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Huber

[11] **3,856,681**

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[54] **CHROMATOGRAPHY APPARATUS AND METHOD**

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[52] **U.S. Cl.** .... **210/198 C,** 55/386
[51] **Int. Cl.** **B01d 15/08**
[58] **Field of Search** .... 210/31 C, 198 C; 55/67, 55/386, 191

[56] **References Cited**

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3,492,794	2/1970	Reynolds et al.	55/386
3,570,673	3/1971	Dutz et al.	55/386
3,664,095	5/1972	Asker et al.	55/387

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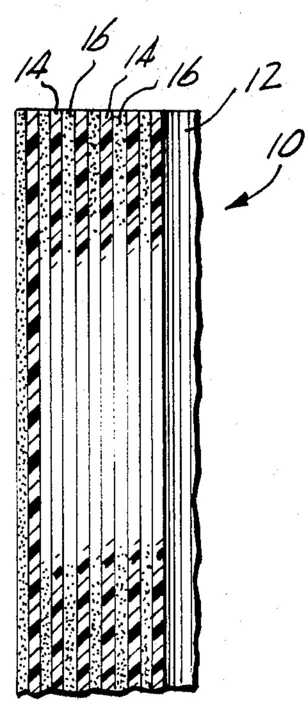
[57] **ABSTRACT**

A preparative and production chromatography column includes a relatively inert core onto which is wound in a spiral pattern a relatively inert sheet of material such as a synthetic polymeric film. Prior to winding the film is coated with a chromatographic media. The completed column contains alternating layers of relatively inert material and layers of chromatographic media. The thickness dimension of the chromatographic media is arranged substantially perpendicularly to the primary direction of fluid flow through the column.

29 Claims, 9 Drawing Figures



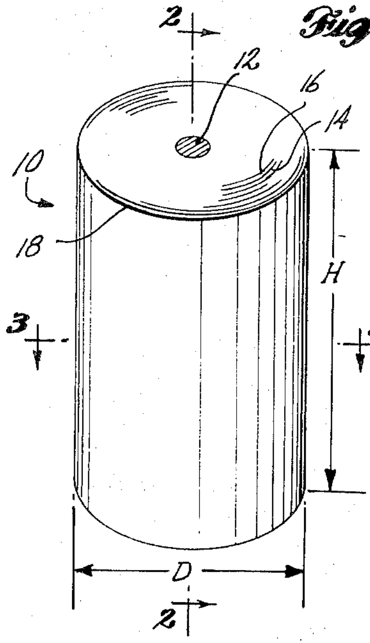


Fig. 1

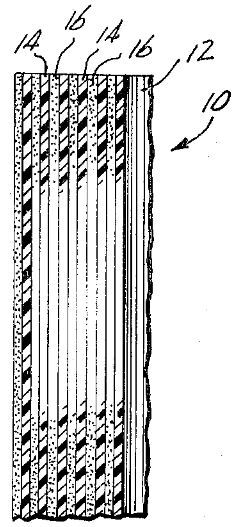


Fig. 2.

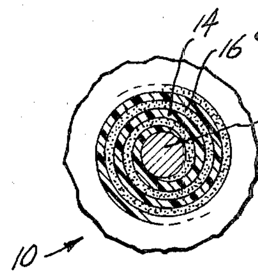


Fig. 3.

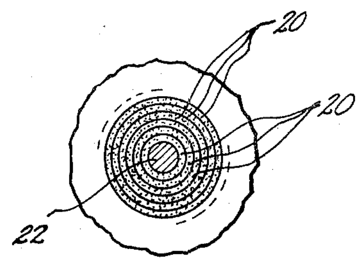
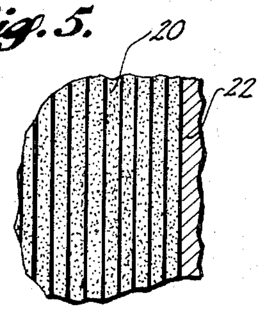


Fig. 4.

Fig. 5.



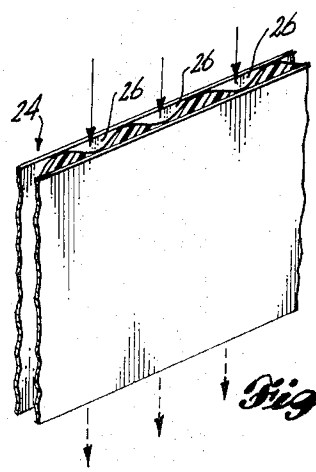


Fig. 6.

