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J. M. McKIBBIN ET AL
CONTAINER

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Fig. 1

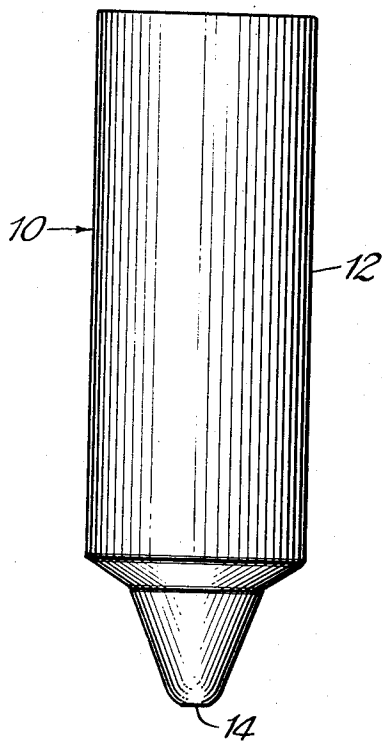
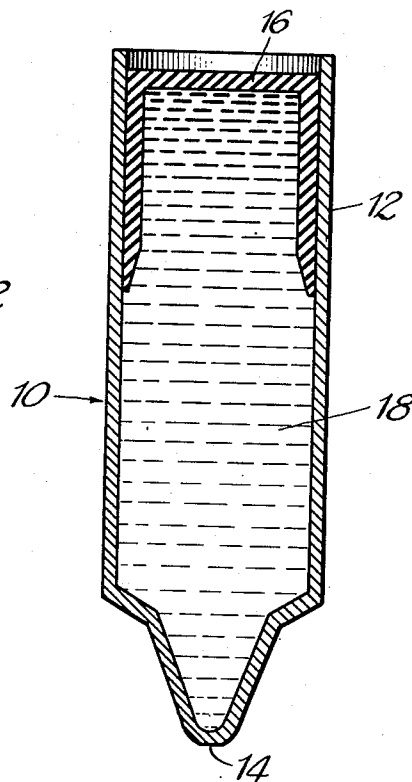


Fig. 2



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CONTAINER

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2 Claims. (Cl. 128—272)

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This invention relates to metal containers or receptacles for liquids to be injected into the living human or animal body for therapeutic, anesthetic or like purposes.

Many liquids conventionally injected by physicians or veterinarians into the living human or animal body are more or less acidic. In the past, such liquids have conventionally been stored in glass containers, such as sealed glass vials or ampules. The glass used in such containers for injectible liquids is of special composition.

In recent years, instruments have been developed for injecting liquids into the living human or animal body without the use of the conventional hypodermic syringe and needle. These recently developed instruments effect injection by generating a high velocity jet of liquid capable of penetrating the skin, the subcutaneous tissues and, if desired, also muscular tissue.

Some of the early instruments effecting jet injection (without the use of a hypodermic needle) were provided with a reservoir or container for the liquid to be injected, which was transferred from a glass container into such a reservoir or container when one or more injections were to be made. In such transfer of liquid into the instrument from a glass container, the liquid was easily contaminated, even when the container or reservoir in the instrument had been made completely sterile, which was not easily effected. The injected liquid could not be administered in exactly predetermined dosages, because of the difficulty in expelling completely the contents of the container or reservoir forming part of the injection device, and because of the difficulty in accurately subdividing the container or reservoir contents into separate doses of desired predetermined magnitude when the reservoir contents were divided between several successive injections. Further, acidic injectible liquids could not be left in the container or reservoir forming part of the injection instrument for any length of time without danger of having metal dissolve from the container or reservoir wall and thus transferred into the liquid to be injected or into liquid left in the container or reservoir after injection had been completed.

Another type of instrument effecting jet injection is completely described in the copending application of R. P. Scherer Serial Number 170,101. In the operation of an instrument of this type, a separate metal ampule is placed in the instrument when injection is to be done. This ampule contains an accurately predetermined amount of a liquid solution or suspension

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of a pharmaceutically active material. When injection is carried out, the whole content of this ampule is completely injected. The instrument is so constructed that either the whole ampule content can be administered parenterally in a single injection or else accurately predetermined amounts of liquid, each less than the total ampule content, may be administered parenterally. The liquid ampule content passes directly from the ampule (through an orifice therein) into and through the skin and into the subcutaneous tissues and, if desired, into muscular tissue, without ever coming in contact with any part of the instrument itself or, indeed, any other surface or body other than the (previously sterilized) limited skin area through which injection is effected. Thus, injection may be carried out without any danger of destroying the initial sterility of the liquid to be injected.

