A STUDY OF THE
OFFICIAL GLYCEROPHOSPHATES

by

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A History of the Glycerophosphates

Glycerophosphoric acid and several of its salts were prepared by Pelouze[1] as early as 1845 while studying the constitution of glycerin. He produced the acid by heating glycerin with phosphoric acid and also with phosphoric anhydride. From the acid the barium and the calcium salts were prepared. Pelouze reported that the calcium salt was less soluble in hot water than in cold. Soon after the synthesis of glycerophosphoric acid by Pelouze, it was obtained by Gobley[2] from egg lecithin by decomposing this substance with acids. Subsequently Liebrich[3] discovered it in diseased brain tissue and in later time it was found in a variety of animal tissues and excretions.

In 1876 Thudichum and Kingzett[4] prepared several salts of glycerophosphoric acid from cephaline (a substance contained in the brains of animals). They prepared the barium, lead, copper, silver, anhydrous calcium and acid calcium salts. This method was however very unprofitable.

In 1894 Portes and Prunier[5] described a process for

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[1] Pelouze, J., Compt. rend. 21, p. 718.
[2] Gobley, P.; Journ. d. Pharm. et d. Chim. /3/, 9, p. 161.
[3] Liebrich. H.; Annal. Chem. Pharm. 134, p. 29.
[4] Thudichun, H. and Kingzett, C.; Journ. Chem. Soc. 30, p.20.
[5] Portes, L. and Prunier, G.; Journ. d. Pharm. et d. Chim., 138, p. 393.

preparing calcium glycerophosphate. These chemists first prepared the acid by heating 3 kg. of 60 per cent phosphoric acid with 3.6 kg. of glycerin at 110° C. for six days with occasional agitation. After cooling, the mixture was saturated with calcium carbonate, the solution filtered and the calcium glycerophosphate in the filtrate precipitated by the addition of alcohol, in which solvent the salt is insoluble. The precipitate was dried in the air, dissolved in water, the solution filtered and the filtrate cautiously evaporated to dryness. The salt prepared by this process was described as a white somewhat crystalline powder, containing 2 molecules of water of hydration. It is soluble in 15 parts of cold water but nearly insoluble in boiling water and in alcohol.

Delage[6] in 1896 devised a more rapid method of preparing calcium glycerophosphate over that of Portes and Prunier's. This new method required but a few hours to complete where as the former method took several days to complete. The method is as follows: - 100 Gm. of phosphoric acid (60 per cent.) and 150 Gm. of glycerin are mixed in a flask; the mixture produces a rise of temperature from 15 to 25° C. The flask is now fitted by means of a doubly perforated cork with a thermometer and a glass tube, and gradually heated up to 120° C., when the mixture begins to boil and

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[6] Delage, G., Nouv. Remed., 8, p. 217.

acquires a yellow color. On continuing the application of heat, the temperature rises rapidly; at 160° C. the liquid becomes brownish-yellow, and at 170-190° dark brown and syrupy, acrolein vapors are given off. The flask is then allowed to cool, and the translucent, gelatinous mass is added in small successive portions and with constant stirring to a mixture of 50 Gm. of precipitated calcium carbonate and 250 cc. of water, the stirring being continued until the effervescence due to the liberation of carbonic acid gas has entirely ceased. The mixture is allowed to stand for 6 hours and then filtered. The filtrate, which is clear and slightly yellow, is next mixed with half its volume of alcohol (90 per cent), which throws down a flocculent precipitate of calcium glycerophosphate. This precipitate is collected and reprecipitated from alcohol again. The calcium salt thus obtained is a white crystalline powder, soluble in 10 parts of cold water and less soluble in hot water. Another salt of the acid is formed simultaneously, which is not precipitated by alcohol, and on evaporating its solution it separates as a flocculent, gelatinous mass.

The first mention of quinine glycerophosphate[7] was in 1897 when it was recommended to be employed in malaria and neuralgia.

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[7] (Committee), Zeit. des. oesterr. Apoth. ver., 35, p. 60.

Adrian and Trillat[8] in 1898 prepared several of the organic glycerophosphates, including those of cocaine, quinine, and phenylhydrazine. They obtained these compounds by the interaction of an acid salt with the organic base.

In 1901 the brothers Lumière, A. and L., and Perrin[9] devised a new method for preparing glycerophosphoric acid. They obtained the acid by treating a slight excess of glycerin with phosphorous trichloride, keeping the mixture cool, and removing the hydrochloric acid from the mixture by means of moist silver oxide. They also mention that free glycerophosphoric acid has not been isolated[10] since it tends to saponify on evaporating its solution.

In contrast to the methods used by all of the above mentioned authors for synthesizing glycerophosphoric esters, Du Bois,[11] finds that the present manufacturing methods, judging from the patent literature, start not from phosphoric acid, but mostly from mono- and dibasic salts of ortho- or metaphosphoric acids. One patent[12] describes the use of a mixture of metaphosphoric acid, disodium phosphate and glycerin; another patent[13] covers the use of monasodium phosphate and glycerin.

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[8] Adrian, H. and Trillat, A., Bull. de la Soc. Chim. de Paris, 19, p. 684.

[9] Lumière, A., Lumière, L., and Perrin, F., Comp. rendu., 133, p. 643.

[10] Ibid., p. 645.

[11] Du Bois, G., Journ. Ind. and Eng. Chem., 6, p. 124.

[12] Ibid., p. 124.

[13] Ibid., p. 124.

The purpose of deviating from the original method of Pelouze (phosphoric acid and glycerin), according to Du Bois,[14] is partly in order to prevent the formation of triglyceroesters, by protecting one of the acid groups by a base, and partly for practical methods of manufacturing.

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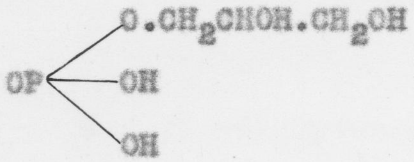
[14] Du Bois, G., Journ. Ind. and Eng. Chem., 6, p. 124.

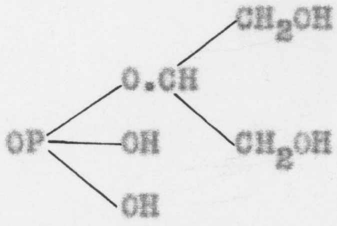
The Chemistry of Glycerophosphoric Acid

Before going into the details of the chemistry and properties of the official glycerophosphates, let us briefly examine what compounds are theoretically possible as a result of the action of phosphoric acid or its salts, on glycerine.

By the interaction of 1 molecule phosphoric acid with one molecule glycerine, two isomeric monoglycerophosphoric acids are possible.[1]



1. α monoglycerophosphoric acid



2. β monoglycerophosphoric acid

These acids can form mono- and dibasic salts. The dibasic calcium salts of the above acids are the main components of calcium glycerophosphate on the market.[2]

If one molecule of phosphoric acid interacts with two molecules of glycerin, again two isomeric diglycerophosphoric acids are possible:[3]

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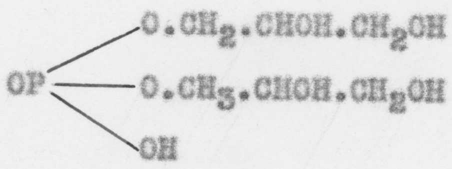
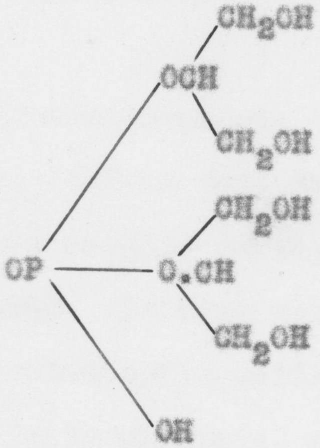
[1] Du Bois, G.; Journ. Ind. and Eng. Chem. V. 6, p. 122 (1914)
[2] Ibid., p. 122.
[3] Ibid., p. 122.

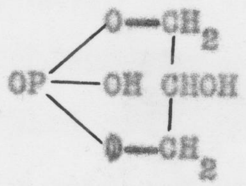


3. α -diglycerophosphoric acid



4. β -diglycerophosphoric acid

Some authors claim diglycerophosphoric acids to have the following constitution:[4]



5. α diglycerophosphoric acid

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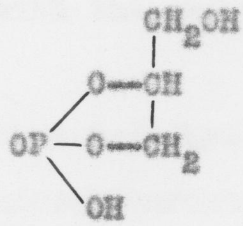
[4] Carré, P., Comptes rend. 137, p. 1070-73, also 138, pp. 47-49.



6. β diglycerophosphoric acid

The diglycerophosphoric acids, whatever their constitution may be, c~~o~~an form only monobasic salts.[5] The salts of these acids are readily partly saponified by the action of alkali hydroxides yielding mainly monoglycerophosphates.[6]

Diglycerophosphoric acids are formed when phosphoric acid is mixed with glycerin, preferably an excess of the latter, and the mixture heated to above 110° C. under reduced or atmospheric pressure. The formation of diglycerides at temperatures above 110° was demonstrated very conclusively by Adrian and Traillat,[7] by Power and Tutin,[8] and also by Carré.[9]

The question, which are the correct formula for the α and β diglycerophosphoric acids, formulas 3 and 4 or 5 and 6 is not settled yet. Adrian and Trillat analyzed diglycerophosphoric acid and obtained figures for C and H

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[5] Du Bois, G., Journ. Ind. and Eng. Chem. V. 6, p. 122 (1914).

[6] Ibid., p. 122.

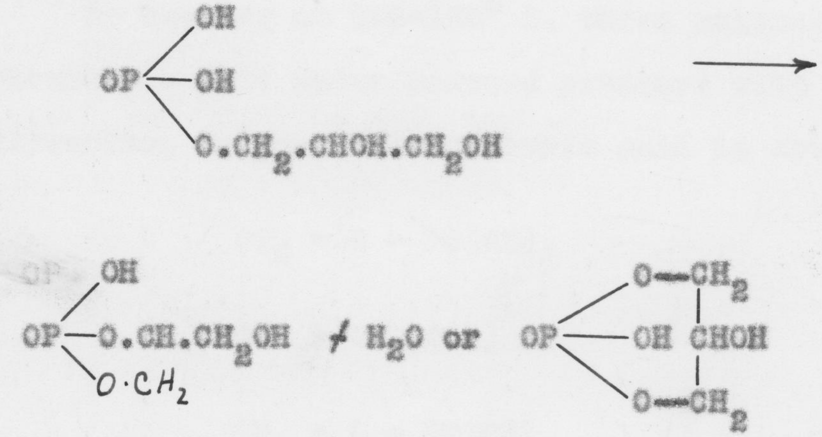
[7] Adrian, H. and Trillat, G., Journ. d. Pharm. et d. Chim. /6/, 7, p. 226-30.

[8] Power, F. and Tutin, G., Journ. Chem. Soc. 87, p. 240-57.

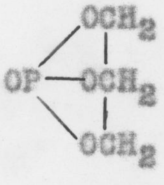
[9] Carré, P., Comptes rendu. 137, p. 1070-73.

corresponding about with the amount contained in formulas 3 and 4.

It is possible that both are correct as it is reasonable to expect that monoglycerophosphoric acid when heated could, by the elimination of water, form diglycerophosphoric acid:[10]



We now come to the last class of esters formed by the action of phosphoric acid on glycerin, the triglycerophosphoric ester. This compound has the following formula:[11]



It is according to Carré,[12] insoluble in water, alcohol

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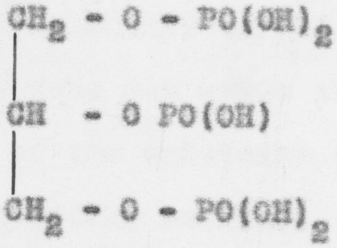
[10] Du Bois, G., Journ. Ind. and Eng. Chem. V.6, p. 122.
[11] Ibid., p. 123.
[12] Carré, P., Comptes rendus., 137, p. 1070-73 also 138, p. 47-49.

and acetone, and forms a hard, spongy mass which can be powdered.

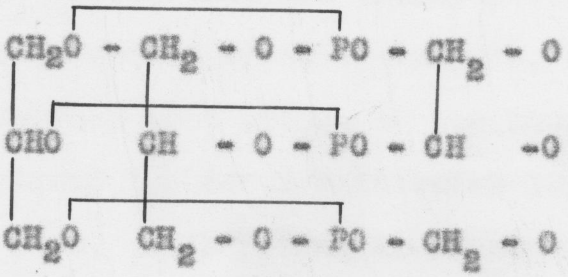
Before leaving the subject of the possible compounds resulting from the esterification of phosphoric acid by glycerine, the investigations by A. Contardi should be briefly mentioned.[13]

By heating at 120-130° C. three molecules crystallized phosphoric acid under reduced pressure with one molecule glycerine, "glycerotriphosphoric acid is obtained:-



$$\begin{array}{l} CH_2 - O - PO(OH)_2 \\ | \\ CH - O\ PO(OH) \\ | \\ CH_2 - O - PO(OH)_2 \end{array}$$

This triphosphoric ester heated with one molecule yields diglycerotriphosphoric ester:



This compound is identical with Carré's[14] triglycerophosphoric ester:

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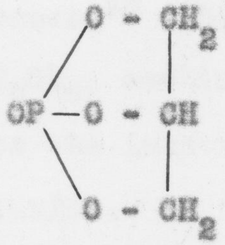
[13] Contardi, A., Gozz. Chim. Ital., 42, II, p. 270-82.
[14] Carré, P., Comptes rend. 137, p. 1070-73.



the latter being just one-third of the formula proposed by Contardi.

The correctness of Contardi's formula for triglycerophosphoric ester has not yet been proved owing to the insolubility of this compound, which makes it impossible to determine the molecular weight.[15]

P. Carré does not agree with Contardi's findings;[16] the question of the existence of above compounds is, therefore, not definitely settled.

Regarding the stability of glycerophosphoric acid or in other words its velocity of hydrolysis, F. Malengrean and G. Prignet,[17] found that the decomposition of glycerophosphoric acid is a case of autocatalysis, caused by the action of the uncombined acid groups of the phosphoric acid, as when neutralized the decomposition at 100° C is practically reduced to zero. With rising temperature the hydrolysis is notably accelerated. There is a certain acidity or concentration of H ions above and below which explains the stability

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[15] Du Bois, G., Journ. Ind. and Eng. Chem. 6, p. 123 (1914).
[16] Carré, P., Compt. rend., 155, p. 1520-21 (1912).
[17] Malengreau, F., and Prignet, G., Ziet. physiol. Chem. 73, pp. 68-84 (1911).

of the compound increases.[18] This explains why strong acids, such as HCl, H_2SO_4, acetic acid etc., retard the decomposition owing to the increase in the concentration of the H ions in the solution. On the other hand weak acids such as oxalic and citric acids and their salts accelerate the hydrolysis of glycerophosphoric acid.[19] The degree of acidity at which the hydrolysis is the greatest is represented by acid salts of glycerophosphoric acid.

The potassium salt decomposes more rapidly than the calcium and sodium salts.[20] The salts of strong acids have mostly but a slight accelerating effect but the salts of weak acids accelerate the hydrolysis reaction considerably.[21]

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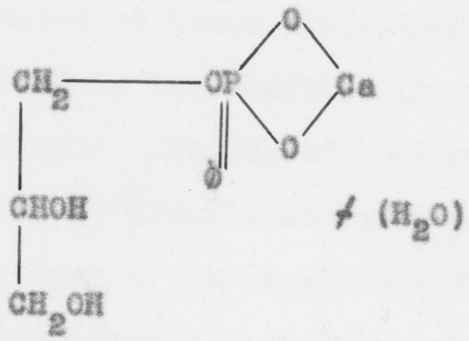
[18] Du Bois, G., Journ. Ind. and Eng. Chem., 6, p. 123 (1914).
[19] Ibid., p. 123.
[20] Ibid., p. 123.
[21] Ibid., p. 123.

