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(54) **Sustained-release bodies of soluble glass tubules**

(57) A liquid soluble body for the controlled release of an active material into a liquid medium comprises a liquid soluble body having an array of microcavities therein, the material being contained in the microcavities and released by exposure of the microcavities as the body dissolves. The body may be in the form of an implant or a bolus for the controlled supply of an organic material, e.g. a drug or hormone, to an animal. The body is preferably a mass of thin tubes or capillaries made of a soluble glass composition, the ends of the tubes being sealed by fusion after the introduction of the active material.

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Fig.1.

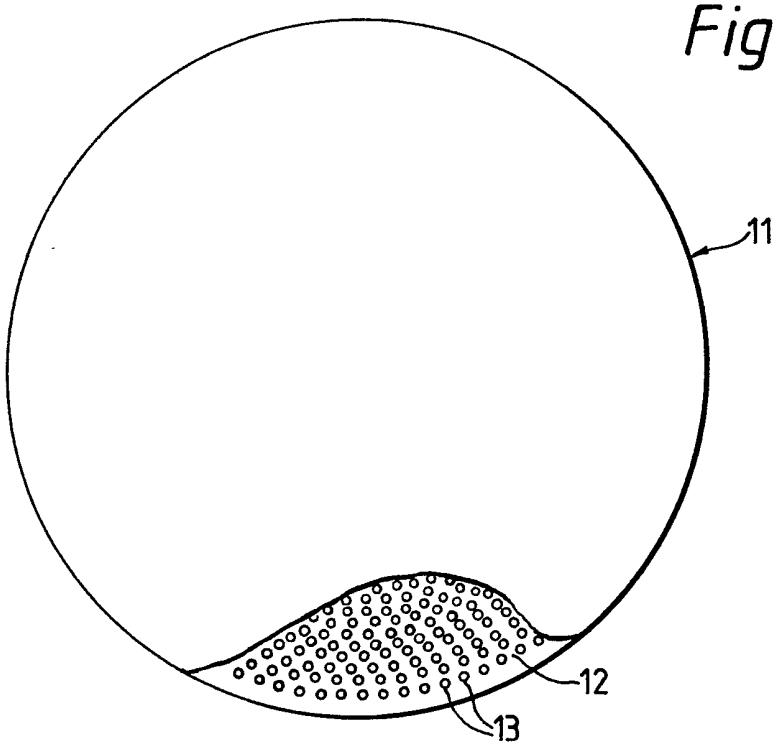


Fig.2.

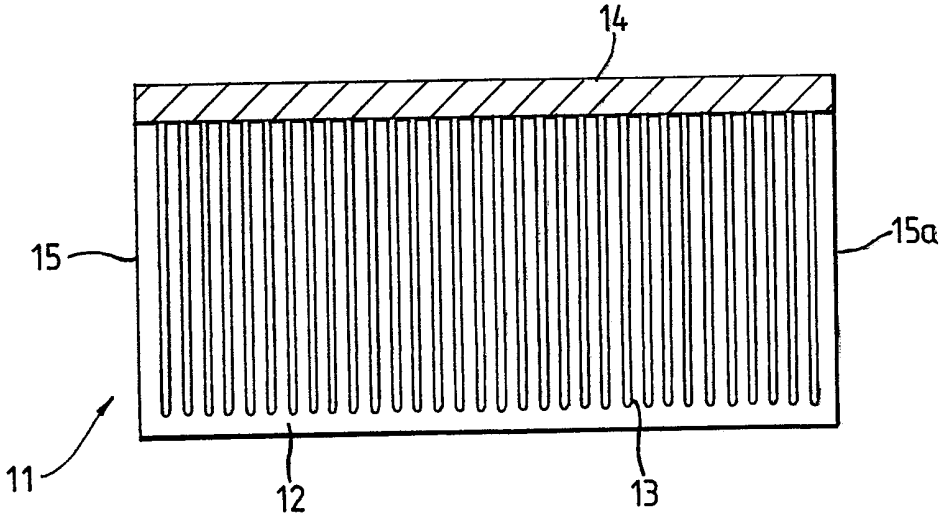


Fig .3.

