shown by oxidation with hot potassium permanganate to *p*-hydroxy isopropyl benzoic acid, melting at 154–155° C.

The oil of higher boiling point was saponified by 3 per cent alcoholic potassium hydroxide for two hours and then submitted to repeated fractionation at 10 mm. into three portions.

Fraction.	Per Cent.	Refraction.
...– 95°	1.07	1.4778
95–120	39.69	1.4744
120–125	1.84	1.4885
Above 125 and loss	23.03	....
Total	65.63	

Borneol.—The first two consisted almost entirely of borneol which was separated in the crystalline state, melting point 203–204° C., phenylurethane 138° C. Oxidation of the oil gave camphor, identified by odor and by the semicarbazone melting at 235–236° C.

Although terpineol was suspected, no nitrosochloride could be obtained from the second fraction. Also cadinene was not present in the last distillate nor in the residue, since no hydrochloride could be obtained.

Combined Acids.—The alkaline liquor from saponification was concentrated, acidified and then distilled with steam. Practically all of the acid was found in the distillate and appeared to consist almost entirely of acetic acid. This was identified as before by conversion to ethyl acetate.

Summary.—The fresh leaves and branches gave 0.36 per cent of oil whose composition was found to be about: bornyl acetate 40; borneol 11; alpha phellandrene, cymene and probably camphene 35; acetic acid 0.2; phenols 0.5; compounds of higher boiling point and loss 14 per cent.

DRUG EXTRACTION. IV. THE EFFECT OF VARIATION IN SOLVENTS ON THE EXTRACTION OF JALAP.[1,2]

BY WILLIAM J. HUSA[3] AND PAUL FEHDER.

Jalap having been selected as a typical resin-containing drug, a study was made of the effect of solvents in relation to swelling, penetration, imbibition and extraction.

EXPERIMENTAL PART.

Material Used.—From a reputable dealer, a 125-lb. shipment of Jalap U. S. P. was obtained, consisting of 10 lbs. whole drug, 40 lbs. of 60 mesh and 25 lbs. each of 20, 40 and 80 mesh, according to the following specifications: "The above samples are to be prepared by taking 125 lbs. of jalap, selecting a representative sample of 10 lbs. for the whole root and a representative 40-lb. sample to be milled to 60 mesh, and three separate 25-lb. samples to be milled to 20, 40 and 80 mesh, respectively. Each portion is to be milled separately so that all portions will be as nearly alike as possible, except for the difference in milling."

[1] Presented before the Scientific Section, A. PH. A., Washington, D. C., 1934.

[2] This paper is based on a thesis presented to the Graduate Council of the University of Florida by Paul Fehder, in partial fulfilment of the requirements for the degree of Master of Science in Pharmacy.

[3] Head Professor of Pharmacy, University of Florida.

A thorough pharmacognostical study showed that the shipment conformed with the U. S. P. requirements.

Swelling of Jalap in Solvents.—The swelling effect of solvents was determined by the technique (1) of measuring the width of thin strips of jalap tissue before and after addition of solvents using a filar micrometer. The strips, 0.25 to 0.50 mm. in width, were cut from sections obtained by use of a small carpenter's plane. The results are expressed on a percentage basis, taking the width of the dry strips as 100 and each value is the average of several determinations. The thickness of the sections was measured by means of a micrometer caliper.

TABLE I.—SWELLING EFFECT OF SOLVENTS ON SECTIONS OF DECORTICATED JALAP TISSUE.

			Width of Section (on Basis Dry = 100). After Time in Minutes.								
		Average Thickness of Section	Dry.	Wet.							
Solvent.	Section.	in Mm.	0.	1.	5.	10.	20.	40.	60.	100.	120.
Water	Cross	0.042	100	133	134	134	133	133	134	134	133
Alcohol	Cross	0.044	100	101	103	106	108	110	109	110	110
Alcohol	Longitudinal	0.066	100	100	100	105	108	111	112	117	117

The results in Table I indicate that swelling equilibrium is attained during the first minute in water but only after 40 minutes or more in alcohol. Further tests showed that longitudinal sections swelled 47% during the first minute in water on the average; the swelling was 60–70% in sections containing much transporting tissue and 35–45% in sections consisting chiefly of starch-bearing parenchyma. The initial swelling of longitudinal sections in alcohol likewise varied from 6% in sections containing much transporting tissue to 0% in those consisting mostly of starch-bearing parenchyma. During the first minute corticular tissue showed neither expansion nor contraction in alcohol, while in water pure cork tissue swelled to about twice its original size, outer bark with a large proportion of cork swelled about 40% and outer bark with little cork swelled about 25%.