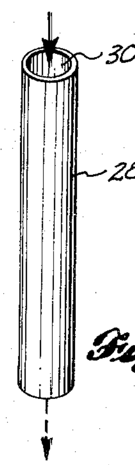


Fig. 7.

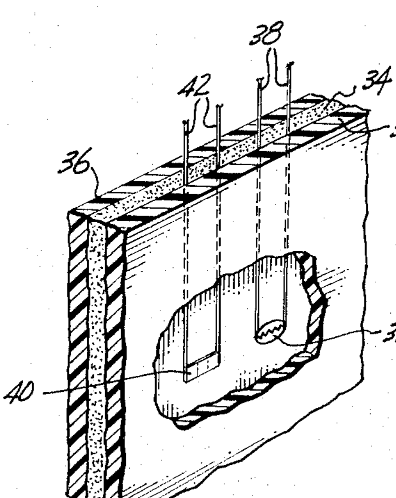


Fig. 8.

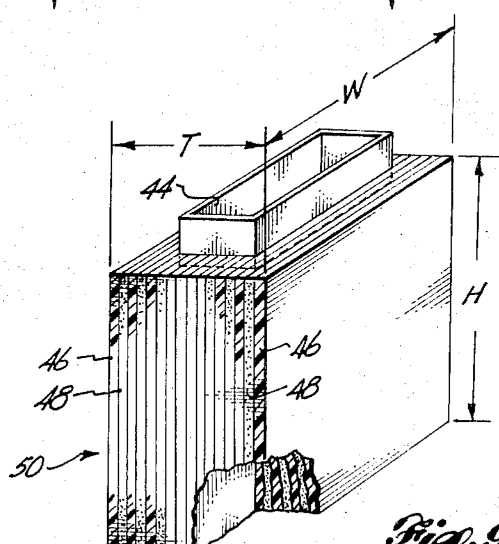


Fig. 9.

CHROMATOGRAPHY APPARATUS AND METHOD

BACKGROUND OF THE INVENTION

The invention relates to chromatography, and more particularly to apparatus and method for effectively conducting preparative and production chromatography. In a chromatographic process, it is customary to pass a mixture of the components to be resolved in a carrier fluid through a chromatographic apparatus or separative zone. The separative or resolving zone generally consists of a material referred to as a chromatographic media, which has an active chromatographic sorptive function for separating or isolating the components in the carrier fluid. The separative zone usually takes the form of a column through which the carrier fluid passes.

A major problem in the art of chromatography is to obtain uniform fluid flow across a column. It is recognized that the solution to this problem resides in an ability to obtain uniform distribution and density of the chromatographic media within a column.

To a large degree the packing problem is surmounted in the laboratory chromatography columns by using columns having a small internal diameter, generally on the order of one-eighth inch to one-half inch. In such columns uneven chromatographic fluid flow resulting from nonuniform packing of the chromatographic media is quickly relaxed across the column diameter and does not significantly affect analytical results. Relaxation of the uneven fluid flow is caused by radial fluid mixing across the column. Radial mixing occurs between the particles in the column, but loses its ability to compensate for nonhomogeneous media distribution when the thickness of the bed exceeds about 75 particle diameters. Optimum chromatographic bed thickness has been treated in *Journal of Gas Chromatography*, 4, 401, 1966 by Willmott and Littlewood.

To provide an economically feasible preparative chromatography column, the column diameter must be larger than one inch and preferably on the order of one foot or more. Attempts to scale up analytical chromatography columns to a size feasible for preparative and/or production chromatography have met with substantial losses in column efficiency. It has been found that as the column diameter or cross-sectional area is increased, the separation or resolving power of the chromatography column decreases. The resolution loss can be attributed primarily to the fluid flow distribution in the column.

It has also been found that uneven chromatographic fluid flow occurs at or near the interface between the bed of chromatographic media and the internal surface of the column wall or support. Fluid flow at or near this interface occurs at a different rate than throughout the bed. The particular type of chromatographic media and the column packing procedure introduce variables which affect fluid flow at or near this interface. This problem has been treated in *Journal of Chromatography Science*, 7,7 (1969) and *Modern Practice of Liquid Chromatography*, Chap. 1, 1970. These references teach that uneven flow at or near the bed-column interface can be minimized by proper column packing procedure to achieve more uniform chromatographic media density across column diameter and by increasing the density of the chromatographic media to eliminate a free fluid flow path at the interface. Increasing the diameter of the chromatography column will also minimize the overall effect of uneven fluid flow at or near the interface. However, an increase of the column diameter over five millimeters will not allow uneven fluid flow to be relaxed across the column diameter because the effect of radial mixing is significantly decreased.