It is, therefore, an important object of the present invention to provide a metal container for liquids to be injected into the living human body which will be substantially as inert as the special glass vials, ampules or like containers conventionally used as receptacles for such liquids.

Another object of the present invention is to provide metal containers for liquids to be injected into the living human body having an inertness so great that substantially no metal will be transferred into the liquid container contents even when these contents are acidic, for instance, due to the inclusion of hydrochloric acid with the liquid contents, and even when the filled containers are stored for very long periods of time.

A further object of this invention is to provide a container for a liquid to be parenterally injected into living human body which will in no manner render the liquid toxic nor render the pharmaceutically active ingredient of the liquid less potent, unstable or subject to deterioration.

A still further object of the present invention is to provide metal containers for liquid solutions or suspensions of pharmaceutically active materials to be injected into the living human subject or animal by the high velocity jet technique rather than by the use of a conventional syringe-hypodermic needle device.

Another object of the present invention is to provide metal containers of the type mentioned in the last paragraph comparable in cost with glass containers and sufficiently inexpensive to permit disposal after use in a single injection.

A further object of the present invention is to

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provide a novel method for safely storing weakly acidic solutions or suspensions of pharmaceutically active materials for long periods of time.

Other and further objects and features of the present invention will become apparent from the following description and appended claims taken in conjunction with the accompanying drawing showing, by way of an illustrative example, a container or ampule according to the present invention. More particularly:

Figure 1 is a side elevational view of a container or ampule according to the present invention; and

Figure 2 is a vertical cross-sectional view through the container or ampule of Figure 1.

For making metal ampules meeting the above noted requirements, we provide an austenitic stainless steel alloy free from precipitated carbides and having a carbon content not in excess of 0.06%. The essential ingredients of this alloy are chromium, nickel, molybdenum and iron. For making ampules to contain liquids that are relatively quite weakly acidic, having, for instance, a pH ranging upwardly from 4.5 to less than 7, the alloy may contain from 18 to 26% chromium, from 11 to 25% nickel, and from 1 to 4% molybdenum, the balance being essentially iron. For making ampules to contain liquids that may be relatively more acidic, having, for instance, a pH ranging between 3.5 and less than 7, the alloy may contain from 20 to 26% chromium, from 15 to 25% nickel, and from 1 to 4% molybdenum the balance being essentially iron. For making ampules to contain liquids that may be relatively quite acidic, having, for instance, a pH ranging from 2.5 to less than 7, the alloy should contain from 24 to 26% chromium, from 20 to 25% nickel, and from 2 to 4% molybdenum, the balance being essentially iron.

In the above disclosed alloys, the molybdenum and chromium contents contribute to the stability of the alloys, i. e. reduce the tendency to transfer of metal into contacting liquids. The upper limit of 26% for the chromium content is set by the difficulty of cold working, particularly drawing, alloys containing much more than 26% chromium. The lower limits for chromium contents are set by the tendencies to nickel transfer (into solutions having the indicated pH values) from alloys having smaller chromium contents. The upper limit of 25% for the nickel content is set by the tendency to nickel transfer from alloys having higher nickel contents. There is no particular advantage in using more than 22% nickel, since this metal serves principally to make the alloy cold workable, which end is attained with a 22% nickel content even at a 26% chromium content.

In making stainless steels and like alloys, it is conventional to determine the composition of the alloys by analyzing samples taken from the molten alloy immediately before the molten alloy is poured into an ingot mold. These analyses, therefore, are designated as "ladle analyses." Such "ladle analyses" do not agree exactly with analyses carried out on the finished articles fabricated from the ingots. In particular, the carbon content of the finished articles will always be found to be higher than the values obtained by "ladle analyses."