The Chemistry of the Official Glycerophosphates

We now come to the chemistry of the official salts of glycerophosphoric acid, the calcium, ferric, manganese, quinine, sodium and strychnine glycerophosphates.

__Calcium Glycerophosphate__: The official calcium glycerophosphate is the normal salt of glycerophosphoric acid[1] and has the following formula:[2]



It is a fine, white odorless and almost tasteless powder.[3] It is somewhat hygroscopic.[4]

When precipitated from a cold, saturated, aqueous solution, by prolonged heating on the water bath, it separates, forming white, irridescent scales of anhydrous calcium

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[1] (Committee), The National Formulary VI, p. 66.
[2] Du Bois, G., Journ. Ind. and Eng. Chem. 6, p. 125.
[3] (Committee), The National Formulary VI, p. 66.
[4] *Ibid*., p. 66.

glycerophosphate.[5]

When precipitated out of a cold aqueous solution by the addition of alcohol, it forms an apparently amorphous precipitate which on drying below 70° C. retains one molecule of water;[6] when, however it is precipitated from the solution of its corresponding sodium salt, by the addition of $CaCl_2$, it forms a crystalline precipitate, containing one molecule of water of crystallization, which is not driven off when the product is dried below 70° C.[7]

One Gm. is soluble in 50 cc. of water at 25° C.[8] It is more soluble in water at lower temperatures.[9] The solubility is greatly increased by the addition of a small proportion of lactic acid, citric acid, or of sodium citrate.[10]

The solubility is diminished by the presence of alcohol, glycerin, or solutions of other glycerophosphates.[11]

It is alkaline towards phenolpthalein T.S. or litmus paper.[12]

The dry salt contains 26.68 per cent CaO and 33.80 per cent P_2O_5 and yields on incineration 60.47 per cent ash.[13]

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[5] (Committee), The National Formulary VI, p. 66.
[6] Du Bois, G., Journ. Ind. and Eng. Chem. 6, p. 125.
[7] *Ibid.*, p. 125.
[8] (Committee), The National Formulary, VI, p. 66.
[9] *Ibid.*, p. 66.
[10] Wood, H., The Dispensatory of the United States of America, 21, p. 253.
[11] *Ibid.*, p. 253.
[12] Du Bois, G., Journ. Ind. and Eng. Chem. 6, p. 126.
[13] *Ibid.*, p. 126.

If a solution of lead acetate is added to a solution of the salt, a precipitate of lead glycerophosphate is formed, which dissolves with difficulty in acetic acid, but readily in nitric acid.[14]

Tests for calcium glycerophosphate can be carried out as follows:

A white precipitate is produced in the aqueous solution (1:40) both by a solution of lead acetate and by a solution of ammonium oxalate.[15]

When 25 cc. of a solution of ammonium molybdate are added to a solution of the salt (1:40) at 15° C., a yellow precipitate should not be produced (phosphoric acid).[16]

When a solution of the salt (1:40) is acidified with nitric acid and solution of silver nitrate is added, it should not become definitely but merely opalescent (chlorides).[17]

If an excess of ammonia is added to the above mixture and the letter is heated, it should not darken or char (phosphides, phosphites, hypophhosphites).[18]

The solution of the calcium salt (1:40) should not be altered by hydrogen sulfide (heavy metals).[19]

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[14] Merck, E., Merck's Annual Report, 25, p. 4.
[15] <u>Ibid</u>., p. 5.
[16] <u>Ibid</u>., p. 5.
[17] <u>Ibid</u>., p. 5.
[18] <u>Ibid</u>., p. 5.
[19] <u>Ibid</u>., p. 5.

For a quantitative estimation of the salt the following test may be carried out:

Dry about 0.4 Gm. of Calcium Glycerophosphate to constant weight at 130° C., weigh accurately, dissolve in 20 cc. of an aqueous solution of acetic acid 1 in 20 and add 30 cc. of distilled water. Heat the mixture to boiling and add an excess of ammonium oxalate T.S. Collect the resulting precipitate, wash, dry, and ignite to constant weight, using a blast or high temperature burner.

Each Gm. of the residue (CaO) is equivalent to 3.7473 Gm. of $CaC_3H_5(OH)_2PO_4$.[20]

The present method of making the official salt is to treat glycerophosphoric acid with calcium hydroxide and purifying the product by treatment with alcohol.[21]

Ferric Glycerophosphate: The official ferric glycerophosphate, when dried to constant weight at 100° C. contains not less than 17 per cent of Fe, corresponding to not less than 95 per cent of $Fe_2(C_3H_5(OH)_2PO_4)_3$.[22]

The salt occurs in amber or yellowish green, transparent, amorphous scales, or in buff-colored or yellowish green powder.[23] It is odorless and nearly tasteless.[24]

One Gm. of the salt is slowly soluble in about 2 cc. of

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[20] (Committee), The National Formulary, VI, p. 56.
[21] Wood, H., The Dispensatory of the United States of America, 21, p. 253.
[22] (Committee), The National Formulary, VI, p. 147.
[23] Ibid., p. 147.
[24] Ibid., p. 147.

water at 25° C.;[25] it is insoluble in alcohol.[26]

Aqueous solutions of the salt are acid to litmus paper.[27]

A 5 per cent aqueous solution of the salt when added to a solution of potassium ferrocyanide, assumes a dark blue color,[28] and on the addition of hydrochloric acid a dark blue color precipitate is formed.[29]

If a solution of lead acetate is added to an aqueous solution of the salt a brown precipitate is immediately formed, which is readily soluble in nitric acid.[30]

When 0.2 Gm. of ferric glycerophosphate is ignited and the resulting ash dissolved in 10 cc. of hydrochloric acid, and the solution filtered, the addition of 25 cc. of solution of ammonium molybdate should give in a short time the phosphoric acid reaction (yellow precipitate).[31] If, however, a solution of 0.5 Gm. of ferric glycerophosphate in 10 cc. of water is added to 25 cc. of solution of ammonium molybdate, only a very small amount of the yellow precipitate should be formed.[32]

On heating a solution of 1 Gm. of ferric glycerophosphate in 20 cc. of water with 10 cc. of caustic soda solution (15 p.c.) and filtering, the filtrate, after being

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[25] (Committee), The National Formulary VI, p. 148.
[26] *Ibid.*, p. 148.
[27] *Ibid.*, p. 148.
[28] Merck, E., Merck's Annual Report, 25, p. 9.
[29] *Ibid.*, p. 9.
[30] *Ibid.*, p. 9.
[31] *Ibid.*, p. 9.
[32] *Ibid.*, p. 9.

acidified with hydrochloric acid, should only become slightly turbid on the addition of solution of barium chloride.[33]

For a quantitative estimation of the salt the following method may be used:

Dissolve about 1 Gm. of ferric glycerophosphate, dried to constant weight at 120° C. and accurately weighed, in 25 cc. of distilled water in a glass-stoppered flask. Add 3 cc. of hydrochloric acid, 1 Gm. of sodium bicarbonate in small portions, and 6 Gm. of potassium iodide; securely stopper the flask, and allow the mixture to stand at least five minutes; add 50 cc. of distilled water, and titrate the liberated iddine with tenth-normal sodium thiosulfate, using starch T.S. as the indicator.

Each cc. of tenth-normal-sodium thiosulfate is equivalent to 0.0311 Gm. of $Fe_2(C_3H_5(OH)_2PO_4)_3$ and to 0.005584 Gm. of Fe.[34]

The present method of preparing ferric glycerophosphate is by dissolving freshly precipitated ferric hydroxide in glycerophosphoric acid, evaporating the solution in vacuo and scaling it upon glass plates.[35]

<u>Manganese Glycerophosphate</u>: Manganese glycerophosphate was formerly official as the soluble salt.[36] It was rendered

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[33] Merck, E., Merck's Annual Report, 25, p. 9.
[34] (Committee), The National Formulary VI, p. 148.
[35] Wood, H., The Dispensatory of the United States of America, 21, p. 475.
[36] (Committee), The National Formulary V, p. 359 and VI, p.265.

soluble by acid of ctric acid.[37] The soluble manganese glycerophosphate contains 70-75 per cent of $MgC_3H_7PO_6$.[38]

It occurred as a yellowish or pinkish white powder, odorless and having an acid taste.[39]

One Gm. dissolves in 4 cc. of water at 25° C.[40] The aqueous solution is strongly acid to litmus[41] and becomes turbid on heating.[42] Alcohol dissolves the citric acid, leaving a residue which is nearly insoluble in water.[43]

The present official manganese glycerophosphate occurs as a white or pinksih white powder.[54] It is odorless, and has almost no taste.[45]

One Gm. of the salt is soluble in 5 cc. of an aqueous solution of citric acid (1 in 4).[46] It is slightly soluble in water and insoluble in alcohol.[47]

As for a quantitative examination of manganese glycerophosphate the following test may be used:

Dissolve about 0.5 Gm. of Manganese Glycerophosphate, dried to constant weight at 110° C. and accurately weighed,

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[37] (Committee), The National Formulary V, p. 359.
[38] _Ibid_., p. 359.
[39] _Ibid_., p. 359.
[40] _Ibid_., p. 359.
[41] _Ibid_., p. 359.
[42] _Ibid_., p. 359.
[43] _Ibid_., p. 359.
[44] _Ibid_., VI, p. 255.
[45] _Ibid_., p. 255.
[46] _Ibid_., p. 255.
[47] _Ibid_., p. 255.

in 100 cc. of a solution prepared by mixing 95 cc. of distilled water and 5 cc. of hydrochloric acid; add 20 cc. of ammonia T.S. and 10 cc. of ammonium sulfide T.S., and boil the mixture until the precipitate has become green. Allow the precipitate to settle, transfer it to a filter, wash with hot distilled water containing, a few drops of ammonium sulfide T.S., dry the filter and contents, and incinerate them in an open crucible, first at a low temperature, then at a strong red heat, until the weight is constant.

Each Gm. of manganous-manganic oxide (Mn_3O_4) is equivalent to 2.95 Gm. of $MnC_3H_5(OH)_2PO_4$.[48]

As for the present method of manufacture of manganese glycerophosphate nothing of recent publication could be found.

<u>Quinine Glycerophosphates</u>: This salt was official in The National Formulary IV,[49] but has not been recognized in the last two revisions of The National Formulary. It has the following formula $[(C_{20}H_{24}O_2N_2)_2\ PO_4H_2(C_3H_7O_2) + 4\ H_2O],$[50] and represents about 72 per cent of quinine.[51]

Quinine glycerophosphate occurs as fine white crystalline needles or as a powder.[52] It is odorless and having a

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[48] (Committee), The National Vormulary VI, p. 255.
[49] <u>Ibid</u>., IV, p. 336.
[50] <u>Ibid</u>., p. 336.
[51] Merck, E., Merck's Annual Report, 25, p. 11.
[52] (Committee), The National Formulary IV, p. 336.

a very bitter taste.[53]

One Gm. dissolves in about 850 cc. of water, or 75 cc. of alcohol at 25° C.; very soluble in boiling alcohol; very slightly soluble in chloroform or ether; soluble in 20 parts of a mixture of one volume of alcohol and two volumes of chloroform.[54]

In aqueous solution it combines with ferric glycerophosphate,[55] but the neutral sodium and calcium glycerophosphates cause the quinine to separate out.[56] Consequently a combination of this sort is only possible when the solutions of the above salts in water are first rendered slightly acid with glycerophosphoric acid.[57]

As for the present method of manufacture of this salt of glycerophosphoric acid nothing could be found in the literature.

Sodium Glycerophosphate: For many years, sodium glycerophosphate was known only in form of a syrupy liquid, or as a very hygroscopic white powder.[58] The crystalline sodium glycerophosphate was discovered by a chemist of the Soc. Anon. des Etabl. Poulenc Frères,[59] and the formation of

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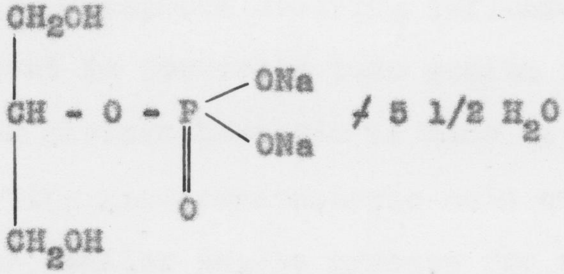
[53] (Committee), The National Formulary IV, p. 336.
[54] Ibid., p. 336.
[55] Merck, E., Merck's Annual Report, 25, p. 11.
[56] Ibid., p. 11.
[57] Ibid., p. 11.
[58] Du Bois, C., Journ. Ind. and Eng. Chem. 6, p. 126.
[59] Ibid., p. 126.

this product was evidently due to a change made at the time in their method of manufacture.[60]

N. Paolini, who was the first to publish results of investigations of this crystalline product,[61] found that it was pure disodium, monoglycerophosphate and concluded that it was the isomeride.[62] It has the following formula:[63]



$$CH_2OH-CH(-O-P(=O)(ONa)_2)-CH_2OH + 5\ 1/2\ H_2O$$

This explains why it could be obtained in a crystalline form, whereas the products obtained by the interaction of glycerin and phosphoric acid at temperatures below 110° C., after conversion into sodium salt, had never been known to crystallize, which can be explained by the fact that in the case, principally the isomeride is formed.[64]

The official sodium glycerophosphate contains 68-74 per cent of anhydrous salt.[65]

The salt occurs in white, monoclinic plates or scales,

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[60] Du Bois, G., Journ. Ind. and Eng. Chem. 6, p. 126.
[61] Ibid., p. 126.
[62] Ibid., p. 126.
[63] Ibid., p. 127.
[64] Ibid., p. 126.
[65] (Committee), The National Formulary VI, p. 329.

or as a white powder.[66] It is odorless, and has a saline taste.[67]

One Gm. of the salt is soluble in about 1.5 cc. of water at 25° C.[68] It is very soluble in hot water, but nearly insoluble in alcohol.[69]

An aqueous solution of the salt (1 in 20) is alkaline to litmus and to phenolphthalein T.S.[70] When strongly heated the salt is decomposed evolving inflammable vapors,[71] and at a red heat is converted into sodium pyrophosphate.[72]

Sodium glycerophosphate is made by two methods. One is by treating glycerophosphoric acid with sodium hydroxide in a manner similar to the process for calcium glycerophosphate. This method affords a salt of alpha-glycerophosphoric acid.[73] The other method is by heating monosodium phosphate with two molecular proportions of glycerin and hydrolyzing the resulting diglyceryl ester with sodium hydroxide. A considerable amount of sodium betaglycerophosphate crystallizes out at first. This constitutes the official salt.[74] The liquor from which no further amount of salt will crystallize constitutes the liquid sodium glycerophosphate of commerce.[75]

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[66] (Committee), The National Formulary VI, p. 329.
[67] _Ibid_., p. 329.
[68] _Ibid_., p. 329.
[69] _Ibid_., p. 329.
[70] _Ibid_., p. 329.
[71] _Ibid_., p. 329.
[72] _Ibid_., p. 329.
[73] Wood, H. The Dispensatory of the U.S., 21, p. 998.
[74] _Ibid_., p. 998.
[75] _Ibid_., p. 998.

As for a quantitative examination of the sodium salt one can proceed as follows:

Dissolve about 3 Gm. of Sodium Glycerophosphate, accurately weighed, in 30 cc. of distilled water, and titrate with half-normal hydrochloric acid, using methyl orange T.S. as the indicator.

