

after the mixture became liquid. The products were then dissolved in hot water or 30% alcohol and allowed to crystallize. Constant melting points were obtained after one or two crystallizations, when the primary pentanols were used, but with the secondary pentanols the reaction did not proceed so readily. Regardless of the length of heating, the mixture of anhydride and secondary pentanol did not become thoroughly liquefied. Thus after heating the secondary alcohol mixtures for thirty minutes the liquid portion was decanted and purified. Water could not be used as crystallizing medium because the compound separated as an oil. Dilute alcoholic solutions acted similarly. Hence the esters of the secondary alcohols were purified by dissolving in chloroform and adding two volumes of ligroin. Slow evaporation of the mixed solvent yielded well-defined crystals. A repetition of the process gave products with constant melting points. The molecular weights of the several compounds not previously described were determined by titration with *N*/10 KOH, using phenolphthalein as an indicator. Tertiary amyl alcohol did not react.

2 Mono-ester of.	M. P. ° C.	M. W.	
		Calc. C <sub>17</sub> H <sub>35</sub> O <sub>2</sub> N.	Found.
Pentanol-1	132-133°	281	280
Methyl 4-butanol-1	165-166°	...	...
Methyl 2-butanol-1	157-158°	...	...
Pentanol-2	102-103°	...	279
Pentanol-3	92°	...	276

## SOME APPLICATIONS OF COLLOIDAL CHEMISTRY TO PHARMACY.\*

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Believing that it is possible to make further applications of colloidal principles in the preparation of pharmaceutical products, this work was undertaken with that end in view. We assumed that a number of our official ointments could be improved and that several insoluble medicinals could be suspended in a semi-colloidal condition, thus adding to their therapeutic value, if colloidal suspension methods were applied in their preparation. Our results indicate that the assumption was justified.

We gave attention to the preparation of ointments of mercury, of metallic silver ointment, of metallic silver suspensions, of suspensions of the halides of silver and of the suspension of calomel. We believed that, if the proper degree of fineness of subdivision could be secured coupled with the proper suspending colloid, we would be able to secure satisfactory preparations. The literature on Colloidal Chemistry was rather carefully covered and suggested methods were tried, modified and tried again or new methods were developed. A bibliography of the literature will be found at end of paper.

### A. OINTMENT OF MERCURY.

*Experiment No. I.*—Ten Gm. of mercuric nitrate in 15 cc. of H<sub>2</sub>O were thoroughly mixed with 45 Gm. of cold lanolin, and 3 Gm. of NaOH dissolved in H<sub>2</sub>O

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added. The product was a smooth yellow ointment, which darkened on standing and appeared to be reducing. Five cc. of 40% formaldehyde were added and the color deepened to a blue-brown. This preparation was too stiff to be worked readily and 15 Gm. of benzoinated lard were added. A fair ointment of mercury resulted.

*Experiment No. II.*—No. I was repeated with  $H_2O_2$  substituted for formaldehyde. The ointment had a tendency to crumble and was therefore discarded.

*Experiment No. III.*—Fifteen Gm. each of lanolin and benzoinated lard were melted together and 20 Gm. of  $Hg(NO_3)_2$ , triturated to a smooth paste with 20 cc. of  $H_2O$ , added and triturated with the mixture of lanolin and lard just before congealing. A very good thick emulsion was formed. Five cc. of 40% HCHO were added and thoroughly incorporated. *No reduction took place after standing several hours.*

A. One-half of above mixture was used and 3 cc. of a saturated solution of NaOH added. Immediate reduction took place with the formation of a good blue ointment, lighter in color than the U. S. P. ointment and with traces of yellow oxide present. Probably not enough NaOH was added.

B. The other half of primary ointments was treated with a slightly larger amount of NaOH and a small amount of HCHO. The result was an ointment lighter than U. S. P. 50% ointment but much darker than the U. S. P. 30% ointment. The amount of Hg present was approximately 30%. This was examined by the microscope and compared with U. S. P. 50% and 30% ointments. The particles of Hg seemed to be 1/10 the diameter of those in the U. S. P. ointments.

*Experiment No. IV.*—Twenty-five Gm. each of anhydrous lanolin and benzoinated lard were melted together and 50 Gm. of mercurous nitrate,  $Hg_2(NO_3)_2$ , triturated with 15 cc. of  $H_2O$  were added and triturated until the fats congealed. A fine white ointment, showing no reduction, was produced.