Penetration of Solvents into Jalap Blocks.—Using a special machine saw at the planing mill, blocks were cut with the grain running the long way, the blocks being 10 mm. square and averaging 2.4 mm. in thickness. Using three blocks for each solvent, these were immersed in water, alcohol and glycerin, respectively, contained in bottles. The bottles were then suspended in a Freas large-size water thermostat, at 30° C. After various intervals, the blocks were removed, excess solvent taken up with filter paper, and the blocks weighed and measured. The chances for error in measuring swelling with a micrometer caliper between surfaces that are somewhat flexible are considerable and may lead to deviations that would not be shown in similar measurements between rigid surfaces. However, by taking the average of several blocks, the degree of error is reduced to an extent which allows helpful conclusions to be drawn.

TABLE II.—PENETRATION OF LIQUIDS INTO JALAP BLOCKS.

(Average Weight of Three Blocks Stated on Basis: Dry Weight = 100%.)

	After Time Intervals in Hours.													
	0.	1.	2.	3.	9.	12.	24.	48.	72.	96.	216.	552.	720.	888.
Water	100	194	224	238	208	213	250	243	238	242	233	229	233	228
Alcohol	100	141	141	141	104	104	143	133	135	138	130	131	133	143
Glycerin	100	130	130	130	102	101	130	121	121	122	117	125	130	141

As shown in Table II, the liquids penetrated rapidly during the first hour. Between three hours and nine hours there was a sharp drop in weight of the blocks in each of the three liquids probably due to loss of soluble constituents, followed by an increase in weight, reaching a maximum at 24 hours and showing only slight changes thereafter.

TABLE III.—SWELLING OF JALAP BLOCKS IN LIQUIDS.

(Average Thickness of Three Blocks Stated on the Basis: Dry = 100%.)

	After Time Intervals in Hours.													
	0.	1.	2.	3.	9.	12.	24.	48.	72.	96.	216.	552.	720.	888.
Water	100	109	119	124	131	130	127	127	128	126	123	123	120	121
Alcohol	100	100	100	100	102	101	101	101	101	101	100	101	101	101
Glycerin	100	100	99	99	99	99	98	98	98	98	98	100	101	102

As shown in Table III swelling by water reaches a maximum of 31 per cent in nine hours. From then on, the thickness of the blocks gradually decreases, due apparently to the loss of water-soluble substances. Alcohol causes very little swelling; a maximum of 2 per cent is observed at the end of nine hours. Glycerin causes a slight shrinkage, due possibly to the abstraction of water from the cells, followed by recovery and very slight swelling.

Effect of Solvents on Powdered Jalap.—In studying the effect of solvents on powdered jalap, a filtration method devised in the present study but previously described by Husa and Magid (1) was used. The filtrates were assayed for total resins by Warren's method (2). The drug was found to contain 7.87 per cent of resin by the U. S. P. method of assay and 6.87 per cent by Warren's method of assay. Warren reported results of his collaborators, showing a similar lower result by his method than by the U. S. P. method, due, apparently, to removal of coloring matter, sugars and other water-soluble extractives from the resin by Warren's method.

TABLE IV.—EFFECT OF SOLVENTS OF JALAP IN NO. 60 POWDER.

Period of Maceration.	Weight in Gm. of. Liquid in Marc.	Dry Marc.	Filtrate.	Loss of Menstruum.	Total Extractive.	Resins in Filtrate.
			Absolute Alcohol.			
15 min.	7.9	8.42	81.5	1.2	0.69	0.55
1 hour	7.9	8.40	81.9	0.8	0.70	0.57
5 hours	8.3	8.39	81.5	0.8	0.72	0.57
24 hours	8.3	8.32	81.8	0.5	0.78	0.57
			Alcohol.*			
15 min.	8.7	8.22	81.5	1.0	0.88	0.61
30 min.	8.4	8.18	81.5	1.2	0.96	0.59
1 hour	8.9	8.18	81.0	0.8	0.93	0.56
5 hours	9.1	8.11	81.1	0.6	1.01	0.57
24 hours	8.5	8.02	81.8	0.6	1.08	0.58
			Alcohol 9 Vol.—Water 1 Vol.			
15 min.	9.9	7.42	80.8	0.6	1.68	0.58
1 hour	10.2	7.36	80.7	0.6	1.76	0.57
5 hours	9.5	7.21	81.6	0.5	1.90	0.59
24 hours	9.5	7.15	81.5	0.6	1.96	0.59

