Labs

MASTE SIZE 2000

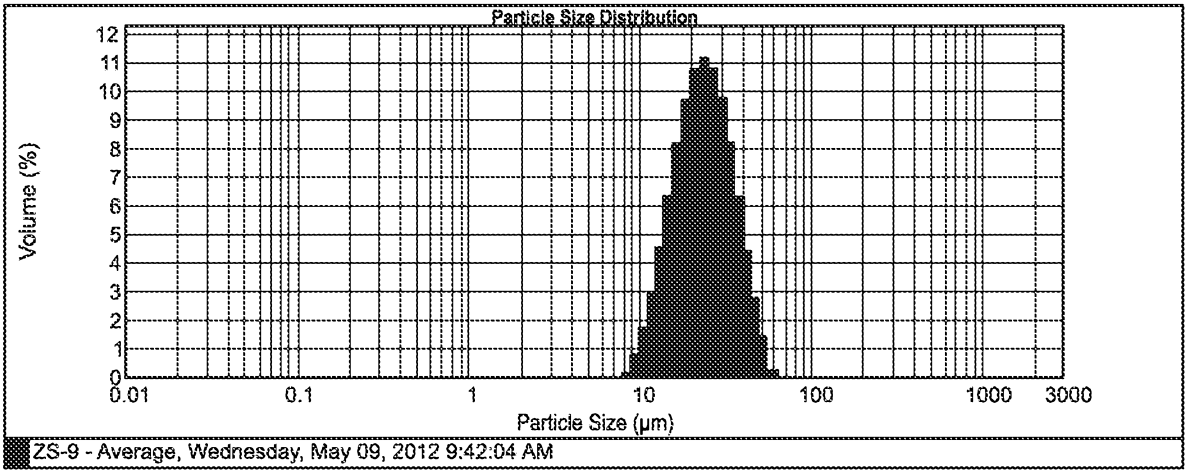
Result Analysis Report

Operator notes:		SOP Name:	Measured:
CEDARBURG HAUSER	ZS - 9	ZS Pharma - ZS-9	Wednesday, May 09, 2012 9:42:04 AM
TM: MM755.03	2724 - 66K	Result Source:	Analyzed:
Analyst: CZ	Aliquot 1	Averaged	Wednesday, May 09, 2012 9:42:05 AM
Particle Technology Labs	*PTL ID#: 90265*	Number of this Measurement:	Number of Measurements:
		1	4

Particle Name:	Accessory Name:	Pump Speed:	Analysis model:	Sensitivity:
ZS-9(0.001)	Hydro 2000S (A)	2000 RPM	General purpose	Normal
Particle RI:	**Absorption:**		**Size range:**	**Obscuration:**
1.550	0.001		0.020 to 2000.000 um	14.34 %
Dispersant Name:	**Dispersant RI:**	**Average Result Records:**	**Weighted Residual:**	**Result Emulation:**
Water	1.330	"51,52,53,54"	0.659 %	Off

Concentration:	Span:	Uniformity:	Result units:
0.0461 %Vol	1.050	0.325	Volume
Specific Surface Area:	**Surface Weighted Mean D[3,2]:**	**Vol. Weighted Mean D[4,3]:**	
0.275 m^2/g	21.798 um	25.257 um	

d(0.1): 14.083 um **d(0.5):** 23.614 um **d(0.9):** 38.888 um



Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.00	50.238	98.40	355.656	100.00
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.04	56.356	98.73	399.052	100.00
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.28	63.246	100.00	447.744	100.00
0.028	0.00	0.200	0.00	1.416	0.00	10.024	1.04	70.963	100.00	502.377	100.00
0.032	0.00	0.224	0.00	1.589	0.00	11.247	2.74	79.621	100.00	589.577	100.00
0.035	0.00	0.252	0.00	1.783	0.00	12.619	5.70	89.337	100.00	632.458	100.00
0.040	0.00	0.283	0.00	2.000	0.00	14.159	10.25	100.237	100.00	709.627	100.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	15.58	112.458	100.00	796.214	100.00
0.050	0.00	0.356	0.00	2.518	0.00	17.825	24.68	126.191	100.00	893.367	100.00
0.058	0.00	0.399	0.00	2.825	0.00	20.000	34.34	141.589	100.00	1002.374	100.00
0.063	0.00	0.448	0.00	3.170	0.00	22.440	45.07	158.866	100.00	1124.683	100.00
0.071	0.00	0.502	0.00	3.557	0.00	25.179	56.22	174.250	100.00	1261.915	100.00
0.080	0.00	0.564	0.00	3.991	0.00	28.251	67.02	200.000	100.00	1415.892	100.00
0.089	0.00	0.632	0.00	4.477	0.00	31.698	76.77	224.404	100.00	1588.656	100.00
0.100	0.00	0.710	0.00	5.024	0.00	35.566	84.84	251.785	100.00	1782.502	100.00
0.112	0.00	0.796	0.00	5.637	0.00	39.905	91.24	282.508	100.00	2000.000	100.00
0.126	0.00	0.893	0.00	6.325	0.00	44.774	95.65	316.979	100.00		