The above disclosed alloy compositions represent analyses of the finished ampules, and not "ladle analyses" of the molten alloys which ultimately make up the ampules. Further, the specified carbon content in the finished ampules of

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not more than 0.06% is critical. It is emphasized that a "ladle analysis" showing a carbon content of not more than 0.06% does by no means signify that the finished ampule will contain not more than 0.06% carbon. Unless the specified carbon content is maintained in the alloy during all the fabricating steps which ultimately yield the finished ampule, objectionable metal transfer into the ampule content of acidic aqueous liquid is apt to occur on long storage of the filled ampule. In other words, the "ladle analysis" must show a carbon content of not more than 0.06%, and in the subsequent handling of the alloy, this carbon content must be maintained.

By way of further specifying the nature of the above disclosed upper limit for the carbon content of our ampule or other container, we note that the analytical method conventionally employed for carbon determination in alloys of this type is accurate within $\pm 0.01\%$. Further, the carbon content of a strip of such an alloy may vary locally by as much as $\pm 0.01\%$. Therefore, a specimen of our alloy is considered to meet our requirements if an analysis of an initial sample shows a carbon content of not more than 0.06%, or if several analyses (say, three or more analyses) show an average carbon content of not more than 0.06%. We prefer a carbon content of not more than 0.04%.

Our statement that the balance of our alloy (after the chromium, nickel and molybdenum) is essentially iron may be further explained as follows: Our alloy is a member of the class of alloys generally referred to as austenitic stainless steels. Our alloy may contain minor amounts of other ingredients than those essential ingredients mentioned hereinabove in the amounts that these other ingredients are normally and usually present in austenitic stainless steels without being purposely added thereto. These minor amounts of other ingredients are not "impurities" in the usual meaning of that term, but are simply materials ordinarily present in commercially available austenitic stainless steels (besides the essential ingredients thereof), the presence of which can be avoided only by extreme measures never resorted to in commercial practice. Thus, our alloy may contain from 1% to 2% manganese, not more than 0.03% phosphorus, not more than 0.03% sulphur and from 0.3 to 0.6% silicon. Titanium should not be added purposely but may be present in very minute amounts. Thus, when we specify that the balance of our alloy (after chromium, nickel and molybdenum) is essentially iron, we mean to include with this balance these minor amounts of other incidentally present materials.

The substantial absence in our alloys of precipitated carbides is as essential as maintaining the carbon content not in excess of 0.06%. A convenient, quick test for the absence of precipitated carbides involves immersing an alloy strip for two minutes in an acidic liquid maintained at about 85° C. and made up of 40% (absolute by weight) of H_2SO_4 , 7.24% of HCl , 3.35% of HNO_3 , 4.04% of CH_3COOH , 0.65% of NaCl and 44.71% H_2O . The presence of a substantial amount of precipitated carbides is then demonstrated by the appearance of a dark surface discoloration on the alloy strip.

In the fabrication of our containers, the molten alloy is initially poured to form an ingot, which is allowed to cool. Next, the surface scale on the ingot is ground off, and the ingot is hot

rolled to form strip that may be, for instance, $\frac{1}{4}$ " thick. This strip is then cold rolled repeatedly, each pass being controlled to effect a reduction in strip thickness of not more than 50%. The final strip thickness may be on the order of 0.02". After each such pass through the rolling mill, the strip is annealed. The cold rolled annealed strip is then drawn into cup form and annealed. The resulting cups are coined and trimmed into their final form and treated at an elevated temperature with a concentrated solution of strong inorganic acid.

During these fabricating steps, conditions are regulated to effect in the finished article a grain size not larger than 8 and preferably not larger than 6 (Timken A. S. T. M. scale), a hardness of from 65 to 72 (Rockwell 30 T scale), a yield strength ranging from, say, 40,000 to 150,000 or more pounds per square inch, a tensile strength in the order of 100,000 pounds per square inch and an elongation ranging from 35 or 40 to 50%.

In carrying out the above fabrication steps, we take precautions to prevent the incorporation with the alloy being worked of any material that would tend to cause metal transfer into the liquid contents of the filled ampule or other container, or else we remove any such material after incorporation with the alloy. An example of such removal is the above noted grinding off of surface scale from the original ingot. One precaution observed for preventing contamination of the alloy with material of the type in question involves carrying out all annealing in an absolutely inert atmosphere, for instance, an atmosphere of pure hydrogen having a dew point of -80° F. or less. Further, before each annealing carried out after each cold-rolling or cup-drawing step, the drawn parts are carefully cleaned to remove substantially all oil or drawing compound adhering to the drawn parts. Ordinary vapor degreasing is not satisfactory for this purpose by itself, but must be followed by rinsing the parts with solutions of chemicals capable of removing the thin film of oil or drawing compound left after conventional vapor degreasing. A number of such solutions are known to those skilled in the art. By way of an example, we can, after vapor degreasing, dip the parts in an aqueous solution of sodium hydroxide and potassium permanganate, then rinse the parts with water, thereafter dip the parts in an aqueous sodium nitrite solution, and finally again rinse the parts with water.