A. To one-half of above mixture was added 5 cc. of 40% HCHO and thoroughly incorporated. No change was apparent.

1. To one-half of A was added 2 cc. of 40% NaOH. Immediate reduction with the production of a dark-blue-to-black ointment resulted. Examined with the microscope the presence of some large dark particles and a great number of exceedingly small particles was indicated. High-power lense showed a myriad of round particles about the size of bacteria. The color indicated a good strong ointment of mercury.

2. To the other half of A was added 4 cc. of 28%  $NH_4OH$ . Results were as in No. 1.

*Experiment No. V.*—To the remainder of material used in Experiment IV (25 Gm. each of lanolin and lard and 50 Gm. of  $Hg_2(NO_3)_2$ ) was added 5 Gm. of oleate of mercury to improve the consistency, and 5 cc. of 28%  $NH_4OH$  was added. A dark brown ointment was produced.

A. To one-half of above was added 5 cc. of 28%  $NH_4OH$ . Color changed to a dark blue. It had the appearance of a good mercury ointment. This led to the assumption that free Hg is produced when  $NH_4OH$  is added to  $Hg_2(NO_3)_2$  because no reducing agent was added in this experiment.

B. To the other half of above mixture was added excess of HCHO. No change in color was produced, evidently no Hg was freed. Next an excess of

NH<sub>4</sub>OH was added and the color immediately changed to that in A. Evidently, the dark color produced when bases are added to mercurous nitrate is not due to the black oxide, as heretofore supposed, but is due to the formation of finely divided mercury.

*Experiment No. VI.*—NH<sub>4</sub>OH was added to a solution of Hg<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub> and a black precipitate was obtained. This was thoroughly washed with HCl. SnCl<sub>2</sub> was added to the washings and a white precipitate of Hg<sub>2</sub>Cl<sub>2</sub>, which turned gray upon standing proved the presence of mercuric salt in the solution. Part of the blue-black residue was dried and it coalesced when rubbed, proving that it was free Hg and that when NH<sub>4</sub>OH is added to a mercurous salt in solution, *free Hg* and *not the black oxide is obtained*. The remainder of the blue-black residue was easily incorporated into an ointment with the usual ointment bases. This method of preparing mercury ointment is unsatisfactory, as not all of the salt is reduced to free Hg and also because the free Hg secured has a strong tendency to coalesce.

*Experiment No. VII.*—A solution of NaOH was added to HgCl<sub>2</sub> in solution and a yellow precipitate of HgO obtained. To this was added a solution of HCHO and the reduction was immediate. However, globules of Hg formed and, hence, it was unsuitable for making an ointment.

*Experiment No. VIII.*—To keep the free Hg in a finely divided condition, we decided to peptize it with tannic acid, 40% NaOH was mixed with equal volumes of 1% tannic acid solution and 40% HCHO. To this mixture was added a concentrated solution of HgCl<sub>2</sub>. There was an immediate reduction to free Hg. The precipitate settled and was washed by decantation until neutral. This removed the excess of NaOH, HCHO, tannic and formic acids. Some of the precipitate was placed under the high-power of a microscope and small, round, nearly transparent particles that showed Brownian movement were seen. This is as near the colloidal state as necessary for smooth ointments. The rest of the precipitate while still moist was incorporated with anhydrous lanolin and an excellent blue ointment resulted.

*Experiment No. IX.*—Attempts were made to secure a weaker base than NaOH for this reduction and thus avoid the work of washing the reduced precipitate. Yellow oxide, HgO, was rubbed to a very fine powder and HCHO added, but no reduction took place. This was repeated and Ca(OH)<sub>2</sub> added; some reduction ensued but not enough to assume complete reduction. It was repeated and NH<sub>4</sub>OH added. Reduction is desirable but the likelihood of the presence of the double salt is objectionable. Repeated and NaOH added. Immediate and complete reduction resulted.

From these experiments we concluded that the presence of some strong base is necessary for complete reduction.

*Experiment No. X.*—From our preceding experiments we developed the following procedure and all of our Freshmen students were required to make the ointment:

Mercuric Chloride	40 Gm.
Sodium Hydroxide, sticks	40 Gm.
Gelatin, leaf	2.5 Gm.
Liq. Formaldehyde, 40%	20 Gm.
Anhyd. Lanolin	25 Gm.
White Petrolatum q. s. ad	100 Gm.

