

## SOME OBSERVATIONS ON THE DISSOLVING OF ZINC CHLORIDE AND SEVERAL SUGGESTED SOLVENTS.\*

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The salts of zinc which are soluble in water, especially the sulphate, acetate and chloride, have long been used in injections, lotions, eye-washes, mouth-washes and other such forms of application, usually in weak solutions, a few grains to the ounce.

The sulphate and acetate of zinc readily dissolve in water without residue; but zinc chloride upon contact with water has a strange behavior, and when treated with water in large proportions leaves an insoluble residue known as oxychloride, or basic chloride of zinc; it matters not which is added to the other. This undissolved portion is bulky, therefore impressive as to quantity especially when resulting from one or two grains of zinc chloride intended for eye-drops. That it does contain both zinc and chlorine, we have assured ourselves by qualitative analysis; it may therefore be rightly termed, basic chloride of zinc, or oxychloride. Whatever of oxide of zinc or oxychloride of zinc was present in the sample dissolved may also be looked for here.

In order to appreciate the quantity of oxychloride usually left undissolved, let us cite a reference found in the Proceedings of the American Pharmaceutical Association, 1896, page 715, "Zinc Chloride-Dissociation by Water" Perrot has observed that when zinc chloride, free from oxide was dissolved in water, a precipitate was formed, which had the composition  $ZnCl_2 \cdot 5ZnO \cdot 6H_2O$ . An inquiry into the relations of the quantity of water to the amount of oxychloride formed resulted in the determination that by employing 100 molecules of water, 3.75 percent of oxychloride was formed, the same quantity was formed with 75 molecules, 3 percent was formed with 50 molecules and 2.6 percent with 25 molecules. "The limit of the reaction is, therefore, with 75 molecules of water, the addition of large quantities giving no increase in the yield of oxychloride." *Pharm. Centralh.*, January 23, 1896, 46 from *Bull. soc. chim.*, 1895, 975.

Commercial zinc chloride may contain some pre-existent oxychloride as an impurity from over-heating in manufacture, and samples of medicinal zinc chloride such as the official grade are expected to show a separation of oxychloride under the condition named; the United States Pharmacopoeia accordingly provides a test for limit of oxychloride.

The equation commonly used to explain the change of zinc chloride through the effect of water into this basic salt is  $ZnCl_2 + H_2O = Zn(OH)Cl + HCl$ .

As already mentioned the precipitate is strikingly bulky, but is by no means a great part of the zinc salt taken. The production of free hydrochloric acid as shown by the equation, is perhaps the reason that all of the zinc is not precipitated by the water. A proper conception of this reaction demonstrates the fact that every clear solution of zinc chloride that is obtained by dissolving zinc chloride in large quantities of water is a solution of zinc chloride plus hydrochloric acid. This is a matter to be noted toward a better understanding of the behavior of this peculiar substance, for although at this point the statement is largely inference it will, in due course, become a proven fact.

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\* Read before Pennsylvania Pharmaceutical Association, 1918 meeting.

Even though the undissolved matter is no great part of the zinc chloride, it does of course represent activity which it is the duty of the pharmacist to vouchsafe to the patient. Therefore, to remove it would be wrong, to dispense it in eye-drops, or similar preparation, would be useless, if not productive of more serious trouble than an explanation.

When first we encountered this behavior we could not take time to investigate it, so acting under the impression that free hydrochloric acid would be present in any event, as shown by the equation, we concluded that the most practical thing to do was to supply that through lack of which the obstacle arose; in other words, add sufficient hydrochloric acid to the zinc chloride itself to enable the water to carry all of the zinc chloride into solution, realizing as already said, that free hydrochloric acid would be present in the finished product whether all or only part of the zinc chloride was in solution, for this procedure assures the zinc to the patient.

The addition of the hydrochloric acid was made in the dispensing of several grains of zinc chloride by putting a single drop of concentrated acid upon the salt, and after mixing by trituration the water was added. When but a grain or two of zinc chloride was to be dissolved, a mere trace or touch of the acid was used, or a portion of a diluted drop. Much less acid is needed if put directly upon the zinc salt. Any mixture prepared without this addition and showing turbidity was rejected because too much acid would have to be added to the fluid. The effect of the acid added is to produce zinc chloride and water;  $Zn(OH)Cl + HCl = ZnCl_2 + H_2O$  the very material desired in the product. We have often wondered "what better can be done?" Theory would indicate that the hydrochloric acid in the liquid could be neutralized by mixing it with zinc oxide or carbonate and filtering off the undissolved portion. This plan however is neither so accurate nor so simple as it appears when tried on a small lot of eye-drops.