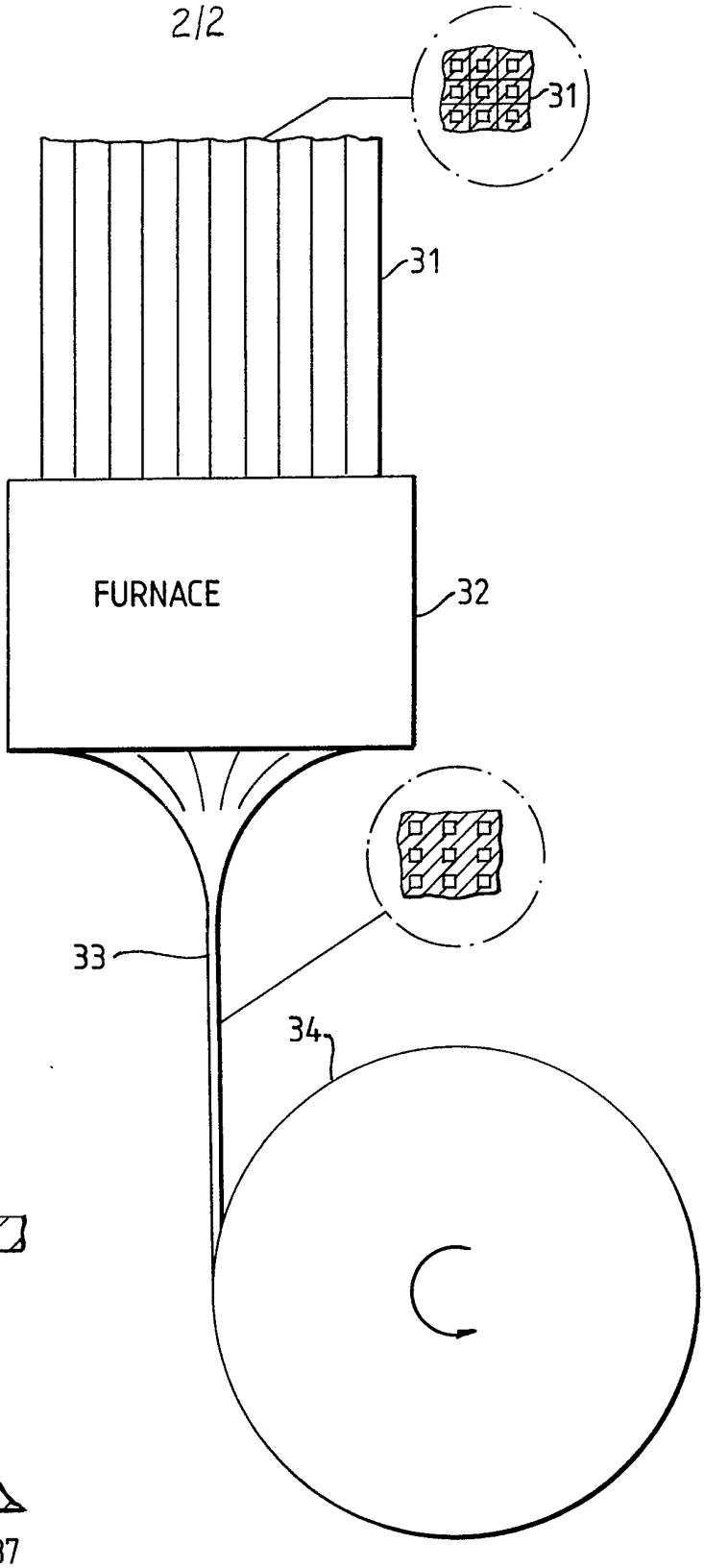
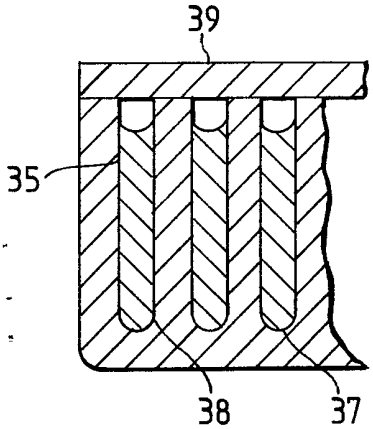


Fig .3a.



SPECIFICATION

Glass encapsulated materials

This invention relates to arrangements for the controlled release of materials into a liquid environment.

