

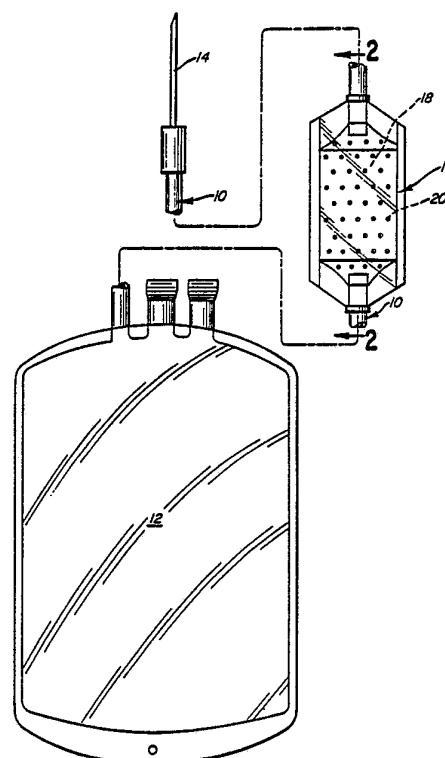


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<p>(21) International Application Number: PCT/US88/03986 (22) International Filing Date: 8 November 1988 (08.11.88) (31) Priority Application Number: 120,892 (32) Priority Date: 16 November 1987 (16.11.87) (33) Priority Country: US (71) Applicant: BAXTER INTERNATIONAL INC. [US/US]; One Baxter Parkway, Deerfield, IL 60015 (US). (72) Inventors: BREILLATT, Julian, P. ; 933 Highland Road, Mundelein, IL 60060 (US). WOO, Lecon ; 1013 Shari Lane, Libertyville, IL 60048 (US). NELSON, Deanna, J. ; 729 Thomas Court, Libertyville, IL 60048 (US). APPL, Richard ; 1111 Robey Avenue, Downers Grove, IL 60068 (US).</p>		<p>(74) Agents: MATTENSON, Charles, R. et al.; One Baxter Parkway, Deerfield, IL 60015 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: GLASSY MATRIX FOR ADMINISTRATION OF BENEFICIAL AGENT**(57) Abstract**

Medical solution is passed in a conduit (10) across a solid mass of beneficial agent (18) to cause the beneficial agent (18) to dissolve in the medical solution. The beneficial agent (18) comprises a sugar in a substantially anhydrous, glass form, the mass being shaped and proportioned so that a controlled amount of the beneficial agent (18) dissolves into passing medical solution in a manner that is preferably substantially predetermined. Typically, the sugar glass of the beneficial agent (18) includes at least one added effective agent for dissolving in the medical solution as the sugar dissolves therein.



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GLASSY MATRIX FOR ADMINISTRATION OF BENEFICIAL AGENT

TECHNICAL FIELD

As blood is collected from the donor, it
5 passes into a container such as a blood bag which
contains an anticoagulant system. Such anticoagulant
systems are typically a small amount of liquid
solution which is stored in the bag, being typically
ACD, CPD, CPD-adenine, or the like. Additionally, it
10 has been suggested that the anticoagulant system may
be placed as a dried coating on the interior of the
blood collection container.

With these systems, as the blood is
introduced into the container, the ratio of the whole
15 blood present to the anticoagulant present is
undesirably high, consequently producing a significant
and detrimental osmotic imbalance. While this problem
is quickly corrected with the addition of subsequent
amounts of blood, it can be damaging to the first
20 aliquot of blood cells administered into the
collection bag.

Accordingly, there is a need for a blood
handling system where beneficial agents such as
anticoagulant/storage agents may be administered to
25 the blood without the initial, undesirable osmotic
effect that currently takes place at the beginning of
the blood collection.

Additionally, in the manufacture of
conventional blood storage bags which contain a liquid
30 anticoagulant, a capital intensive and closely
controlled manufacturing process is required,

including a liquid filling operation (which requires a clean room), batch steam sterilization procedures, and packaging of the blood bag in an additional moisture barrier container for storage. If it were possible to
5 make use of blood bags which did not contain a liquid anticoagulant system, it would be possible to greatly simplify the manufacturing process, making use of continuous radiation sterilization, and eliminating the additional moisture barrier packing which is
10 currently necessary.

Additionally, blood storage bags which contain either a liquid anticoagulant or a dried coating thereof on the interior walls result in a container that must be completely filled with blood in
15 order to be usable. If, for any reason, the donor is unable to donate one complete unit of blood, the entire, underfilled unit typically is not used, due to an excess concentration of anticoagulation agent present in the reduced volume of blood, since the
20 anticoagulant present in the bag is intended for one complete unit of blood. If empty, anticoagulant-free blood storage bags were used in which the blood was still properly provided with anticoagulant/storage agents, these underfilled units could still be used
25 for pediatric or partial transfusion purposes, and would not have to be discarded.

In a United States patent application entitled Controlled Administration of Beneficial Agent to Blood, assigned to Baxter Travenol Laboratories,
30 Inc. and filed on the same day as this present application, a technique and apparatus for solving the above problems is provided, to permit the application of a beneficial agent such as anticoagulant/storage agent to blood while the blood is passing through a
35 conduit into a container. Thus, blood storage

containers without any beneficial agent therein may be manufactured and used, for the significant manufacturing advantages described above.