Fig. 8

PSA Summary Table 2724-60E & G, Engineering Run #2, 62h and 63.75h Aliquots

SAMPLE ID	CUMULATIVE VOLUME % LESS			MEAN
	D[v,0.10]	D[v,0.50]	D[v,0.90]	
2724 - 60E				
Measurement 1	4.7	9.0	16.7	10.0
Measurement 2	4.7	9.0	16.7	10.0
Measurement 3	4.7	9.0	16.7	10.0
Measurement 4	4.7	9.0	16.7	10.0
Calculated	4.7	9.0	16.7	10.0
Standard	0.0	0.0	0.0	0.0
% RSD	0.0	0.0	0.0	0.1
2724 - 60E				
Measurement 1	4.7	9.0	16.7	10.0
Measurement 2	4.7	9.1	16.8	10.0
Measurement 3	4.7	9.1	16.9	10.1
Measurement 4	4.7	9.1	16.8	10.0
Calculated	4.7	9.1	16.8	10.0
Standard	0.0	0.0	0.1	0.0
% RSD	0.0	0.6	0.5	0.5
2724 - 60G				
Measurement 1	7.0	11.9	20.1	12.9
Measurement 2	7.0	12.0	20.1	12.9
Measurement 3	7.0	11.9	20.1	12.9
Measurement 4	7.0	11.9	20.1	12.9
Calculated	7.0	11.9	20.1	12.9
Standard	0.0	0.0	0.0	0.0
% RSD	0.0	0.4	0.0	0.0
2724 - 60G				
Measurement 1	6.9	11.9	20.0	12.8
Measurement 2	6.9	11.9	19.9	12.8
Measurement 3	6.9	11.9	19.9	12.8
Measurement 4	6.9	11.9	19.9	12.8
Calculated	6.9	11.9	19.9	12.8
Standard	0.0	0.0	0.1	0.0
% RSD	0.0	0.0	0.3	0.0

Fig. 9

Representative PSD Graph 2724-60G, Engineering Run #2, 63.75h Aliquot

PTL Particle Technology Labs

MASTE SIZE 2000

Result Analysis Report

Operator notes:
CEDARBURG HAUSER ZS - 9
TM: MM755.03 2724 - 60G
Analyst: CZ Aliquot 1
Particle Technology Labs *PTL ID#: 90317*

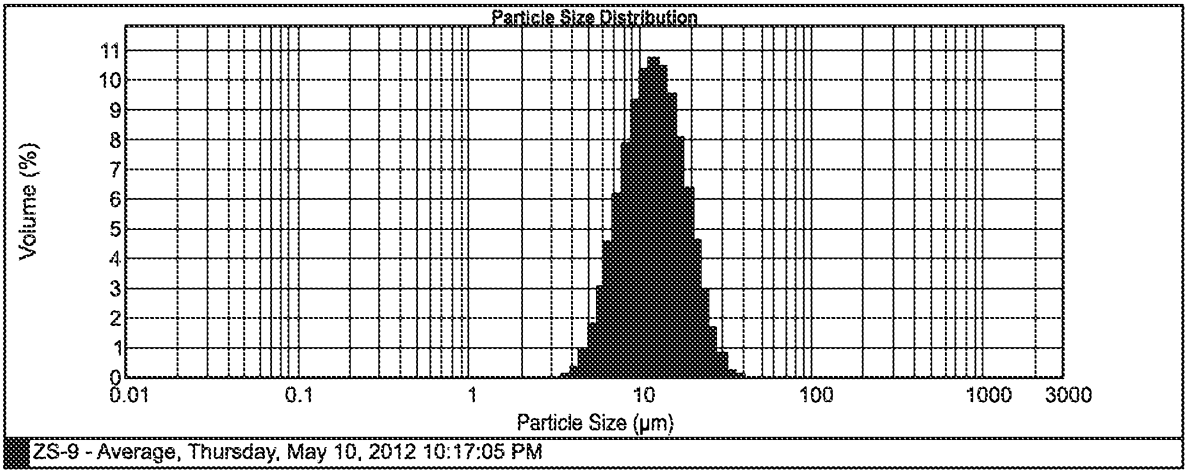
SOP Name: ZS Pharma - ZS-9
Result Source: Averaged
Number of this Measurement: 1