Dissolve gelatin and NaOH in 200 cc. of  $H_2O$  with heat. Cool and add solution of HCHO. Dissolve the  $HgCl_2$  in 200 cc.  $H_2O$  by aid of heat. While still hot, add slowly and with stirring to solution of NaOH, HCHO and gelatin. This should be done slowly and with care. Allow the precipitate to settle completely and decant. Wash the precipitate by decantation with two successive portions of 200 cc. of  $H_2O$ , allowing the precipitate to settle each time. Filter and transfer precipitate *while still moist* to a mortar and add 25 Gm. of anhydrous lanolin and thoroughly mix. Add enough white petrolatum to make 100 Gm. and mix thoroughly.

Caution. Do not allow precipitate to dry on filter.

All of our freshmen students made good mercurial ointments by this method and the time required was about one hour. The proportion of Hg up to 60% can be varied at will. We do claim that this method is better than the one in vogue for the following reasons:

1. The ointment can be prepared in less time.
2. It is easier to prepare it.
3. The free Hg is in a much finer divided condition and therefore of greater therapeutic value.

*Experiment No. XI.*—The Ointment of Mercury was also prepared by a modified Carey Lea's method of preparing silver sols. as follows: Four Gm. of dextrin and 4 Gm. of KOH were dissolved in 100 cc. of  $H_2O$ . Three Gm. of  $HgCl_2$  were dissolved in 20 cc. of  $H_2O$  with heat. The two solutions were mixed while hot and 5 cc. of 40% HCHO added. A very fine blue-black precipitate was obtained, almost colloidal in nature. Washed until neutral to litmus and the moist precipitate incorporated in sufficient lanolin to make the desired per cent of Hg in the ointment. This made an ointment with the Hg more finely divided and hence of greater therapeutic value, but considerable time was consumed in washing because the finely divided Hg settled very slowly.

#### SILVER OINTMENT.

*Experiment No. I.*—A good appearing ointment of silver was made by Hatschek's method "Laboratory Manual of Colloidal Chemistry" by Emil Hatschek, pp. 39-40. Silver nitrate is dissolved in  $H_2O$  and mixed with anhydrous. This method is objectionable for an ointment because NaOH may be present in the finished product. The procedure was therefore modified.

*Experiment No. II.*—A solution of  $AgNO_3$  was added to a solution of  $Ca(OH)_2$  and a brown precipitate of  $Ag_2O$  was obtained. This turned in the sunlight to a black precipitate of Ag. So much lime water was required that it was almost impossible to mix the solution with anhydrous lanolin and secure a fair percentage of Ag in the ointment. Therefore this method was abandoned.

*Experiment No. III.*—Modified Carey Lea's method. Four Gm. of dextrin were dissolved in 100 cc. of  $H_2O$  and 4 Gm. of stick NaOH added; 3 Gm. of  $AgNO_3$  were dissolved in 20 cc. of  $H_2O$  and this solution was added, with stirring, to the dextrin soda solution. A precipitate of  $Ag_2O$  was obtained which was gradually reduced by the dextrin to Ag. This was precipitated by alcohol and the precipitate washed free from alkali by alcohol. While the precipitate was moist it was incorporated in anhydrous lanolin making an excellent Ag ointment.

## COLLOIDAL SILVER HALIDES.

*Experiment No. I.*—Prepared a 2% gelatin solution and added NaCl. AgNO<sub>3</sub> dissolved in water was added to above with agitation. A milk-white thick suspension of AgCl was secured. A drop of this added to 10 cc. of H<sub>2</sub>O forms a homogenous white suspension. This was stable in the dark but sunlight reduced it.

*Experiment No. II.*—A solution of AgNO<sub>3</sub> was added to a 2% gelatin solution and mixed. HCl was added drop by drop with agitation. The solution was definitely acid to methyl orange. A curdy white precipitate settled out. Upon standing this was peptized and a stable suspension formed. This reduced in the sunlight.

*Experiment No. III.*—Repeated No. I but controlled the  $p_H$  by use of NaOH. Had a  $p_H$  of 10 when the AgNO<sub>3</sub> solution was added. A heavy white precipitate was obtained which was easily peptized in an excess of NaCl. This suspension was stable in the dark but reduced by sunlight.

All of the above suspensions of AgCl were precipitated by alcohol but are not reversible to any great extent.