Each cc. of half-normal hydrochloric acid is equivalent to 0.10803 Gm. of $Na_2C_3H_5(OH)_2PO_4$.[76]

Stychnine Glycerophosphate: This strychnine salt was official in The National Formulary IV.[77]

This salt occurs in white, rhombic crystals, or as a white powder.[78] It is odorless, having at first a faint, sweet taste, afterward becoming intensely bitter.[79]

One Gm. is soluble in about 350 cc. of water,[80] the solution being neutral or slightly alkaline to litmus,[81] also in about 310 cc. of alcohol;[82] slightly soluble in chloroform,[83] and very slightly soluble in ether.[84]

In aqueous solution it reacts in the same was as quinine glycerophosphate with the other salts of glycero-

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[76] (Committee), The National Formulary VI, p. 329.
[77] *Ibid.*, IV, p. 344.
[78] *Ibid.*, p. 344.
[79] *Ibid.*, p. 344.
[80] *Ibid.*, p. 344.
[81] *Ibid.*, p. 344.
[82] *Ibid.*, p. 344.
[83] *Ibid.*, p. 344.
[84] *Ibid.*, p. 344.

phosphoric acid.[85]

The addition of sulfuric acid to the salt produces no color, or at most only a slight yellowish coloration, but on subsequently adding a fragment of potassium dichromate a deep blue color is obtained, which changes to deep violet, then to purplish-red, cherry-red and finally to orange yellow.[86]

An excess of ammonia water added to a saturated aqueous solution of the salt produces a white precipitate, which is readily soluble in chloroform.[87]

As to the present manufacture of strychnine glycerophosphate nothing could be found in the present literature of preparing this salt.

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[85] Merck, E., Merck's Annual Report, 25, p. 11.
[86] (Committee), The National Formulary IV, p. 344.
[87] _Ibid_., p. 344.

The Therapeutics of the Official Glycerophosphates

Except as chemical curiosities little attention was paid to the glycerophosphates until 1894, when they were introduced into medicine by Robin[1] in the belief that they were of value in malnutrition. He recommended sodium glycerophosphate[2] as a nerve tonic to be given by mouth and subcutaneously and obtained excellent results in convalescence from influenza and other infective diseases, and also in nervous asthenia of any origin.

Robin[3] and Pasqualis[4] were the first to describe the therapeutic use of calcium glycerophosphate. The latter author pointed out that the action of calcium phosphate and of calcium glycerophosphate differed both physiologically and pharmacologically. Thus the excretion of phosphoric acid with constant diet is increased in the first 24 hours when calcium glycerophosphate is administered, whereas with calcium phosphate an increase of phosphate metabolism can only be recognized after two days.[5] The explanation of this observation was that glycerophosphate was more readily absorbed and utilised by the organism than was the phosphate.

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[1] Robin, A., Bulletin Acad. Med. /3/, 31, p. 419 (1894).

[2] Robin, A. Journ. des praticiens, 1906, p. 409.

[3] Robin, A., Gazette médicale de Paris 1894, p. 193; Bulletin général de therapeutique 1895, p. 385 and 433.

[4] Pasqualis, Annalidi chimical de farmacologia 1894, p. 94 and 145.

[5] *Ibid*., p. 96.

According to Robin,[6] calcium glycerophosphate not only increases phosphate metabolism, but it also increases the solid constituents of the urine, as for example the urea content rises from 23 per cent to 32 per cent, and of the chlorides and sulfates, and further the oxidation of nitrogen from 87 per cent to 90 per cent. But uric acid excretion, according to the author, is not influenced. He concludes that the use of glycerophosphate is only indicated in those diseases in which a dimunition in the exchange of nitrogen and sulphur can be demonstrated. He considers calcium glycerophosphates specially suitable in conditions of depression in patients suffering from phosphaturia, in convalescence from influenza, and from other infective diseases, in neurarasthenia, in torpid chlorosis with diminished nitrogen exchange, in phosphaturia either with or without albuminuria, in rickets, Addison's disease, sciatica, facial neuralgia, scrofula and tabes dorsalis. He considered the subcutaneous administration of the preparation to be more effective as a rule, but he also obtained satisfactory results by prescribing it internally. It may be noted that Gay[7] also prescribed calcium glycerophosphate in effervesing mixtures, prepared by adding a suitable amount of sodium bicarbonate and citric

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[6] Robin, A., Gazette médicale de Paris 1894, p. 196.
[7] Gay, H., Journ. d. Pharm. et d. Chim. 1895, I, p. 247.

acid to the aqueous solution.

Calcium glycerophosphate also deserves due consideration in the treatment of pulmonery tuberculosis. Michelozzi and Angiulli[8] have tested its value both pharmacologically and clinically. Michellozzi gave infected rabbits daily doses of 3 grams and obtained clinical and structural cures. Angiulli prescribed it in human practice both internally and subcutaneously with very good results. The ingestion of calcium salts is necessary, in his experience, because the excretion of calcium is increased in tuberculosis, thus causing poverty of calcium salts in the body; also the impregnation of the tuberculous focus with calcium salts may initiate or hasten the healing process. Therefore he gave subcutaneous injections daily. The author brought about a cure on an average by means of 90 injections. These were always well borne and markedly contributed to the improvement in the clinical signs. He also recorded direct cures in patients in the first and second stages of the diseases.

Ferric glycerophosphate is distinguished from most of the usual iron compounds by its ready absorption and rapid action, and it is therefore regarded with increasing favor in the treatment of chlorosis and anaemia. Robin[9] recog-

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[8] Michelozzi, A., Il Morgagni, 1906, p. 621.
[9] Robin, A., Bulletin général de thérapeutique 1895, p. 433.

nized the good qualities of iron glycerophosphate and prescribed it with marked benefit.

The therapeutic use of manganese glycerophosphate[10] is indicated in chronic constipation. It can be given alone or in combination with ferric glycerophosphate.

According to Moncourt[11] quinine glycerophosphate has the advantage over the other quinine salts in that it has no noxious by-effects. It does not upset the stomach, nor does it cause buzzing in the ears and it can be taken for a prolonged period, as the patient does not become habituated to the drug and its efficacy is thus not diminished. Moncourt[12] assumes that a diminuition in efficiency of the other quinine salts after prolonged use occurs owing to the quinine gradually causing poisoning of the nerve cells. But if the medicament be united to a substance which promotes the new formation of nerve tissue, as in the case with glycerophosphoric acid, the disadvantage mentioned above is eliminated and the beneficial action of the quinine is in no way interfered with, even after prolonged administration. In malaria this circumstance is said to especially noteworthy.[13]

Strychnine glycerophosphate can be prescribed in the same way as strychnine nitrate.[14] It is specially suitable

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[10] Merck's Annual Report, (1911), V. 25, p. 27.
[11] Moncourt, Presse médicale 1898, V. 99, p. 167.
[12] Ibid., p. 170.
[13] Ibid., Nouv. reméd. (1907), V. 19, p. 263.
[14] Merck's Annual Report, (1911), V. 25, p. 29.

in cases such as tuberculosis, anaemia and debility, in which the glycerophosphates of calcium, sodium or iron are to be administered in combination with strychnine. Given by itself, strychnine glycerophosphate has no advantage over strychnine nitrate,[15] because its maximum dose (1/6 grain) a day contains such a small amount of glycerophosphoric acid that it can have no therapeutic significance.

Now available evidence indicates that as a source of phosphorous to the animal organism the glycerophosphates passes no advantages over the ordinary inorganic phosphates.[16] The glycerophosphates are split up in the intestine, and liberate inorganic phosphates.[17] In this form they are absorbed and utilized; if they are utilized at all. The theory that organic phosphorous compounds are more readily assimilated than inorganic compounds and hence a better means of introducing phosphorous into the system is still kept alive in the promotion of certain proprietary mixtures, in spite of the scientific evidence that the organism can assimilate phosphorous quite readily from inorganic as from organic phosphorous compounds.[18] McCollun and Halpin[19] have shown that the animal organisms can build up lecithins and nucleoproteids, and other phosphorous containing com-

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[15] Merck's Annual Report, V. 25, p. 29.
[16] (Editorial), Journ. Amer. Med. Assoc., 66, p. 1205.
[17] Ibid., p. 1206.
[18] Ibid., p. 1206.
[19] McCollun, E.V., and Halpin, J.G., Journ. Biol. Chem., V. 11, p. 13.

pounds quite as readily from inorganic phosphates as from organic phosphorous compounds.

Forbes,[20] too, in an elaborate research upon swine, reaches the conclusion that there is no fundamental differences in the nutritive values of the glycerophosphates and phosphates, except that the former are less likely to disturb the digestive track. Also in a review of the literature on this subject for the Council on Pharmacy and Chemistry, Marshall[21] concluded "that organic phosphorous is of no more value as a food than inorganic."

Granting this to be true, however, does not necessarily disprove their therapeutic utility. It is possible to conceive that the unbroken molecule of glycerophosphoric acid, circulating in the blood, may in some way exercise a stimulating action on the metabolism of the central nervous system. While there is considerable clinical evidence of the usefulness of the glycerophosphates in various conditions of deproved metabolism, the testimony is not unanimous. We must regard, therefore, the question of value of the glycerophosphates as a remedy in conditions of general debility, as still "subjudice."

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[20] Forbes, H., Ohio Technical Bull. No. 6, 1914.
[21] Marshal, K., Journ. Am. Med. Assoc. 1915, V. 64, p. 573.

United States Pharmacopoeia (0-XI)
1820-1930
National Formulary (I-VI)
1888-1935

History of Glycerophosphates

U. S. P. IX p. 91

5 Calcii Glycerophosphos

Calcium Glycerophosphate

Calc. Glycerophos. - Calcium Glycerinophosphate

The normal calcium salt of glycerophosphoric acid [$C_3H_5(OH)_2PO_4H_2$ /= 172.11], containing, when dried to constant weight at 130° C., not less/then 98 per cent. of $CaC_2H_7PO_6$ or $C_3H_5(OH)_2PO_4Ca$ (210.17). Pre-/serve it in well-closed containers.

Calcium Glycerophosphate occurs as a fine white powder; odorless and almost/tasteless, somewhat hygroscopic.

One Gm. of Calcium Glycerophosphate dissolves in about 50 mils of water/at 25° C.; soluble in less water at a lower temperature; citric acid increases its/solubility; insoluble in alcohol.

A saturated aqueous solution of the salt is alkaline to litmus and to phenol-/phthalein.

A cold, saturated aqueous solution of the salt yields white, iridescent scales/of anhydrous calcium glycerophosphate when heated to boiling.

When heated above 170° C. the salt is decomposed, evolving inflammable/vapors, and at a red heat it is converted into calcium pyrophosphate.

A saturated aqueous solution of the salt yields with ammonium oxalate T.S./a white precipitate, insoluble in acetic acid but soluble in hydrochloric acid. With lead acetate T.S. the saturated solution yields a white curdy precipitate which is soluble in nitric acid.

Dissolve 1 Gm. of Calcium Glycerophosphate in 10 mils of diluted nitric acid and add an equal volume of cold ammonium molybdate T.S.; no precipitate is formed within one hour (phosphates) but on heating the mixture a yellow precipitate is formed.

An aqueous solution of the salt does not respond to the Test for heavy metals (see Part II, Test No. 3).

Dissolve 0.1 Gm. of the salt in 10 mils of diluted nitric acid and add 1 mil of silver nitrate T.S.; an opolescence but no precipitate may appear within one minute (chloride).

Dissolve 0.1 Gm. of the salt in 10 mils of diluted hydrochloric acid and add 1 mill of barium chloride T.S.; no distinct turbidity appears within one minute (sulphate).

Shake 1 Gm. of finely powdered Calcium Glycerophosphate with 25 mils of dehydrated alcohol, filter the mixture, evaporate the filtrate on a water bath and dry the residue for an hour at a temperature not exceeding 70° C. The resulting residue weighs not more than 0.01 Gm. (alcohol-soluble impurities, etc.)

Dry a portion of the finely powdered salt to constant

U. S. P. IX

(Calcium Glycerophosphate)

weight at 130° C.; the/loss does not exceed 10 per cent (water).

Assay -- Dissolve about 0.4 Gm. of the salt, previously dried to constant/weight at 130° C. and accurately weighed, in 20 mils of a 5 per cent solution of/acetic acid and add 30 mils of distilled water. Heat the mixture to boiling and/add an excess of ammonium oxalate T.S. Collect the resulting precipitate, wash,/dry, and then ignite it until of constant weight. This residue of calcium oxide/corresponds to not less than 26.1 per cent of the weight of Calcium Gly-cerophos-/phate taken.

Dry a portion of Calcium Glycerophosphate to constant weight at 130° C.,/and ignite it to constant weight; the weight of calcium pyrophosphate corre-/sponds to not less than 59.2 per cent of the weight of Calcium Glycerophos-/phate taken.

Average Dose - Metric, 0.25 Gm. - Apothecaries, 4 grains.

U. S. P. X p. 89

Calcii Glycerophosphos

Calcium Glycerophosphate

Calc. Glycerophos. - Calcium Glycerinophosphate

The normal calcium salt of glycerophosphoric acid [$C_3H_5(OH)_2PO_4H_2$] containing, when dried to constant weight at 130° C. not less than 98 per cent of $C_3H_5(OH)_2PO_4Ca$.

Description and physical properties — A fine, white, odorless powder. It is somewhat hygroscopic.

One Gm. of Calcium Glycerophosphate is soluble in about 50 cc. of water at 25° C. It is more soluble in water at a lower temperature; citric acid increases its solubility in water. It is insoluble in alcohol.

Tests for identity — A saturated aqueous solution of the salt upon boiling yields white, iridescent scales of anhydrous calcium glycerophosphate. When heated above 170° C., the salt is decomposed, evolving inflamable vapors, and at a red heat is converted in calcium pyrophosphate.

A saturated aqueous solution of the salt responds to the reactions for calcium page 441, and for glycerophosphate, page 442.

With lead acetate T. S. a saturated aqueous solution of the salt yields a white curdy precipitate, which is soluble

U. S. P. X

(Calcium Glycerophosphate)

in nitric acid.

Tests for purity -- Dissolve 1 Gm. of Calcium Glycerophosphate in 10 cc. of diluted nitric acid, and add an equal volume of cold molybdate T.S.: no precipitate is formed within one hour (phosphates).

An aqueous solution of the salt meets the requirements of the test for heavy metals, page 439.

One Gm. of Calcium Glycerophosphate shows no more chloride than 1 cc. of fiftieth-normal hydrochloric acid, page 462.

Two-tenths of 1 Gm. of Calcium Glycerophosphate shows no more sulphate than 1 cc. of fiftieth-normal sulphuric acid, page 462.

Shake 1 Gm. of finely powdered Calcium Glycerophosphate with 25 cc. of dehydrated alcohol filter the mixture, evaporate the filtrate on a water bath, and dry the residue for an hour at a temperature not exceeding 70° C.: the resulting residue weighs not more than 0.01 Gm. (alcohol-soluble substances).

The loss on drying a portion of the finely powdered salt to constant weight at 130° C., does not exceed 10 per cent (water).

U. S. P. X

(Calcium Glycerophosphate)

Dry about 3 Gm. of Calcium Glycerophosphate to constant weight at about/130° C., weigh accurately, dissolve it in 250 cc. of distilled water, and then/titrate with half-normal hydrochloric acid, using methyl orange T.S. as indi-/cator, to a slight yet distinct pink. Each Gm. of dry Calcium Glycerophos-/phate requires not less than 9 cc. of half-normal hydrochloric acid (minimum/limit for glycerophosphate).