Although the plan of adding acid had been used for many years, without any untoward effects, there might have arisen a comparison between the work of dispensers, wherein the reason for such an addition might be difficult of explanation to the lay mind, for although we believed we were acting within the bounds of right judgment, it might not have been possible to satisfy the patient that such was the case. Nor was the patient the only one who might have to be convinced of the common-sense of the plan, as we shall soon learn, and it was this apprehension, perhaps, more than any other influence that persuaded us to look for another solvent. Since undertaking this study of the subject, we find that others have practiced this method as the only practical means of dissolving zinc chloride. Indeed we find that this problem had been referred to a commission of apothecaries and physicians in Belgium, because physicians were objecting to the use of the acid. This body discountenanced the use of the acid, and recommended the use of a turbid solution or the clear liquid therefrom, either of which as has been pointed out will contain the same amount of free hydrochloric acid, *produced but not added*. Referring to the report of this commission, Dr. Paul Wiskirchen, in the *Pharm. Zeitung*, 1899, page 268, states that he finds "the addition of acid is unnecessary. He finds that if it is attempted to dissolve pure zinc chloride in cold water, or if cold water is added to a clear solution of zinc chloride, turbidity is invariably produced, but

if the solution is effected with hot water, or if the dilution is made with hot water, clear solutions result, and so remain permanently." This quotation is from the proceedings of the American Pharmaceutical Association, 1900, page 717, for which it was abstracted from the *Pharm. Centralhalle* of August 17, 1899, page 508. In the same proceedings for 1907, page 850 we find another abstract which we quote in its entirety.

*"Zinc Chloride—Simple Method to Effect a Clear Solution.*—Franz Wipperfurth directs attention to the fact that while pure zinc chloride usually produces a turbid solution when it is dissolved in cold water, it dissolves perfectly clear in hot water and the solution remains clear on cooling (*Pharm. Zeitung*, Li, No. 73 (1906) 807)." Wondering whether we had shut our minds to such a simple and efficient agent as hot water, we hastened to try the suggestion, but only to be utterly disappointed, for we found no appreciable difference in either the immediate or prolonged effect of hot or cold water, in dissolving the salt, or diluting concentrated solutions. If there is any perceptible difference in the effect of hot water from that of cold water, it is merely in making the sediment more dense and to settle somewhat faster, perhaps to be overlooked more easily. Not satisfied to record a refutation of these statements without sufficient proof, we made dozens of tests under varying conditions and quantities, but all to no avail. The statements are erroneous. It was now decided to look into the properties of zinc chloride itself as the most rational starting point of our quest.

One of the characters of zinc chloride which should be borne in mind throughout the consideration of this subject is that property of its solutions to turn litmus from blue to red, or, as usually described, its acid reaction. As is well known this property is common to many of the soluble salts of the metals; we merely want to remind ourselves at this time that it does not indicate free acid. The sample of zinc chloride which was employed for these experiments conformed to the U. S. P. requirements as to limit of oxychloride content and production; it also conformed to the other tests of the same standard. After a number of experiments made more or less at random to determine features which seemed to have bearing upon the matter in hand, a series of experiments was outlined through which it was purposed to follow some zinc chloride in order to note its behavior under varying conditions. Accordingly, a convenient portion of it was placed in a vessel and water added drop by drop with constant stirring. Approximately an equal weight of water dissolved it—the mixture becoming warm as solution progressed—and a practically clear solution resulted. The addition of water in small portions was continued until a decided precipitate made its appearance. These experiments were repeated several times with different amounts of zinc chloride. On an average it required over five times as much water as zinc chloride to produce a permanent turbidity or precipitate. The further dilution of these turbid solutions with water threw out more precipitate, so the addition of water was continued until to all appearances no more oxychloride was being produced. This condition appeared to be attained when twenty or more parts of water had been added. One of these mixtures was allowed to settle and the clear supernatant liquid decanted upon asbestos wool. The filtrate was placed upon a water bath for evaporation. The undissolved portion (oxychloride) was washed and boiled with

sodium carbonate to separate the zinc and chlorine, both of which were shown to be present.