Still another problem which has been encountered with larger diameter chromatography columns is the occurrence of temperature gradients through the column. These temperature gradients are caused by increased sample loading. For a discussion of this subject see *Gas Chromatography*, A. B. Littlewood, pp. 219, Academic Press (1970). Small diameter analytical columns have a favorable column surface area to volume ratio, which allows rapid equilibration of column temperature. In larger diameter columns, the migration of a sample peak through the column is accompanied by thermal gradients. These thermal gradients cause an enlargement of the sample peak and a resulting loss in chromatographic resolution. In larger columns the dissipation of heat required to eliminate the thermal gradients cannot be accomplished through the column wall because of the decrease in the column surface to column volume ratio, i.e., the increase in column diameter.

Various internal column devices have been proposed to overcome the difficulties of producing large diameter preparative and production chromatography columns which will yield a sharp sample separation. Such devices have been described in U.S. Pat. No. 3,250,058, South African application 66/3,204, U.S. Pat. No. 3,310,932, U.S. Pat. No. 3,436,897 and U.S. Pat. No. 3,492,794. Several of these references disclose partition elements which are placed perpendicularly to the primary flow axis of the chromatography column. Such partition elements are introduced into the column in an attempt to correct the uneven fluid flow by inducing lateral flow and radial mixing of the normally axially flowing fluid streams. These partition elements must also subsequently redirect the lateral fluid flow in an axial direction. These attempts at solving the uneven fluid flow problems still result in reduced efficiency for large scale applications when compared to analytical results.

Another approach to resolve the problems encountered in large scale preparative and production chromatography has been to limit the bed diameter or thickness over which radial mixing can function, while increasing the overall cross-sectional area of the chromatography column. U.S. Pat. No. 3,386,035 describes a technique whereby elongated rod-like elements are arranged parallel to the axis of the column. These rod-like elements produce unsymmetrical column cross sections causing difficult column packing and uneven fluid flow. The elements also limit overall productive output of the column.

To build an effective preparative or production chromatography column, a homogeneous distribution of chromatographic media and maintenance of uniform media density across the column must be achieved. This thesis has been set forth in several published articles, among which are those appearing in "Journal of Chromatography Science," 7,1 (1969), "Journal of Chromatography Science," 7,257 (1969) and "Journal of Chromatography Science," 8,434 (1970).

The present invention provides a chromatography column which achieves results on a scale which have heretofore eluded others' attempts. An object of the present invention, therefore, is to provide an efficient, large diameter, preparative or production chromatography column for use with both gas and liquid chromatographic techniques. Other objects of the present invention are to provide: a relatively simply constructed, inexpensive, and effective preparative and production chromatography column which embodies a homogeneous chromatographic media distribution and uniform chromatographic media density; means of determining temperature at any preselected point within the column; means for controlling temperature and minimizing temperature gradients throughout a chromatography column; a chromatography column having essentially no diametric size limitation; a column which can be produced in many desired cross-sectional shapes; a chromatography column which can be quickly and relatively inexpensively manufactured; a chromatography column which resolves the uneven fluid flow problems encountered when attempting to scale up analytical columns to preparative and production columns; and a chromatography column which can also be utilized for analytical procedures.

SUMMARY OF THE INVENTION

The present invention invention therefore provides a chromatography column in which primary fluid flow occurs along a predetermined axis comprising a plurality of layers of chromatographic media arranged adjacent each other, the thickness dimension of said layers extending substantially perpendicularly to said axis. Preferably the chromatography column comprises a plurality of layers of chromatographic media spaced laterally from each other by relatively inert partitioning means interposed between the layers.

BRIEF DESCRIPTION OF THE DRAWINGS

A better understanding of the present invention can be acquired by reading the ensuing specification in conjunction with the accompanying drawings wherein:

FIG. **1** is a pictorial isometric view of a preferred embodiment of the chromatography column of the present invention;

FIG. **2** is an enlarged cross-sectional view of a portion of the preferred chromatography column taken along section line **2—2** of FIG. **1**;

FIG. **3** is an enlarged cross-sectional view of a portion of the preferred chromatography column taken along section line **3—3** of FIG. **1**;

FIG. **4** is an enlarged cross-sectional view similar to that of FIG. **3** of a second embodiment of the chromatography column of the present invention;

FIG. **5** is a cross-sectional view of a portion of a third embodiment of the present invention;

FIG. **6** is a pictorial isometric view of one type of partitioning layer which can be utilized with the present invention;

FIG. **7** is a pictorial isometric view of one type of core which can be utilized with the present invention;

FIG. **8** is a pictorial isometric view of a temperature sensing and heating means positioned within a portion of the preferred chromatography column of the present invention; and

FIG. **9** is a pictorial isometric view of a fourth embodiment of the present invention.

DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention broadly relates to preparative and production chromatography columns. A chromatography column in accord with the present invention is made by arranging a plurality of layers of chromatographic media adjacent and/or contiguous each other. The layers of chromatographic media are preferably preconstructed in relatively thin lamina so that the length and width dimensions of each layer are relatively large in comparison to the thickness of the layer. The thin layers are then formed into a column of desired shape and dimension to provide a usable preparative chromatography column having overall dimensions dependent upon the length and width of the original preconstructed layers and a total thickness dependent upon the number of preconstructed layers employed. Depending on whether a continuous preconstructed layer or whether individual preconstructed layers of equal size are initially prepared, a chromatography column can be constructed in accord with the present invention which has a circular cross section or which has a rectangular cross section. Other cross-sectional configurations can be constructed as desired.

To form a rectangular chromatography column, the thin layers of chromatographic media are stacked on each other with the surfaces of the layers adjacent each other. A sufficient number of layers are superposed on each other until a chromatography column of desired overall thickness is produced. The thickness (T) of the chromatography column is directly proportional to the number of thin layers of thickness (t) used in the column. The width (W) of the column is substantially equal to the width (w) of the original layer of chromatographic media utilized to build the column. The height (H) of the column corresponds to the length (l) of the original layers.

Likewise a chromatography column of substantially circular cross section can be formed from a single, elongate, preconstructed layer of chromatographic media of width (w), length (l) and thickness (t). A core rod of height (h) is placed along one end of an elongated, preconstructed layer of chromatographic media. The layer of chromatographic media is then rolled in a spiral pattern about the core rod to build up successive layers of material of chromatographic media to form a chromatography column of height (H) corresponding to the original width (w) of the elongate layer of chromatographic media, and having a diameter (D) which is a function of both the original thickness (t) and the length (l) of the elongate layer of chromatographic media.

It is important when constructing a chromatography column in accord with the present invention that the preconstructed layer of chromatographic media be of uniform thickness throughout its length and width and that the media in the thin layer have a uniform density throughout. It is preferred that the layer of media be substantially homogeneous with respect to itself; however, for certain applications and materials it is to be understood that nonhomogeneous construction can be employed.

A chromatography column prepared in accord with the present invention, whether rectangular, circular, or other desired cross section, can be formed from a continuous layer or successive discrete layers of chromatographic media. For example, a substantially cylindrical column can be formed from successive cylindrical shells of chromatographic media, each of which increase in diameter approximately 2(t) for each successive shell. Likewise a column of rectangular cross section can be prepared in an accordion-like manner or can be prepared by stacking individual sheets or layers of media contiguous with or adjacent with the immediately preceding layer to form a stack.

The present invention is adaptable to use with both gas and liquid chromatography. As those of ordinary skill in the art are aware, the chromatographic media may change when utilizing gas and liquid chromatography. In addition, of course, the chromatographic media will change depending upon the particular liquid or gas system encountered as a starting material or carrier, and will vary with the particular separation to be effected or particular application of the individual column.

As stated, it is important that the process conditions, primarily formation of homogeneous, uniformly dense, and thick individual layers of chromatographic media, be maintained with care. If reproducibility of results among columns of dissimilar or similar cross-sectional structure is desired, then uniformity in density and thickness should be maintained for the layers utilized in building each of the different columns. An additional criteria of the present invention is homogeneity or perfect distribution of the chromatographic media within the individual media layers. This is much easier to achieve when forming thin layers of chromatographic media. Thus it is much easier to maintain homogeneity in a layer having a 2 millimeter thickness than one having a 25 millimeter thickness.

Additionally, it is preferred that the thickness (t) of an individual layer of chromatographic media does not exceed a thickness at which a substantial temperature gradient appears across that dimension. Resultantly, there will be substantially no temperature gradient appearing through the multiplicity of layers in the column. In most instances, the thickness of a single layer of chromatographic media should not exceed about 15 percent of the total chromatographic column diameter or thickness. Most preferably the thickness of an individual layer is about 1 percent or less of the column thickness or diameter. For example, for a column having a diameter of 500 millimeters it is preferred that the average thickness of an individual layer be less than above 5 millimeters. A preferred chromatographic media layer thickness is on the order of less than 1 centimeter.

