The loss of 1.87% of ethyl nitrite during this period shows the inadivsability of placing a small quantity in a container that allows a large air space above the liquid.

Experiment No. 7.

One-ounce bottles were completely filled, then exposed to direct sunlight, and assayed weekly.

	Flint, %.	Amber, %.
Original strength	5.25	5.25
After one week	4.10	5.24
After two weeks	2.62	5.20
After three weeks	1.89	5.18
After four weeks	1.18	5.19

Results show surprisingly little change in the contents of amber bottles, and that the contents of the flint bottles show marked deterioration.

Experiment No. 8.

Desiring to determine the relative volatility of ethyl nitrite and alcohol when in admixture, 16 ounces were heated on a steam-bath. When a quantity equal to the amount of ethyl nitrite present had been driven off it was found to contain 2.5% ethyl nitrite which was a loss of 2.08%. Upon continuing the evaporation until all of the ethyl nitrite had been eliminated, it was found that 2.5 ounces had been vaporized, about 1.75 ounces of which were alcohol.

Experiment No. 9.

Exposure to the atmosphere in a porcelain evaporating dish.

Original strength.	After 1/2 hour.	After 1 hour.	After 1 1/2 hours.
4.58%	1.4%	0.275%	0.038%

The pronounced volatility of the ethyl nitrite is well illustrated in this test which shows the elimination of practically all of it in 1 1/2 hours.

Experiment No. 10.

Exposure to the atmosphere and agitation in a porcelain dish.

Original strength.	After stirring 1 minute.	After stirring 3 min.	After stirring 5 min.
4.56%	3.58%	2.19%	1.54%

After stirring 10 minutes.	After stirring 15 minutes.
0.57%	0.19%

The rate of elimination was substantially increased by stirring, as most of the ethyl nitrite was dissipated in 10 minutes and practically all in 15 minutes.

As a result of this study we[1] find that ethyl nitrite is easily dissipated from an alcoholic solution; that the action of direct sunlight is very destructive to it in flint glass containers; that partly filled containers are objectionable and that it is bad practice to dispense numerous orders from the same container. The ideal method of storage is in small *completely filled*, amber bottles kept in a refrigerator or ice-box.

ANALYTICAL LABORATORY OF
SMITH, KLINE & FRENCH CO.

A CONTRIBUTION TO THE HISTORY OF THE DEVELOPMENT OF THE ENTERIC CAPSULE.

BY A. G. DUMEZ.

During the years 1914 and 1915, at least four articles concerning the hardening of gelatin capsules with formaldehyde appeared in American journals,

[1] The writer desires to express his appreciation of the services rendered by Mr. T. R. Singer in this investigation.

medical and pharmaceutical. These several articles appearing in such a short space of time, and the manner in which the subject was treated therein, would lead one to infer that the enteric capsule was of comparatively recent invention, and but little known to the medical profession. Such, however, is not the case.

The matter of preparing medicines intended for internal administration in such a manner that they might not be liberated until reaching the intestines has given rise to numerous investigations on the part of both the physician and the pharmacist. The first work along this line appears to have been done in connection with vile-tasting medicines which are liable to be regurgitated, or substances which, upon administration in the ordinary manner, give rise to gastric disturbances. The pill was the form of medication which appealed to the early investigators as offering the best means of solving this problem. Attempts were made to form the mass with the aid of some substances not acted upon by the gastric juice or to apply these substances to the exterior as a protective coating. Fats, waxes, resins, paraffin, collodion, salol, *et cetera*, were employed for this purpose, but with little avail, as disintegration in the stomach was only partially prevented or the pills passed intact through the intestines as well as the stomach. Such was the extent of the progress made in this matter up to the time of the introduction of keratin as a pill coating in the latter part of the 19th century.

At about this time, Dr. Unna[1] began experimenting with various pill coatings in an endeavor to discover a substance which, unlike the fats, did not depend for its usefulness upon its melting point, which would not be rendered soluble or be disintegrated by the acid secretion of the stomach and would still be soluble in the alkaline secretions of the intestines. The results of his investigations were published in 1884. As a result, there was made available to the practitioner the first real enteric pill, the keratin coated pill. Pills coated in this manner were marketed in Germany almost immediately under the name of "Keratinirte Pillen" or "Dündarmpillen." These were followed two years later by "Kapsulae keratinosae," or "Dündarmkapseln," which were also first placed upon the market in Germany.[2] In the case of the enteric capsule, however, the keratin was not applied as a coating, but was used as an ingredient of the material from which the capsule was formed. According to the patent[3] issued to the firm of G. G. Pohl of Schönbaum near Danzig, the mass used in making these capsules was prepared by mixing together the following:

(*a*) An ammoniacal solution of keratin evaporated to the consistence of a syrup.

(*b*) An aqueous solution of wax-free shellac and borax, also of the consistence of a syrup.

(*c*) A small amount of an ammoniacal solution of colophony.