*Experiment No. IV.*—Stable suspensions of AgI were made, using method described in N. N. R. 1925, under Neo-Silvol. Prepared a colloidal precipitate of Ag by precipitating Ag<sub>2</sub>O in the presence of gelatin with an excess of NaOH and reducing with HCHO. Treated this preparation with Wagner's Reagent (I<sub>2</sub> in KI) and secured a brown to cream suspension of AgI. In dilute suspension this is stable in sunlight but stronger suspensions reduce in sunlight. Evidently a very fine suspension well protected by gelatin is stable in sunlight.

*Experiment No. V.*—Repeated above, using Br<sub>2</sub> in KBr and secured a sunlight-stable suspension of AgBr.

*Experiment No. VI.*—Attempted to secure the same kind of suspension of AgCl by passing chlorine gas into a silver sol. No reaction took place. Apparently a chloride is necessary or the Cl<sub>2</sub> in the gas was not sufficiently concentrated to cause a union with the Ag sol.

*Experiment No. VII.*—Repeated No. VI, using KCl and changing the  $p_H$  value, but was unable to secure a suspension that was sunlight stable.

*Experiment No. VIII.*—Since it seemed impossible to secure a sunlight-stable suspension of AgCl by using chlorine gas or the ordinary chlorides with AgNO<sub>3</sub> or with the silver sol, we next tried dichloramine T as a source of chlorine. The silver sol and a solution of dichloramine T were heated on a water-bath. The brown color of the silver sol disappeared and a white suspension of AgCl was formed. The dichloramine T was filtered out and the dilute solution of colloidal AgCl was exposed for several days to the action of sunlight. *It was stable* in sunlight.

## COLLOIDAL CALOMEL.

*Experiment No. I.*—A solution of NaCl was added to a 2% solution of gelatin and dilute solution of Hg<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub> was prepared and added slowly and with agitation to the gelatin-NaCl solution. A stable suspension of Hg<sub>2</sub>Cl<sub>2</sub> resulted.

## YELLOW WASH N. F.

Yellow Wash of the N. F. settles out and has to be dispensed with a "shake label." Attempts were made to stabilize this precipitate as follows:

*Experiment No. I.*—A solution of 2 Gm. of acacia tears was made and mixed with a solution of 0.6 Gm. of  $\text{HgCl}_2$ ; 200 cc. of  $\text{Ca}(\text{OH})_2$  were added. No precipitate of yellow oxide was formed. The solution turned a pearl grey and upon standing 24 hours a bluish black precipitate of Hg formed.  $\text{HgO}$  must be very unstable when first formed and easily reduced by the organic acacia.

*Experiment No. II.*—A 5% solution of gelatin was used and molecular proportions of  $\text{HgCl}_2$  and  $\text{Ca}(\text{OH})_2$ . The gelatin prevented the precipitation of  $\text{HgO}$ . Solution became opalescent and upon standing a white flocculent precipitate settled out.

*Experiment No. III.*—Repeated Experiment II but added the gelatin last and after the yellow  $\text{HgO}$  was formed. The yellow oxide settled slowly and adhered to bottom of container.

*Experiment No. IV.*—Repeated Experiment I and added a solution of  $\text{NaOH}$ . No yellow precipitate formed. Heated the preparation and a grey-blue precipitate of metallic Hg formed. It is evident that it will be impossible to peptonize  $\text{HgO}$  precipitate if the peptizing agent is present when the  $\text{HgO}$  is formed. Time did not permit a series of experiments to determine whether it is possible to peptize this precipitate after it is formed.

#### CONCLUSIONS.

1. A new and, we believe, a better method of preparing ointment of mercury is described.
2. A method of preparing an ointment of metallic silver is described.
3. Methods for preparing sunlight-stable silver iodide, bromide and chloride have been developed.
4. A method of preparing colloidal suspension of calomel is given.

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#### THE ORGANIZATION OF THE DRUGGISTS' RESEARCH BUREAU.

Secretary E. L. Newcomb advises that some publications have credited the organization of the Druggists' Research Bureau solely to the National Wholesale Druggists' Association, whereas the National Association of Retail Druggists should share the credit equally. The N. W. D. A., through its work and activities, made the original recommendations which

led to organization of the Bureau. The Secretary also states that the Druggists' Research Bureau is now being directed by a joint committee representing the National Association of Retail Druggists, the American Association of Colleges of Pharmacy and wholesale and manufacturing members of the National Wholesale Druggists' Association. Splendid progress is being made in promoting the work of the Bureau.