In a preferred form of the chromatography column of the present invention, a layer of partitioning material can be interposed between the successive layers of chromatographic media. The partitioning layer functions to maintain uniform temperature within the layer of chromatographic media and functions to relax fluid flow unevenness across the thin media layer. A layer of partitioning material also maintains uniform thickness and density in the layer of chromatographic media prior to and during use. In addition the layer of partitioning layer can serve as a backing or support for the layer of chromatographic media. It is preferred that the thickness of the partitioning layer be less than the thickness of the media layer. In this manner the overall width of the column does not greatly exceed the effective width of the column, i.e., the additive width of the individual layers of chromatographic media. Moreover, when using a partitioning material, it is important that the portion of the layer of chromatographic media next to the partitioning material be maintained at the same uniform density as the interior of the media layer. Good physical contact must also be present between the media layer and the surface of the partitioning material.

The partitioning layer can be constructed from a variety of materials as pointed out hereinafter. It is preferred that the partitioning layer is composed of a material which is relatively inert with respect to the chromatographic process. By relatively inert it is meant the material does not adversely affect the chromatographic process. Depending upon, among other things, the particular application of a column, the type of materials being separated, the composition of the carrier, and whether gas or liquid chromatography is being used, the partitioning layer can have a smooth or rough surface texture, can be pervious or substantially impervious to chromatographic fluid, and need not be uniformly dense.

Referring now to FIGS. **1**, **2** and **3** a preferred embodiment of the present invention is illustrated. A pictorial isometric view of a chromatography column **10** in accord with the present invention is shown in FIG. **1**. Column **10** is formed by initially positioning a central core **12**, preferably composed of relatively inert material, horizontally on a temporary support structure. Although it is not preferred, a core prepared from chromatographic media could be utilized. Exemplary preferred materials for the central core **12** include a dowel composed of a nonporous, rigid synthetic polymeric material, such as polytetrafluoroethylene, or a dowel composed of stainless steel.

A long sheet of material which will form a partition layer **14** is then attached to the central core **12** by heat sealing or affixation with adhesive. The width (w) of the sheet of material forming the layer **14** will correspond to the height (H) of the column **10**. A uniformly dense and constant thickness layer **16** of chromatographic media is then contacted with or applied to the partitioning layer **14**. The central core **12** is then rotated so as to roll the superposed layer **16** of chromatographic media and partitioning layer **14** onto the core. The rolling process is continued until a column of desired diameter (D) has been constructed. The diameter (D) will correspond to the diameter of the core **12** and the multiple thicknesses of the layers **16** and **14** of chromatographic media and partitioning material, respectively.

As shown in FIGS. **2** and **3** the resultant chromatography column will thus be composed of the central core **12** and, viewing in a lateral direction with respect to the column **10**, a plurality of adjacent layers **16** of chromatographic media which have a uniform thickness and packing density. The composition of chromatographic material from which the layers **16** are constructed will be dependent upon the particular chromatographic application. Factors to be considered are whether gas or liquid chromatography will be utilized, in addition to the components of the mixture of fluid which will be separated. Herein when the word fluid or chromatography fluid is utilized it is to be understood that reference is being made to carrier gas or liquid and the components in the carrier gas or liquid which are transported through the column for purposes of separation. Exemplary chromatographic media used in liquid chromatography can be cellulose, silica, alumina, kieselguhr, silicone grease, glass fibers, carbon and several others. Gas chromatography can use these media in addition to certain others, such as crushed firebrick, squalane and apiezone grease.

The chromatographic media layer **16** can be applied to the partitioning layer in a variety of ways. If the chromatographic media is in particulate or powder form, a layer of uniform thickness can be distributed over the sheet of partitioning material prior to the time it is rolled onto the core. The chromatographic media may be put into a liquid suspension and then applied to the partitioning layer. An adhesive or binder can be used to coalesce particulate media into a uniformly dense and mechanically stable layer. A suitable adhesive or binder is calcium sulfate or polymerizable ethylene monomer. The chromatographic media itself may also act as a binder to the partitioning layer. Additionally, the chromatographic media can be a liquid alone, such as silicone oil, and can be applied in a uniform layer to the support film or partitioning layer. If desired, relatively large particles, composed of media or relatively inert material, can be uniformly distributed throughout the media layer. Such particles can function to reduce the overall pressure drop through the final column.

In the embodiment of FIGS. **1** through **3**, the partition layer can be composed of a relatively inert, support film of a synthetic polymeric material, such as polytetrafluoroethylene, having a thickness on the order of 0.004 inches. For other applications, a metallic sheet or film of aluminum or other material compatible with the chromatographic solvents, pressures and temperatures can be used. As stated above, it is preferred that the materials utilized for the partition layer be composed of a material relatively inert with respect to the chromatography process. Other support films, such as nonwoven fibrous mats or woven cloth of either synthetic polymeric or metallic filaments, or glass fiber mats can be effectively employed.