Assay -- Dry about 0.4 Gm. of Calcium Glycerophosphate to constant weight at/130° C., weigh accurately, dissolve in 20 cc. of a 5 per cent solution of acetic/acid, and add 30 cc. of distilled water. Heat the mixture to boiling, and add an/excess of ammonium oxalate T. S. Collect the resulting precipitate, wash, dry,/and ignite to constant weight. This residue of calcium oxide corresponds to not/ less than 26.1 per cent of the weight of dried Calcium Glycerophosphate taken.

Dry a portion of Calcium Glycerophosphate to constant weight at 130° C.,/and ignite it to constant weight. The weight of calcium pyrophosphate cor-/responds to not less than 59.2 per cent of the weight of Calcium Glycero-/phosphate taken.

U. S. P. X

(Calcium Glycerophosphate)

Preserve in well-closed containers.

Average Dose -- Metric, 0.3 Gm. - Apothecaries, 5 grains.

N. F. VI p. 66

Calcii Glycerophosphas
Calcium Glycerophosphate
Calc. Glycerophos

Calcium Glycerophosphate is the normal calcium salt of glycerophos-/phoric acid, and, when dried to constant weight at 130° C., contains not/less than 98 per cent of $CaC_3H_5(OH)_2PO_4$(210.15).

Description and physical properties.

Calcium Glycerophosphate is a fine, white, odorless, almost tasteless powder. /It is somewhat hygroscopic.

One Gm. of Calcium Glycerophosphate is soluble in 50 cc. of water at 25° C. /It is more soluble in water at a lower temperature; citric acid increases its solu-/bility in water. It is insoluble in alcohol.

Tests for identity and purity.

A saturated aqueous solution of Calcium Glycerophosphate is alkaline to litmus/paper and to phenolphthalein T.S. and responds to the tests for calcium, and for/glycerophosphate.

Prepare a cold, saturated aqueous solution of the salt and boil it: white, iri-/descent scales of anhydrous calcium glycerophosphate form.

N. F. VI

(Calcium Glycerophosphate)

When heated above 170° C., the salt is decomposed, evolving inflammable vapors, and at a red heat is converted into calcium pyrophosphate.

With lead acetate T.S., a saturated aqueous solution of the salt yields a white, crudy precipitate, which is soluble in nitric acid.

Dissolve 1 Gm. of Calcium Glycerophosphate in 10 cc. of diluted nitric acid, and add an equal volume of cold ammonium molybdate T.S.: no precipitate is formed on standing for one hour at 20° to 25° C. (phosphate).

Dissolve 1 Gm. of the salt in 60 cc. of distilled water, and add 3 drops of phenol-phthalein T.S.: any red color produced is discharged by the addition of not more than 1.5 cc. of tenth-normal sulfuric acid (free alkali).

One Gm. of the salt shows no more chloride than corresponds to 1 cc. of fiftieth-normal hydrochloric acid.

Two-tenths Gm. of the salt shows no more sulfate than corresponds to 1 cc. of fiftieth-normal sulfuric acid.

Shake 1 Gm. of the finely powdered salt with 25 cc. of dehydrated alcohol, filter the mixture, evaporate the filtrate on a water bath, and dry the residue for an hour at a temperature not exceeding 70° C.: the resulting residue weighs not more than 0.01 Gm. (alcohol-soluble substances).

N. F. VI

(Calcium Glycerophosphate)

When dried to constant weight at 130° C., the salt loses not more than 10 per cent in weight (water).

The salt meets the requirements of the test for arsenic and the test for heavy metals.

Assay.

Dry about 0.4 Gm. of Calcium Glycerophosphate to constant weight at 130° C., weigh accurately, dissolve in 20 cc. of an aqueous solution of acetic 1 in 20, and add 30 cc. of distilled water. Heat the mixture to boiling and add an excess of ammonium oxalate T.S. Collect the resulting precipitate, wash, dry, and ignite to constant weight, using a blast or high temperature burner.

Each Gm. of the residue (calcium oxide) is equivalent to 3.7473 Gm. of $CaC_3H_5 - (OH)_2PO_4$.

Storage.

Keep the salt in well-closed containers.

Preparations: Elixir Calcii et Sodii Glycerophosphatum, Elixir Glycerophosphatum Compositum.

Average Dose: Metric, 0.3 Gm. - Apothecaries, 5 grains.

Summary of U.S.P. and N.F. data of
Calcium Glycerophosphate

When Official:

U.S.P., IX; X; N.F. VI.

Official Latin Title:

Calcii Glycerophosphas: U.S.P., IX, X; N.F. VI.

Official English Title:

Clacium Glycerophosphate: U.S.P. IX; X; N.F. VI.

Official Abbreviation:

Calc. Glycerophos.: U.S.P. IX, X; N.F. VI.

Official Synonym:

Calcium Glycerinophosphate, U.S.P. IX; X.

Official Description:

The normal calcium salt of glycerophosphoric acid [$C_3H_5(OH)_2PO_4H_2$ = 172.11], containing, when dried to constant weight at 130°, not less 98 per cent of a $CaC_3H_7PO_6$ or $C_3H_5(OH)_2PO_4Ca$ (210.17). Preserve it in well-closed containers.

U. S. P. IX

The normal calcium salt of glycerophosphoric acid

$[C_3H_5(OH)_2PO_4H_2]$ containing, when dried to constant weight at 130° C. not less than 98 per cent of $C_3H_5\ (OH)_2PO_4Ca$.

U.S.P. X.

Calcium Glycerophosphate is the normal calcium salt of glycerophosphoric acid, and, when dried to constant weight at 130° C., contains not less than 98 per cent of $CaC_3H_5(OH)_2PO_4$ (210.15).

N. F. VI

Official Preparations:

Elixir Calcii et Sodii Glycerophosphatum, Elixir Glycerophosphatum Compositum.

N. F. VI

Official Dose:

Metric, 0. 25 Gm. - Apothecaries, 4 grains.

U. S. P. IX

Metric, 0.3 Gm. - Apothecaries, 5 grains.

U. S. P. X; N. F. VI.

N. F. IV S. p. 297

Ferri Glycerophosphas

Ferric Glycerophosphate

Ferr. Glycerophos. Ferric Glycerinophosphate

It contains a variable quantity of $Fe_2(C_3H_7O_6P)_3$ (621.97) corresponding to not less than 14 per cent nor more than 16 per cent of Fe. Preserve it in well-closed containers, protected from light.

Ferric Glycerophosphate occurs as yellowish-green, transparent, amorphous scales or as a greenish-yellow powder; odorless and nearly tasteless.

One gramme dissolves slowly in about 2 mils of water at 25° C.; insoluble in alcohol. An aqueous solution is acid to litmus and becomes turbid when heated.

An aqueous solution of the salt (1 in 20) is colored dark blue by potassium ferro-cyanide T.S.; on the subsequent addition of hydrochloric acid a dark blue precipitate is produced.

Heat a powdered mixture of about 0.1 Gm. of the salt with about 0.5 Gm. of potassium bisulphate; the pungent vapors of acrolein are evolved.

Incinerate 0.5 Gm. of the salt; it yields a red-brown residue, which is not alkaline to moistened litmus paper.

N. F. IV

(Ferri Glycerophosphas)

Not more than a slight yellow turbidity is produced at once on mixing 5 mils of an aqueous solution of the salt (1 in 50) with 10 mils of ammonium molybdate T.S. (phosphate), but on standing or on warming, a yellow precipitate is formed.

An aqueous solution of the salt (1 in 50), acidulated with hydrochloric acid, does not become more than slightly turbid on the addition of barium chloride T.S. (sulphate).

Another portion of this aqueous solution, acidulated with nitric acid, does not become more than slightly turbid on the addition of silver nitrate T.S. (chloride).

Assay. -- Dissolve about 0.5 Gm. of Ferric Glycerophosphate, accurately weighed, in 50 mils of distilled water, in a 100 mil glass-stoppered flask, add 5 mils of hydrochloric acid and about 3 Gm. of potassium iodide. Warm to 40° C., and allow the mixture to stand one-half hour at this temperature, in the stoppered flask, cool, and then titrate the liberated iodine with tenth-normal sodium thiosulphate V.S., using starch T.S. as indicator. It shows not less than 14 per cent nor more than 16 per cent of Fe.

Each mil of tenth-normal sodium thiosulphate V.S. used corresponds to 0.005584 Gm. of Fe. Each gramme of Ferric

N. F. IV

(Ferri Glycerophophas)

Glycerophosphate corresposds to not less than/25.07 mils nor more than 28.65 mils of tenth-normals sodium thiosulphate V.S.

Average Dose -- Metric, 0.2 Gm. -- Apothecaries, 3 grains.

N. F. V S. p. 326

Ferri Glycerophosphas

Ferric Glycerophosphate

Ferr. Glycerophos. Ferric Glycerinophosphate

Ferric Glycerophosphate contains a variable quantity of/$Fe_2(C_3H_7O_6P)_3$ (622.02) corresponding to not less than 14 per cent and/not more than 16 per cent of Fe.

Description and physical properties.

Ferric Glycerophosphate occurs as yellowish green,/ transparent, amorphous scales or as a greenish yellow powder; odorless/and nearly tasteless.

One Gm. dissolves slowly in about 2 cc. of water at 25° C.; insoluble in alco-/hol. An aqueous solution is acid to litmus and becomes turbid when heated.

Tests of identity: An aqueous solution of the salt 91 in 20) is colored dark blue/by potassium ferrocyanide, T.S.; on the subsequent addition of hydrochloric/acid a dark blue precipitate is produced.

Heat a powdered mixture of about 0.1 Gm. of the salt with about 0.5 Gm./of potassium bisulphate; the pungent vapors of acrolein are evolved.

Tests for purity: Not more than a slight yellow turbidity is produced at once on/mixing 5 cc. of an aqueous solution of the salt (1 in 50) with 10 cc. of ammonium/

N. F. V

(Ferric Glycerophosphate)

molybdate T.S. (phosphate), but on standing or on warming a yellow precipi-/tate is formed.

An aqueous solution of the salt (1 in 50), acidulated with hydrochloric acid, does/not become more than slightly turbid on the addition of barium chloride/T.S. (sulphate).

Another portion of this squeous solution, acidulated with nitric acid, does not/become more than slightly turbid on the addition of silver nitrate T.S. (chloride).

Assay. - Dissolve about 0.5 Gm. of Ferric Glycerophosphate, accurately weighed,/in 50 cc. of distilled water, in a 100 cc. glass-stoppered flask, add 5 cc. of hydro-/chloric acid and about 3 Gm. of potassium iodide. Warm to 40° C., and allow/the mixture to stand one-half hour at this temperature in the stoppered flask,/cool, and then titrate the liberated iodine with tenth-normal sodium thiosulphate,/ using starch T.S. as indicator.

Each cc. of tenth-normal sodium thiosulphate corresponds to 0.005584 Gm./of Fe. Each gram of Ferric Glycerophosphate corresponds to not less than/25.07 cc. nor more than 28.65 cc. of tenth-normal sodium thiosulphate.

Preserve it in well-closed containers, protected from light.

N. F. V

(Ferric Glycerophosphate)

Preparation: Elixir Glycerophosphatum Compositum.

Average Dose: Metric, 0.2 Gm. -- Apothecaries, 3 grains.

N. F. VI p. 147

Ferri Glycerophosphas
Ferric Glycerophosphate
Ferr. Glycerophos.

Ferric Glycerophosphate, when dried to constant weight at 110° C., contains not less than 17 per cent of Fe. corresponding to not less than 95 per cent of $Fe_2(C_3H_5(OH)_2PO_4)_3$ (621.96).

Description and physical properties.

Ferric Glycerophosphate occurs in amber or yellowish green, transparent, amorphous scales, or in buff-colored or yellowish green powder. It is ordorless, and nearly tasteless.

One Gm. of the salt is slowly soluble in about 2 cc. of water at 25° C., it is insoluble in alcohol.

Tests for identity and purity.

An aqueous solution of Ferric Glycerophosphate (1-20) is acid to litmus paper and responds to the tests for ferric iron and for glycerophosphate.

When 5 cc. of an aqueous solution of Ferric Glycerophosphate (1- in 20) is mixed with 10 cc. of ammonium molybdate T.S., no yellow turbidity is immediately produced (phosphate).

N. F. VI

(Ferric Glycerophosphate)

When dried to constant weight at 110° C., the salt loses not more than 5 per cent in weight (water).

Separate 0.5 Gm. portions of the salt show no more chloride than corresponds to 1 cc. of fiftieth-normal hydrochloric acid, and no more sulfate than corresponds to 0.1 cc. of fiftieth-normal sulfuric acid.

An aqueous solution of the salt meets the requirements of the test for arsenic.

To an aqueous solution of the salt (1 in 20), add sodium hydroxide T.S. until there is no further precipitation, and filter: the filtrate is colorless; when acidullated with hydrochloric acid, it meets the requirements of the test for heavy metals.

Assay.

4Dissolve about 1 Gm. of Ferric Glycerophosphate, dried to constant weight at 110° C. and accurately weighed, in 25 cc. of distilled water in a glass-stoppered flask. Add 3 cc. of hydrochloric acid, 1 Gm. of sodium bicarbonate in small portions, and 6 Gm. of potassium iodide; securely stopper the flask, and allow the mixture to stand for at least five minutes; add 50 cc. of distilled water, and titrate the liberated iodine with tenth-normal sodium thiosulfate, using starch T.S. as the/indicator.

Each cc. of tenth-normal sodium thiosulphate is equivalent to 0.0311 Gm. of/$Fe_2 (C_3H_5(OH)_2PO_4)_3$ and to 0.005584 Gm. of Fe.

Storage.

Keep the salt in well-closed containers, protected from light.

Preparation: Elixir Glycerophosphatum Compositum.

Agerage Dose: Metric, 0.2 Gm. -- Apothecaries, 3 grains.

Summary of U.S.P. and N.F. data of
Ferric Glycerophosphate

When Official:

N.F. IV, V, VI.

Official Latin Title:

Ferri Glycerophosphas.

N.F. IV, V, VI.

Official English Title:

Ferric Glycerophosphate.

N.F. IV, V, VI.

Official Abbreviation:

Ferr. Glycerophos.

N.F. IV, V, VI.

Official Synonym:

Ferric Glycerinophosphate.

N.F. IV, V, VI.

Official Description:

It contains a variable quantity of $Fe_2(C_3H_7O_6P)_3$ (621.97) corresponding to not less than 14 per cent nor more than 16 per cent of Fe. Preserve it in well-closed containers, protected from light.

N.F. IV

N. F. IV

(Ferric Glycerophosphate)

Ferric Glycerophosphate contains a variable quantity of $Fe_2(C_3H_7O_6P)_3$ (622.02) corresponding to not less than 14 per cent and not more than 16 per cent of Fe.

N.F. V.

Ferric Glycerophosphate, when dried to constant weight at 110° C., contains not less than 17 per cent of Fe, corresponding to not less than 95 per cent of $Fe_2(C_3H_5(OH)_2PO_4)_3$ (621.96).

N.F. VI.

Official Preparations:

Elixir Glycerophosphatum Compositum.

N.F. V, VI.

Official Dose:

Metric, 0.2 Gm. - Apothecaries, 3 grains.

N.F. IV, V, VI.

N. F. IV S. p. 317

Mangani Glycerophosphas Solubilis

Soluble Manganese Glycerophosphate

Mangan. Glycerophos. Sol. Soluble Manganous Glycerinophosphate

Manganous Glycerophosphate rendered soluble by the aid of citric acid. It contains not less than 70 per cent nor more than 75 per cent of $MnC_3H_7PO_6$ (225.03). Preserve it in well-closed containers.