			Alcohol 4 Vol.—Water 1 Vol.			
15 min.	10.8	6.81	80.2	0.7	2.29	0.57
1 hour	11.7	6.74	79.5	0.5	2.34	0.56
5 hours	11.4	6.75	79.5	0.8	2.34	0.56
24 hours	11.6	6.76	79.5	0.6	2.33	0.56
			Alcohol 3 Vol.—Water 2 Vol.			
15 min.	13.0	6.34	78.4	0.6	2.77	0.50
1 hour	12.9	6.34	78.2	0.7	2.76	0.49
5 hours	13.1	6.40	78.0	0.7	2.70	0.49
24 hours	13.1	6.38	78.2	0.6	2.74	0.50
			Alcohol 1 Vol.—Water 2 Vol.			
15 min.	17.1	6.52	73.6	0.6	2.57	0.22
1 hour	17.0	6.46	74.0	0.4	2.66	0.18
5 hours	17.1	6.32	73.9	0.5	2.80	0.20
24 hours	16.7	6.10	74.4	0.5	3.00	0.19
			Alcohol 1 Vol.—Water 7 Vol.*			
15 min.	22.1	6.7	68.4	0.9	2.4	Less than 0.1%
1 hour	23.7	6.6	67.1	0.7	2.5	Less than 0.1%
5 hours	23.5	6.6	66.9	1.0	2.5	Less than 0.1%
24 hours	22.8	6.5	68.1	0.7	2.6	Less than 0.1%
			Distilled Water.*			
15 min.	27.0	6.8	63.2	0.9	2.3	Negligible
1 hour	27.5	6.7	62.2	1.6	2.4	Negligible
5 hours	28.7	7.2	60.3	0.4	2.1	Negligible
24 hours	27.9	6.7	61.5	0.9	2.6	Negligible

* Conducted at room temperature; all others conducted in thermostat at 30° C.

From the results in Table IV, it appears that the extraction of resin is as complete in 15 minutes as in 24 hours, but the percentage of total extractive in the filtrates increases with time. With higher percentages of alcohol, imbibition decreases and less extraneous matter is extracted along with the resins. The higher percentages of alcohol extract the same amount of resin but with alcohol 4 vol.—water 1 vol. and more aqueous mixtures, less resin is extracted.

DISCUSSION OF RESULTS.

Effect of Solvents on Thin Strips.—Swelling equilibrium in thin strips of jalap tissue was reached within 1 minute, as was the case with chestnut wood (1) and the wood of belladonna root (3). For the same type of jalap tissue, swelling across the grain in liquids was greater in longitudinal sections than in cross sections. Perhaps this means that in a cross section of a fibre or vessel, there is more mechanical resistance to swelling than when the fibre or vessel is split longitudinally.

Penetration and Swelling of Jalap Blocks.—There is no direct relationship between the rate of swelling and the rate of increase in weight. At nine hours, the swelling with water and with alcohol is at a maximum, while the weight of the blocks is at a minimum. The blocks immersed in alcohol gained about 40% in weight, while the swelling was not over 2%.

Imbibition and Extraction of Powdered Jalap.—Using belladonna root in No. 40 powder, Husa and Magid (1) found that imbibition of alcohol-water mixtures increased with decreasing alcohol content; similar results were obtained in the present study using jalap in No. 60 powder. As far as present results go, alcohol of U. S. P. strength and absolute alcohol seem to be the best solvents for the extraction of jalap resin; with more aqueous mixtures a greater proportion of inert extractive is removed along with the resin.

SUMMARY.

Alcohol, water and glycerin have been studied from the standpoint of swelling effects and rate of penetration, using jalap in the form of thin strips and blocks. Using a series of alcohol-water mixtures in a study of imbibition and extraction of powdered jalap, it was found that with increasing concentration of alcohol there is a decrease in imbibition and a decrease in the proportion of extraneous matter extracted along with the resins.

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THE APPLICATION OF STATISTICAL METHODS TO PHARMACEUTICAL RESEARCH. IV. METHODS OF RECORDING DRUG ACTION.

BY J. C. MUNCH[1] AND F. E. GARLOUGH.[2]

How much of a drug is required to produce a definite action? This question constantly arises in discussing the narcotic potency of a drug like cocaine, the relative soporific value of several barbiturates, the anesthetic concentration of ether, the cathartic dose of cascara, the lethal or the convulsant dose of strychnine. Official compendiums list the "doses" of drugs as a matter of convenience and of practicality. Many original articles dealing with quantitative measures of drug action, as well as compilations of toxic and lethal doses (9) give tables showing doses per animal or per kilo, which are withstood, which produce injury, which produce the desired type of response, or which produce death within stated time limits.

The general impression is regarding relationship of dose to effect results from the usual method of laboratory study. A series of doses of a product is given to animals and the effects observed. Too small a dose fails to produce discernible or detectable effects: this is a "subminimal" or "subliminal" quantity. As the dose is increased there is a change in the normal appearance of the test animal, which is attributed to the action of the drug. After showing the characteristic response for some time, the effect passes off and the animal recovers. The smallest concentration that produces such a response is often called the "minimum effective dose" (MED). Increases in dose cause greater intensity or prolongation of action until a quantity is reached that causes some of the test animals to die. This dose may be

[1] Director, Pharmacological Research, Sharp and Dohme, Philadelphia, Pa., and Consulting Pharmacologist, Bureau Biological Survey, Washington, D. C.
[2] Director, Control Methods Research Laboratory, Denver, Colo.