As shown in FIG. **1** column **10** also contains an outer shell **18** which is present primarily for structural purposes. The exterior shell **18** is formed by continuing to wrap the partitioning layer **14** about the column **10**, while omitting the step of coating the partitioning material **14** with a layer **16** of chromatographic media. Thus a plurality of wraps around the exterior of the column can consist solely of the partitioning material. The structural integrity can thus be enhanced. As an alternate, different structural material can be interposed between or substituted for the layers of material composing the outer shell **18** to provide enhanced structural integrity. For example, if a polymeric film is utilized for layers **14**, a metal sheet can be placed on the film as it is being wrapped about the column **10** to form the outer shell **18**. In addition, an adhesive or other suitable fastening means can be applied to the last wraps of the material which form the outer shell **18** to provide a secured outer shell.

If desired a suitable casing can be employed to surround the column **10**. For example, column **10** can be inserted into a glass, metal or polymeric tube having an internal diameter corresponding to the external diameter of the column **10**. Suitable fluid admission, collection and monitoring systems can also be employed with the present column as in conventional analytical columns.

Referring now to FIGS. **4** and **5** an alternate embodiment of the present invention is illustrated. In this embodiment a plurality of layers **20** of chromatographic media are built up in the form of successively larger diameter, coaxial cylindrical shells. These shells are applied to a central structural core **22**. Referring to the enlarged cross section of FIG. **5**, cylindrical shells can be formed by suspending chromatographic media in a carrier and incorporating an adhesive. The suspension can then be sprayed onto the cylindrical core **22** as it is being axially rotated to provide uniform layers **20**. Thus, a plurality of uniformly dense and thick layers can be achieved as long as the producton conditions are well regulated. This coaxial layer configuration can be formed with or without partitioning layers alternating and coaxial with media layers.

Referring now to FIG. **6** an alternate embodiment for a layer **24** of partitioning material is illustrated. The partitioning layer **24** includes a plurality of heat transfer fluid flow channels **26**. Flow channels **26** as shown are formed integrally with the partitioning sheet **24**. As will be noted, the partitioning sheet **24** has a uniform thickness (t) between which the flow channels are situated in a corrugated pattern. A preferable material for this embodiment of the partitioning layer **24** is a material of relatively high thermal conductivity such as aluminum or some other metallic substance. It should be understood that if such heat transfer channels are to be utilized with a column such as shown in FIGS. **1** through **3**, a suitable manifold system must be utilized to introduce the heat transfer fluid, such as water, into channels **26** and to exhaust the fluid from channels **26** in the direction exemplified by the arrows.

FIG. **7** shows an alternate core **28** which can be utilized for the purpose of transmitting heat to or from the interior of a chromatography column constructed in accord with the invention. Hollow core **28** can be utilized to construct a column similar to that of FIGS. **1** through **3**. Core **28** contains a channel **30** formed in the interior of the core **28**. Again suitable inlet and outlet connections are required for ingress and egress of a heat transfer fluid. Core **28** can be composed of a material of relatively high thermal conductivity such as a metal, for example, aluminum.

As shown in FIG. **8**, the heating function can alternatively be performed by an electric resistance heater **32**, shown schematically. Heater **32** can be interposed between a layer **34** of chromatographic media and a partitioning layer **36**. Electric resistance heater **32** is powered through leads **38** which extend outside the column to a suitable source of electrical energy. One or more resistance heaters can be energized at selected locations within the column as required.

For conjunctive use with heat transfer means such as that shown in FIGS. **6** through **8**, a temperature monitoring system is also of great value. One means by which the temperature can be monitored within the column is by interposing a thermocouple **40** adjacent layer **34** of chromatographic media. This can be accomplished by positioning the thermocouple **40** on a layer of chromatographic media **34** as the column is being rolled up in accord with the embodiment of FIG. **1**. Leads **42** associated with the thermocouple **40** will run away from the thermocouple to the exterior of the column and will be connected to a suitable monitoring instrumentation system. Thus, for appropriately placing suitable thermocouples **40** throughout the column the appearance of a thermal gradient across the column can be detected. In response to the detection of a thermal gradient a heat transfer fluid can be pumped through the flow channel such as **26** in FIG. **6** to either add or remove heat as required. Similarly, an electric resistance heater **32** can be energized to add heat to the appropriate location in the system. It is to be understood that resistance heaters **32** can be more strategically located than heat transfer channels such as **26** to provide a more localized control of the thermal conditions within the column. It should also be realized that for many applications sole use of a thermally conductive partitioning layer **36** can provide adequate heat transfer to equalize a thermal gradient throughout the column.