Our published specification No. 1,512,637 (C. F. Drake — 49) and our co-pending application No. 7 930 041 (C. F. Drake — 70) describes water soluble glass compositions designed to release one or more active materials into a liquid environment. Typically such glasses comprise a glass-forming axide together with one or more glass-modifying oxides, the ratio of the former to the latter and the proportions and nature of the constituents being selected so as to provide the glass with a desired rate of dissolution in water. The materials to be released are incorporated in the glass, generally in oxide form. Such materials are restricted to those which have a reasonable stability at the glass forming temperatures. In particular, organic materials cannot be incorporated in the glass in this way.

Our published specification No. 1,565,906 (C. F. Drake — H. Des Forges 56–1) describes and claims a liquid soluble body adapted to provide for the controlled release of a material into solution in a surrounding liquid, the body being formed from a glass soluble in the liquid and having an array of cavities therein, each said cavity containing a quantity of said material.

Typically the material to be released from such a body is a drug or other biologically active material which is released into the bloodstream of an animal into which the body is implanted. The glass body or pellet is formed by providing an array of indentations in the heat-softened glass, allowing the glass to cool, filling the indentations with the active material and sealing the body with a glass lid.

We have now found that more acceptable results are obtained from a body in which the relatively large cavities are replaced by much finer cavities obtained by employing a porous glass body.

According to one aspect of the present invention there is provided a liquid-soluble body for the controlled release of an active material into the liquid medium, the body having a plurality of pores or microcavities distributed therein and within which the active material is contained such that the material will be released at a predetermined rate as the body dissolves.

According to another aspect of the invention there is provided a water-soluble body or pellet for the controlled release of an active material into the body fluid of an animal to which the pellet is administered either orally or in the form of a subcutaneous implant or into other water-containing systems, the pellet comprising a water-soluble body having distributed therein a plurality of pores or microcavities containing the active material such that the material will be released at a predetermined rate by continuous dissolution of the pellet by the intestinal or body fluid of the animal.

As the microcavities containing the active material are small relative to the size of the liquid soluble body the material is released at a substantially continuous rate upon dissolution of the body. In some applications, e.g. where certain drugs are to be released into the bloodstream of a human or non-human animal, this continuous release rate is highly advantageous.

A number of materials may be employed to form the body, but we prefer to use a water soluble glass composition. The cavities may be provided either by forming a sponge like body or, advantageously, by providing an array of capillaries in the body.

Embodiments of the invention will now be described with reference to the accompanying drawings in which:—

Fig. 1 is a cut-away plan view of the water soluble body;

Fig. 2 is a cross-section of the body of Fig. 1;

Fig. 3 shows in schematic form an apparatus for producing the body of Figs. 1 and 2,

and Figs. 3*a* shows the body during manufacture.

Referring to Figs. 1 and 2, the water-soluble body, which advantageously is made of a water-soluble glass, is shown in plan view and cross section respectively. The body 11 comprises a solid matrix 12 in which an array of microcavities 13 is provided. The cavities 13 are filled each with the same or with different active materials and are closed by a seal 14 which should be made of a material of lower rate of water dissolution than that of the matrix 12. Alternatively the thickness of the seal 14 may be such that although its rate of solution is comparable to that of the material of the body 12, the body dissolves from the lateral faces before the seal 14 has been completely dissolved.

When immersed in an aqueous medium the body 11 slowly dissolves from the faces 15, 15*a* (Fig. 2) such that the microcavities 13 are successively opened and can thus release their contents into the aqueous medium. Typically the aqueous medium is the body fluid of an animal and the active material comprises a medicament which is thereby released at a controlled rate into the animals bloodstream.

The rate of release of the active material, which rate may or may not be constant depending on the application, can be determined in a number of ways either separately or in combination. Examples of such techniques are:—

1. Controlling the thickness of the glass matrix between the microcavities at various regions of the body.
2. Providing a particular density distribution of the microcavities in the body.
3. Controlling the glass dissolution rate which may be constant throughout the body or may be different in different regions.
4. Controlling the dimensions of the cavities.
5. Controlling the degree of filling of the cavities or the concentration of the active material in the cavity contents.

The material released from the cavities may be solid, liquid or gas, and the cavities may be filled by capillary suction, vacuum filling. All the cavities can be filled with the same material or there may be two or more materials distribtuted in a particular way amongst the cavities.