Before passing on to the consideration of the evaporated filtrate let us observe some of the behaviors of the clear solution of equal parts of zinc chloride and water. The statement is common in works of reference that zinc oxychloride is dissolved by zinc chloride solution; now the fact, that up to a certain dilution a clear solution of zinc chloride is possible must certainly be conceded to be proof of this statement. The inference then would be that the total acidity of the zinc chloride solution is sufficiently powerful in that certain concentration to hold in solution any oxychloride which existed in the sample as well as to prevent the separation of the incipient oxychloride which will be manifested upon a further dilution.

Looked at from the view point which attaches to precipitated oxychloride, another significance to be gathered from this phenomenon is that there is a limit to the ability of the acidity of the zinc chloride solution to hold the oxychloride in solution, and, as through gradual dilution this power suffers attenuation the separation of oxychloride progresses until exhaustion is attained when down comes such balance of zinc in the form of oxychloride as the weakened acidity of the solution can no longer hold dissolved. The present acidity of the solution must, therefore, be looked upon as the only reason that all of the zinc is not thrown out in preparing clear zinc chloride solutions by dissolving or diluting with water.

That this acidity must be sufficient, though not necessarily of a related form, was proven through a fortunate thought which occurred just before finishing the work upon these tests, namely, zinc chloride can be dissolved in a well charged carbonic acid water, without residue of oxychloride, and further evidence that acidity is the essential was shown by the fact that if this same solution is boiled or agitated to expel the carbon dioxide, the insoluble oxychloride appears. Boiling caused its immediate separation, agitation revealed it but slowly, while quiet maintained a clear solution for over four days, when afterwards the application of heat caused the escape of a few bubbles of gas, and the looked-for precipitate appeared. But for its fleeting nature, what could be better for our need? That there may be a trace of oxychloride yet held in solution by the combined acidities of the zinc chloride and free acid which have ever enveloped it, would be difficult indeed to prove, but it was proven that a clear solution of zinc chloride of greatest strength possible will not dissolve oxychloride which has been previously separated from a solution. A portion of the cold, clear concentrated solution of zinc chloride was mixed with a small amount of zinc carbonate without change in appearance, but upon boiling the mixture the zinc carbonate dissolved. Even after no more carbonate would be taken up the solution retained its power to redden litmus. On the other hand, a clear solution of zinc chloride from which oxychloride has been completely separated by sufficient dilution, did not dissolve zinc oxide or carbonate, even upon prolonged digestion with heat, thus indicating that in this dilution the affinity between the zinc oxychloride and hydrochloric acid as a balanced condition within the solution is greater than between the zinc oxide and hydrochloric acid.

The liquid which was placed upon the water bath was evaporated to nearly constant weight. It was now in the form of a thick, syrupy liquid, for zinc chloride cannot readily be dried on a water bath under atmospheric pressure. Besides,

what moisture it retains this syrupy residue would be expected to also contain the hydrochloric acid from the reaction producing the oxychloride from which it had been filtered; later it will be shown that it does contain this hydrochloric acid.