The efficiency of the keratin coated pill and the keratinized capsule, however, seems to have been somewhat exaggerated in the beginning as certain disadvantages in the use of both were brought to notice later, when they became more generally known to the medical profession.

Dr. Sahli[4] of Berne, Switzerland, pointed out the fact that the efficiency of the

[1] *Pharm. Centralh.*, 25, 577, 1884; from *Fortschr. d. Med.*, 15, 507, 1884.

[2] *Pharm. Ztg.*, 31, 432, 1886.

[3] D. R. Patent No. 35976, November 1885.

[4] *Deutsch. Med. Wchnschr.*, 23, 62, 1897.

keratin coating, in the case of the pill, and of the capsule manufactured from keratinized material depended to a large extent on the contents of the pill or capsule, and that pills or capsules containing certain substances were prone to swell and burst before reaching the intestines. He, therefore, undertook to discover a means whereby this disadvantage might be overcome and intestinal medication further improved. Realizing that the capsule was of more practical value than the pill, he directed his efforts toward perfecting a process of hardening the ordinary gelatin capsule[1] in such a manner that it would withstand the solvent action of the gastric juice, regardless of the contents, and still be completely dissolved in the intestines. After several unsuccessful attempts, in which he employed tannin, catechu, kino, tannic acid, chromic acid, *et cetera*, as the hardening agent, he called to his aid the pharmacist Hausmann of St. Gallen, Switzerland. Hausmann apparently turned the work over to his assistant, Dr. Weyland.

Shortly before Dr. Weyland became interested in the subject, there appeared on the market a new antiseptic powder under the name of "Glutol."[2] Chemically, this substance was formalin gelatin. It appears that Dr. Weyland was informed as to the composition and properties[3] of this preparation and made use of the information in his attempts at hardening the ordinary gelatin capsule. At any rate, he employed an aqueous solution of formaldehyde for this purpose, and obtained results so satisfactory that the process was patented by Hausmann in 1895, and the capsules were marketed soon after under the name of "Glutoidkapseln." The process as patented by Hausmann is as follows:[4]

> "Immerse the previously filled gelatin capsules for 18 minutes in an 0.8% aqueous solution of formaldehyde, wash with water and dry at 50° C."

The specifications state that the capsules thus treated dissolve in artificial pancreatic juice in 2 to 3 hours, that traces of uncombined formaldehyde may be removed by treatment with ammonia water, and that the degree of hardness may be varied by varying the strength of the formaldehyde solution or the length of the period of immersion.

Hausmann also secured a second patent[5] in which an aldehyde was employed as the hardening agent, namely, acroleïn. The process, very similar to that given above, is described in the patent literature as follows:

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[1] The ordinary gelatin capsule was already in common use at this time. It was invented by Mothes, a Frenchman, in 1833. Mothes and Dublanc applied for a patent on the same in 1834. The first elastic capsule was made by Adolph Steeger, an apothecary of Bukarest, in 1843. *Apoth.-Ztg.*, 12, 275, 1897.

[2] "Formalin gelatin" or "formaldehyde gelatin" was first brought to the notice of the medical profession by Dr. Schleich of Berlin. He called the substance "Glutol." *Therap. Monatsh.*, 10, 608, 1896.

[3] Dr. Arnold Voswinkel published a short article on the composition and properties of "Glutol" in March 1896. In this article, he calls attention to the insolubility of the compound in dilute acids. *Pharm. Ztg.*, 41, 222, 1896.

Dr. Weyland in an article entitled "Ueber Formaldehydegelatine" published during the same year (1896), but later, mentions having seen the publication of Voswinkel, *Pharm. Centralh.*, 37, 483, 1896.

[4] D. R. Patent No. 85,807, August 1895.

[5] D. R. Patent No. 124,678, August 1895.

"Immerse the previously filled gelatin capsules for 10 to 20 minutes in a 0.5 to 1.0% aqueous solution of allyl aldehyde (acroleïn), wash and dry at 30° to 50° C."

It will be observed that in both of the above processes, it is necessary that the capsules be filled previous to immersing them in the hardening fluid. This was found to be an inconvenience in ordinary practice as considerable time was consumed in drying the capsules treated in this manner. Hardening the capsules previous to filling by immersing in the aqueous formaldehyde solution was found to be impracticable as they became distorted on drying and could not be properly closed. Furthermore, capsules treated according to Hausmann's method were found to increase in hardness with age, finally becoming insoluble in the intestinal as well as the gastric secretions.