FIG. **9** shows another embodiment of the chromatography column of the present invention. In this embodiment a central core or dike **44** is formed from any suitable relative inert composition, such as a polytetrafluoroethylene block. Sheets or layers **46** of partitioning material are prepared and coated with a layer **48** of appropriate chromatographic media. Layers **46** and **48** are then alternately superposed until a column **50** of desired thickness (T) is completed. The length dimension of the individual sheets or layers **46** of partitioning material will determine the overall height (H) of the column while the total combined thickness of the partitioning layers **46** and media layers **48** will determine the overall thickness (T). The width (w) of the layers **46** of partitioning material will determine the final width (W) of the column. Although not necessary, dike **44** can be incorporated into column **50** as an aid to the separation process. Dike **44** is formed of a relatively inert material and can be recessed into the top of the column to a depth on the order of one-eighth inch. Dike **44** is used to hold the carrier fluid and sample at the top of the column when a separation is begun. If desired, structural side plates can be placed on all four sides of the column **50.**

At this point it should be noted that all chromatography columns have a primary direction of fluid flow. Generally chromatography columns are arranged in a vertical direction with the chromatographic fluid either flowing upwardly or downwardly through the column. According to the embodiments of the present invention as illustrated, the thickness dimension of the successive adjacent layers of chromatographic media are arranged so that the thickness dimension is substantially perpendicular to the column axis, i.e., the primary direction of fluid flow.

The present invention provides variety and flexibility in constructing different types of chromatography columns. For example, materials which can be utilized in the chromatographic layer include glass beads, porous layer beads, molecular sieves, gels for gel filtration, alumina, carbon, fibers or filaments, woven cloth, mesh, porous films and the like. Whenever the term chromatographic media is utilized herein it is intended to refer primarily to the active chromatographic composition. When layer of chromatographic media or similar phrase is used, the layer can include not only the chromatographic media itself, but also materials for reducing pressure drop, materials to assist in homogeneous distribution of the chromatographic media, adhesive compositions and the like. Any conventional treatment utilized for the chromatographic media can be applied to the chromatographic layer of the present invention. The present invention as conceived utilizes conventional media and conventional media preparation techniques. The invention as conceived relates to the method and manner of forming a chromatography column and to the column itself.

EXAMPLE

An example of a chromatography column prepared in accord with the present invention follows. A porous chromatographic media composed of silica powder with a particle diameter on the average of 10 microns is conventionally prepared as normal. One end of a sheet of aluminum film, 0.004 inches thick, 12 inches wide and 50 feet long, is connected to a stainless steel core rod, 12 inches long by 0.75 inches in diameter. The prepared chromatographic media is then laid down on one surface of the aluminum sheet by spreading it onto the surface to a uniformly packed thickness of 1.0 millimeter. As the silica powder is spread onto the aluminum sheet, the sheet and layer of chromatographic media are carefully rolled onto the steel core rod. This construction provides a cylindrical column with alternating adjacent layers of aluminum film and silica.

The foregoing example illustrates the basic technique of forming a chromatography column in accord with the present invention. The diameter of the column has been limited to a plurality of thin layers of chromatographic media. The column thus produced is 12 inches high in the direction of longitudinal solvent flow, which height is dictated by the width of the original aluminum film. The dimension of the individual layers of chromatographic media are limited to a finite value, taking into consideration such variables as type of chromatographic media, activity of chromatographic media, column diameter, column operating pressure and temperature, solvent flow rate, separation time, longitudinal diffusion of samples in the moving solvent phase, and the mass transfer rates of a sample between the moving and stationary phases of the chromatographic solvent or carrier.

The overall width of the column in accord with the present invention can be infinite, the actual diameter being limited only by practical considerations such as space requirements. Since the diameter or width of the overall column can be increased without theoretical limitation, the sample size or amount of substance to be separated in the bed is not limited. Thus the diameter can be increased to separate the desired amount of the sample substance to be produced.

To reiterate, the present invention is applicable to both liquid and gas chromatography, various porous chromatographic media in most physical states, for example, powders, pastes, liquids, gels, beads, fibers etc., can be utilized to produce a column in accord with the present invention. The partitioning layers and core rods utilized in the preferred embodiment to partition the adjacent layers of chromatographic media can be of any material that is compatible with the physical requirements and chemical reactivity of the chromatographic system. The partitioning material is preferably relatively inert. By appropriate selection of core rod material and partitioning material, a reinforced chromatography column can be constructed to allow the use of higher pressures during the chromatography process.

It should also be understood that the present invention is applicable not only to preparative and production chromatography, but is equally applicable to analytical techniques. The main thrust of the invention has been directed toward the former since these are the areas in which larger chromatography columns are normally required.