Two series of experiments, with this syrupy residue, were arranged. In the first of these it was mixed with water gradually added and finally increased to a considerable bulk to find that it dissolved clear throughout. It was then re-evaporated under the same condition to a syrupy consistency and again found to dissolve clear; a third such treatment was given to it, and a third time it dissolved clear. The reason for its doing so was the presence of a sufficient amount of said hydrochloric acid, tenaciously retained throughout the evaporation, to effect solution, as was proven to be the case by treating the syrupy liquid of the second series of experiments with zinc carbonate. When put into the syrupy liquid the zinc carbonate made no demonstration of the presence of acid until the mixture was thinned with just sufficient water to permit of enough motion for reaction. Effervescence then took place with the disappearance of the small amount of zinc carbonate which had been added. More zinc carbonate was now added until in excess, and the solution warmed, gradually but abundantly diluted with water, and filtered. The clear liquid would now be considered as containing no free hydrochloric acid. Next, it was evaporated to a syrupy consistency on a water bath, and then mixed with water as had been done in the experiment just preceding it. Instead of dissolving clear as the preceding one, the present experiment gave with the first portion of water a clear solution but upon further dilution an abundant residue of oxychloride. This was separated and the filtrate evaporated as before, and upon treatment with water gave a clear solution, thus showing that the acid which was produced in the solution, along with the oxychloride was sufficient to redissolve all of the zinc chloride. Another evaporation and solution substantiated this opinion. The liquid of the first series was now evaporated for the fourth time, and after it had reached the syrupy consistence, the vessel was placed over a direct flame, and the heat continued, while tests were made from time to time, by removing a drop with a glass rod, until a point was reached when the drop gave a turbidity with water. This stage was not attained until after and in succession the last trace of moisture which had been held so tenaciously by the zinc and the adhering hydrochloric acid had been driven off and the zinc chloride had been liquefied by the heat, giving additional evidence that adhering hydrochloric acid had been the reason for this syrupy liquid persistently dissolving clear. The fused residue was now treated with an abundance of water and the mixture filtered. This filtrate was evaporated to a syrupy condition as before and found to dissolve clear in water. Another fused mass corresponding to that just described was treated with a limited quantity of water and upon filtering, evaporating and again diluting, oxychloride separated, because when the mass was treated with the limited quantity of water not enough water was present to adjust the acidity so that the full production of oxychloride might take place. The insoluble portions of the fused masses were all shown by tests to be oxychloride.

In order to observe a specimen of zinc chloride which had never been in a solid state and thus avoid oxychloride due to overheating, a concentrated solution was prepared by saturating warm hydrochloric acid with zinc oxide added in excess.

The clear supernatant liquid from this mixture precipitated with both hot and cold water and in all respects corresponding dilutions behaved exactly as those obtained from the dissolved salt. One could imagine nothing more likely to be chemically neutral than this solution prepared by neutralizing the acid with the zinc base, and its precipitation by water must convince the most skeptical that free acid is not only present in every diluted zinc chloride solution prepared with water alone as the solvent, but also needed to insure complete solution.

Neutralize such diluted solution in part, and simultaneously with the precision of natural law readjustment takes place between the zinc chloride and the water present, with the formation of oxychloride and the production of a corresponding amount of free acid; there will be free hydrochloric acid in a diluted solution made with water alone while there is zinc chloride left in it.

Any amplification of these experiments will but reiterate the proven fact at first but inference—that when this dilution is reached there has been formed and retained enough hydrochloric acid sufficient to re-dissolve the residue in any amount of water that may be added.

So much for our study of zinc chloride under the conditions of ordinary manipulation by the pharmacist, and like every definite chemical substance it always behaves the same under identical conditions no matter how often they recur. And still the problem—to get zinc chloride into solutions of such strength as ordinarily called for in prescriptions, without loss—remained unsolved. Left as we were to make the best of what cannot be changed, one might decide, and with sanction of authority, as previously pointed out, to prepare a solution of zinc chloride and ignoring the slight precipitate, ascribe to it an approximately definite strength and of this take sufficient quantity as needed. Such course is perhaps the next best plan to getting the zinc salt entirely dissolved, but the accomplishment of the latter was what had prompted the work; and yet meditation seemed to be but closing the door to possibility.

While reviewing numerous experiences with zinc chloride in prescription work, it was thought that there was a possibility of boric acid being the agent sought. It had been used a great many times in eye-washes with zinc chloride but had never been depended upon for solvent effect. Its suitability to eye-washes and its mild acidity, however, strongly urged a trial, and the first experiment showed that it has the very property desired, while subsequent trials established the fact that boric acid will give clear solutions with zinc chloride, grain for grain, in any dilution, hot or cold, up to about twenty grains per ounce. Boric acid applied to the zinc chloride will prevent the precipitation of zinc oxychloride; it will also redissolve a precipitate of oxychloride, although proportionately more is then required than is needed to prevent the precipitate. A saturated solution of boric acid is a convenient form in which to employ the agent, adding it directly to the zinc chloride, or the reverse. Saturated solutions of boric acid at ordinary indoor temperatures contain about twenty grains of boric acid to the fluid ounce; these solutions will dissolve an equal amount of zinc chloride. If such concentrated solutions of zinc chloride are exposed to a lower temperature, they become cloudy, peculiarly so, and though cleared by warmth they do not retain their transparency.