Soluble Manganese Glycerophosphate occurs as a yellowish or pinkish-white powder, odorless, and having an acid taste.

One gramme dissolves in 4 mils of water at 25° C. The aqueous solution is strongly acid to litmus and becomes turbid on heating. Alcohol dissolves the citric acid, leaving a residue which is nearly insoluble in water.

Add an excess of ammonium sulphide T.S. to an aqueous solution of Soluble Manganese Glycerophosphate; on standing, it yields a salmon-colored precipitate soluble in acetic acid.

No yellow turbidity is produced immediately on mixing 5 mils of an aqueous solution (1 in 20) with 10 mils of ammonium molybdate T.S. (phosphate), but on prolonged standing, or on heating, a yellow precipitate is formed.

N. F. IV

(Soluble Manganese Glycerophosphate)

Heat a powdered mixture of about 0.1 Gm. of Soluble Manganese Glycerophos-/phate and about 0.5 Gm. of potassium bisulphate; pungent vapors of acrolein are/evolved.

Separate portions of 10 mils each of an aqueous solution of Soluble Manganese/Glycerophosphate (1 in 20) are not rendered more than slightly turbid by barium/chloride. T.S. when mixed with a few drops of hydrochloric acid (sulphate); nor by/silver nitrate T.S., after acidulation with nitric acid (chloride).

Add a few drops of hydrochloric acid and 1 mil of chlorine T.S. to 10 mils of an/aqueous solution of Soluble Manganese Glycerophosphate (1 in 200) and boil; no/reddish color is produced in the liquid by potassium sulphocyanate T.S. after cooling/(iron).

An aqueous solution of Soluble Manganese Glycerophosphate does not respond/to the Test for heavy metals (see page 357).

Assay. -- Dissolve about 0.5 Gm. of Soluble Manganese Glycerophosphate, accu-/rately weighed, in 100 mils of distilled water, add 10 mils of ammonia water and 5/mils of ammonium sulphide T.S. and boil the mixture until the precipitate formed has/become greenish. Allow the precipitate to settle, then transfer it to a filter, wash/with hot distilled water containing a few drops of ammonium sulphide T.S., dry the/filter and contents and incinerate them in an open crucible, first at a low temperature/and then at strong red heat, until the weight is constant. The residue of manganous-/manganic oxide (Mn_3O_4) so obtained is not less than 23.7 percent. nor more than/25.4 per cent of the weight taken, corresponding to not less than 70 per cent nor/more than 75 per cent of $MnC_3H_7PO_6$.

Each gramme of manganous-manganic oxide is equivalent to 2.95 Gm. of $MnC_3H_7PO_6$.

Aberage Dose -- Metric, 0.2 Gm. -- Apothecaries, 3 grains.

N. F. V S. p. 359

Mangani Glycerophosphas Solubilis

Soluble Manganese Glycerophosphate

Mangan. Glycerophos. Sol. Soluble Manganous Glycerinophosphate

Manganous Glycerophosphate rendered soluble by the presence of/citric acid. It contains not less than 70 per cent nor more than 75 per cent/of $MnC_3H_7PO_6$ (225.04).

Description and physical properties.

Soluble manganese Glycerophosphate oc-/curs as a yellowish or pinkish white powder, odorless, and having an acid taste.

One Gm. dissolves in 4 cc. of water at 25° C. The aqueous solution is/strongly acid to litmus and becomes turbid on heating. Alcohol dissolves the/citric acid, leaving a residue which is nearly insoluble in water.

Tests for identity: Add an excess of ammonium sulphide T.S. to an aqueous solu-/tion of Soluble Manganese Glycerophosphate; on standing, it yields a salmon-/colored precipitate soluble in acetic acid.

No Yellow turbidity is produced immediately on mixing 5 cc. of an aqueous/solution (1 in 20) with 10 cc. of ammonium molybdate T.S. (phosphate), but on/prolonged standing, or on heating,a yellow precipitate is formed.

Heat a powdered mixture of about 0.1 Gm. of Soluble Manganese Glycero-/phosphate and about 0.5 Gm. potassium bisulphate; pungent vapors of acro-/lein are evolved.

Tests for purity: Separate portions of 10 cc. each of an aqueous solution of Soluble/Manganese Glycerophosphate (1 in 20) are not rendered more than slightly/turbid by barium chloride T.S. when mixed with a few drops of hydrochloric acid /(Sulphate); nor by silver nitrate T.S., after acidulation with nitric acid (chloride).

Add a few drops of hydrochloric acid and 1 cc. of chlorine T.S. to 10 cc. of an/aqueous solution of Soluble Manganese Glycerophosphate (1 in 200) and boil;/no reddish color is produced in the liquid by potassium theocyanate T.S. after/cooling (iron).

An aqueous solution of Soluble Manganese Glycerophosphate does not re-/spond to the Test for heavy metals (see page 418).

Assay. — Dissolve about 0.5 Gm. of Soluble Manganese Glycerophosphate, ac-/curately weighed, in 100 cc. of distilled water, add 10 cc. of ammonia water and /5 cc. of ammonium sulphide T.S., and boil the mixture until the precipitate/formed has become greenish. Allow the precipitate to settle, then transfer it to/a filter, wash with hot distilled water containing a few drops of ammonium sul-/phide T.S., dry the filter and contents, and incinerate them in an

N. F. V

(Soluble Manganese Glycerophosphate)

open crucible, first at a low temperature and then at strong red heat, until the weight is constant. The residue of manganous-manganic oxide (Mn_3O_4) so obtained is not less than 23.7 per cent or more than 25.4 per cent of the weight taken, corresponding to not less than 70 per cent or more than 75 per cent of $MnC_3H_7PO_6$.

Each Gm. of manganous-manganic oxide is equivalent to 2.95 Gm. of $MnC_3 - H_7PO_6$.

Preparation: Elixir Glycerophosphatum Compositum.

Average Dose: Metric, 0.2 Gm. - Apothecaries, 3 grains.

N. F. VI

Mangani Glycerophosphas
Manganese Glycerophosphate
Mangan. Glycerophos.

Manganese Glycerophosphate, when dried to constant weight at 110° C., contains not less than 98 per cent of $MnC_3H_5(OH)_2PO_4$ (225.00).

Description and physical properties.

Manganese Glycerophosphate is a white or pinkish white powder. It is odorless, and has almost no taste.

One Gm. of the salt is soluble in 5 cc. of an aqueous solution of citric acid (1 in 4). It is slightly soluble in water and insoluble in alcohol.

Tests for identity and purity.

A solution of Manganese Glycerophosphate (1 in 20) in diluted hydrochloric acid responds to the tests for manganese and glycerophosphate.

When a mixture of 0.1 Gm. of the salt and 0.5 Gm. of potassium bisulfate is heated, pungent vapors of acrolein are evolved (glycerin).

When 5 cc. of a solution of Manganese Glycerophosphate (1 in 20) in diluted hydrochloric acid is mixed with 10 cc.

of ammonium molybdate T.S., no yellow/turbidity is immediately produced (phosphate).

Separate portions of 0.5 Gm. each of the salt show no more chloride than cor-/responds to 1 cc. of fiftieth-normal hydrochloric acid and no more sulfate than corresponds to 0.1 cc. of fiftieth-normal sulfuric acid.

The salt, dissolved in diluted hydrochloric acid, meets the requirements of the/test for arsenic and the test for heavy metals.

Dissolve 0.1 Gm. of the salt in 20 cc. of a solution prepared by mixing 18 cc. of/water and 2 cc. of hydrochloric acid. Add 1 cc. of chlorine T.S. to the solution;/boil and cool; no red color is produced in the liquid by ammonium thiocyanate/T. S. (iron).

When dried to constant weight at 110° C., the salt loses not more than 10 per/cent in weight (water).

Assay.

Dissolve about 0.5 Gm. of Manganese Glycerophosphate, dried to constant/weight at 110° C. and accurately weighed, in 100 cc. of a solution prepared by/mixing 95 cc. of distilled water and 5 cc. of hydrochloric acid; add 20 cc. of ammonia/T.S. and 10 cc. of ammonium sulfide T.S., and boil the mixture until the precipitate/has become green. Allow the precipitate to settle, transfer it to a filter, wash/

with hot distilled water containing a few drops of ammonium sulfide T.S., dry the filter and contents, and incinerate them in an open crucible, first at a low temperature, then at a strong red heat, until the weight is constant.

Each Gm. of manganous-manganic oxide (Mn_3O_4) is equivalent to 2.95 Gm. of $MnC_3H_5(OH)_2PO_4$.

Preparation: Elixir Glycerophosphatum Compositum.

Average Dose: Metric, 0.2 Gm. - Apothecaries, 3 grains.

Summary of U.S.P. and N.F. data of Manganese Glycerophosphate

When Official:

N. F. IV, V, VI.

Official Latin Title:

Mangani Glycerophosphas Solubilis

N. F. IV, V.

Mangani Glycerophosphas

N. F. VI.

Official English Title:

Soluble Manganese Glycerophosphate

N. F. IV, V.

Manganese Glycerophosphate

N. F. VI.

Official Abbreviation:

Mangan. Glycerophos. Sol.

N. F. IV, V.

Mangan. Glycerophos.

N. F. VI.

Official Synonym:

Soluble Manganous Glycerinophosphate

N. F. IV, V.

Official Description:

Manganous Glycerophosphate rendered soluble by the aid of citric acid. It contains not less than 70 per cent nor more than 75 per cent of $MnC_3H_7PO_6$ (225.03). Preserve it in well-closed containers.

N. F. IV.

Manganous Glycerophosphate rendered soluble by the presence of citric acid. It contains not less than 70 per cent nor more than 75 per cent of $MnC_3H_7PO_6$ (225.04).

N. F. V.

Manganese Glycerophosphate, when dried to constant weight at 110° C., contains not less than 98 per cent of $MnC_3H_5(OH)_2PO_4$ (225.00).

N. F. VI.

Official Preparations:

Elixir Glycerophosphatum Compositum.

N. F. V, VI.

Official Dose:

Metric, 0.2 Gm. - Apothecaries, 3 grains.

N. F. IV, V, VI.

N. F. IV S. p. 336

Quininae Glycerophosphas

Quinine Glycerophosphate

Quin. Glycerophos. Quinine Glycerinophosphate

The glycerophosphate $[C_{20}H_{24}O_2N_2)_2\ PO_4H_2(C_3H_7O_2) +$ $4\ H_2O =$ /892.60] of the alkaloid quinine. Preserve it in well-stoppered, amber- /colored bottles.

Quinine Glycerophosphate occurs as fine, white crystalline needles or as a powder; odorless and having a very bitter taste.

One gramme dissolves in about 850 mils of water, or 75 mils of alcohol at 25° C.;/very soluble in boiling alcohol; very slightly soluble in chloroform or ether; soluble in/20 parts of a mixture of one volume of alcohol and two volumes of chloroform.

Quinine Glycerophosphate slowly loses part of its water of crystallization at room/temperature and when heated to 100° C. becomes anhydrous. Incinerate 0.2 Gm./of the salt; no weighable residue remains.

The salt yields a clear solution with undiluted sulphuric acid. An aqueous solution/is not fluorescent, but becomes so upon the addition of a few drops of diluted sulphuric/acid.

N. F. IV

(Quinine Glycerophosphate)

Add 1 mil of bromine T.S. to 10 mils of a suturated aqueous solution of the salt, and then follow with 1 mil of ammonia water; the liquid acquires an emerald-green color.

When the salt is heated with potassium bisulphate the odor of acreolein is given off.

An aqueous solution of 0.1 Gm. of the salt in 10 mils of distilled water, made with the aid of acetic acid, does not produce a precipitate on the addition of ammonium oxalate T.S. (calcium).

Dissolve 0.1 Gm. of the salt in 10 mils of diluted hydrochloric acid; the solution does not become more than faintly turbid upon the addition of a few drops of barium chloride T.S. (sulphate).

Dissolve 0.1 Gm. of the salt in 10 mils of diluted nitric acid; the solution is not rendered more than faintly turbid on the addition of silver nitrate T.S. (chloride).

Add a slight excess of ammonia water to a saturated aqueous solution of the salt, and filter; the clear filtrate does not show more than a slight turbidity with magnesia mixture T.S. (phosphate).

Mix about 2.5 Gm. of the salt in a separatory funnel with 15 mils of distilled water, add 5 mils of ammonia water,

N. F. IV

(QUinine Glycerophosphate)

shake with three successive portions of 25, 15 and 10/mils of chloroform, respectively, and evaporate the chloroform solutions to dryness/on a water bath. Dissolve 1.5 Gm. of this dry residue in 25 mils of alcohol, add 50 mils of hot distilled water, neutralize the liquid with normal sulphuric acid V.S.,/using methyl red T.S. as indicator and evaporate the liquid to dryness on a water/bath. Powder the residue, mix it with 20 mils of distilled water and maintain the/ temperature of the mixture at 65° C., for thirty minutes, agitating frequently. Now/cool the mixture to 15° C., maurate it at this temperature for two hours with/occasional shaking, then filter it through a dry filter, of from 8 to 10 cm. in diameter,/into a dry test tube. Transfer 5 mils of this filtrate to a test tube and mix it gently/(without shaking) with 7 mils of ammonia water, which must contain not less than/10 per cent nor more than 10.2 per cent of NH_3, must have a temperature of 15° C./and be added at once. A clear liquid is produced (other cinchona alkaloids).

If the temperature during the maceration has been 16° C., add 7.5 mils of am-/monia; if 17° C., add 8 mils.

Average Dose -- Tonic, Metric 0.1 Gm. - Apothecaries 1½ grains. Anti-malarial, Metric 1 Gm. - Apothecaries 15 grains, daily.

Summary of U.S.P. and N.F. data of
Quinine Glycerophosphate

Since Quinine Glycerophosphate was official only in the National Formulary IV there is no need for making a summary of this salt.

U.S.P. IX p. 389

Sodii Glycerophosphas

Sodium Glycerophosphate

Sod. Glycerophos. - Sodium Glycerinophosphate

Hydrated Sodium Glycerophosphate containing not less than 68 per cent of the anhydrous salt [$Na_2C_3H_7PO_6$ or $C_3H_5(OH)_2PO_4Na_2$ =/216.10].

Sodium Glycerophosphate occurs as white, monoclinic plates or scales, or as/a white powder, having a saline taste; odorless.

It is very soluble in cold or hot water; nearly insoluble in alcohol.

An aqueous solution of the salt (1 in 20) is alkaline to litmus and to phenol-/phthalein T.S.

When strongly heated the salt is decomposed, evolving inflammable vapors,/and at a red heat is converted into sodium pyrophosphate.

Dissolve 1 Gm. of Sodium Glycerophosphate in 10 mils of distilled water and/add 3 drops of phenolphthalein T.S.; the red color produced is discharged by/the addition of 1.5 mils of tenth-normal sulphuric acid V.S. (free alkali).

An aqueous solution of the salt does not respond to the Test for heavy/metals (see Part II, Test No. 3).

U.S.P. IX

(Sodium Glycerophosphate)

Add an equal volume of cold ammonium molybdate T.S. to 10 mils of an/aqueous solution of the salt (1 in 20); no precipitate is formed within one hour/(phosphates). On heating this mixture a yellow precipitate is formed.

Triturate 1 Gm. of the salt with 20 mils of dehydrated alcohol, filter the/mixture, evaporate the filtrate on a water bath and dry the residue for one/hour at a temperature not exceeding 70° C.; the weight of this residue does not/ exceed 0.01 Gm. (alcohol-soluble impurities).