Measured: Thursday, May 10, 2012 10:17:05 PM
Analyzed: Thursday, May 10, 2012 10:17:07 PM
Number of Measurements: 4

Particle Name:	Accessory Name:	Pump Speed:	Analysis model:	Sensitivity:
ZS-9(0.001)	Hydro 2000S (A)	2000 RPM	General purpose	Normal
Particle RI:	**Absorption:**		**Size range:**	**Obscuration:**
1.550	0.001		0.020 to 2000.000 um	14.37 %
Dispersant Name:	**Dispersant RI:**	**Average Result Records:**	**Weighted Residual:**	**Result Emulation:**
Water	1.330	"31,32,33,34"	0.680 %	Off

Concentration:	Span:	Uniformity:	Result units:
0.0226 %Vol	1.098	0.343	Volume
Specific Surface Area:	**Surface Weighted Mean D[3,2]:**	**Vol. Weighted Mean D[4,3]:**	
0.547 m²/g	10.978 um	12.898 um	

d(0.1): 6.999 um **d(0.5):** 11.950 um **d(0.9):** 20.115 um



Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	10.68	50.238	100.00	355.656	100.00
0.022	0.00	0.159	0.00	1.125	0.00	7.962	16.61	56.356	100.00	399.052	100.00
0.025	0.00	0.178	0.00	1.262	0.00	8.934	24.88	63.248	100.00	447.744	100.00
0.028	0.00	0.200	0.00	1.416	0.00	10.024	33.09	70.963	100.00	502.377	100.00
0.032	0.00	0.224	0.00	1.589	0.00	11.247	44.34	79.621	100.00	589.577	100.00
0.035	0.00	0.252	0.00	1.783	0.00	12.619	55.11	89.337	100.00	632.458	100.00
0.040	0.00	0.283	0.00	2.000	0.00	14.159	65.62	100.237	100.00	709.627	100.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	75.20	112.458	100.00	796.214	100.00
0.050	0.00	0.356	0.00	2.518	0.00	17.825	83.35	126.191	100.00	893.367	100.00
0.058	0.00	0.399	0.00	2.825	0.00	20.000	89.73	141.589	100.00	1002.374	100.00
0.063	0.00	0.448	0.00	3.170	0.00	22.440	94.33	158.866	100.00	1124.683	100.00
0.071	0.00	0.502	0.00	3.557	0.00	25.179	97.26	174.250	100.00	1261.915	100.00
0.080	0.00	0.564	0.00	3.991	0.08	28.251	98.95	200.000	100.00	1415.892	100.00
0.089	0.00	0.632	0.00	4.477	0.38	31.698	99.74	224.404	100.00	1588.656	100.00
0.100	0.00	0.710	0.00	5.024	1.31	35.566	99.95	251.785	100.00	1782.502	100.00
0.112	0.00	0.796	0.00	5.637	3.10	39.905	100.00	282.508	100.00	2000.000	100.00
0.126	0.00	0.893	0.00	6.325	6.11	44.774	100.00	316.979	100.00		