Solution by means of boric acid may also be accomplished by mixing the boric acid intimately with the zinc chloride before the aqueous solvent is applied. This plan involves some allowance for the slow solubility of the boric acid itself. Solutions of zinc chloride by means of an equal amount of boric acid are permanent, with the exception of the saturated solution as already mentioned. Less than an equal amount of boric acid does not appear to insure permanency.

The limit of solubility of boric acid is the only shortcoming of this agent so far observed. It is of interest to note for subsequent comparison, that upon boiling zinc oxide or zinc carbonate and boric acid together, no zinc enters solution.

While little, if any, objection can be raised to the use of boric acid in this connection, yet because of its limited effect we sought for another solvent less restricted. Attention had been arrested by a reference to the soluble double salts which zinc chloride forms with ammonium chloride, and effort was turned in that direction. The results with boric acid had strengthened the belief that an acidulated medium is essential to the purpose, and associating this thought with the fact that solutions of ammonium chloride are prone to redden litmus, unquestionably through the presence of a trace of free hydrochloric acid, it was undertaken to learn what effect ammonium chloride would have in the dissolving of zinc chloride. Gratifying, indeed, was it to find in the substance a very efficient solvent, and more powerful than boric acid, for applied directly to the zinc chloride one grain of ammonium chloride will dissolve five grains of zinc chloride. If used to dissolve a precipitate of oxychloride an additional amount may be needed, apparently dependent on strength of solution. The solutions with ammonium chloride are permanent.

There would seem to be no objection to the use of the few grains of ammonium chloride which would be needed to prepare an application for a mucous membrane since such parts are constantly saturated with solution of chlorides and likewise inured to the presence of ammonium compounds. Should a very strong solution of zinc chloride be needed as for powerful local effect, ammonium chloride may be depended upon to yield a clear solution.

The possibility of decomposing ammonium chloride in solution with zinc oxide, in the capacity of an alkali or alkaline earth, had not come to mind until now. Upon boiling zinc oxide with a solution of ammonium chloride it was found that the zinc oxide dissolved, of course, with the inevitable liberation of ammonia. Zinc carbonate behaves in this same manner with ammonium chloride. A parallel test with water was made to check up these results against any soluble zinc impurities in the oxide and carbonate. Herein may be considered to abide the solvent effect of ammonium chloride on zinc oxychloride—an effect again attributable to acidity of medium.

Representing the action by the equation  $\text{Zn(OH)Cl} + \text{NH}_4\text{Cl} = \text{ZnCl}_2 + \text{H}_2\text{O} + \text{NH}_3$ , ammonia gas might at first be expected to be in evidence. But when it is recalled that free hydrochloric acid is present or producible in a quantity definitely proportionate to the oxychloride to be dealt with, it is readily understood that no ammonia should be evolved, nor was any, as proven by test.

Sodium and potassium chlorides have no solvent effect upon zinc chloride, but ammonium chloride gives a clear solution of zinc chloride in normal salt solution, and so does boric acid.

A sample of zinc ammonium chloride was prepared by adding to a solution of zinc chloride of known strength the calculated amount of ammonium chloride to supply an equal number of molecules of the two salts. Crystallization of this solution yielded a product which was recrystallized to obtain the sample shown at this time. The identity of the product was established by tests.

Zinc ammonium chloride forms colorless, transparent crystals, without odor and having an intensely caustic taste. It is readily and completely soluble in water; the aqueous solution is acid to litmus; the solution remains permanently clear. This salt is not an article of commerce in channels through which the pharmacist trades, nor is its use suggested, for the acquisition of it needlessly increases one's stock, especially since boric acid and ammonium chloride must always be at hand.

Since medicated waters are frequently used in solutions for treating conditions wherein zinc chloride is likely to be employed, some experiments were made to observe the behavior of these liquids toward zinc chloride. Peppermint water was found to act as does distilled water, boric acid and ammonium chloride but yield clear solutions. Camphor water was found to possess acidity sufficient to dissolve zinc chloride up to ten grains per ounce. Beyond that strength camphor water takes on a satiny opalescence due to the separation of microscopic crystals of camphor. The addition of ammonium chloride increases this opalescence. But with or without ammonium chloride these camphor crystals re-enter solution within a few days, or immediately upon the addition of a few drops of alcohol. The samples of rose water at our disposal were neutral to litmus; they did not dissolve zinc chloride completely until boric acid or ammonium chloride was added. A past experience but well remembered, leads us to believe that specimens of rose water may be encountered which will give clear solutions.