Assay -- Dissolve about 3 Gm. of the salt, accurately weighed, in 30 mils of/distilled water and titrate with half-normal hydrochloric acid V.S., using methyl/orange T.S. as indicator. It shows not less than 68 per cent of $Na_2C_3H_7PO_6$.

Each mil of half-normal hydrochloric acid V.S. used corresponds to/0.10805 Gm. of $Na_2C_3H_7PO_6$. Each gramme of Sodium Glycerophosphate/corresponds to not less than 6.29 mils of half-normal hydrochloric acid V.S.

Average Dose -- Metric, 0.25 Gm. - Apothecaries, 4 grains.

Sodii Glycerophosphas

Sodium Glycerophosphate

(U.S.P. IX)

Sod. Glycerophos. Sodium Glycerinophosphate

Hydrated Sodium Glycerophosphate containing not less than 68 per cent of the anhydrous salt ($Na_2C_3H_7PO_6$ or $C_3H_5(OH)_2PO_4Na_2$ = 216.11).

Description and physical properties.

Sodium Glycerophosphate occurs as white, monoclinic plates or scales, or as a white powder, having a saline taste; odorless.

It is very soluble in cold or hot water; nearly insoluble in alcohol.

Tests for identity.

An aqueous solution of the salt (1 in 20) is alkaline to litmus and to phenolphthalein T.S.

When strongly heated the salt is decomposed, evolving inflammable vapors, and at a red heat is converted into sodium pyrophosphate.

N. F. V

(Sodium Glycerophosphate)

Tests for purity.

Dissolve 1 Gm. of Sodium Glycerophosphate in 10 cc. of distilled/water and add 3 drops of phenolphthalein T.S.; the red color produced is dis-/charged by the addition of 1.5 cc. of tenth-normal sulfuric acid (free alkali).

An aqueous solution of the salt does not respond to the Test for heavy metals/(see page 418).

Add an equal volume of cold ammonium molybdate T.S. to 10 cc. of an aque-/ous solution of the salt (1 in 20); no precipitate is formed within one hour/(phosphates). On heating this mixture a yellow precipitate is formed.

Triturate 1 Gm. of the salt with 20 cc. of dehydrated alcohol, filter the mix-/ture, evaporate the filtrate on a water bath, and dry the residue for one hour at a/temperature not exceeding 70° C.; the weight of this residue does not exceed/0.01 Gm. (alcohol-soluble impurities).

Assay. -- Dissolve about 3 Gm. of the salt, accurately weighed, in 30 cc. of distilled/water, and titrate with half-normal hydrochloric acid, using methyl orange T.S./as indicator.

Each cc. of half-normal hydrochloric acid used corresponds to 0.10805 Gm./of $Na_2C_3H_7PO_6$. Each Gm. of Sodium

N. F. V.

(Sodium Glycerophosphate)

Glycerophosphate corresponds to not/less than 6.29 cc. of half-normal hydrochloric acid.

Preparations: Elixir Calcii et Sodii Glycerophosphatum, Elixir Glycerophospha-/tum Compositum, Elixir Terpini Hydrastis et Creosoti Compositum.

Average Dose: Metric, 0. 25 Gm. - Apothecaries, 4 grains.

N. F. VI p. 329

Sodii Glycerophosphas

Sodium Glycerophosphate

Sod. Glycerophos.

Sodium Glycerophosphate contains not less than 66 per cent and /not more than 74 per cent of the anhydrous salt, $Na_2C_3H_5(OH)_2PO_4$ (216.06).

Description and physical properties.

Sodium Glycerophosphate occurs in white, monoclinic plates or scales, or as a /white powder. It is odorless, and has a saline taste.

One Gm. of the salt is soluble in about 1.5 cc. of water at 25° C. It is very solu-/ble in hot water, but nearly insoluble in alcohol.

Tests for identity and purity.

An aqueous solution of Sodium Glycerophosphate (1 in 20) is alkaline to litmus/paper and to phenolphthalein T.S., and responds to the tests for sodium and for/glycerophosphate.

When strongly heated, the salt is decomposed, evolving inflammable vapors,/and at a red heat is converted into sodium pyrophosphate.

Dissolve 1 Gm. of the salt in 10 cc. of distilled water, and add 3 drops of phenol-/phthalein T.S.: the red color produced is discharged by the addition of not more/than 1.5 cc. of tenth-normal sulfuric acid (free alkali).

Add an equal volume of cold ammonium molybdate T.S. to 10 cc. of an aqueous/solution of the salt (1 in 20); no precipitate is formed on standing one hour at/20° to 25° C. (phosphate).

Triturate 1 Gm. of the salt with 20 cc. of dehydrate alcohol, filter the mixture,/evaporate the filtrate on a water bath, and dry the residue for one hour at a tem-/perature not exceeding 70° C.: the weight of this residue does not exceed 0.01 Gm. /(alcohol-soluble impurities).

The salt meets the requirements of the test for arsenic and the test for heavy/metals.

Assay.

Dissolve about 3 Gm. of Sodium Glycerophosphate, accurately weighed, in/30 cc. of distilled water, and titrate with half-normal hydrochloric acid, using methyl/ orange T.S. as the indicator.

Each cc. of half-normal hydrochloric acid is equivalent to 0.10803 Gm. of/$Na_2C_3H_5(OH)_2PO_4$.

Storage.

Keep the salt in well-closed containers.

Preparations: Elixir Calcii et Sodii Glycerophosphatum, Elixir Glycerophosphatum/Compositum.

Average Dose: Metric, 0.25 Gm. - Apothecaries, 4 grains.

Summary of U.S.P. and N.F. data of
Sodium Glycerophosphate

When Official:

U.S.P. IX; N.F. V, VI.

Official Latin Title:

Sodii Glycerophosphas.

U.S.P. IX; N.F. V, VI.

Official English Title:

Sodium Glycerophosphate

U.S.P. IX; N.F. V, VI.

Official Abbreviation:

Sod. Glycerophos.

U.S.P. IX; N.F. V? VI.

Official Synonym:

Sodium Glycerinophosphate

U.S.P. IX; N.F. V.

Official Description:

Hydrated Sodium Glycerophosphate containing not less than 68 per cent of the anhydrous salt [$Na_2C_3H_7PO_6$ or $C_3H_5(OH)_2PO_4Na_2$ = 216.10].

U.S.P. IX; N.F. V.

Sodium Glycerophosphate contains not less than 68 per cent and not more than 74 of the anhydrous salt $Na_2C_3H_5(OH)_2PO_4$ (216.06).

N. F. VI.

Official Preparations:

Elixir Calcii et Sodii Glycerophosphatum, Elixir Glycerophosphatum Compositum, Elixir Terpini Hydrastis et Creosoti Compositum.

N. F. V.

Elixir Calcii et Sodii Glycerophosphatum, Elixir Glycerophosphatum Compositum.

N. F. VI.

Official Dose:

Metric, 0. 25 Gm. - Apothecaries, 4 grains.

U.S.P. IX; N.F. V, VI.

N. F. IV S. p. 344

Strychninae Glycerophosphas

Strychnine Glycerophosphate

Strych. Glycerophos. Strychnine Glycerinophosphate

The glycerophosphate [$(C_{21}H_{22}O_2N_2)_2PO_4H_2(C_3H_7O_2) + 6\ H_2O$ =/948.60] of the alkaloid strychnine. Preserve it in well-stoppered bottles.

Strychnine Glycerophosphate occurs in white, rhombic crystals or as a white pow-/der; odorless; having at first a faint, sweet taste, afterward becoming intensely bitter.

One gramme dissolves in about 350 mils of water, the solution being neutral or/slightly alkaline to litmus; also in about 310 mils of alcohol; slightly soluble in/chloroform, and very slightly soluble in ether.

On incinerating 0.2 Gm. of the salt it yields no weighable residue.

The addition of sulphuric acid to the salt produces no color, or at most only a/slight yellowish coloration, but on subsequently adding a fragment of potassium/dichromate a deep blue color is obtained, which changes to deep violet, then to/purplish-red, cherry-red and finally to orange or yellow.

Add ammonia water in slight excess to a saturated aqueous solution of the salt; a/white precipitate is formed which is readily soluble in chloroform.

A saturated aqueous solution of the salt acidulated with diluted nitric acid, is not rendered more than faintly turbid on the addition of silver nitrate T.S. (chloride).

A saturated aqueous solution of the salt, acidulated with hydrochloric acid, shows not more than a slight turbidity on the addition of barium chloride T.S. (sulphate).

Add a slight excess of ammonia water to anaaqueous solution of the salt, and filter the mixture; the filtrate shows not more than a slight turbidity with magnesia mixture T.S. (phosphate).

Average Dose: Metric, 0.0015 Gm. - Apothecaries, 1/40 grain.

Summary of U.S.P. and N.F. data of
Strychnine Glycerophosphate

Since Strychnine Glycerophosphate was official only in the National Formulary IV there is no need for making a summary of this salt.

Glycerophosphates Official in the United States Pharmacopoeias

Glycerophosphate	1820	'30$_A$	'30$_B$	'40	'50	'60	'70	'80	'90	1900	'10	'20	'30
Calcium											+	+	
Sodium											+		

Glycerophosphates Official in the National Formuleries

Glycerophosphate	1888	'96	1906	'16	'26	'36
Calcium						+
Ferric				+	+	+
Manganese				+	+	+
Quinine				+		
Sodium					+	+
Strychnine				+		

Experimental

The statements of the solubilities of official substances are given primarily for the information of physicians and pharmacists for use in the preparation and dispensing of medicines. They should not always be regarded as exact physical constants upon which the identification or the determination of the purity of a substance may be based. Frequently, the official standards are descriptive terms to indicate the approximately solubility of substances, viz: (1) "Very soluble", 1 part of the substance is soluble in less than 1 part of the solvent; (2) "freely soluble", 1 part of the substance is soluble in from 1 to 10 parts of solvent; (3) "soluble", 1 part of the substance is soluble in from 10 to 30 parts of solvent, (4) "sparingly soluble", 1 part of the substance is soluble in from 30 to 100 parts of solvent; (5) "slightly soluble", 1 part of the substance is soluble in from 100 to 1000 parts of solvent; (6) "very slightly soluble", 1 part of substance is soluble in from 1,000 to 10,000 parts of solvent; and (7) "practically insoluble", more than 10,000 parts of solvent are required to dissolve 1 part of substance.[1]

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[1] (Committee), The Pharmacopoeia of The United States of America, XI, p. 466.

There are nine possible classes of solutions, namely:[2] (1) a gas in a gas; (2) a gas in a liquid; (3) a gas in a solid; (4) a liquid in a gas; (5) a liquid in a liquid; (6) a liquid in a solid; (7) a solid in a gas; (8) a solid in a liquid; and (9) a solid in a solid. Although examples of all of these different types of solutions are known, the only classes of pharmaceutical importance are solutions of gases in liquids, of liquids in liquids, and of solids in liquids.

The official determination of the solubility of gases in water, such as HCl and NH_3, is generally effected by chemical titration methods,[3] while the solubility of liquids in liquids and of solids in liquids is determined by physical methods.[4]

Numerous factors affect the rate and the extent of the solubility of a substance in a given solvent as follows:[5]

1. The solubility of most of the official substances is increased by a rise in temperature at which solution is effected.[6] There are numerous exceptions to the generality, however; e.g., gases, calcium salts, and ether are less soluble in hot than in cold water.[7] Since the solubility of

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[2] Jenkins, G. and Du Mez, A., Quantitative Pharmaceutical Chemistry (1931), p. 173.
[3] *Ibid.*, p. 173.
[4] *Ibid.*, p. 173.
[5] *Ibid.*, p. 173.
[6] *Ibid.*, p. 174.
[7] *Ibid.*, p. 174.

substances varies markedly with slight changes in temperature, it is very important that a constant temperature be accurately maintained throughout a solubility determination.[8]

2. Substances in a fine state of division dissolve more rapidly than large crystals or particles because the total surface area exposed to the action of the solvent is much greater when the substance is powdered.[9]

3. The purity of the substance and of the solvent must be assured in all solubility determinations, since slight amounts of impurity in either may cause considerable variation in the results.[10]

4. The position of the solute in the solvent affects the rate of solution. If the solute is allowed to lie on the bottom of the vessel, it becomes surrounded by a layer of concentrated solution which prevents the access of fresh portions of the solvent to the surface of the solute.[11]

The determination of the solubility of a solid in a liquid necessitates the preparation of a saaturated solution.[12] The production of saturated solution of this type was carried out as follows. The apparatus consisted of four hard-glass test tubes of medium size, one for each of

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[8] Jenkins, G. and Du Mez, A., Quantitative Pharmaceutical Chemistry (1931), p. 174.
[9] *Ibid.*, p. 174.
[10] *Ibid.*, p. 174.
[11] *Ibid.*, p. 174.
[12] *Ibid.*, p. 174.

the present official salts, the calcium, ferric, manganese and sodium glycerophosphates. Into these tubes the solvents and solutes were placed and stirred vigorously for three hours by means of a motor-driven glass screw stirrer. The stem of the stirrers passed through a glass tube, inserted through a rubber stopper by which the solubility tubes were closed to prevent evaporation. The glass tubes selected were of such a size that the stem of the stirrers just passed through, the area of contacts were well lubricated with petrolatum. When solubility determinations were made, the required materials were placed in the tubes. The solubility tubes were immersed in the thermostat bath, to maintain a constant temperature throughout the mixture, since as mentioned before, the solubility varies appreciably with a slight change in temperature. The temperature in the thermostat was regulated so that there was no more variation than 0.1° C. above or below 25° C., during the determination. After running the stated amount of time the stirrers were stopped and removed from the tubes, and the latter stoppered securely, allowing the undissolved crystals to settle. About 5 cc. of the clear solution was removed from the solubility tubes by means of a pipette, and accurately weighed. This portion of the solution was evaporated to dryness in an electric oven at 110° C to constant weight, and the residue weighed.

The weight of the residue, subtracted from the weight of the solution analyzed, gives the weight of the solvent in which the substance was dissolved.

The stirrers were attached again and allowed the stirring to continue for about one hour. Again a 5 cc. portion of the solution was removed and accurately weighed again, and determined the weight of the residue as before.

When this result agreed with the former determinations, it showed that saturation of the solution was complete.

If a 6.0533 Gm. portion of a saturated ferric glycerophosphate solution yielded 2.1629 Gm. of ferric glycerophosphate upon drying to constant weight, the 2.1629 Gm. of ferric glycerophosphate was dissolved in 6.0533 - 2.1629 = 3.8904 Gm. of water. The amount of ferric glycerophosphate soluble in 100 Gm. of water at 25° C. was therefore calculated from the simple proportion.

$$2.1629 : 3.8904 :: X : 100$$

$$x = 55.8$$

in which x = the number of grams of ferric glycerophosphate soluble in 100 Gm. of water at 25° C.

The solubility of the salts were first determined using water as a solvent in order that the operator could acquire some technique before attempting the solvents intended for testing the solubility of the official glycerophosphates.

Data

Using Water as a solvent:

<u>Calcium Glycerophosphate</u>:	I	II
Weight of saturated Calcium Glycerophosphate solution	5.4173 Gm.	5.8170 Gm.
Weight of residue after evaporation	0.1252 Gm.	0.1336 Gm.
Weight of Water salt dissolved in	5.2921 Gm.	5.6834 Gm.
One Gm. of Calcium Glycerophosphate soluble in	42.2 cc.	48.5 cc.