5 Additionally, partial units of blood may be collected and used.

As described in the patent application cited above, the beneficial agent may be carried in a conduit through which medical solution, typically blood, passes, typically on its way to a container.
10 As it passes through the beneficial agent, a controlled amount of beneficial agent dissolves into each aliquot of medical solution which passes. In accordance with this invention, improved uniformity of transfer of the beneficial agent to the various
15 aliquots of medical solution may be obtained, along with desirable improvement in control and precision in the process.

Additionally, the controlled or sustained delivery of chemical agents or drugs is commonly
20 obtained by diffusion from a permanent matrix that contains and serves as a reservoir of the agent. In some cases, the porosity of the matrix fixes the diffusion rate of the chemical into the surrounding environment. In other cases, a rate-limiting membrane
25 is juxtaposed between the reservoir and the target. Examples include pesticide dissemination, transdermal drug delivery and administration of therapeutic agents into parenteral fluids or blood.

In the case of delivery into blood or
30 parenteral fluids, the introduction of a permanent matrix entails an additional material whose biocompatibility must be assured, and that will not shed particles into the circulation. Moreover, it is difficult to determine when a permanent matrix has
35 delivered its total dose of entrapped agent to a

parenteral fluid or to blood, since neither the visual appearance nor the density of the matrix will necessarily change with depletion of the agent. Further, because matrices allowing outward diffusion of the agent must have a finite porosity, they cannot act as a barrier to moisture or gas diffusion into the matrix and the agent formulation therein entrapped.

The ideal matrix for parenteral or blood delivery would be one that protects and stabilizes the active agent in the dry state, then disappears as the agent is delivered into the flowing stream. The matrix could be the agent itself or a component thereof, a beneficial metabolite, or a non-toxic, excretable molecular species that dissolves in the stream of parenteral fluid or blood passing over it, thus releasing the entrapped agent.

Ideally, the matrix dissolution rate determines the delivery rate of the active agent; as the matrix dissolves and disappears, the agent is contacted by the surrounding fluid and itself dissolves. However, one of the factors limiting the delivery rate of the agent into the fluid stream is its own solubility. In the extreme case the matrix could dissolve away leaving the agent as an insoluble mass in the fluid. To ensure that the dissolution of the agent is equal to or greater than that of the matrix, chemical buffers or reactants can be entrapped in the matrix with the agent, under conditions that they would not react during the formation of the filled matrix, but such that when the dissolving fluid reaches the agent, a localized environment will be established that favors its dissolution.

Alternately, an agent may be stable to storage only in a pharmacologically inactive form. Chemical reactants that transform the pro-drug into

its active form may be co-entrapped in the matrix. As the fluid dissolves the matrix and its contents, a high concentration of the various dissolving chemical species will occur at the solid-liquid interface, providing conditions that enhance the desired chemical transformation.

In this invention, a matrix is provided for delivery of anticoagulant during blood collection, for parenteral drug delivery, and for any other controlled release of beneficial agent into a fluid stream.

DESCRIPTION OF THE INVENTION

In this invention, a method is provided for passing solution, typically medical solution such as blood, any desired parenteral solution, enteral nutrient solution, or the like, through a conduit, typically into a container or the circulatory system, the digestive system, the peritoneal cavity, or the like. In accordance with this invention, one passes the medical solution in the conduit across a solid mass of beneficial agent, wherein the beneficial agent is typically dispersed within a substantially anhydrous glassy sugar matrix, although the beneficial agent may be the glassy sugar matrix itself.

The term "sugar" shall include monosaccharides or polymers thereof having a degree of polymerization (d.p.) of preferably about 1 or 2, but optionally up to the hundreds. The term "sugar" also includes the corresponding sugar alcohols. The term "glass" or "glassy" refers to the amorphous, non-crystalline form assumed by viscous sugars, although local areas of crystallization may occur within such a glassy matrix without impairing its overall classification as a glass.

The mass of beneficial agent may, in one

embodiment, be shaped and proportioned whereby a controlled amount of the beneficial agent dissolves into passing medical solution in a manner that is substantially uniform or otherwise predetermined. As
5 a result of this, no substantial portion of the medical solution needs to be exposed to a significantly higher concentration of the beneficial agent than other portions of the medical solution.

For example, the tablet of beneficial agent
10 used herein may comprise a sugar selected from the group consisting of glucose, lactose, sorbitol, fructose, and xylitol in a substantially anhydrous glass form, the tablet also including at least one added effective agent for dissolving in medical
15 solution as the sugar dissolves in the medical solution.

In one typical use of the invention of this application, the medical solution may be blood, for example blood which is in the process of being
20 collected from a donor and passed into the donor bag of a single or multiple blood bag system which may be of conventional design and use, but for the modifications provided by this invention. In this circumstance, the beneficial agent may include an
25 anticoagulant which is dispersed in the sugar glass. Any known anticoagulant or other blood cell preservative, such as platelet preservatives, may be so incorporated into such a sugar glass. For example, the sugar that forms the glass may be glucose, which
30 may also include a water soluble, non-toxic source of citrate in sufficient concentration to have an anticoagulating effect on passing blood. Additionally, a water soluble, non-toxic source of phosphate may be present in a concentration effective
35 to promote blood storage in known manner. Adenine may

be present, if desired, as well as any other ingredient which is desired for the storage of blood or components thereof.

By the term "blood", it is intended to include not only whole blood, but components of blood as may be desired, for example blood plasma (either platelet rich or platelet poor) or suspensions of packed red cells, white cells, or platelets in saline solution, any other appropriate suspension of blood cells, or the like.

