Keyphrases

Homatropine HBr—stability determination
Cerimetric titration, direct—analysis
Hydrolysis, homatropine HBr—detection

Technical Articles

Study on Dosage Variations of Individual Capsules and Tablets of Desipramine and Imipramine Hydrochloride

By S. AHUJA, C. SPITZER, and F. R. BROFAZI

Automated methods of analyses based on UV absorption of desipramine and imipramine hydrochloride were developed in order to obtain information on intercapsule and intertablet variations of the following six dosage forms: desipramine hydrochloride capsules 10, 25, and 50 mg. and imipramine hydrochloride tablets 10, 25, and 50 mg. The automated methods require the use of an automatic analyzer and the same manifold is used for all six dosage forms. A careful review of the results obtained on individual capsules and tablets reveals that almost all of the capsules and tablets analyzed by these methods were within ±15 percent limits of the indicated dosage.

THE PHARMACEUTICAL INDUSTRY has long been interested in obtaining more information on drug content of individual tablets or capsules to assure high standard of drugs, from the standpoint of production, quality control, and therapeutic activity. This information is necessary for establishing suitable control measures in production and quality control in order to obtain reasonable dosage uniformity of drugs.

Analytical methods which are based on the analysis of sample composites cannot provide reliable indications of content uniformity because they express product dosage on individual dosage forms, whereas the analyses are actually run on sample composites. Therefore, such analyses not only average out small variations in composition between individual tablets or capsules, but may also mask large deviations.

Quantitative analysis of the active ingredient itself, in each of the individual capsules or tablets, should provide a good approach for studying dosage variations. However, this approach was rather difficult to carry out until the recent introduction of automated methods of analyses.

The automated methods of analyses based on UV absorption of desipramine hydrochloride[1] [10,11 - dihydro - 5 - (3-methylaminopropyl) - 5*H*-dibenz[*b*,*f*] azepine hydrochloride] and imipramine hydrochloride[2] [10,11 - dihydro - 5 - (3-dimethylaminopropyl) - 5*H*-dibenz[*b*,*f*]azepine hydrochloride] were developed with the object of gaining information on intercapsule and intertablet variations on the following six dosage forms: (*a*) desipramine hydrochloride capsules (hard gelatin) 10, 25, and 50 mg., and (*b*) imipramine hydrochloride tablets (sugar coated) 10, 25, and 50 mg.

A variety of methods (1–8) have been used for the analysis of desipramine and imipramine hydrochloride. For several years manual UV methods have been used for the analysis of these compounds in these laboratories. These pro-

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[1] Pertofrane, Geigy Chemical Corp., Ardsley, N. Y.
[2] Tofranil, Geigy Chemical Corp., Ardsley, N. Y.

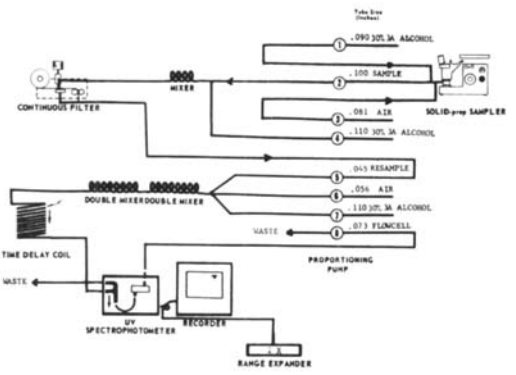

Fig. 1—Flow diagram.

cedures were automated by the use of the automatic analyzer.[3]

EXPERIMENTAL

Materials and Methods—Figure 1 shows a flow diagram of the analytical system including tubing sizes. The Solidprep sampler is programmed to operate at a rate of 13 samples/hr. The sample (tablet or capsule) is deposited in a cup placed on the turntable of the sampler. In turn, each sample is dumped into the homogenizer and homogenized with 125 ml. of 30% 3A alcohol[4] and a 0.9 ml./min. sample (segmented with air) is pumped from the sampler. The sample is diluted with 30% 3A alcohol, mixed, and filtered with the continuous filter. About 17% of it is resampled and diluted with additional 30% 3A alcohol, segmented with air, mixed with two double mixers, and then passed through a time delay coil.