Note:

The N.F. VI requires 1 Gm. to be soluble in 50 cc. of water. The reason for error in this test is most likely due to the fault of the operator, who isn't perfect with the technique of running solubility tests as yet.

<u>Ferric Glycerophosphate</u>	I	II
Weight of saturated Ferric Glycerophosphate solution	6.0533 Gm.	6.4300 Gm.
Weight of residue after evaporation	2.1629 Gm.	2.1433 Gm.
Weight of Water salt dissolved in	3.8904 Gm.	4.2867 Gm.
One Gm. of Ferric Glycerophosphate soluble in	1.79 cc.	1.98 cc.

Note:

The N.F. VI standard for this salt is 1 Gm. soluble in about 2 cc. of water. The solubility of this salt checks with the N.F. standard.

Manganese Glycerophosphate	Samples I	 II
Weight of saturated Manganese Glycerophosphate solution	4.9603 Gm.	6.1703 Gm.
Weight of residue after evaporation	0.0475 Gm.	0.0610 Gm.
Weight of Water salt dissolved in	4.9128 Gm.	6.1093 Gm.
One Gm. of Manganese Glycerophosphate soluble in	103.42 cc.	100.32 cc.

Note:

The N.F. VI standard for manganese glycerophosphate is, that it should be slightly soluble in water. The N. F. means by "slightly soluble" in water, that 1 part of solute is soluble in 100-1,000 parts solvent. This salt then agrees with the N.F. standard.

Sodium Glycerophosphate	Samples I	 II
Weight of saturated Sodium Glycerophosphate solution	6.6891 Gm.	6.7202 Gm.
Weight of residue after evaporation	3.0405 Gm.	2.8734 Gm.
Weight of Water salt dissolved in	3.6486 Gm.	3.8468 Gm.
One Gm. of Sodium Glycerophosphate soluble in	1.2 cc.	1.38 cc.

Note:

The N.F. VI standard for sodium glycerophosphate is 1 Gm. soluble in about 1.5 cc. of water. This "about" again allows the sodium salt tested to agree with the N. F. standard.

Using Ethylene Dichloride as a solvent:

Ethylene Dichloride is a colorless liquid, with a chloroform like odor.[1] It is an exceedingly good solvent for oils, fat, waxes, gums and resins.[2] While ethylene dichloride is not a solvent for nitrocellulose or cellulose acetate, it readily dissolves both the cellulose ester when mixed with alcohol.[3]

<u>Calcium Glycerophosphate</u>	Samples I	 II
Weight of saturated Calcium Glycerophosphate solution	5.9471 Gm.	6.1393 Gm.
Weight of residue after evaporation	0.0011 Gm.	0.0011 Gm.
Weight of Ethylene Dichloride salt dissolved in	5.9460 Gm.	6.1382 Gm.
One Gm. of Calcium Glycerophosphate soluble in	5,405.45 cc.	5,403.45 cc.

Average solubility of 1 Gm. = 5,404.5 cc.

<u>Ferric Glycerophosphate</u>	Samples I	 II
Weight of saturated Ferric Glycerophosphate solution	6.1148 Gm.	6.2083 Gm.
Weight of residue after evaporation	0.0005 Gm.	0.0010 Gm.
Weight of Ethylene Dichloride salt dissolved in	6.1143 Gm.	6.2073 Gm.
One Gm. of Ferric Glycerophosphate soluble in	12,227.6 cc.	6,207.3 cc.

Average solubility of 1 Gm. = 9,217.45 cc.

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[1] Carbide and Carbon Chemicals Corporation, A Summary of the Products of the Carbide and Carbon Chemical Corporation, 5, March 15, 1933, p. 24.

[2] <u>Ibid</u>., p. 24.

[3] <u>Ibid</u>., p. 24.

Manganese Glycerophosphate

	Samples	
	I	II
Weight of saturated Manganese Glycerophosphate solution	5.9187 Gm.	5.9734 Gm.
Weight of residue after evaporation	0.0006 Gm.	0.0009 Gm.
Weight of Ethylene Dichloride salt dissolved in	5.9181 Gm.	5.9725 Gm.
One Gm. of Manganese Glycerophosphate soluble in	9,863.5 cc.	6,636.11 cc.

Average solubility of 1 Gm. = 8,249.80 cc.

Sodium Glycerophosphate

	Samples	
	I	II
Weight of saturated Sodium Glycerophosphate solution	6,0064 Gm.	5.8348 Gm.
Weight of residue after evaporation	0.0000 Gm.	0.0003 Gm.
Weight of Ethylene Dichloride salt dissolved in	6.0064 Gm.	5.8345 Gm.
One Gm. of Sodium Glycerophosphate soluble in	Insoluble for amount of sample taken	19,445. cc

Conclusion: Ethylene Dichloride is a very poor solvent for the official glycerophosphates, as the test indicated.

Using Morpholine as a solvent:

Morpholine is a cyclic ether of amine,[4] $NH(C_2H_4)_2O$. It is a colorless, mobile liquid of a penetrating ammoniacal, but not unpleasant, odor.[5] One of the most prominent characteristics of morpholine is high and varied solvent power.[6] It is a good solvent for dyes and has been recommended as a leveling agent in dye baths, vat printing pastes, etc.,[7] and as a general textile assistant for scouring, stripping, and boiling off.[8] It has been suggested as a solvent for certain dyestuffs, to be volatilized during steaming, and also as a solvent for naphthol-type developers for the ingrain dyeing of silks and woolens.[9] It has been found useful in removing the color and otherwise purifying gasolines and lubricating oils.[10]

Calcium Glycerophosphate	Samples I	 II
Weight of saturated Calcium Glycerophosphate solution	5.0782 Gm.	6.2056 Gm.
Weight of residue after evaporation	0.2808 Gm.	0.3408 Gm.
Weight of Morpholine, salt dissolved in	4.7974 Gm.	5.8648 Gm.
One Gm. of Calcium Glycerophosphate soluble in	17.09 cc.	17.2 cc.

Average solubility of 1 Gm. = 17.14 cc.

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[4] Wilson, A. L., Industrial and Engineering Chemistry, 27, p. 870.
[5] Ibid., p. 870.
[6] Ibid., p. 870.
[7] Ibid., p. 870.
[8] Ibid., p. 870.
[9] Ibid., p. 870.
[10] Ibid., p. 870.

Ferric Glycerophosphate

	Samples I	Samples II
Weight of saturated Ferric Glycerophosphate solution	4.3981 Gm.	4.5073 Gm.
Weight of residue after evaporation	0.240 Gm.	0.2490 Gm.
Weight of Morpholine, salt dissolved in	4.1581 Gm.	4.2583 Gm.
One Gm. of Ferric Glycerophosphate soluble in	17.2 cc.	17.1 cc.

Average solubility of 1 Gm. = 17.15 cc.

Manganese Glycerophosphate

	Samples I	Samples II
Weight of saturated Manganese Glycerophosphate solution	5.0662 Gm.	4.2394 Gm.
Weight of residue after evaporation	0.2911 Gm.	0.2408 Gm.
Weight of Morpholine, salt dissolved in	4.7751 Gm.	3.9986 Gm.
One Gm. of Manganese Glycerophosphate soluble in	16.4 cc.	16.6 cc.

Average solubility of 1 Gm. = 16.5 cc.

Sodium Glycerophosphate

	Samples I	Samples II
Weight of saturated Sodium Glycerophosphate solution	5.0896 Gm.	5.6197 Gm.
Weight of residue after evaporation	0.2249 Gm.	0.2459 Gm.
Weight of Morpholine, salt dissolved in	4.8647 Gm.	5.3648 Gm.
One Gm. of Sodium Glycerophosphate soluble in	21.6 cc.	21.9 cc.

Conclusion:

Morpholine is a fairly good solvent for the official glycerophosphates, dissolving them all in a fairly even range.

Note: The manganese salt colored its solution pink and on standing gradually turned dark brown. Evidently decomposition had taken place.

It required 5 days before the salts settled out of the stirred solutions. The sodium salt settled out in 3 days, the calcium and manganese salt in 4 1/2 days and the iron salt 5 days. The salts appeared to be in a sort of colloidal suspension.

All the salts after drying to constant weight turned dark brown in color. They evidently all decomposed.

<u>Using Carbitol</u> as a solvent:

Carbitol is the monolthyl ether of diethylene glycol. It is a colorless, slightly hygroscopic liquid of mild and odor.[11] It is an excellent solvent for nitrocellulose and resins.[12] Its low rate of evaporation have brought about the use of Carbitol as a solvent for nitrocellulose in lacquers.[13] In the printing and dyeing of textiles the use of Carbitol as a solvent for dyestuff results in better penetration as well as deeper and brighter shades.[14]

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[11] Carbide and Carbon Chemicals Corp., A Summary of the Products of the Carbide and Carbon Chemical Corporation, 5, March 15, 1933, p. 15.
[12] <u>Ibid</u>., p. 16.
[13] <u>Ibid</u>., p. 16.
[14] <u>Ibid</u>., p. 16.

Calcium Glycerophosphate

	Samples	
	I	II
Weight of saturated Calcium Glycerophosphate solution	4.8914 Gm.	4.8856 Gm.
Weight of residue after evaporation	0.3050 Gm.	0.3053 Gm.
Weight of Carbutanol, salt dissolved in	4.5864 Gm.	4.5803 Gm.
One Gm. of Calcium Glycerophosphate soluble in	15.05 cc.	15.03 cc.

Average solubility of 1 Gm. = 15.04 cc.

Ferric Glycerophosphate

	Samples	
	I	II
Weight of saturated Ferric Glycerophosphate solution	5.0631 Gm.	5.1136 Gm.
Weight of residue after evaporation	0.3233 Gm.	0.3468 Gm.
Weight of Carbutanol, salt dissolved in	4.7398 Gm.	4.7668 Gm.
One Gm. of Ferric Glycerop phosphate soluble in	14.6 cc.	14.7 cc.

Average solubility of 1 Gm. = 14.65 cc.

Magnesium Glycerophosphate

	Samples	
	I	II
Weight of saturated Magnesium Glycerophosphate solution	5.1572 Gm.	5.2428 Gm.
Weight of residue after evaporation	0.2700 Gm.	0.2743 Gm.
Weight of Carbutanol, salt dissolved in	4.8872 Gm.	4.9685 Gm.
One Gm. of Manganese Glycerophosphate soluble in	18.1 cc.	18.4 cc

Average solubility of 1 Gm. = 18.25 cc.

Sodium Glycerophosphate	Samples I	Samples II
Weight of saturated Sodium Glycerophosphate solution	5.1688 Gm.	5.6404 Gm.
Weight of residue after evaporation	0.2333 Gm.	0.2538 Gm.
Weight of Carbutanol, salt dissolved in	4.9355 Gm.	5.3866 Gm.
One Gm. of Sodium Glycerophosphate soluble in	21.1 cc.	21.2 cc.

Average solubility of 1 Gm. = 21.15 cc.

Conclusion:

As the tests indicate the solubilities of the Glycerophosphates in Carbutanol is about the same as with Morpholine.

Using Dioxon as solvent:

Dioxan (diethylene oxide) is a colorless liquid of a faint, pleasant odor, miscible in all proportions with water and the usual organic solvents.[15] It is an excellent solvent for cellulose acetate, ethyl cellulose, benzyl cellulose and for a wide variety of resins including both the alcohol-and oil-soluble type.[16] Practically all evegetable and mineral oils are soluble in all proportions in Dioxan.[17] Several of the waxes such as beeswax, carnauba, montan and paraffin are only slightly soluble in the cold but are soluble when heated.[18] In addition Dioxan is a very good solvent for many orgahic and inorganic compounds.[19]

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[15] Carbide and Carbon Chemicals Corporation, A Summary of the Products of the Carbide and Carbon Chemical Corporation, 5, March 15, 1933, p. 17.

[16] Ibid., p. 17.

[17] Ibid., p. 18.

[18] Ibid., p. 18.

[19] Ibid., p. 18.

Calcium Glycerophosphate

	Samples	
	I	II
Weight of saturated Calcium Glycerophosphate solution	5.6807 Gm.	6.1166 Gm.
Weight of residue after evaporation	0.1048 Gm.	0.1126 Gm.
Weight of Dioxan, salt dissolved in	5.5759 Gm.	6.0036 Gm.
One Gm. of Calcium Glycerophosphate soluble in	53.2 cc.	53.2 cc.

Average solubility of 1 Gm. = 53.2 cc.

Ferric Glycerophosphate

	Samples	
	I	II
Weight of saturated Ferric Glycerophosphate solution	5.1668 Gm.	5.8283 Gm.
Weight of residue after evaporation	0.2214 Gm.	0.1429 Gm.
Weight of Dioxan, salt dissolved in	5.1454 Gm.	5.5854 Gm.
One Gm. of Ferric Glycerophosphate soluble in	23.2 cc.	49.8 cc.

Average solubility of 1 Gm. = 36.5 cc.

Magnesium Glycerophosphate

	Samples	
	I	II
Weight of saturated Magnesium Glycerophosphate solution	5.0583 Gm.	5.6498 Gm.
Weight of residue after evaporation	0.1002 Gm.	0.1126 Gm.
Weight of Dioxan, salt dissolved in	4.9581 Gm.	5.5372 Gm.
One Gm. of Magnesium Glycerophosphate soluble in	49.4 cc.	49.1 cc.

Average solubility of 1 Gm. = 49.25 cc.

Sodium Glycerophosphate

	Samples	
	I	II
Weight of saturated Sodium Glycerophosphate solution	4.7874 Gm.	5.2440 Gm.
Weight of residue after evaporation	0.1003 Gm.	0.1098 Gm.
Weight of Dioxan, salt dissolved in	4.6871 Gm.	5.1342 Gm.
One Gm. of Sodium Glycerophosphate soluble in	46.7 cc.	47.6 cc.

Average solubility of 1 Gm. = 47.15 cc.

Note:

The reason for the large difference in the two solubility samples of Ferric Glycerophosphate is due to the fault of the experimenter. The saturated solution was shaken while taking the saturated solution and a small amount of the undissolved salt was carried over in the pipette, so that on evaporation a larger amount was deposited then should have been. There wasn't time to check the results of the second sample, but it seems to be in accord with the rest of the salts, so the operator left it be.

Conclusion:

The solubility of all the official glycerophosphates in Dioxan seem to agree fairly well, but they are not as soluble as in the case when Morpholine or Carbutanol was used.

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Pelouze, J. 1845

Recherches sur la glycérine

Comptes rendus, 21, p. 718 (Journ. d. Pharm. et d. Chim., 42, p. 166; Ibid., 144, p. 433;

Gives the analysis of the composition of glycerine. Then the preparation of glycerophosphoric acid from glycerine is mentioned and continues to say that the calcium salt and barium was formed from the glycerophosphoric acid. Continues with several physical properties of the salts and an analysis to determine the empirical formula. Concludes that the lead salt of glycerophosphoric acid was also prepared. A few of its physical properties determined but not an analysis as to the empirical formula was given.

Gobley, P. 1846

Recherches chimiques sur le jaune d'oeuf

Journ. d. Pharm. et d. Chim. [3], 9, p. 161 (Journ. Am. Pharm. Assoc., 1, p. 749;

Gives a method for the preparation of glycerophosphoric acid.

Portes, L. & Prunier, G. 1894

Du phosphoglycérate de chaux de d'un moyen pratique de le préparer

Journ. d. Pharm. et d. Chim., 138, p. 393. (Jour. d. Pharm. et d. Chim., 144, p. 433; Proc. Am. Pharm. Assoc., 43, p. 686;

Gives a new method for the preparation of calcium glycerophosphate over the method used by Pelouze which was a very expensive one. A new method was sought because the salt was being used very much after the salts of the acid were used in 1894 by Dr. Albert Robbin in the hospitals of Paris and elsewhere, in the administration of phosphorous to the human system. It being reasoned that the phosphorous in the glycerophosphate exists in the same state as in the nerve tissue of the body, and therefore a natural form of administering phosphorous.