Typical sugars which may be used are, of course, soluble, non-toxic sugars which may or may not be metabolizable as a nutrient according to the desires of the formulator and the use to which the glassy mass of beneficial agent is to be put. Specifically, the sugar may be one or more of those selected from the group described above.

Examples of usable citrates and phosphates which may be used in the manner described above include sodium citrate, citric acid, and monosodium or disodium phosphate. The proportions of sodium citrate and citric acid may be adjusted to obtain the pH desired.

The glassy mass of beneficial agent is preferably provided in the form of one or more dry tablets, with means provided in the conduit for carrying the solid mass of beneficial agents and permitting blood or other medical solution to pass through the conduit to enter into contact with the solid mass. As solution passes through the solid mass, it picks up a substantially predetermined amount of beneficial agent, and carries it away. The specific geometry of the preferred tablet may be specifically shaped to provide a desired, controlled, relatively constant release of the beneficial agent as

the solution passes across it. Specifically, a single tablet may be provided which is relatively long and wide relative to its thickness. With such a configuration, as the tablet erodes, there is little change in the surface area of the tablet, so that the amount of beneficial agent which dissolves into passing medical solution remains substantially uniform, at least until the tablet begins to disintegrate. One may have the tablet or tablets of a desired size and thickness so that the last of the medical solution has passed through the conduit before the tablet or tablets erode away so much that they begin to break up, at which point a significant difference in the transfer rate of beneficial agent into the solution can take place. Otherwise, the tablet may be proportioned to completely dissolve before flow terminates to provide visual indication of complete dosage.

The dry, glassy beneficial agent may be a molded or pressed tablet structure, which may be flat and thin as described above, or the tablet may be a pressed, solid structure having multiple flow channels through it for flow of medical solution therethrough, or a cylinder positioned so that medical solution flows through its bore, or any other shape or structure as desired.

By this invention, since the geometry, state, and size of the glassy mass of beneficial agent can be controlled, improvements in control of transfer of the beneficial agent to the medical solution are obtained. For example, a variable rate of dosage may be provided by the shape of the tablet, if desired. A large, initial bolus dose may be provided, for example, if the outer portion of the tablet is more porous than an inner portion thereof.

When the beneficial agent desired is an anticoagulant/preservative preparation, it may comprise a solid mass or tablet of a sugar such as dextrose, formed in the shape as described above, with
5 the solid, glassy mass containing an effective anticoagulating amount of a soluble, non-toxic citrate, as described above, so that the dextrose and the citrate dissolve together in a controlled release manner in the passing blood. Similarly, the
10 anticoagulant/preservative formulation may include an amount of soluble, non-toxic phosphate as stated above.

Thus, the use of the substantially dry glassy mass of beneficial agent, positioned in a
15 conduit, provides significant advantages. The specific advantages of the empty bag or the receptacle which thus may be used for blood or other medical solution have been described above. Additionally, transportation and handling advantages are achieved,
20 when compared particularly with containers of frozen drug solution, which must be transported in frozen condition. In many cases, the drug is simply incorporated into the glassy mass of sugar. If desired, a parenteral solution such as saline may be
25 passed over the glassy mass and directly into the patient, carrying the dissolved sugar and a controlled amount of drug with it. Thus, critical drugs may be administered to a patient without a special step of reformulation of the dry drug into a parenteral
30 solution.

Thus, significant advantages of manufacturing, transportation, storage, and handling are provided in accordance with this invention.

35 Additionally, sugar glasses having a low water content (for example 1 to 4 percent by weight)

are good oxygen barriers. Thus, oxygen-sensitive drugs may be protected while incorporated in the glassy mass of beneficial agent used in this invention. Additionally, the system of this invention
5 is well suited for gamma irradiation sterilization, and moisture sensitive drugs are also protected by storage in the glassy mass of beneficial agent in accordance with this invention. It is believed that the sugar present can exert a protective action on
10 drugs or other effective agents which are mixed in the glassy mass with the sugar prior to contact with the medical solution for use, providing protection against moisture, oxygen, and even gamma radiation, to reduce loss of effective agent during gamma irradiation
15 sterilization.

Additionally, the glassy sugar masses used in this invention are resistant to bacterial attack due to their low water content. It is generally preferred for the water content of such glassy masses
20 to be about 1 to 2 percent, and typically no more than about 5 percent by weight.

Also, the glassy mass of this invention can be effectively molded during manufacture to form a tablet or tablets of desired dimensions to obtain the
25 exact, desired dissolution rate as medical or other solution passes in contact therewith.

Enough amorphous, glassy sugar or sugar alcohol should be present to serve as a binder for other materials present. Typically, at least about 20
30 weight percent of amorphous, glassy sugar is present in the dry, beneficial agent of this invention, surrounding and protecting other inclusions therein.

If desired, a substantially pure glassy sugar mass may be used as the beneficial agent.
35 Tablets of such material may be used to form glucose

parenteral solutions at their site of use, for example, from sterile water at the site, to avoid transporting the water from elsewhere.

Other ingredients such as soluble fillers
5 and coloring agents may also be present in the glassy mass.