Mucilage of sassafras pith did not dissolve the zinc chloride, until boric acid or ammonium chloride was added; but though the zinc oxychloride went into solution the mucilage was rendered cloudy by its contents.

The statement that zinc chloride forms soluble double salts with some alkalis as well as with ammonium chloride was tried out with some of those used in eye-washes, with the following results: Equal parts of morphine hydrochloride and zinc chloride did not yield a clear solution, until ammonium chloride was added. Equal parts of pilocarpine hydrochloride and zinc chloride did dissolve clear. Equal parts of cocaine hydrochloride and zinc chloride did not dissolve clear, without the addition of ammonium chloride; boric acid likewise carried the mixture into solution. Ammonium chloride produced clear solutions when zinc chloride was brought together with morphine sulphate and atropine sulphate.

#### CONCLUSIONS.

Our conclusions from this mass of experiments and words may be summed up in short as follows: the separation of zinc oxychloride when zinc chloride is dissolved in water is always accompanied by liberation of free hydrochloric acid which remains in the solution; at the same time a loss of zinc is experienced. Both of these objections may be overcome in solutions up to approximately twenty grains to the ounce by the use of boric acid, weight for weight of zinc chloride taken. For solutions exceeding this strength, or for any strength, ammonium



chloride in quantity of not less than one-fifth of the amount of zinc chloride used, will insure complete and permanent solution. Camphor water will dissolve a few grains of zinc chloride per ounce. Carbonic acid water may be employed if intended for immediate use. And finally the comparative ease with which a minute quantity of either boric acid or ammonium chloride prevents a precipitate as against the larger quantity needed to redissolve oxychloride once formed may be impressed upon our minds by the wisdom of the maxim: "An ounce of prevention is worth a pound of cure."

THE MANUFACTURE OF ASPIRIN TABLETS.\*

BY ROBERT C. WHITE.

The data presented by the author are based on his investigations of Aspirin tablets of American manufacturers, including also the original Aspirin tablet. No report is made on the content of aspirin, but only of the tests involving the physical operation of making the tablets. The author states that manufacturers are constantly improving their product and as the tablets reported on are of different dates of manufacture, no names of manufacturers are given and the tablets are referred to by number. The table following has been prepared from Doctor White's report in order to condense this matter; that which follows thereafter is printed from the original.—EDITOR.

The manufacture of Aspirin tablets may be placed in what is considered by manufacturers the "delicate" group. Many things coming in contact with aspirin can exercise either physical or chemical function, and so either contaminate or break down the aspirin content. In the manufacture of any tablet there are several important features to which the manufacturers give considerable atten-

EXAMINATION OF ASPIRIN TABLETS.

Quality, description and composition.	Sample No. 1. Examined May 1918.	Sample No. 2. From eastern manufacturer Examined May 1918.	Sample No. 3. From eastern manufacturer. Examined June 1918.
Appearance.....	Poor	Fair	Poor
Color.....	Good	Fair	Dark
Die.....	Satisfactory	Poor	Good
Punch.....	Poorly engraved	Plain	Very poor
Monogram.....	Indistinct	None	Poor, engraving worn
Carrying Qualities....	Very poor	Good	Poor
Disintegration.....	Good	Good	Fair
Disintegration Agent..	Evidently potato starch	Potato starch	Corn starch
Uniformity of Weight.	Poor	Average, good	Poor
Maximum Weight.....	7.3	6.4	7.7
Minimum Weight.....	4.7	5.7	5.3
Excipient.....	Weak starch paste	Weak gum solution	Gelatin solution
Other Filler.....	Corn starch	Corn starch	Corn Starch
Lubricants.....	Oil, none.	Oil, small amount Tal- cum, large quantity	Oil, large quantity Talcum " "
Contamination.....	None	Iron	Bad. Evidently iron stains
Packing.....	Fair	Poor and loose	Poor

\* From a paper read before Pennsylvania Pharmaceutical Association, 1918 meeting.