It should be understood that ingots or parts made of our alloy tend to adsorb and/or absorb on their surfaces materials which effect metal transfer into the contents of the filled ampules when such parts are exposed to the high temperature required to anneal the parts. This is the reason for the removal of the surface scale from the ingots, for the complete removal of oil and of drawing compound before annealing and for the provision of an absolutely inert atmosphere in the annealing. Essentially, the precautionary steps carried out in connection with the annealing involve carrying out the annealing steps under conditions such that no contaminating material (such as nitrogen, which forms nitrides tending to cause metal transfer) will then be absorbed by the parts in question. Any conventional procedure effective for this purpose may be used in place of the specific steps disclosed hereinabove by way of examples.

The above noted annealing steps are carried out to effect a fine-grained structure in the alloy

that permits easier working, as by cold rolling and drawing. For this purpose, the alloy is annealed for from three to six minutes at 2050° to 2150° F. To avoid the precipitation of carbides, the cooling from this high temperature is carried out as quickly as possible. The drawn cups should be cooled to 900° F. and preferably 800° F. within three minutes.

Thus, our ampules or other containers are fabricated from an austenitic stainless steel alloy devoid of precipitated carbides and having the above disclosed composition including a carbon content not in excess of 0.06%, and in this fabrication such a composition is maintained, precautions being taken to prevent the absorption by the parts being fabricated of contaminating material tending to effect metal transfer into the liquid container contents, or else such contaminating material is removed if absorbed.

Over and above originally establishing and thereafter maintaining the above disclosed metallurgical composition, it is also necessary, after the ampules or other containers have been fabricated, to subject the otherwise finished ampules to the action at an elevated temperature of a concentrated solution of strong inorganic acid. Such acids include hydrochloric acid, sulphuric acid, nitric acid or mixtures thereof. Such acid treatment reduces the transfer of metal to the liquid contents of filled ampules to one-third or less of that which would take place in the absence of such a treatment. The acid treatment disclosed hereinbelow as effecting polishing reduces the metal transfer to one-tenth or less of that noted in the case of untreated metal.

The time of ampule exposure to inorganic acid may vary from one-half to five minutes, and ordinarily runs from one to three minutes. The temperature may vary from 70° C. to the boiling point of the acid solution being used. Ordinarily, the time and temperature of treatment are related inversely, i. e. a shorter treatment may be carried out at a more elevated temperature, and vice versa. At relatively low temperatures, treatment may require 20 to 30 minutes. The inorganic acid concentration should be at least 25% of saturation, and preferably 30% of saturation. This solution should be aqueous, but may also contain organic liquids, for instance, acetic acid, along with the water. A rather wide range of acid solutions can be used, for instance, concentrated hydrochloric acid (20% up to saturated aqueous HCl at the boiling point for one minute); 25% nitric acid (at 50° C. for 20 to 30 minutes); a mixture of 30 ml. concentrated (35%) hydrochloric acid, 3 ml. concentrated (60 to 70%) nitric acid, 1 gram sodium chloride, 35 ml. water, 20 ml. concentrated (95%) sulfuric acid and 3 ml. glacial acetic acid (3 minutes at 70° — 85° C. which also brings about polishing of the alloy to a mirror finish); a mixture of 30 ml. concentrated hydrochloric acid, 10 ml. concentrated nitric acid, 1 gram sodium chloride, 20 ml. concentrated sulfuric acid, 3 ml. glacial acetic acid and 35 ml. water (3 minutes at 70° — 75° , which also brings about polishing of the alloy to a mirror finish); a mixture of 30 ml. concentrated hydrochloric acid, 3 ml. concentrated nitric acid, 1 gram sodium chloride, 20 ml. concentrated sulfuric acid, 3 ml. glacial acetic acid and 40 ml. water ($1\frac{1}{2}$ minutes at 70° — 75° C., which also brings about polishing of the alloy to a mirror finish); a mixture of 20 ml. concentrated hydrochloric acid, 20 ml. concentrated nitric acid and 60 ml. water (1