The present invention has been described in relation to several embodiments. Upon reading the specification one of ordinary skill in the art will be able to effect various alterations, changes and substitutions of equivalents to the present invention as disclosed. It is intended that the invention as conceived be limited only by the definition of the invention contained in the appended claims.

What is claimed is:

1. In a chromatography column in which flow of a fluid to be separated occurs primarily along a predetermined axis, said column having a height dimension, a packing for said column comprising:

a plurality of layers of chromatographic media arranged contiguous to each other, said layers having a thickness dimension and a height dimension, said thickness dimension of said layers extending substantially perpendicularly to said predetermined axis, said height dimension of said layers extending substantially parallel to said predetermined axis, said layers being substantially continuous and homogeneous to form a uniformly dense layer in both the thickness and height dimensions of said layers, said height dimension of said layers being substantially equal to the height dimension of said column.

2. The column of claim **1** wherein said layers are composed of sheets of chromatographic media, said sheets having surfaces arranged contiguous to the surface of a next adjacent sheet.

3. The column of claim **1** wherein said sheets are serially interconnected to form an integral, continuous roll of chromatographic media.

4. In a chromatography column in which the flow of fluid to be separated occurs primarily along a predetermined axis, packing means for said column comprising:

a plurality of layers of chromatographic media being arranged adjacent each other having the surfaces thereof extending substantially along said axis, said surfaces being arranged adjacent each other, said layers having a thickness dimension extending in a direction substantially perpendicular to said axis,

partitioning means interposed between adjacent ones of said plurality of layers for separating said layers and maintaining said layers at a substantially uniform thickness, said partitioning means being substantially impervious to fluid, said partitioning means contacting said surfaces to prevent substantial fluid flow between said surfaces and said partitioning means.

5. The column of claim **4** wherein said layers of chromatographic media are of substantially uniform thickness and density.

6. The column of claim **4** wherein said partitioning means comprises at least one sheet of relatively inert material, said layers being adhered to said partitioning means.

7. The column of claim **4** wherein said partitioning means is a structural component of said packing.

8. The column of claim **7** wherein said partitioning means has a thickness less than the thickness of said layer.

9. The column of claim **4** wherein said column has a substantially cylindrical shape, said partitioning means comprising a continuous sheet of partitioning material arranged in a spiral pattern to form said cylinder, said chromatographic media forming a continuous spiral layer adjacent said partitioning means.

10. The column of claim **4** wherein said column is composed of separate layers of media alternating with separate layers of said partitioning means to form a laminated structure.

11. The column of claim **10** wherein said column is substantially cylindrical, said layers of chromatographic media comprising coaxial substantially cylindrical shells and wherein said partitioning means comprises separate substantially cylindrical coaxial shells interposed between said layers of chromatographic media.

12. The column of claim **10** wherein said column is a parallelepiped of separate layers of chromatographic media alternating with separate layers comprising said partitioning means to form a sandwich structure.

13. The column of claim **4** wherein said partitioning means comprises a sheet of relatively inert material.

14. The column of claim **13** wherein said sheet comprises a material of relatively high thermal conductivity.

15. The column of claim **14** wherein said thermally conductive material comprises a metal.

16. The column of claim **13** wherein said sheet comprises a synthetic polymer.

17. The column of claim **4** further comprising:

means in said column for thermally conditioning selected locations within said column.

18. The column of claim **17** wherein said means for thermally conditioning comprises means for heating selected portions of said column.

19. The column of claim **17** wherein said means for thermally conditioning comprises means for cooling selected portions of said column.

20. The column of claim **17** wherein said means for thermally conditioning selected portions of said column further comprises means for transmitting heat from a first portion of said column to a second portion of said column.

21. The column of claim **4** further comprising:

heat transfer conduit means interposed between said layers of chromatographic media.

22. The column of claim **21** wherein said heat transfer conduit means comprise channels formed in said partitioning means.

23. The column of claim **4** wherein the thickness of said individual layer of chromatographic media does not exceed a thickness at which a substantial temperature gradient will occur across said multiple layers of chromatographic media.

24. The column of claim **23** wherein said thickness is less than about one centimeter.

25. The column of claim **4** wherein said column has substantially a cylindrical shape, said column further comprising a core composed of a relatively inert material.

26. The column of claim **25**, said core having a channel means therein for circulating a heat transfer fluid therethrough.

27. The column of claim **4** further comprising:

means in said column contacting said layers of chromatographic media for sensing the temperature at selected locations in said column.

28. The column of claim **4** further comprising an outer shell surrounding said column, said shell providing structural support for said column.

29. The column of claim **28** wherein said outer shell comprises the same material as said partitioning means.

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