The suitably diluted sample thus obtained is passed through a 15-mm. tubular continuous flow cell and its absorbance is recorded at an appropriate wavelength (imipramine = 250 mμ and desipramine = 252 mμ). Standards are run at various intervals to provide a means of sample concentration calculation and also to keep a check on any instrumental variations. The same manifold is used for all of the formulations and can handle concentrations of imipramine and desipramine ranging from 10 to 50 mg. per sample (tablet or capsule). Range Expander at 2× setting is used only for 10-mg. dosage forms.

The manifold was designed so that it can handle all six dosage forms without any loss of time in changeover procedures. Thirteen determinations can be made per hour with the automated methods as compared to 10 per day with the manual methods.

[3] AutoAnalyzer, Technicon, Chauncey, N. Y.
[4] US Industrial Chemical, Newark, N. J.

RESULTS AND DISCUSSION

A linear relationship was observed between the concentration of imipramine and desipramine hydrochloride and absorbance in the range of concentrations studied for this investigation. The precision of the method was checked by running standards and synthetic formulations (prepared in a manner similar to commercial formulations). Table I shows the precision of the results obtained on standards in various concentrations.

The percentage recovery (an average of 10 individual determinations) of two synthetic formulations, each containing 50 mg. of imipramine and desipramine hydrochloride, was 100.2% (*SD* = ±0.94) and 100.1% (*SD* = ±0.91), respectively. By running placebos of these formulations, it could be shown that there was no significant interference from the excipients. Examples of the recordings obtained for these formulations are shown in Figs. 2 and 3.

In order to study dosage variation a very large number of individual capsules (590) and tablets (730) were analyzed by these methods. The distribution of dosage in each of these dosage forms is presented in the form of a histogram in Figs. 4–9, where the ordinate indicates the number of capsules or tablets, and the abcissa, the number of milligrams of active ingredient present in an individual capsule or tablet. The capsules and tablets used for this study were randomly selected from several production batches, where possible, in order to obtain a good overall picture of dosage variation. The results on interbatch and intrabatch variations will be the subject matter of another publication. The results of the present investigations are summarized in Table II.

Of the 590 individual desipramine capsules analyzed, over 94% were within ±10% limits of the indicated dosage while 100% were within ±15% limits of indicated dosage. Of the 730 individual imipramine tablets analyzed, over 90% were within

Table I—Precision of the Automated Methods

No.	Sample	Results (Av. Abs.)	No. Determinations	Range Expander	*SD*
1	Imipramine HCl, 50 mg.[a]	0.372	10	—	±0.004
2	Imipramine HCl, 25 mg.[a]	0.176	10	—	±0.003
3	Imipramine HCl, 10 mg.[b]	0.152	10	2×	±0.003
4	Desipramine HCl, 50 mg.[a]	0.403	10	—	±0.004
5	Desipramine HCl, 25 mg.[a]	0.191	10	—	±0.001
6	Desipramine HCl, 10 mg.[b]	0.170	10	2×	±0.002

[a] In solid form. [b] In solution form.

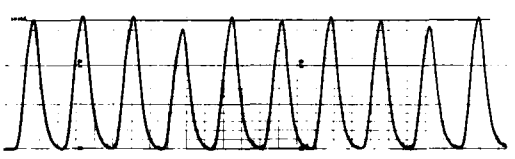

Fig. 2—Typical recording of desipramine capsules, 10 mg.

TABLE II—DOSAGE VARIATION OF DESIPRAMINE CAPSULES AND IMIPRAMINE TABLETS

Dosage, mg.	% Capsules or Tablets Within Indicated Dosage							
	± 2%		± 5%		± 10%		± 15%	
	Tabs.	Caps.	Tabs	Caps.	Tabs.	Caps.	Tabs.	Caps.
10	27.7	32.5	57.4	65.0	90.3	96.7	99.4	100.0
25	38.1	49.7	79.6	67.8	99.2	94.1	100.0	100.0
50	45.2	42.0	82.9	88.7	99.0	100.0	100.0	100.0

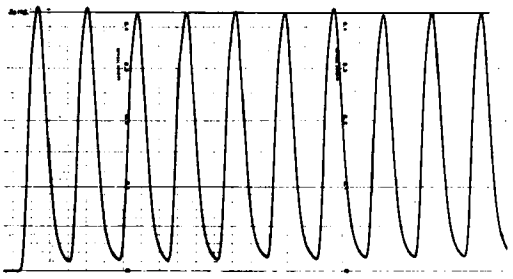

Fig. 3—Typical recording of imipramine tablets, 50 mg.