The glassy mass of this invention may be manufactured by dispersing a substantially dry, powdered beneficial agent into a substantially dry,
10 soluble fluid phase material and thereafter allowing the dispersion thus formed to assume a solid state. The fluid phase material may be a molten sugar, especially those listed above, sodium citrate, citric acid, mannitol, or mixtures thereof, for example. The
15 molten material may be heated to dryness. Then, the dry, powdered beneficial agent is added, being, for example, powdered sugar to promote solidification. A drug or the like may also be used as the powdered beneficial agent. Then the dispersion is allowed to
20 cool and solidify, typically being molded into tablet form for use as described herein.

DESCRIPTION OF DRAWINGS

Fig. 1 is a plan view of a blood collecting set made in accordance with this invention, shown to
25 be integrally connected to a blood storage bag; and

Fig. 2 is a sectional view taken along line 2-2 of Fig. 1.

DESCRIPTION OF SPECIFIC EMBODIMENTS

Referring to the drawings, there is shown a
30 set 10 for collecting blood from a patient and conveying it to blood storage container 12, which may

be made in substantially conventional manner. Set 10 carries at one end a conventional blood connection needle 14 for collecting blood from the venous system of the patient, which blood then passes through set 10 into blood bag 12.

In accordance with this invention, the conduit of set 10 defines an enlarged portion 16 which includes a glassy, solid mass 18 of dry blood storage anticoagulant preparation, typically having a water content on the order of no more than about 2 percent by weight. Anticoagulant tablet 18 is shown to be made in the form of a thin, rectangular member positioned within enlarged portion 16. The inner walls of both sides of enlarged portion 16 define an array of small projections 20 which project inwardly to define flow passages between the inner wall of enlarged portion 16 and the surface of anticoagulant preparation tablet 18.

Specifically, anticoagulant preparation tablet 18 may comprise, for example, a dried mixture of:

Wt. % Present

	Dextrose	44
	Sodium Citrate	46
25	Citric Acid	6
	Sodium Biphosphate	4

The above dextrose is dissolved as a near saturated solution in water by heating to boiling. Then, water is removed by boiling under a vacuum of about 2 inches of mercury and up to about 310 degrees F., until the dextrose reaches the desired water content of 2 weight percent or less (as defined by its

temperature at the air pressure obtained by the vacuum system). The viscous mass is then cooled to avoid crystallization, to obtain a supercooled solution.

The other ingredients are added when the
5 temperature of the molten dextrose falls to about 200 degrees F., with vigorous stirring or alternatively in a twin screw extruder, to form a homogeneous mass. This material is molded into the desired shape and allowed to solidify, to form a white, glassy mass in
10 the shape of tablet 18, which may be then placed in portion 16.

Blood bag 12 may be initially free of any anticoagulant. The entire system, including tablet 18, is typically radiation sterilizable, since it is
15 substantially free of moisture. Additionally, no overpouch or other outer package is required to prevent the loss of water from a liquid anticoagulant present, which constitutes a significant advantage over the conventional present blood collection
20 equipment.

For use, a conventional phlebotomy is made into a vein of a blood donor with needle 14, and the blood flows through conduit 10. As it flows, it enters enlarged portion 16, where it flows in a pair
25 of opposed flow paths 22 between the walls 24 of enlarged portion 16 and the flat surfaces of tablet 18. As the blood so flows, the substance of tablet 18 is dissolved away into the flow blood at a relatively uniform rate of dissolution, so that each individual
30 portion of the flowing blood passing through conduit 10 picks up a substantially similar amount of the dissolved substance of tablet 18 as it flows across it. From there, the flowing blood, carrying the dissolved anticoagulant, glucose, etc. passes into bag
35 12 for storage, without encountering an excessive

concentration of anticoagulant or other agent.

Other dry forms of beneficial agents, particularly anticoagulant/preservatives, may also be used as desired, as a substitute for the specific forms of beneficial agent illustrated above with respect to tablet 18.

Any design of blood bag or other container may also be utilized in accordance with this invention. If desired, the tablet 18 or an equivalent mixture of materials may be encapsulated and released via diffusion through a semipermeable membrane.

Additionally, the invention of this application may be used in conjunction with various apheresis procedures, for example bag apheresis hardware collection, apheresis, or continuous apheresis procedures. For example, medications may be administered to blood in accordance with this invention by an apheresis procedure or the like.

Alternatively, an antibiotic or other drug may be mixed into the molten sugar when it is at a temperature of about 200 degrees F. or below. For example, aspirin may be added to dextrose sugar glass. Antibiotics and other peptides may be added with advantage to sorbitol glass. After intimate mixing, the molten mixture is molded into tablet form, or any other desired shape, and allowed to solidify to a solid, glassy form. Such glassy tablets may be stronger than compressed powder tablets, having more uniform dissolution rates for more accurate dosage, and higher dissolution rates than compressed powder tablets with conventional binders. The resulting tablets may be placed into a chamber similar to enlarged portion 16 of set 10, which may be adapted for connection, or integrally connected with, a bag of parenteral solution. Fig. 1 in this circumstance can

represent such a system, in which bag 12 contains, for example, sterile normal saline solution, or even pure water, although such a latter system might not be fail safe since intravenously administered water is very
5 damaging to blood cells.

In this instance, connection with the venous system of a patient is made by needle 14, and the parenteral solution in bag 12 is allowed to pass from bag 12 through set 10 into the patient's venous
10 system. As it passes through enlarged portion 16, the sugar and admixed drug of table 18 dissolves into the passing parenteral solution at a predetermined rate, so that the desired amount of drug may be administered simply by administering a desired quantity of
15 parenteral solution from bag 12 at a predetermined rate of flow.