Fig. 10

PXRD 2724-69E, Engineering Run #5, Final Product

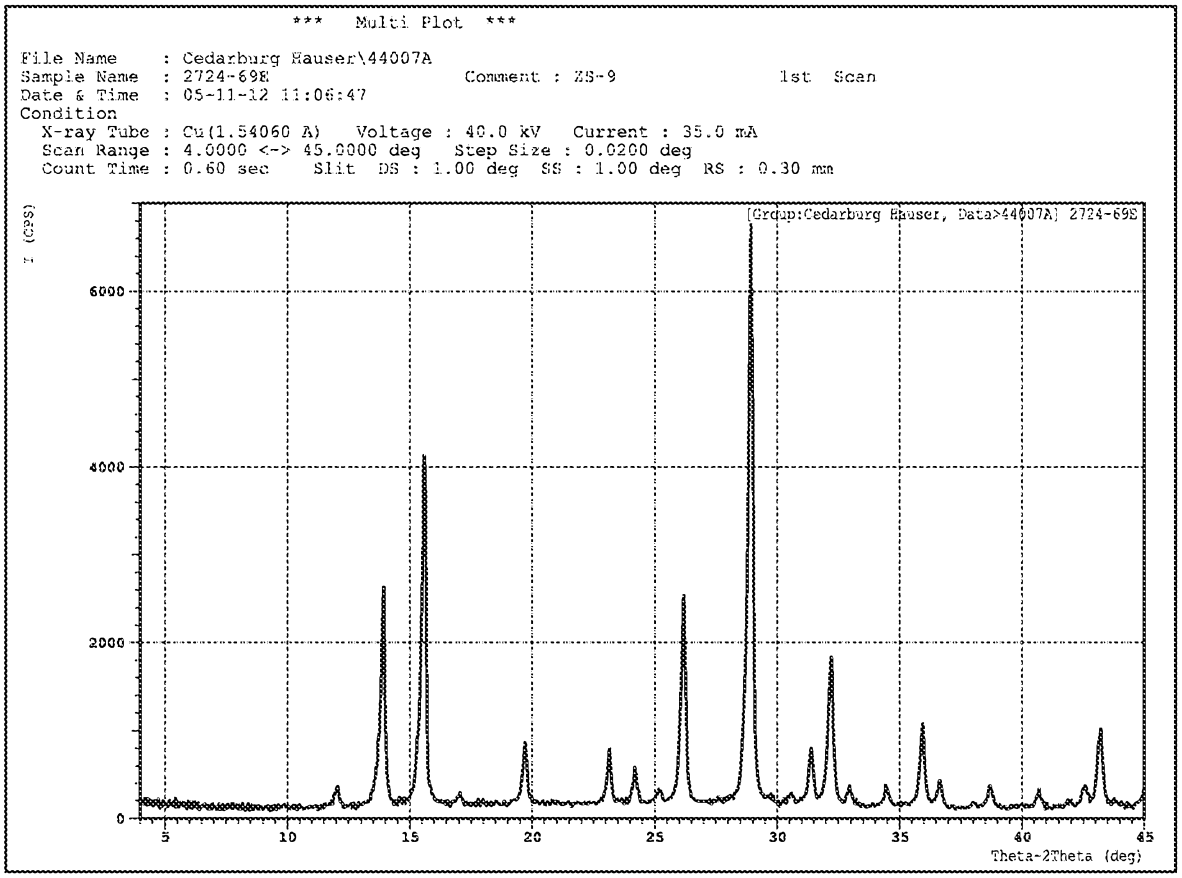


Fig. 11

PSA Summary Table 2724-69E, Engineering Run #5, Final Product

SAMPLE ID	CUMULATIVE VOLUME % LESS			MEAN
	D[v,0.10]	D[v,0.50]	D[v,0.90]	
2724 - 69E				
Measurement 1	4.6	8.5	14.8	9.2
Measurement 2	4.6	8.5	14.8	9.2
Measurement 3	4.6	8.5	14.8	9.2
Measurement 4	4.6	8.5	14.8	9.2
Calculated	4.6	8.5	14.8	9.2
Standard	0.0	0.0	0.0	0.0
% RSD	0.0	0.1	0.0	0.0
2724 - 69E				
Measurement 1	4.6	8.4	14.6	9.1
Measurement 2	4.6	8.4	14.6	9.1
Measurement 3	4.6	8.4	14.6	9.1
Measurement 4	4.6	8.4	14.6	9.1
Calculated	4.6	8.4	14.6	9.1
Standard	0.0	0.0	0.0	0.0
% RSD	0.0	0.0	0.0	0.0

Fig. 12

Representative PSD Graph 2724-69E, Engineering Run #5, Final Product

PTL Particle Technology Labs

MASTE SIZE 2000

Result Analysis Report

Operator notes:
CEDARBURG HAUSER ZS - 9
TM: MM755.03 2724 - 69E
Analyst: CZ Aliquot 1
Particle Technology Labs *PTL ID#: 90443*