±10% limits of indicated dosage, and all except one tablet (10 mg.) were within ±15% limits of indicated dosage. The results, therefore, very strongly suggest that in the case of these capsules, the content uniformity is at least as good, if not better than that of tablets, in the dosage range studied for these formulations.

The current specifications for tablets requiring a content uniformity test are: the first 10 tablets analyzed out of a representative sample of 30 tablets (or 29 out of 30 tablets) should be within the limits of 85 and 115% of the average of the specified tolerances in the monograph. A content uniformity test for capsules is presently being considered for the new editions of USP and NF. Needless to say, these capsules and tablets would have passed the content uniformity test of tablets of the compendia. Furthermore, these results provide some indications as to the type of specifications that could be set for capsules.

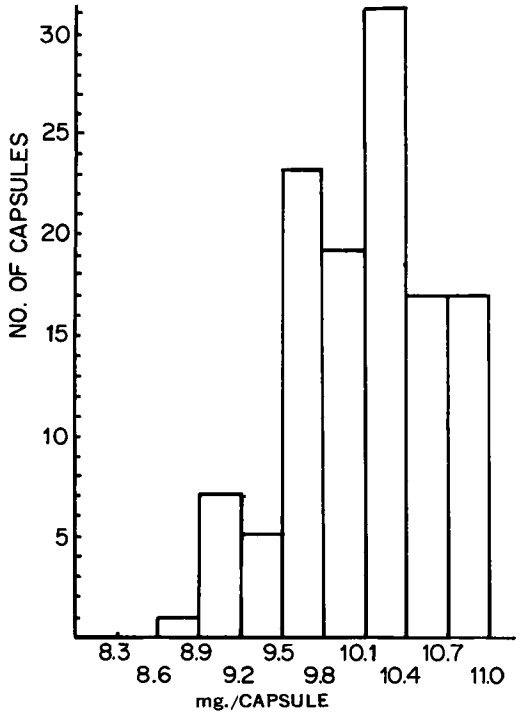

Fig. 4—Histogram of desipramine capsules, 10 mg.

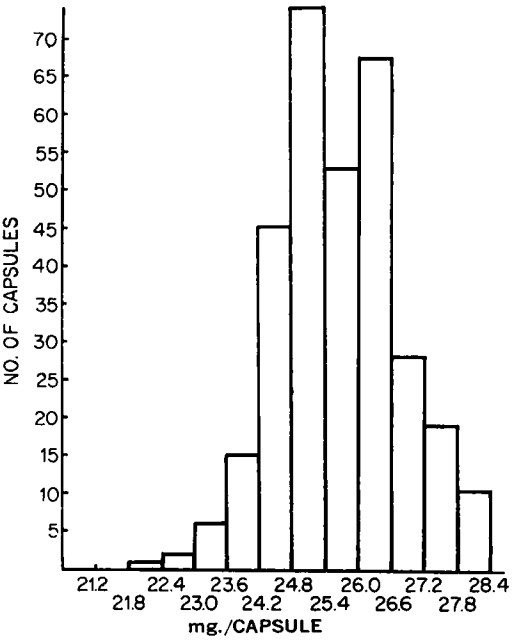

Fig. 5—Histogram of desipramine capsules, 25 mg.

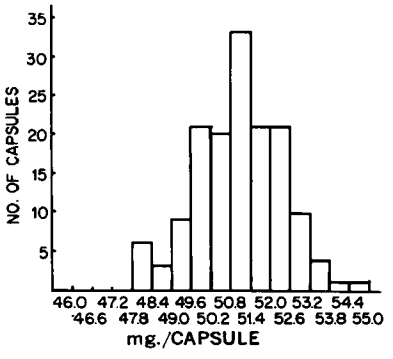

Fig. 6—Histogram of desipramine capsules, 50 mg.