The microcavities may contain a variety of materials into an aqueous medium. Thus, in addition to drugs or other curative materials the body 11 may also be used to release fungicides, algicides, nematocides, batericides, molluscicides, spermicides or mixtures thereof. Other applications include the release of an attractant for a species which it is intended to destroy. Thus, e.g. in the treatment of water courses for the prevention of bilharzia, a snail attractant can be released to attract the snails to a molluscicide which is released simultaneously or in conjunction with the attractant. In a further application two materials may be released together, the materials reacting in situ to form a compound with a short half-life and which therefore cannot be readily applied by conventional means.

Referring now to Fig. 2, this shows one example of an apparatus for manufacturing the water-soluble bodies of Fig. 1. The bodies are prepared by a technique somewhat analogous to the manufacture of channel plates for image-intensifier tubes.

The bodies are formed from a plurality of glass capillaries that are formed by drawing down a bundle of glass tubes 31 which are passed under tension through a furnace 32 so as to form a relatively thin multibore rod or fibre 33. The bundle of glass tubes 31 is formed by heating an assembly of individual glass tubes in a closed mould to a temperature at which they fuse together over their outer face. The fibre 35 is wound up or to a drum 34 to form a relatively thick layer, the fibre being wound up. When sufficient thickness of fibre has been wound up on the drum drawing is stopped. Bundles of fibres are then fused together as already described above and the fused fibres are sawn into sections 35 (Fig. 3*a*). To produce very fine capillaries it may be desirable to further pull the assembly and wind the consequent product on the drum. As can be seen from Fig. 3*a* each section comprises a bundle of substantially parallel capillaries 35 fused together to form a pellet like body. One face 36 of each body is briefly fused, e.g. by flash heating to seal the one ends 37 of the capillaries 35. The capillaries 38 e.g. by capillary motion or by vacuum filling and the open ends of the capillaries are then sealed with a cover plate 39 typically of glass. The plate may be secured with an adhesive or by flash heating to fuse the plate to the body. The plate may optionally contain a small proportion (~ 1-5%) of an oxide strongly absorbing in the infra-red (e.g. iron oxide) to ensure that when the source of heat for flash-sealing is an infra-red lamp most of the energy is dissipated in the plate and the part of the body immediately adjacent thereto.

To prevent premature discharge of the active material it is essential that the cover plate 38 and the fusion sealed ends of the capillaries are dissolved at a slower rate than that of the glass matrix. This may be achieved by various techniques. For example the cover plate may be made of a glass of lower solubility than the bulk material of the body, a similar plate being applied to the other face of the body to prevent attack of the fusion sealed capillary ends. Alternatively the cover plate 38 may be of the same composition as the body, the top and bottom faces of the body being protected by a layer (not shown) of a substantially insoluble wax material. This latter method is preferred where the body is to be implanted into the body of an animal as, if the wax is of the biodegradable type, no solid residues remain after the curative or remedial action of the implant is completed.

Other method of sealing of the capillaries include plasma spraying of a glass or a metal, or moulding of a polymeric material layer to the body.

The water-soluble body or pellet may be used in a variety of applications. Typically it may be employed in the form of a subcutaneous implant for the controlled supply of a drug, medicament or curative material to a human or non-human animal. To implant the pellet in an animal it is conveniently inserted with the aid of a hypodermic gun into or adjacent the ear lope where it is thus in contact with the body fluids, the material contained in the pellet being transported from the implantation site by the animal's bloodstream. Where poultry are to be treated the pellet may be administered orally as it will then lodge in the gizzard, the active material being released into the intestine and from there, via the intestinal wall, to the bloodstream. Similarly, a pellet may be administered orally in the form of a bolus to ruminant animals for lodgement in the reticulum. Such techniques of administration will of course be apparent to those skilled in veterinary medicine.

As previously stated it is preferred to form the body or pellet from a water-soluble glass. The glass must be workable, i.e. it must be drawable into tube and fibres, it must have a suitable solubility for the particular application, and, where the pellet or body is to be administered to an animal, it must be non-toxic. Furthermore, where such a body is administered to an animal that is subsequently slaughtered for meat, the glass must not contain elements that could be undesirable or even harmful for human consumption.