Thus, the invention of this application may not only be used for the handling of blood, but it may be used for the administration of drugs or other
20 beneficial agents directly to the patient, or to another container in which solution from a bag is passed through a chamber which contains a glassy mass of a sugar, containing the desired beneficial agent. Such a system is very flexible as to the amount of
25 beneficial agent which is delivered, contrary to many present systems. If one wishes to deliver only one third of the available beneficial agent in tablet 18, one can simply administer a predetermined amount of solution from bag 12 through set 10 to the patient,
30 and then terminating such administration when the desired amount of beneficial agent has been delivered. Additionally, the enlarged chamber 16 may be manufactured in a form of a cartridge for connection to parenteral solution sets, with the various
35 cartridges carrying different types of drugs as may be

desired in the glassy mass of sugar. The doctor then
needs to only select a cartridge which carries the
drug of the desired type and concentration, and
administer it to the patient without a special drug
5 reconstitution step previous to the administration.

Other examples of drugs which may be
inserted into the glassy mass of this invention
include anti-clotting agents such as heparin,
antibiotics of any type such as gentamycin,
10 penicillin, or erythromycin, other strongly
biologically active drugs that require controlled
administration to the patient such as thyroid hormones
or insulin, and the like.

Not only can the glassy mass of this
15 invention be stored in a tubular set, but the glassy
mass may be placed within an empty bag or other
storage container, to dissolve into an aliquot of
solution that passes into the container, should that
alternative technique be deemed desirable.

20 Added specific examples are found below
showing the manufacture of specific glassy, sugar
tablets containing beneficial agents.

As an example of how acetylsalicylic acid
may be incorporated into a glassy dextrose tablet, 250
25 grams of dextrose monohydrate may be dissolved in
water at a near saturated solution and boiled to about
250 degrees F. under vacuum of about two inches of
mercury, until the dextrose reaches the desired water
content of 2-4 wt. percent or less in the manner
30 previously described, but remains in liquid form.

A well-mixed powder containing 78 grams of
anhydrous sodium citrate and 55 grams of
acetylsalicylic acid is then dispersed in the dextrose
liquid after it has cooled to about 200 degrees F.,
35 with vigorous stirring or alternatively in a twin

screw extruder, to form a homogenous mass. This material is molded into the desired shape and desired to solidify to form tablets 18 of a shape desired. These tablets may then be placed in portion 16 of an administration set, or otherwise used.

When water flows over a tablet containing aspirin dispersed alone in a dextrose matrix, the dextrose matrix dissolves, leaving an undissolved mass of aspirin, since aspirin has a low solubility in water. The sodium citrate ingredient is thus included to continuously establish an acidic pH (4.9-5.0) at the surface of the dissolving tablet, under which conditions the aspirin is readily soluble, and dissolves at a comparable rate to the matrix. This mixture of aspirin and citrate is only possible in an anhydrous system since aspirin reacts with citrate if they are heated together in the presence of a significant amount of water. Also, the aspirin will deacetylate in the presence of water. Thus, by this method, aspirin and citric acid are incorporated together into a glassy tablet, for later i.v. or other administration while strongly suppressing undesired reactions.

Preferably, 25 parts by weight of sugar such as dextrose may be reduced to fluid, anhydrous form according to this invention, and the temperature reduced to 180-240 degrees F.. From 6-10 parts by weight of sodium citrate and from 4-7 parts by weight of acetylsalicylic acid may then be added to the liquid, anhydrous dextrose, followed by mixing and formation by molding of tablets for use in accordance with this invention.

As another example of the manufacturing of another kind of tablet 18 which may be used in the manner previously described, 250 grams of sorbitol is

dissolved in water by boiling to 392 degrees F., followed by cooling to about 100-150 degrees F. There is then added to the fluid sorbitol 100 mg. of freeze-dried, powdered peptide mixed with 25 grams of powdered sorbitol as a dispersing agent. The mixture is rendered homogeneous by vigorous stirring, or by twin screw extruder or the like. This material may be formed by molding into tablets or the like, as desired, for use in controlled dosage administration, intravenously or otherwise, of the peptide.

The peptide may be substantially any bioactive protein or polypeptide, for example, antibiotics or the like. Additionally, other low dosage, biologically active materials may be similarly formed into tablets in highly diluted form for similar administration.

One advantage of this technique is that sorbitol or mixtures thereof with other sugars may be cooled to below 200 degrees F. in anhydrous form while retaining significant fluid characteristics, to permit the physical mixing of a heat sensitive desired ingredient. Thus, temperature sensitive ingredients may be administered in accordance with this invention by the use of sorbitol or other materials in accordance with this invention.

Accordingly, by the invention of this application, a system is provided in which a solid drug or other beneficial agent can be reconstituted into its beneficial form at the site of use without an intermediate diluent, if desired. In other words, the beneficial agent of this invention can be directly reconstituted into blood, where its beneficial action takes place directly on the blood without the need of an intermediate diluent. On the other hand, the glassy mass tablet of this invention may be

reconstituted into a diluent, for purposes of drug delivery or the like, if desired.

The above has been offered for illustrative purposes only, and is not intended to limit the scope of the invention of this application, which is as
5 defined in the claims below.