minute at 75° C.); a mixture consisting of 40% (absolute by weight) of H₂SO₄, 7.24% of HCl, 3.36% of HNO₃, 4.04% of glacial acetic acid, 0.65% of NaCl and 44.71% of water (2 minutes at 85° C., which brings about polishing of the alloy); a mixture of 30 ml. concentrated hydrochloric acid, 3 ml. concentrated nitric acid, 20 ml. concentrated sulfuric acid and 20 ml. water (5 minutes at 70°—80° C.); a mixture of 35 ml. hydrochloric acid, 3 ml. concentrated nitric acid, 20 ml. concentrated sulfuric acid and 50 ml. water (5 minutes at 70°—80° C.); and 30 ml. concentrated hydrochloric acid, 3 ml. concentrated nitric acid, 20 ml. concentrated sulfuric acid, 20 ml. water and 2 ml. glacial acetic acid (4 minutes at 75°—80° C.). For best results, the acid composition should be one capable of effecting polishing of the metal parts being treated or of effecting a surface finish of not more than 15 micro inches. Such compositions include, among others, those consisting essentially of sulfuric acid, water in an amount ranging from ½ to less than 1½ parts (by weight) of the sulfuric acid and preferably less than 60% (by weight) of the total composition, hydrochloric acid in an amount ranging from ⅓ to ½ parts (by weight) of the sulfuric acid, nitric acid in an amount ranging from ⅓ to ½ parts of the hydrochloric acid and acetic acid in an amount ranging from 1 to 10% (by weight) of the total composition. The parts by weight and percentages here referred to signify 100% of the material in question, not including any water. These polishing compositions may also contain from ⅓ to 2% by weight of the total composition of sodium ions.

Mechanical polishing cannot be used in place of the above disclosed chemical polishing, for mechanical polishing introduces foreign matter into the surface of the metal and also sets up strains in the metal surface which tend to cause metal transfer into the acidic liquid contained in the ampules.

A container according to the present invention is illustrated in Figures 1 and 2 and there indicated generally by the reference numeral 10. As shown, the container or ampule 10 is generally cylindrical, having tubular side walls 12 and a curved and pointed bottom 14 which may be formed with a minute aperture (not shown). The ampule 10 may be closed by a rubber stopper 16 to confine within the ampule a liquid indicated at 18.

The container of Figures 1 and 2 is made up of the above described alloy except for the stopper, which may be made of rubber or like resinous material. It should be understood, however, that other parts of the wall structure may be made up of resinous material, as long as at least the tip portion defining the above noted minute aperture is made up of the above described alloy.

A container such as that shown in Figures 1 and 2 made of the indicated alloy will meet very rigorous requirements. Thus, we have found that such a container can be exposed to contact with an acidic solution for 8000 hours with the resultant transfer into the solution of only 1 part of nickel per 5 million parts of solution. More particularly, this result was obtained by proceeding as follows:

A strip of metal was prepared by rolling from an alloy containing 24.08% chromium, 21.21% nickel, 2.05% molybdenum and 0.046% carbon, the remainder being essentially iron. Prior to rolling, the surface scale of the bar or billet of the alloy was ground off and the bar or billet

had been annealed at 2150° F. for three minutes and cooled to below 800° F. within 3 minutes. The annealed alloy rolled easily. Physical testing showed a grain size of about 5 to 6 (ASTM standard), a yield strength of 43,000, a tensile strength of 91,000 and an elongation of 47%. All the carbides were in solution. The rolled strip was drawn into the form of cups.

In the above rolling and drawing steps, the metal was carefully cleaned before being annealed, in the manner described hereinabove. Further, after each cold working step, the metal was annealed at 2150° F. for three minutes in an atmosphere of pure hydrogen having a dew point of 80° F. or less. After such annealing, the metal was cooled to below 800° F. within three minutes.