We have found that glasses based on the Na_2O (K_2O): CaO: P_2O_5 system are suitable for such applications. These glasses contain no harmful or toxic elements and are readily workable. The glass solubility can be controlled by adjusting the ratio of the glass-former to glass-modifiers and the relative proportions of the alkali metal oxide and the calcium oxide constituents relative to the glass forming oxide. In general an increase in the proportion of calcium oxide produces a decrease in solubility and vice versa. In some applications some or all of the calcium oxide may be replaced by magnesium oxide, strontium oxide or barium oxide all of the latter having a similar effect of reducing the water solubility of the glass. In many applications a small proportion of alumina may be added to the glass to further reduce its water dissolution rate. The technique of controlling the solution-rate of a glass is more fully described in our published specification No. 1,512,637 (C. F. Drake — 49) and in our co-pending application No. 7 930 041 (C. F. Drake — 70). It will be apparent that other glass modifying metal oxides may be incorporated in the glass depending on the particular application envisaged.

To illustrate the typical glass compositions that

may be employed a series of glass compositions within the following composition range, which is by no means limiting, was prepared. The composition range is listed in Table I.

TABLE I

Glass constituent	Proportion Range Mole %
Na_2O	20-50
K_2O	0-2
CaO	0-30
ZnO	0-30
MgO	0-30
P_2O_5	30-60

It should be noted that although each constituent is expressed in the form of its oxide it is not necessarily present in this form in the glass composition. The glasses can be prepared from the oxide constituents, but in the present case the glass constituents were as follows:—

NaH_2PO_4	Sodium dihydrogen phosphate.
KH_2PO_4	Potassium dihydrogen phosphate.
$CaCO_3$	Calcium carbonate
or $Ca(H_2PO_4)_2$	Calcium dihydrogen phosphate.
$ZnCO_3$	Zinc carbonate.
$MgCO_3$	Magnesium carbonate.
P_2O_5	Phosphorus pentoxide.

These glasses were prepared by mixing weighed quantities of the batch constituents followed by fusion at 1000 to 1100°C in a platinum crucible to form a homogeneous glass. As some phosphorus pentoxide is always lost by evaporation the composition of the finished glass was determined in each case.

A major application of the liquid soluble body is the controlled delivery of organic compounds to animals, the body being administered as an implant which is thus in contact with the interstitial fluid of the animal. Hence the dissolution rate of each glass composition in an interstitial fluid was examined. Weighed quantities of each glass were placed in the fluid at a temperature of 38°C and the glass weight loss was periodically determined. The interstitutial fluid employed had the following composition:—

$NaHCO_3$	0.43 gm	
NaCl	5.85 gms.	
$MgSO_4 7H_2O$	0.37 gms.	
K H PO_4	0.435 gms.	In 1 litre of solution.
$CaCl_2 6H_2O$	0.545 gms.	
Na Acetate $3H_2O$	0.816 gms.	
Bovine serum albumin	1.0 gms.	

The results of the dissolution tests are summarised in Table II below.

TABLE II

Specific Glass Composition with Dissolution Rate in IF at 38°C

Glass No.	Mole %	Na_2O	K_2O	CaO	ZnO	MgO	P_2O_5	Diss. rate. mgm/cm²/ 24 hr.
180480.1		20.7	–	13.2	13.2	–	52.9	4.0
290480.12		34.7	1.0	14.3	14.3	–	35.6	4.8
090580.4		40.6	1.3	8.4	8.4	–	41.3	13.8
090580.5		40.9	1.4	8.4	–	8.4	40.9	0.4
140580.7		36.0	1.2	7.4	–	7.4	47.9	2.7

These results illustrate the feasibility of providing suitable glass compositions for the construction of the liquid soluble body.

The techniques described herein are not of course limited to the use of glass compositions. Thus, in some applications liquid soluble and/or biodegradable polymeric materials may be employed. However, glasses are to be preferred as they provide a continuously variable range of composition and dissolution rate.

CLAIMS:

1. A liquid soluble body for the controlled release of an active material into the liquid medium, the body having a plurality of pores or microcavities distribtued therein and within which the material is contained such that the material will be released at a predetermined rate as the body dissolves.

