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The Solubility of Ephedrine in Liquid Petrolatum*

By Joseph Rosin, G. K. Eger and Harry Mack

Ephedrine base is extensively used as a therapeutic agent. It is generally formulated as a solution in light liquid petrolatum, commonly called "spray" or "inhalation." Accurate knowledge of the solubility of ephedrine in this solvent is, therefore, very desirable. There is, however, very little information on this subject in the literature. Moreover, ephedrine base is available in the form of a hemihydrate and also as the anhydrous article. The U. S. P. specifications permit both the hemihydrate and the anhydrous, and some difference in the degree of solubility might be expected.

The laboratory of the AMERICAN PHARMACEUTICAL ASSOCIATION (1) has reported the solubility of ephedrine in light and heavy liquid petrolatum at 25° C. It is not, however, clear from their report what type of ephedrine they used, whether anhydrous or the hydrated, and if the latter, how much water it contained and whether or not it was dried before use in their determinations. As will be shown, the water content of the ephedrine has a profound effect on the degree of solubility.

In addition to the solubility at 25° C. we also determined the solubility at 20° C.—a temperature which is frequently met with in the stock rooms of manufacturers and retail pharmacists.

EXPERIMENTAL

The solubility determinations at 20° and 25° C. were made with different lots of ephedrine and of liquid petrolatum. The hydrated ephedrine used at 20° C. showed by titration 95.26% anhydrous ephedrine, and by toluene distillation it indicated 4.65% of water. The "anhydrous" ephedrine titrated 99.8%, and by toluene distillation showed 0.27% water. The light liquid petrolatum used in these determinations had a specific gravity of 0.845^{25}_{25}.

* Presented to the Scientific Section of the A. PH. A., Detroit meeting, 1941.

For the solubility determinations at 25° C. the hydrated ephedrine used titrated 95.12% of anhydrous ephedrine and the "anhydrous" alkaloid 99.37%. The light liquid petrolatum used in these tests had a specific gravity of 0.852, and the heavy, 0.868 at 25/25. The kinematic viscosity at 37.8° C. of the light oil was 0.183, and of the heavy, 0.438.

The solubilities at 20° C. were made as follows, except 24[a] which was obtained with the ephedrines and the oils used for solubilities at 25° C.

The liquid petrolatum was heated between 45° and 50° C. An excess of the ephedrine amounting to 50–100% of the assumed solubility was added, and the mixture shaken in a mechanical shaker for about 6 hours. After allowing to stand over night or longer, at room temperature, the mixture was maintained at 20° C. for 5 to 6 hours with frequent agitation. A portion of the mixture was filtered through a glass filter, and the ephedrine determined in an accurately measured volume of 10 or 15 cc. of the clear filtrate. The remainder of the mixture was again shaken at room temperature in a mechanical shaker for several hours and on the following day kept at 20° C. for 5 to 6 hours with frequent shaking, and the ephedrine again determined in a filtered portion. The results are shown in Table I.

Table I.—Solubility of Ephedrine in Light Liquid Petrolatum at 20° C.

Number of Hours of Contact	Hemihydrated Ephedrine Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.	Anhydrous Ephedrine Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.
48	0.87	2.26
96	0.81	2.24
24[a]		2.207
Av.	0.84	2.235

The solubility at 25° C. was determined in a similar manner, except that the petrolatum was not preheated. The ephedrine was added to the petrolatum at room temperature (about 25° C.), the mixture shaken at room temperature for 6 hours or longer, and before withdrawal of a portion for the determination, the mixture was maintained at 25° C. for 5 to 6 hours with frequent shaking. The solubility at 25° C. was also determined for light and heavy liquid petrolatum. The results are shown in Table II.

The extraction of the alkaloid from the oil solution was effected with a moderate excess of approximately half-normal sulfuric acid. The acid solution was alkalinized with sodium hydroxide and shaken with 6 to 8 portions of ether. The combined ether extracts were shaken with two 10-cc. portions of water to remove any sodium hydroxide, and the water washings were extracted with two 10-cc. portions of ether and the latter added to the main ether solution. The bulk of the ether was allowed to evaporate at practically room temperature, then a measured excess of twentieth-normal sulfuric acid added. The mixture was then heated gently to expel all the ether, cooled, and the excess acid titrated

Table II.—Solubility of Ephedrine in Light and Heavy Liquid Petrolatum at 25° C.