The problem of hardening the empty capsule without detracting from its practical value or therapeutic efficiency is said to have been solved by Dr. Hans Rumpel of Breslau. The following are the specifications of his patent[1] taken out in 1904:

1. "Immerse the open capsules for 15 to 20 minutes in a sufficient quantity of a mixture consisting of 35 parts by weight of a 40% aqueous solution of formaldehyde and 2 parts by weight of 90 to 91% alcohol by volume. Dry at room temperature."
2. "Immerse the open capsules for $^1/_2$ hour in a solution consisting of 2.5 kilos of acetone and 1 kilo of 35 to 40% aqueous solution of formaldehyde. Dry at room temperature."
3. "Immerse the open capsules for 10 minutes in a solution consisting of 1 kilo of a 40% aqueous solution of formaldehyde, 1 kilo of 90% alcohol and 2 kilos of ether. Dry at room temperature."
4. "Immerse the capsules for 20 minutes in a solution prepared by dissolving 80.0 grammes of chromic acid anhydride in 720 grammes of water and pouring the resulting solution slowly into 3.2 kilos of 90% alcohol. The solution should be chilled before immersing the capsules."

For Hardening Capsules Consisting of Two Parts.

"Immerse 500 of the opened capsules (20 mm. long × 5 to 6 mm. in dia.) for 1 to $1^1/_2$ minutes in 1000 grammes of a mixture consisting of 3 parts by weight of 35 to 40% aqueous formaldehyde solution and 10 parts by weight of 70% alcohol by volume. Remove the capsules from the liquid, spread out on blotting paper and dry at room temperature. After filling with the medicament, the capsules may be sealed by penciling with collodion or a solution of gelatin and again immersing in the formaldehyde solution."

Capsules treated according to Rumpel's process are at present being manufactured by the firm of Pohl in Schönbaum near Danzig[2] and are known in Europe as "Kapsulae geloderatae." In America, they are more commonly known as "Pohl's enteric capsules."[3] These capsules are, however, not for sale in the empty state, but are filled with various remedies and marketed by the firm of Pohl in the form of specialties.

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[1] D. R. Patent No. 167,318, October 1904.

[2] *Pharm. Centralh.*, 48, 256, 1907.

[3] *Drug. Circ.*, 58, No. 11, 64, 1914.

With the exception of the experiments of Vaudin, Donard and Labbé,[1] in 1906, on the use of concentrated solutions of maisin in alcohol or glacial acetic acid as the material for the manufacture of capsules, no further work along this line appears to have been attempted until the subject suddenly received attention in America in 1914. The American experimenters appear to have had no knowledge of the earlier work done in Europe, and the processes developed by them are, with one exception, similar to that patented by Hausmann as is shown by the following descriptions:

Method of Smith.[2]—"Immerse the filled capsules in a 10% aqueous solution of formaldehyde during 15 minutes. Wash in running water for 20 minutes and dry in a dish on a water-bath for 5 hours, or until free from the odor of formaldehyde."

Ballenger and Elder (Method No. 1).[3]—"Immerse the filled capsules for 1 minute in a dilution of 1 part of 40% formaldehyde solution to from 40 to 60 parts of water. The strength should vary with the aging allowed. From the time that the dilution mentioned is used, 2 weeks should be allowed to intervene before administering the capsules."

Ballenger and Elder (Method No. 2).[3]—"Place the capsules in an open box in a closed vessel in which they may be subjected to the vapor of Liquor Formaldehydi. About 15 Cc. of the solution should be used for each cubic foot of space in the closed vessel and should be placed on cotton or gauze in a saucer or tray. Six hours' exposure or less is sufficient for capsules which are not to be administered at once, while 12 hours may be necessary in preparing capsules for immediate use."

Method of DeLanney.[4]—"Number 00 capsules were soaked for a few hours in a 20% solution of formaldehyde and then dried. They became very brittle and somewhat distorted, but not so much as to prevent subsequent filling."

Method of Scoville.[5]—"Immerse the filled capsules for 30 seconds in a 1% aqueous solution of formaldehyde at ordinary temperature, drain them quickly, dry them, and store for 2 weeks before using."

Scoville calls attention to the fact that capsules treated as described by the American investigators increase in hardness with age and are unfit for use after about a year. Rumpel claims that capsules treated according to his process are not subject to this change. The final chapter in the history of the development of the enteric capsule, therefore, must be added at some future time.

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GENERAL USES OF DISINFECTANTS.*

BY L. E. SAYRE.

Disinfectants are used for the prevention of germ activated waste. They are

[1] Maisin is prepared from corn by treating the ground material first with benzol to remove the fat and then digesting with hot amyl alcohol for 8 hours. The amyl alcohol extract is filtered and the maisin precipitated by adding 3 volumes of benzol. Maisin is stated to be more resistant to the acid secretions of the stomach than either keratin or glutin and, in concentrated solution, to be more easily moulded into capsules than gelatin. *Bull. Comm.*, 33, 465, through "Year-Book Pharm. and Trans.," p. 142, 1906.

[2] Cited by E. F. Cook, *Am. J. Pharm.* 86, 185, 1914.

[3] *J. Am. M. Assoc.*, 62, 197, 1914.

[4] *The Military Surg.*, 35, 320, 1914.

[5] *The Southern Pharm. J.*, 7, 745, 1915.

* Presented before Kansas Academy of Science, a contribution for public information.