2. A water-soluble body or pellet for the controlled release of an active material into the body fluid of an animal to which the pellet is administered either orally or in the form of a subcutaneous implant, or in other water-containing systems, the pellet comprising a water-soluble body having distributed therein a plurality of pores or microcavities containing the active material such that the material will be released at a predetermined rate by continuous dissolution of the pellet by the intestinal or body fluid of the animal.

3. A body as claimed in claim 1 or 2, in which said cavities are in the form of substantially parallel cylinders sealed at each end and in which the soluble body dissolves in such a way as to break through the cylinder walls in turn without breaking through the end face of the cylinder.

4. A body as claimed in claim 3, in which the solubility beyond the end faces of the cylinder is lower than at right angles to any part of the cylindrical faces of the cylinder.

5. A body as claimed in any one of claims 1 to 4, and which is constructed such that, on dissolution, the number of cavities exposed to the aqueous system per unit time is a function of time defined by a predetermined profile.

6. A body as claimed in claim 5, and in which the soluble solid is uniform with respect to solution rate and in which the spacial distribution of the cavities is such as to provide the predetermined time function of the rate of exposure of said cavities to the aqueous phase.

7. A body as claimed in claim 5, and in which the

rate of solution of said solid varies in such a way as to provide the predetermined time function of the rate of exposure of said cavities to the aqueous phase.

8. A body as claimed in claim 5, 6 and 7 in which the delivery rate is substantially constant.

9. A body as claimed in claim 5, 6 or 7, in which the delivery rate profile is a discontinuous function of time providing pulsed release with an interval between release periods in which no release occurs.

10. A body as claimed in any one of the preceding claims and which is made from soluble glass composition.

11. A body as claimed in claim 10, and wherein said glass is an alkali metal phosphate glass.

12. A body as claimed in claim 11, and wherein said glass further includes calcium oxide, alumina, magnesium oxide, strontium oxide, barium oxide, zinc oxide, or mixtures thereof.

13. A body as claimed in any one of the preceding claims, wherein the active material includes a drug or other curative material, a hormone, an insecticide, a nematocide, a fungicide, an algicide, a bactericide, a molluscicide, a spermicide, or mixtures thereof.

14. A liquid soluble body substantially as described herein with reference to the accompanying drawings.

15. A method of controlled delivery of an active material into water or other aqueous system, in which the active material is encapsulating within a multiplicity of microcavities or pores distributed in the body of a solid, said solid being soluble in said aqueous system at a predetermined rate so as to release the contents of each cavity as said cavity comes in contact with said aqueous phase as the solid dissolves.

16. A method as claimed in claim 15, in which said solid is an inorganic glass.

17. A method as claimed in claim 15 or 16, wherein the glass is an alkali metal phosphate glass.

18. A method as claimed in claim 15, 16 or 17, wherein said cavities are provided as a plurality of substantially parallel capillaries.

19. A method of controlled release of an active material substantially as described herein with reference to the accompanying drawings.

20. A method of treating an animal, including administering to the animal, a liquid soluble body as claimed in any of claims 1 to 12 or claim 14.

21. A method as claimed in claim 19, wherein the active material is a drug medicament or curative, a hormone, a nematocide, bactericide or insecticide or mixtures thereof.

22. A method of animal treatment substantially as described herein.

23. An animal treated by the method of claim 20, 21 or 22.

24. A method of making a liquid soluble body for the release of an active material into an aqueous medium, including drawing a water soluble glass composition, into a plurality of tubes, assembling said tubes into a bundle and drawing the bundles down so as to form a multibore fibre, assembling portion of said fibre into a bundle and fusing said portion together to form a multibore rod, forming said rod into sections, each section comprising a pellet like body having a plurality of substantially parallel capillary bores therethrough.

25. A method as claimed in claim 24, wherein one end of the capillary bores is sealed and the bores are filled with one or more active materials and their other ends are closed by a seal.

26. A method as claimed in claim 25, wherein said seal is a glass plate secured to the body.

27. A method as claimed in claim 26, wherein the plate is secured to the body by fusion.

28. A method as claimed in any one of claims 24 to 27, wherein the glass is an alkali metal phosphate type glass.

29. A method of making a liquid soluble body substantially as described herein with reference to the accompanying drawings.

30. A body made by the method of any one of claims 24 to 29.

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