Number of Hours of Contact	Light Liquid Petrolatum: Hemihydrated Ephedrine, Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.	Light Liquid Petrolatum: Anhydrous Ephedrine, Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.
36	1.240	3.137
	1.248	3.111
60	1.237	3.149
	1.243	3.134
Av.	1.242	3.133

Number of Hours of Contact	Heavy Liquid Petrolatum: Hemihydrated Ephedrine, Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.	Heavy Liquid Petrolatum: Anhydrous Ephedrine, Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.
36	1.092	2.842
	1.118	2.855
60	1.110	2.876
	1.119	2.920
Av.	1.110	2.873

with fiftieth-normal sodium hydroxide using methyl red indicator.

In the determinations at 25° C., and also the one marked 24° in Table I, the acid solution from the extraction of the oil was saturated with sodium chloride and alkalinized with an excess of 10% ammonia water instead of sodium hydroxide. By saturating the solution with sodium chloride the complete extraction of the alkaloid was attained with four portions of ether. Also, the use of ammonia water eliminated the necessity of washing the ether with water. Any ammonia retained in the ether solution was removed by gentle suction.

The results reveal a striking effect of the 5% of water in the hydrated ephedrine on its solubility in liquid petrolatum. The ratio of the solubility of the hydrated ephedrine to the anhydrous is 1:2.67 at 20° C., and 1:2.52 at 25° C. in light liquid petrolatum. For the heavy liquid petrolatum the ratio is 1:2.58 at 25° C. At the temperatures of 20° and 25° C. substantially anhydrous ephedrine is, in round numbers, $2^1/_2$ times as soluble as the hemihydrate.

It is interesting to call attention to another curious distinction in the properties of hydrated and anhydrous ephedrine. Whereas anhydrous ephedrine melts at about 34° C., the hemihydrate melts at about 40° C.

The difference in the degree of solubility between 20° and 25° is also noteworthy. At 20°, 100 cc. of the solution hold 0.84 Gm. of ephedrine calculated as anhydrous, and at 25° 1.24 Gm.—a difference of 0.40 Gm. or a little over 30%. The difference in solubility of the anhydrous at 20° and 25° is 0.64 Gm. or a little over 20%. We observed crystallization of ephedrine to take place from a saturated solution in light liquid petrolatum prepared at 25° after the solution has stood over night during which the temperature was only a few degrees below 25° C.

The results presented in Table II indicate that the difference in the solubility at 25° C. between the light and the heavy liquid petrolatum used is only about 10%.

REFERENCE

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Enteric Coating*

By Paul V. Maney† and Ruldoph A. Kuever‡

INTRODUCTION

Interest in the mode of administering medicine in individual doses, protected by enteric coating, is on the increase. The purpose is to deliver the medication to the intestinal tract for optimum disintegration in the duodenum or jejunum. Drugs delivered in such a manner are of value because:

1. Prolonged contact of highly irritating concentrations with the mucous membrane of the stomach is eliminated.
2. Possible interference with the digestive processes of the stomach by forming precipitates with pepsin and peptones is avoided.
3. Those that are otherwise rendered inactive by the secretions of the stomach, are delivered to the intestinal tract in their therapeutically active form.
4. Delivery of a high concentration to the desired portion of the intestinal tract is possible.
5. Recently it has been disclosed that it may be possible, by means of administering medicine with delayed action, to avoid sleep interruption.

Many drugs are at present administered in enteric form. A common list follows: sodium and potassium chloride; magnesium sulfate; potassium nitrate; ammonium nitrate; ammonium chloride; ferrous sulfate; salts of salicylic acid; methenamine, sodium biphosphate combinations; mandelic acid, ammonium chloride combinations; emetine, and bismuth compounds; aminophyllin;

* Presented to the Scientific Section, A. PH. A., Detroit meeting, 1941.

† Abstract from a thesis presented to the Graduate College of the State University of Iowa in partial fulfilment of the requirements for the degree of Master of Science.

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