THAT WHICH IS CLAIMED IS:

1. The method of passing medical solution through a conduit, the improvement comprising:
passing said medical solution in the conduit across a solid mass of beneficial agent, said
5 beneficial agent comprising a sugar in a substantially anhydrous, glass form, said mass of beneficial agent being shaped and proportioned whereby a controlled amount of said beneficial agent dissolves into passing
10 medical solution in a manner that is substantially predetermined.
2. The method of Claim 1 in which said beneficial agent dissolves in substantially uniform manner, whereby no substantial portion of said medical solution is exposed at a relatively constant flow to a
5 significantly higher concentration of said beneficial agent than other flowing portions of said medical solution.
3. The method of Claim 1 in which said medical solution is blood, and said beneficial agent includes an anticoagulant mixed in the sugar glass.
4. The method of Claim 1 in which said sugar is selected from the group consisting of glucose, lactose, sorbitol, fructose, and xylitol.
5. The method of Claim 1 in which said
sugar glass of the beneficial agent includes at least
one added effective agent for dissolving in the
medical solution as the sugar dissolves in the medical
5 solution.

6. The method of Claim 5 in which said added effective agent is a drug which is sensitive to at least one of moisture, oxygen, and gamma radiation, whereby said sugar exerts protective action on said effective agent prior to contact with said medical solution.

7. The method of Claim 1 in which said beneficial agent comprises glucose as said sugar and also includes a water soluble, non-toxic source of citrate in sufficient concentration to have an anticoagulating effect on passing blood.

8. The method of Claim 7 in which said beneficial agent also includes a water soluble, nontoxic source of phosphate in a concentration effective to promote blood storage.

9. The method of Claim 1 in which said medical solution is an artificial parenteral solution, and said beneficial agent includes a drug admixed in the sugar glass.

10. The method of passing blood through a conduit into a container, the improvement comprising: passing said blood in the conduit across a solid mass of beneficial agent, said beneficial agent comprising at least one sugar selected from the group consisting of glucose, lactose, sorbitol, fructose, and xylitol in a substantially anhydrous, glass form, said solid mass also containing an effective amount of anticoagulant therein, said mass of beneficial agent being shaped and proportioned whereby a controlled amount of said beneficial agent dissolves into passing blood in a manner to permit an anticoagulating

effect on said blood.

11. The method of Claim 10 in which said beneficial agent dissolves in substantially uniform manner, whereby no substantial portion of said blood is exposed to a significantly higher concentration of said beneficial agent than other portions of said blood.

12. The method of Claim 11 in which said beneficial agent comprises glucose as said sugar and also includes a water soluble, non-toxic source of citrate.

13. The method of Claim 12 in which said beneficial agent also includes a water soluble, non-toxic source of phosphate in a concentration effective to promote blood storage.

14. In a set for conveying solution from one location to another which comprises a conduit, the improvement comprising:

a portion of said conduit carrying a solid mass of beneficial agent, said beneficial agent comprising a sugar in substantially anhydrous, glass form, said mass of beneficial agent being shaped and proportioned whereby a controlled amount of said beneficial agent dissolves into passing solution in a manner that is substantially predetermined.

15. The set of Claim 14 in which said mass of beneficial agent is shaped and proportioned to cause said beneficial agent to dissolve in substantially uniform manner, whereby no substantial portion of medical solution passing through said

conduit at relatively constant flow is exposed to a significantly higher concentration of said beneficial agent than other portions of said flowing solution.

16. The set of Claim 14 in which said beneficial agent includes an anticoagulant mixed in the sugar glass.

17. The set of Claim 14 in which said sugar is selected from the group of glucose, lactose, sorbitol, fructose and xylitol.

18. The set of Claim 14 in which said sugar glass of the beneficial agent includes at least one added effective agent for dissolving in the solution as the sugar dissolves in the solution.

19. The set of Claim 18 in which said added effective agent is a drug which is sensitive to at least one of moisture, oxygen, and gamma radiation, whereby said sugar exerts protective action on said
5 effective agent prior to contact with said solution.

20. The set of Claim 14 in which said beneficial agent comprises glucose as said sugar and also includes a water soluble, non-toxic source of citrate in sufficient concentration to have an
5 anticoagulating effect on passing blood.

21. The set of Claim 20 in which said beneficial agent also includes a water soluble, non-toxic source of phosphate in a concentration effective to promote blood storage.

22. The set of Claim 14 in which said

beneficial agent includes a drug admixed in the sugar glass, said set being attached to a container of artificial parenteral solution at one end and carrying
5 means at the other end for communication with the venous system of a patient.

23. The set of claim 14 in which said beneficial agent is substantially pure sugar.

24. In a set for conveying medical solution from one location to another which comprises a conduit, the improvement comprising:

a portion of said conduit carrying a solid
5 mass of beneficial agent, said beneficial agent comprising a sugar selected from the group consisting of glucose, lactose, sorbitol, fructose, and xylitol in a substantially anhydrous, glass form, said
beneficial agent also including at least one added
10 effective agent for dissolving in the medical solution as the sugar dissolves in the medical solution, said mass of beneficial agent being shaped and proportioned whereby a controlled amount of said beneficial agent
dissolves into passing medical solution in a manner
15 that is substantially predetermined.

25. The set of Claim 24 in which said beneficial agent is shaped and proportioned to dissolve in substantially uniform manner, whereby no substantial portion of said medical solution is
5 exposed at a relatively constant flow to a significantly higher concentration of said beneficial agent than other flowing portions of said medical solution.