The finished cups were immersed for three minutes in a solution consisting of 30 ml. of concentrated hydrochloric acid, 3 ml. concentrated nitric acid, 20 ml. concentrated sulfuric acid, 35 ml. water, 1 gr. sodium chloride and 3 ml. glacial acetic acid. The temperature of this acid solution ranged from 70° to 85° C. The cups were thereafter washed in hot water, rinsed with and boiled in distilled water and heat dried. The cups were thereafter each placed in a glass stoppered bottle and 0.001 normal hydrochloric acid was added, the pH of the hydrochloric acid solution having been adjusted to 3.0. 22.44 square inch of cup surface area was exposed to 15 ml. of hydrochloric acid solution. The ground glass stopper was then sealed with paraffin and the bottle was allowed to stand for 8000 hours. At the expiration of this time, the nickel content of the hydrochloric acid solution was determined by a modified Sandell method and found to be 1 part of nickel for each 5 million parts of hydrochloric acid solution. This is less than 1% of the amount of nickel theoretically capable of combining with the amount of hydrochloric acid present in the hydrochloric acid solution. It may be noted in this connection that chromium tends to be dissolved by the solution to a lesser extent than the nickel, and that nickel, of the metals making up the alloy, is the one metal that is particularly objectionable when transferred into the acidic contents of the ampule.

Another cup prepared exactly as described was tested by exposure for 8000 hours to 15 ml. of an aqueous solution having a pH of 3.0 and consisting of 50 ml. of ½ molar potassium acid phthalate and 20.4 ml. of ½ molar hydrochloric acid, the resulting mixture being diluted with water to 200 ml. After 8000 hours, the nickel content of the solution was found to be 1 part of nickel for each 5 million parts of buffered hydrochloric acid solution.

Similar low nickel transfers were found in testing in exactly the same manner, but at other and higher pH values, cups prepared in the same manner from alloys having lower chromium and nickel contents. For instance, in the case of cups prepared from an alloy consisting essentially of 19% chromium, 14% nickel and 3% molybdenum, the balance being essentially iron, nickel transfers were less than one part per five million parts of contacting solution acidified to a pH of 4.6. In the case of cups prepared from an alloy consisting essentially of 21% chromium, 18% nickel and 3% molybdenum, the balance being essentially iron, nickel transfers were less than one part per five million parts of contacting solution acidified to a pH of 3.7.

While specific reference has been made hereinabove to transfer of nickel into a solution contained within the ampule, it should be understood that the other metals are transferred into the solution to an even smaller extent than the nickel. Further, while reference has been made hereinabove to transfer of nickel into an extremely dilute hydrochloric acid solution, similar results have been obtained when using other similar dilute hydrochloric acid solutions, solutions of hydrochloric acid salts having pH values as low as 3.0 or less, such as epinephrine hydrochloride, which is administered at concentration of 1:1000 and has a pH of 2.9 or acidic solutions of other acids and salts.

Many details of composition and procedure may be varied without departing from the principles of this invention and it is, therefore, not our purpose to limit the patent granted on this invention otherwise than necessitated by the scope of the appended claims.

This application is a continuation-in-part of our copending application Serial No. 93,286, filed May 14, 1949, entitled "Alloy and Container Made Therefrom," now abandoned.

We claim as our invention:

1. As a new article of commerce a container filled with a liquid, said liquid being an acidic aqueous pharmaceutical composition suitable in the absence of added metals for injection into the human or animal body, said composition tending to effect dissolution of metal whenever said composition is subjected to prolonged contact with a metal article comprising a metal other than a noble metal, said container having walls made up of an austenitic stainless steel having the following strip analysis:

Chromium	24-26%.
Nickel	20-25%.
Molybdenum	2- 4%.
Manganese	1- 2%.
Phosphorous	.03% maximum.
Silicon	.3-.6%.
Sulfur	.03% maximum.
Carbon	.05% maximum.
Iron	Balance.

and being free from precipitated carbides, whereby metal transferred from said container wall into the liquid composition filling said container is substantially eliminated even on prolonged storage of said article.

2. As a new article of commerce a container filled with a liquid, said liquid being an acidic aqueous pharmaceutical composition suitable in the absence of added metals for injection into the human or animal body, said composition tending to effect dissolution of metal whenever said composition is subjected to prolonged contact with a metal article comprising a metal other than a noble metal, said container having walls made up of an austenitic stainless steel having the following strip analysis:

Chromium	24-26%.
Nickel	20-25%.
Molybdenum	2- 4%.
Carbon	0.5% maximum.
Iron	Balance.

and being essentially free from precipitated carbides, whereby metal transferred from said container wall into the liquid composition filling said container is substantially eliminated even on prolonged storage of said article.

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