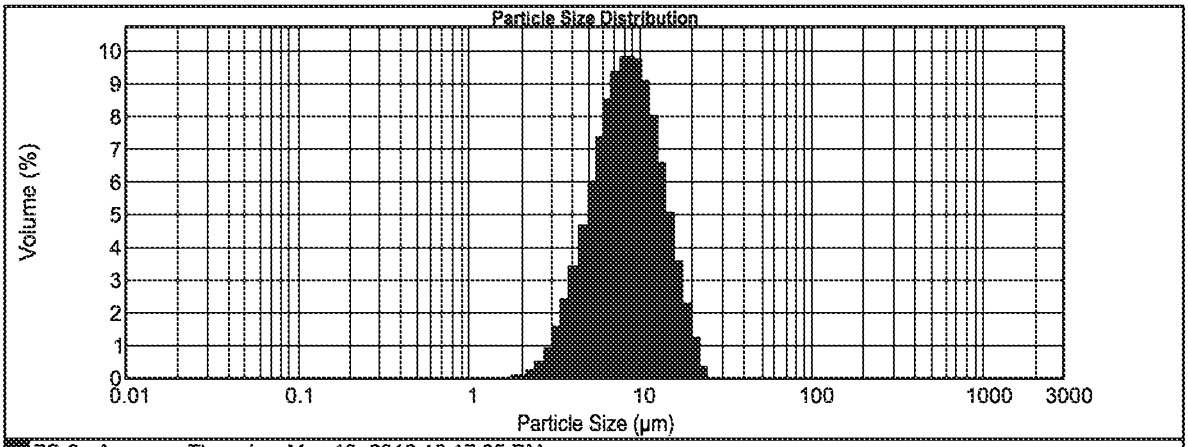
SOP Name: ZS Pharma - ZS-9
Result Source: Averaged
Number of this Measurement: 1

Measured: Thursday, May 10, 2012 8:20:21 PM
Analyzed: Thursday, May 10, 2012 08:20:22 PM
Number of Measurements: 4

Particle Name:	Accessory Name:	Pump Speed:	Analysis model:	Sensitivity:
ZS-9(0.001)	Hydro 2000S (A)	2000 RPM	General purpose	Normal
Particle RI:	**Absorption:**		**Size range:**	**Obscuration:**
1.550	0.001		0.020 to 2000.000 um	16.32 %
Dispersant Name:	**Dispersant RI:**	**Average Result Records:**	**Weighted Residual:**	**Result Emulation:**
Water	1.330	"21,22,23,24"	0.484 %	Off

Concentration:	Span:	Uniformity:	Result units:
0.0177 %Vol	1.201	0.373	Volume
Specific Surface Area:	**Surface Weighted Mean D[3,2]:**	**Vol. Weighted Mean D[4,3]:**	
0.791 m²/g	7.582 um	9.212 um	

d(0.1): 4.647 um **d(0.5):** 8.491 um **d(0.9):** 14.843 um



Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	35.14	50.238	100.00	355.656	100.00
0.022	0.00	0.159	0.00	1.125	0.00	7.962	44.53	56.356	100.00	399.052	100.00
0.025	0.00	0.178	0.00	1.262	0.00	8.934	54.35	63.248	100.00	447.744	100.00
0.028	0.00	0.200	0.00	1.416	0.00	10.024	64.07	70.963	100.00	502.377	100.00
0.032	0.00	0.224	0.00	1.589	0.00	11.247	73.18	79.621	100.00	589.577	100.00
0.035	0.00	0.252	0.00	1.783	0.00	12.619	81.18	89.337	100.00	632.458	100.00
0.040	0.00	0.283	0.00	2.000	0.01	14.159	87.75	100.237	100.00	709.627	100.00
0.045	0.00	0.317	0.00	2.244	0.08	15.887	92.78	112.458	100.00	796.214	100.00
0.050	0.00	0.356	0.00	2.518	0.23	17.825	96.31	126.191	100.00	893.367	100.00
0.058	0.00	0.399	0.00	2.825	0.85	20.000	98.54	141.589	100.00	1002.374	100.00
0.063	0.00	0.448	0.00	3.170	1.49	22.440	99.70	158.866	100.00	1124.683	100.00
0.071	0.00	0.502	0.00	3.557	2.85	25.179	100.00	174.250	100.00	1261.915	100.00
0.080	0.00	0.564	0.00	3.991	5.27	28.251	100.00	200.000	100.00	1415.892	100.00
0.089	0.00	0.632	0.00	4.477	8.04	31.698	100.00	224.404	100.00	1588.656	100.00
0.100	0.00	0.710	0.00	5.024	13.27	35.566	100.00	251.785	100.00	1782.502	100.00
0.112	0.00	0.796	0.00	5.637	19.28	39.905	100.00	282.508	100.00	2000.000	100.00
0.126	0.00	0.893	0.00	6.325	28.81	44.774	100.00	316.979	100.00		