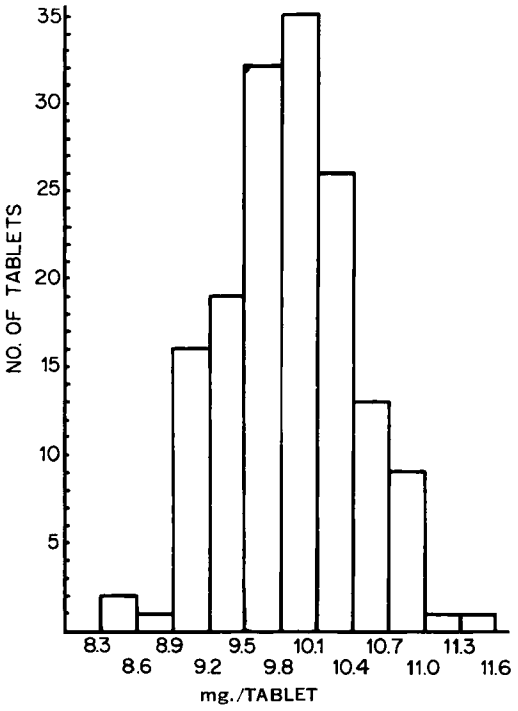

Fig. 7—Histogram of imipramine tablets, 10 mg.

CONCLUS ONS

A careful review of the results obtained from a large number of individual capsules and tablets reveals that of the 1,320 individual capsules and

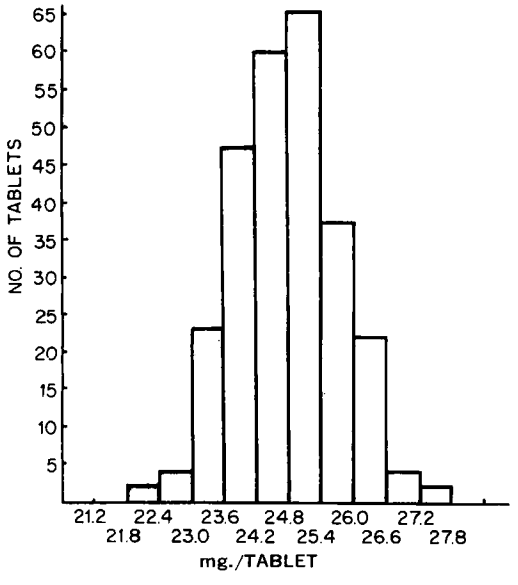

Fig. 8—Histogram of imipramine tablets, 25 mg.

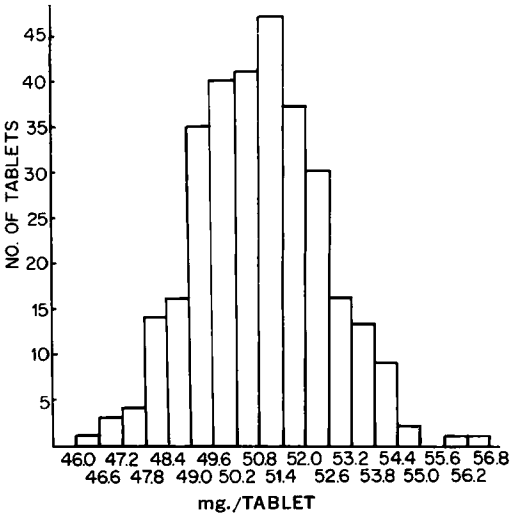

Fig. 9—Histogram of imipramine tablets, 50 mg.

tablets analyzed by the automated methods, only one tablet (10 mg.) was found to be outside the ±15% limits of the indicated dosage. Therefore, it may be logically concluded that with these formulations and with the equipment used to manufacture these tablets and capsules,[5] it is possible to produce capsules with dosage uniformity comparable to that of tablets.

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[5] Hard-shelled gelatin capsules (No. 4), used for these formulations, are filled with the Zanasi machines. The percentages (w/w) of the active ingredient in the capsule fills of the 10, 25, and 50-mg. capsules are 5.50, 13.75, and 27.50, respectively.

Keyphrases

Dosage variation—individual capsules, tablets
Desipramine HCl capsules, individual—analysis
Imipramine HCl tablets, individual—analysis
UV spectrophotometer—analysis
Diagram—automated apparatus