Petit, A. & Polonovski, M. 1894

Essai des glycérophosphates employés en thérapeutique

Journ. d. Pharm. et d. Chim., 139, p. 193 (Journ. d. Pharm. de d. Chim., 144, p. 433; Proc. Am. Pharm. Assoc., 43, p. 686;

Gives the general properties of the glycerophosphates, a means for calculating the dose according to the individual glycerophosphate.

Then gives a table of the properties and reactions for the iron, calcium, strontium, magnesium, lithium, sodium and potassium glycerophosphates.

Delage, G. & Gaillard, M. 1896

(Preparation of the Glycerophosphate of Lime)

Nouv. Reméd., 8, p. 217 (Yrbk. Brit. Pharm. Conf. 33, p. 27;

(Describes a more rapid method of preparing calcium glycerophosphate than Porter and Prunier's method, which takes several days to complete. This method can be finished in a few hours.)

Original reference not available.

(Committee) 1897

Chinium glycerino-phosphoricum

Zeitschr. des oesterr. Apoth. Ver., 35, p. 60. (Yrbk. Brit. Pharm. Conf., 34, p. 233;

Under the heading of Neue Arzneimettel, occurs the mention of quinine glycerophosphate, giving the following information of it: The empirical formula occurs as colorless needle-shaped crystals, which are readily soluble in hot water and alcohol, and contain 68 per cent of quinine. It is employed in malaria, neuralgia, and during convalescence after fevers. It is administered in the form of pills.

Adrian, H. and Trillot, A. 1897

Sur le phosphoglycérate de chaux

Jour. d. Pharm. et d. Chim., 144, p. 433 and 481. (Am. Journ. Pharm., 70, p. 165; Yrbk. Brit. Pharm. Conf., 35, p. 36;

Gives a review of the work done by Petit and Polonovski in 1894 in preparing the calcium salt of glycerophosphoric acid. Then continues with the result of assays of several commercial salts as to their per cent of calcium and phosphoric acid; the solubility of the calcium salt in alkali, netsal or acid solutions; analysis of the residue; the action of heat on the salt; and concludes with a method of preparing a pure calcium glycerophosphate.

Astruc, A. 1898

Contribution á l'étude des glycérophosphates

Journ. de Pharm. et d. Chim., 146, p. 5. (Yrbk. Brit. Pharm. Conf., 35, p. 105; Pharm. Journ., 60, p. 163.

Gives a rapid method for determining the amount of phosphoric acid present in the glycerophosphates.

Adrian, H. & Trillat, A. 1898

(Organic Glycerophosphates)

Bull. de la Soc. Chim. de Paris 19, p. 684 (Pharm. Journ. 61, p. 241;

(The authors have prepared several of the organic glycerophosphates, including those of cocaine, quinine, and phenylhydrozine. They find that these compounds are better obtained by the interaction of an acid salt with the organic base than by using glycerophosphoric acid itself. Their paper gives some of the properties of these important substances which are now engaging considerable attention among the medical profession.)

Original reference not available.

Fallieres, E. 1898

Sur les glycérophosphates de quinine

Journ. d. Pharm. et d. Chemie., 146, p. 294. (Pharm. Journ., 60, p. 410;

There are two glycerophosphates of quinine, -- basic and neutral according to the author and he gives a method of how they may be obtained; and concludes that the basic salt is to be preferred for general use. Gives structural formula for basic and neutral salt.

Hoseason, J. H. 1900

Commercial Glycerophosphates

Pharm. Journ., 64, p. 419. (Yrbk. Brit. Pharm. Conf., 37, p. 31;

Gives a table of the results of an examination of a number of samples of glycerophosphates, among those examined were the sodium, potassium, calcium, iron and quinine salts.

Lumière, A., Lumière, L., & Perrin, F. 1901

Sur l'acide glycérophosphoreux et les glycérophosphites

Comptes rend., 133, p. 643. (Yrbk. Brit. Pharm. Conf., 39, p. 88;

Gives a new method of preparing glycerophosphorous acid, that by treating a slight excess of glycerin with phosphorous trichloride, keeping the mixture cool, and removing the hydrochloric acid from the mixture by means of moist silver oxide. Also states that free glycerophosphorous acid has not been isolated, since it tends to saponify on evaporating its solutions. Most of the salts are soluble in water. And concludes that the alkaline glycerophosphites are soluble in alcohol, those of barium and calcium insoluble.

Barthe, L. 1902

Le glycérophosphate de bismuth

L'Union Pharm., 43, p. 498. (Yrbk. Brit. Pharm. Conf., 40, p. 41;

Gives a method for the preparation of bismuth glycerophosphate.

Eigelburner, H. B. 1904

Calcium Glycerophosphate

Am. Journ. Pharm., 76, p. 212. (Proc. Am. Pharm. Assoc., 52, p. 901;

Gives a review on the discovery of the acid by Pelouze, and the method of manufacture as proposed by Portes and Prunier in 1894. The salts of the acid were introduced by Dr. Albert Robbin of Paris. Then gives the results of the assay suggested by Fresenius -- precipitating as the oxalate and weighing as the oxide. Concludes that the examination is not exhaustive, but is rapid, approximately accurate, and enables the pharmacist to arrive at comparative valuation between different samples of calcium glycerophosphate.

Reidel, J. D. 1905

Über die Prüfung der Glycerophosphates

Pharm. Ztg., 50, p. 166. (Proc. Am. Pharm. Assoc., 53, p. 790;

Gives a method for determining the absence of free phosphoric acid and free glycerin in the glycerophosphates.

Self, P.A.W. 1908

The Acid Glycerophosphates

Pharm. Journ., 80, p. 626. (Yrbk. Brit. Pharm. Conf., 45, p. 86;

Gives the general formula of the acid glycerophosphates, and the general methods for the preparation of the following acid glycerophosphate salts, Ba, Sr, Mg, Zn, Ca, Na, K, and Cu, and follows with their general properties; concludes with an analytical characterization of these acid salts.

Cohn, G. 1910

Die Veredlung der natürlichen Alkaloide

Pharm. Zentralh., 51, pp. 265, 289. (Yrbk. Brit. Pharm. Conf., 47, p. 9;

Gives a method for preparing neutral and acid quinine glycerophosphate.

Beringer, G. M. 1912

Report of Committee on Unofficial Standards

Journ. Am. Pharm., Assoc., 1, p. 255;

In the report of the Committee on Unofficial Standards of certain crude drugs and chemicals suggested for inclusion in the next revision of the National Formulary occurs the mention of Potassii Glycerophosphas.

Beringer, G. M. 1913

Report of Committee on Unofficial Standards

Journ. Am. Pharm. Assoc., 2, pp. 371 and 520;

In the report of the Committee on Unofficial Standards of certain crude drugs and chemicals suggested for inclusion in the next revision of the National Formulary occurs; Ferri Glycerophosphas, Mangani Glycerophosphas, Quinine Glycerophosphate, Sodii Glycesophosphate, and Strychninae Glycerophosphas.

Rogier, -- and Fiore, -- 1913

Étude sur les glycérophosphates cristallisés

Bull. Sci. Pharm. 20, p. 7, 72. (Yrbk. Brit. Pharm. Conf., 50, p. 197;

After reviewing the published literature of the subject it deals in detail with the following salts; Sodium Glycerophosphate, Calcium Glycerophosphate, Barium Glycerophosphate, Strantium Glycerophosphate, Quinine Glycerophosphate, Strychnine Glycerophosphate, Brucine Glycerophosphate, and two Copper glycerophosphates.

Engelhardt, H. 1913

Purity of Chemicals and Drugs

Journ. Am. Pharm. Assoc., 2, p. 163.

Gives the result of an analysis of Calcium Glycerophosphate.

Umney, J. C. and Bennett, C. T. 1914

The Composition of the Glycerophosphates of Commerce

Yrbk. Brit. Pharm. Conf., 51, p. 401.

Gives a report on the commercial products on the market, showing how far they comply with the descriptions given in British Pharmaceutical Codex. The salts examined were Calcium, Ferric, Magnesium, Potassium and Sodium Glycerophosphates.

Remington, J. P. 1914

Abstract of Proposed Changes with New Standards and Descriptions. United States Pharmacopoeia, Ninth Revision

Journ. Am. Pharm. Assoc., 3, pp. 1566, and 1575;
(Yrbk. Brit. Pharm. Conf., 52, p. 327;

Among the Proposed Changes with New Standards and Descriptions occurs the mention of Calcium Glycerophosphate and Sodium Glycerophosphate.

Du Bois, G. 1914

Commercial Glycerophosphates

Journ. Ind. and Eng. Chem., 6, p. 122. (Yrbk. Brit. Pharm. Conf., 51, p.132;

After discussing at length the structure and methods of formation of the various phosphoric esters of glycerin, the author deals with the following commercial glycerophosphates; calcium, sodium and potassium.

Umney, J.C. and Bennett, C.T. 1914

The Composition of the Glycerophosphates of Commerce

Pharm. Journ., 93, p. 134 (Am. Journ. Pharm., 86, p. 423;

Gives the composition of the following salts; the calcium, potassium, sodium, magnesium, and iron glycerophosphate.

Grimbert, L. and Bailly, O. 1915

Sur un procédé de diagnose des monoétheis glycérophosphoriques et sur la constitution du glycérophosphate de sodium cristallisé

Comptes rendus, 160, p. 207 (Yrbk. Brit. Pharm. Conf., 52, p. 174.

Gives a method for distinguishing between the two sodium salts of glycerophosphoric acid as prepared by Poulenc.

Hegland, J.M.A. 1916

Bereiding Van Glycerophosphas Natricus

Pharm. Weekblad, 53, p. 1645. (Yrbk. Am. Pharm. Assoc., 5, p. 357;

Gives a method for preparing sodium glycerophosphate.

Deschamps, A. 1916

L'action thérapeutique du magnesium et des sels de magnésie

Jour. d. Pharm. et d. Chem. [7], 14, p. 27. (Yrbk. Brit. Pharm. Conf. 43, p. 224;

Mg cacodylate and notably Mg glycerophosphate, have great therapeutic activity. They are specially valuable in the treatment of nervous cases and asthenia due to insufficient elimination of MgO.

Smith, C.E. 1916

Note on Testing Calcium Compounds

Am. Jour. Pharm., 88, p. 215.

States that the U.S.P. tests for calcium compounds is deficient, and for the detection of certain possible contaminations, such as might easily lead to serious results because of the false sense of security the official tests give. Also that the tests are not sufficient for differentiating calcium from other alkaline earth compounds. Suggest that the tests be made characteristic enough to distinguish it from everything else.

Couch, J. F. 1917

The Pharmacy of Calcium Glycerophosphate

Am. Jour. Pharm., 89, p. 243.

Gives an account of experiments of the behavior of calcium glycerophosphate in solution and the effect upon the salt of those substances commonly associated with it in pharmaceutical mixtures.

Éwe, G.E. 1920

Suggestions for Pharmacopoeial Revision

Journ. Am. Pharm. Assoc., 9, p. 419.

Under the Suggestions for Pharmcopoeial Revision occurs the mention of Sodium Glycerophosphate, it is recommended that the U.S.P. standard of not less than 68 per cent of anhydrous $Na_2C_3H_7PO_6$ is too low. A standard of not less than 95 per cent is suggested.

Dizius, J. L. 1921

The Determination of Small Quantities of Phosphate in Glycerophosphates

Pharm. Journ., 106, p. 478. (Am. Journ. Pharm., 93, p. 806.

Gives a tintometric method for the determination of minute quantities phosphate in the glycerophosphates.

Bailly, O. and Gaumé, J. 1925

Sur la composition et l'essai des glycérophosphates de calcium officinaux

Journ. d. pharm. et d. chim., S. 8, V. 1, p. 241.
(Yrbk. Am. Pharm. Assoc., 14, p. 365;

Gives the results of eight commercial samples of calcium glycerophosphate assayed according to the official method of The French Codex, and also the determination of their composition.

Maccone, G. 1927

Incomptabilità nelle soluzioni ipodermiche di glicerofasfato

Schweiz. Apoth. Zeit., 65, p. 350. (Yrbk. Am. Pharm. Assoc., 16-17, p. 106;

Discusses the incompatibilities of the glycerophosphates in the preparation of solutions for hypodermic use, and gives two methods for overcoming the incompatibilities.

Lambote, H. 1927

Glicerofasfato di calcio liquido

Boll. chim. farm., 66, p. 543. (Yrbk. Am. Pharm. Assoc., 16-17, p. 335.

Gives a method for the manufacture of a 50% solution of calcium glycerophosphate.

Kogan, G. 1928

Über Calcium glycerinophosphoricum solubile und einige Glyzerophosphate

Pharm. Zentr. 69, p. 49 (Quat. Journ. and Yrbk. Brit. Pharm. Conf., 1, p. 247;

Because the commercial glycerophosphates occur many times in commerce together with ctric acid to increase their solubility the quantitative figures for the content of salt and ash do not agree even though the qualitative reactions were in agreement, this author gives a method by which this may be overcome. He gives it for the Calcium, Iron, Sodium and Magnesium salts.

de Coquet, C. 1929

(Assay of Calcium Glycerophosphates and their Saccharides)

Bull. Soc. Pharm., Bordeaux, 67, p. 15. (Quat. Journ. and Yrbk. Brit. Pharm. Conf., 2, p. 416;

Gives the assays for the neutral Calcium -Glycerophosphate, the neutral Calcium -Glycerophosphate, the Calcium Acid Glycerophosphate, and the Calcium Glycerophosphate Saccharides, and concludes that these methods are simpler and quicker the official French Codex Method.

Ekkert, L. 1931

Breitrag zu den Reaktionen des Glyzerins und glyzerin phosphorsauren Kalziums

Pharm. Zentralkl., 72, p. 85. (Yrbk. Am. Pharm. Assoc., 20-21, p. 186.

Gives a quick color method for the determination of the presence of glycerin or calcium glycerophosphate.

Bennett, C. T. and Campbell, N. R. 1932

Note on Calcium Glycerophosphate

Pharm. Journ., 129, p. 253. (Yrbk. Am. Pharm. Assoc., 20-21, p. 591; Yrbk. Brit. Pharm. Conf., 5, p. 517;

Gives the following methods for analysis of the calcium salt: Determination of Calcium by Ignition; Titration of Precipitated Calcium Oxalate; Direct Titration; Terry's Titration Method.

Carpentier, A., and Bocquet, G. 1932

Sur l'a-glycérophosphate de sodium crystallisé

Compt. rendu., 194, p. 104. (Yrbk. Brit. Pharm. Conf., 5, p. 705.

Gives a method for obtaining the crystal salts of
and sodium glycerophosphate.

Hitchens, R. M. and McCauley, M.S. 1936

Analysis of Glycerophosphates II. Determination of Small Amounts of Orthophosphates in Glycerophosphates

Journ. Am. Pharm. Assoc., 25, p. 990.

A rapid, simple method for the quantitative determination of orthophosphates in glycerophosphate, based upon their precipitation as ammonium phosphomolybdate, is described.

Hitchens, R. M. 1936

Analysis Glycerophosphates. I. Discussion of Assay Methods for Ferric Glycerophosphate and Manganese Glycerophosphates.

Journ. Am. Pharm. Assoc., 25, p. 985.

Gives an improved method over the N. F. VI for assaying ferric and manganese glycerophosphates.