26. The set of Claim 25 in which said

beneficial agent includes an anticoagulant mixed in the sugar glass in sufficient concentration to have an anticoagulating effect on passing blood.

27. The set of Claim 26 in which said anticoagulant is a water soluble, non-toxic source of citrate.

28. The set of Claim 27 in which said beneficial agent also includes a water soluble, non-toxic source of phosphate in a concentration effective to promote blood storage.

29. The set of Claim 24 in which said beneficial agent includes a drug admixed in the sugar glass.

30. The set of Claim 29 in which said set is connected at one end to a container of artificial parenteral solution and at the other end to means for communicating with the venous system of a patient.

31. The set of Claim 29 in which said sugar glass of the beneficial agent includes a drug which is sensitive to at least one of moisture, oxygen, and gamma radiation, whereby said sugar exerts protective action on said effective agent prior to contact with said medical solution.

32. The method of bringing into contact under substantially aseptic conditions a medical solution and a beneficial agent which comprises a sugar in a substantially anhydrous glass form plus at least one added effective agent, said mass of beneficial agent being shaped and proportioned whereby

a controlled amount of said beneficial agent dissolves into said medical solution at a rate that is substantially predetermined.

33. A tablet of beneficial agent which comprises a sugar selected from the group consisting of glucose, lactose, sorbitol, fructose, and xylitol in a substantially anhydrous, glass form, said tablet
5 of beneficial agent including at least one added effective agent for dissolving in medical solution as the sugar dissolves in the medical solution.

34. The tablet of Claim 33 which comprises glucose as said sugar and also includes a water soluble, non-toxic source of citrate in sufficient concentration to have an anticoagulating effect on
5 passing blood.

35. The tablet of Claim 34 which includes a water soluble, non-toxic source of phosphate in a concentration effective to promote blood storage.

36. The tablet of Claim 35 which contains approximately 44 weight percent dextrose, 46 weight percent citrate, 6 weight percent of citric acid, and 4 weight percent of sodium biphosphate.

37. The tablet of Claim 37 in which said added, effective agent is a drug which is sensitive to at least one of moisture, oxygen and gamma radiation, whereby said sugar exerts protective action on said
5 effective agent prior to contact with medical solution.

38. The tablet of claim 33 in which said

sugar is dextrose and said tablet contains mixed therewith from 6 to 10 parts by weight of sodium citrate and 4 to 7 parts by weight of acetylsalicylic acid per 25 parts by weight of dextrose present.

39. The tablet of claim 33 in which said sugar is sorbitol and said tablet contains admixed therewith a powdered peptide.

40. The method of dispersing a dry, powdered beneficial agent into a substantially dry, soluble, fluid phase material, and thereafter allowing said dispersion of beneficial agent and material to assume a solid state.

41. The method of claim 40 in which said dispersion is formed into a tablet of predetermined shape and placed in chamber means capable of providing a flowing stream of solution to pass across said dispersion, to cause controlled-rate dissolution of said dispersion into said flowing stream.

42. The method of claim 41 in which said substantially dry, soluble fluid phase material is a sugar.

FIG. 1

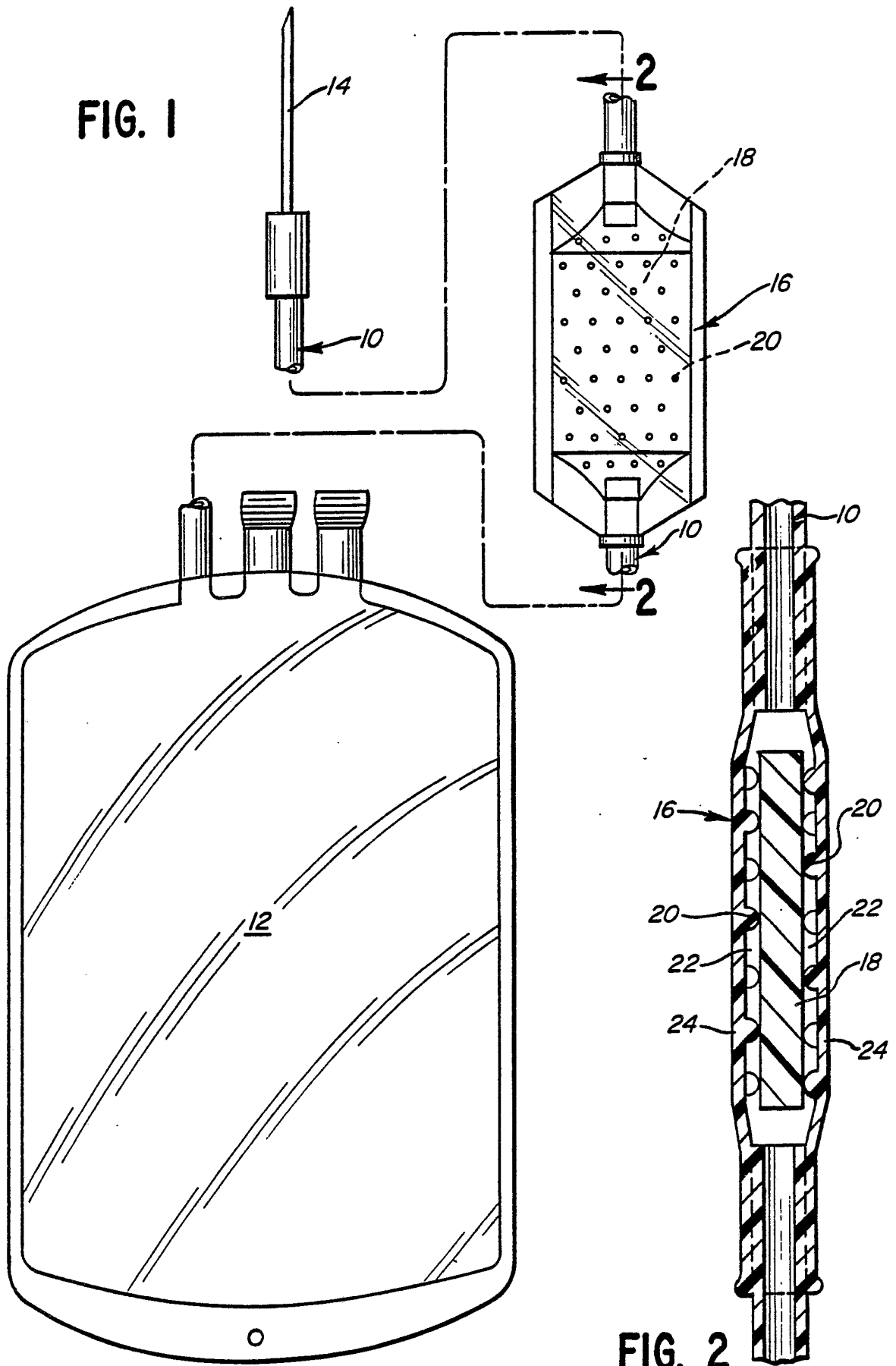
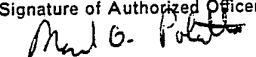


FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03986

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶				
According to International Patent Classification (IPC) or to both National Classification and IPC				
IPC(4)	A6 IM 31/00	US CL 604/890		
IPC(4)	B27N 3/00	US CL 264/109		
II. FIELDS SEARCHED				
Minimum Documentation Searched ⁷				
Classification System	Classification Symbols			
US	604/4, 6, 56, 82-85, 92, 185, 251, 252, 262, 890, 892 424/467, 479 264/109			
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸				
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹				
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³		
Y	US, A, 4,552,555 (THEEUWES), 12 November 1985, See Abstract, Column 4, lines 8-36.	1-32,41		
Y,P	US, A, 4,753,800 (MOZDA), 28 June 1988, See column 5, lines 28-52.	1-32,41		
Y	US, A, 4,257,426 (BAILEY), 24 March 1981, See Abstract.	3,7,8,10-13, 16,20,21,26-28		
Y	Transfusion, Volume 24, no. 6, issued 1984 (Philadelphia), B.A. MYHRE et al., 'Preservation of red cell antigens during storage of blood with different anticoagulents,' See pages 499-501.	3,7,8,10-13 16,20,21,26-28		
Y,P	US, A, 4,758,430 (Sabin), 19 July 1988, See column 3, lines 32-36, 65-5	33-39		
Y	US, A, 4,130,647 (TAYLOR), 19 December 1978, See column 3, lines 7-31.	33-39		
Y	US, A, 4,235,236 (THEEUWES), 25 November 1980, See column 6, lines 10-28, lines 51-60, column 5, lines 20-21.	33-39		
Y	US, A, 4,684,516 (BHUTANI), 04 August 1987, See column 2, lines 3-68.	40-42		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 2px;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="width: 50%; vertical-align: top; padding: 2px;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>			
IV. CERTIFICATION				
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report			
15 February 1989	03 APR 1989			
International Searching Authority	Signature of Authorized Officer			
ISA/US	 Mark O. Polutta			

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	US,A, 3,558,768 (KIPPEL), 26 January 1971, See column 2, lines 4-40.	40-42
Y	US,A, 3,365,365 (BUTLER), 23 January 1968, See column 3, lines 70-35.	40-42
Y	US,A, 2,996,43L (BARRY), 15 August 1961, See column 4, lines 1-17.	40-42
A	US,A, 4,381,776 (LATHAM), 03 May 1983, See column 1, lines 32-36,65-5.	
A	US,A, RE 25,129 (WALTER), 02 February 1962, See column 4, lines 15-25.	
A	CH, 497,181 (FOKIANOS), 30 November 1970, See Fig. 1, column 3, lines 5-10.	

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers because they relate to subject matter¹² not required to be searched by this Authority, namely:

2. Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out¹³, specifically:

3. Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

I. Claims 1-32 drawn to an administration set; class 604 subclass 56.

II. Claims 33-42 drawn to a tablet; class 424 subclass 469, class 264 subclass 109.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application. Telephone Practice

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.

No protest accompanied the payment of additional search fees.

ATTACHMENT TO FORM PCT/ISA/210, PART VI. 1

\$140 payment approved by Mr. Mathenson on 16 February 1989 for Group II; charge to Deposit Account No. 021440. Counsel advised that he has no right to protest for any group not paid for and that any protest must be filed no later than 15 days from the date of mailing of the search report (Form 210).

The invention as defined by group I (claims 1-32,) is drawn to an administration set which is classified in Class 604, Subclass 56 and which does not require the tablet defined by Group II (Claims 33-42) which is drawn to a tablet and method of making a tablet and is classified in Classes 424, and 264, Subclasses 469 and 109.

Applicant is hereby given 15 days from the mailing date of this Search Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 40.2 applicant may protest the holding of lack of unity only with respect to groups paid for.