from the tablet mass. No difficulties were encountered with the remainder of the preparations.

CONCLUSION

Several methods are described for the identification of 13 substituted phenothiazines with tranquilizing properties. The methods are rapid and the manipulative techniques are simple.

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Stability Assays of Pharmaceutical Preparations by Quantitative Paper Chromatography II

Quantitation by Spectrophotofluorometry

By HENRY R. ROBERTS and MARIA RITA SIINO

A quantitative paper chromatographic method has been developed which is routinely used as a stability assay for estrogenic hormones in castor oil and tablet formulations. The method involves: (*a*) A separation of the estrogenic hormone from interfering degradation products. (*b*) The location of the estrogenic hormone on the chromatogram by the guide strip technique employing a chromogenic agent. (*c*) The elution of the estrogenic hormone from the chromatogram. (*d*) A quantitative spectrophotofluorometric analysis of the eluate. Recoveries in excess of 95% are obtained by simultaneously chromatographing replicates of standard and sample solutions on the same chromatogram. A detailed account of the procedure is presented using as examples the assay of estradiol valerate in castor oil formulations and ethinyl estradiol in tablets.

RECENTLY we have described methods for the quantitative determination of hormone preparations using paper chromatographic separations followed by spectrophotometric analysis (1). In this paper we wish to report on techniques which permit the quantitation of estrogens in ethanol eluates by spectrophotofluorometry. The examples chosen are the quantitative determination of two estradiol derivatives, estradiol valerate in castor oil and ethinyl estradiol in tablets.

The sensitivity of the method permits the chromatography and quantitation of 10 and 20 mcg. quantities. This is important since estrogens, because of their physiological potency, are generally compounded in low concentrations, for example, 0.5% in oil formulations and 0.05% in tablets.

Fluorometric methods may be classified according to whether the fluorescence measured is that of the compound in its native state or is induced by chemical transformations. Most accepted procedures for the quantitation of estrogens fall in this second category. The fluorescence is developed in sulfuric acid and measured in the visible range (2).

The development of the spectrophotofluorometer, capable of activating and measuring fluorescence throughout the visible and ultraviolet regions, has revealed the presence of useful ultraviolet fluorescence in many compounds not previously known to fluoresce in solution.

Duggan, *et al.* (3), in studying the fluorescent properties of a number of compounds of biologi-

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The authors wish to thank Mr. Raymond Poet for his instructions and help in the use of the spectrophotofluorometer.

TABLE I.—PAPER CHROMATOGRAPHIC CONDITIONS FOR ASSAY OF ESTROGENIC HORMONES

Compound	Paper Impregnating Solution	Developing Solvent	Time, hr.
Estradiol Valerate	20% Carbitol in Chloroform	Methylcyclohexane saturated with Carbitol	3
Ethinyl Estradiol	25% Propylene Glycol in Chloroform	Toluene saturated with Propylene Glycol	16

cal interest found that estradiol fluoresced in the ultraviolet region in the absence of sulfuric acid.

Based on this observation, a sensitive quantitative paper chromatographic assay has been developed which is used routinely for the analyses of estradiol derivatives in castor oil and tablet formulations.

EXPERIMENTAL

The paper chromatographic procedure involves essentially four steps: (*a*) The separation of the intact estrogenic hormone from interfering degradation products. (*b*) The location of the intact estrogenic hormone on the chromatogram by the guide strip technique employing a chromogenic agent. (*c*) The elution of the intact estrogenic hormone from the chromatogram. (*d*) A quantitative spectrophotofluorometric analysis of the eluate.

Preparation of Standard

The reference standard solution should contain 0.2 mg. of the estrogenic hormone per ml. of solution. In a volumetric flask, the appropriate amount of steroid is dissolved in the smallest volume of N,N-dimethylformamide. Then methyl isobutyl ketone is added to the mark. The reference standard material should be from the same lot as the formulation undergoing analysis.

Preparation of Sample

Oil Preparations.—For the assay of estradiol valerate in castor oil, the amount of sample which will yield, based on theory, 0.2 mg. of the hormone per ml. of solution is weighed into a volumetric flask, dissolved and diluted to the mark with methyl isobutyl ketone.

Tablet Preparations.—For the assay of ethinyl estradiol in tablets containing ethinyl estradiol and norethindrone acetate,[1] 10 tablets are reduced to a fine powder using a mortar and pestle and an amount of the powdered tablet mix which contains, based on theory, 250 mcg. of the steroid are transferred to a 60 ml. glass-stoppered bottle. Two ml. of N,N-dimethylformamide are added, the bottle stoppered, and shaken mechanically for 10 minutes, after which 3 ml. of methyl isobutyl ketone are added and the bottle shaken mechanically for an additional 10 minutes. The extract is then filtered under reduced pressure through a 15 ml. Buchner funnel (fine porosity fritted disk). If the filtrate is not clear, an asbestos pad should be used with the filter.

The filter paper used is the same as described previously (1). Methylcyclohexane saturated with Carbitol [2-(2-ethoxyethoxy) ethanol] (4) and toluene saturated with propylene glycol (5) are the two developing solvents used. Any conventional chamber used for descending paper chromatography is suitable. The chromogenic agent is made up of one part of Folin-Ciocalteu phenol reagent plus 4 parts of water (6). The eluting solvent used was 95% ethanol.

Paper Chromatographic Procedure.—Two chromatograms are run per sample. The slotted filter paper, which has been described previously (1), contains six 3/4 in. strips which are spotted for the estradiol valerate assay at 1-in. intervals along the line of origin as follows:

ORIGIN 1 2 3 4 5 6

No. 1 Chromatogram	No. 2 Chromatogram
1 = Sample, 0.05 ml.	Sample, 0.10 ml.
2 = Standard, 0.05 ml.	Standard, 0.05 ml.
3 = Standard, 0.10 ml.	Standard, 0.10 ml.
4 = Sample, 0.05 ml.	Sample, 0.10 ml.
5 = Sample, 0.05 ml.	Sample, 0.10 ml.
6 = Paper blank	Paper blank

For the ethinyl estradiol assay, both strips are spotted as follows:

ORIGIN 1 2 3 4 5 6

1 = Sample, 0.20 ml.; 2 = Standard, 0.05 ml.; 3 = Standard, 0.10 ml.; 4 = Sample, 0.20 ml.; 5 = Sample, 0.20 ml.; 6 = Paper blank.

Blow-out pipets, of 1- and 2-ml. capacity, graduated in 0.01 ml., are used to apply the standards and the sample to the paper. The spotted strips are impregnated with the stationary phase by dipping them into the appropriate chloroform solution (Table I). The procedure has been described in detail previously (1). Following solvent development (Table I), the strips are removed from the chamber and dried in a mechanical convection oven for 20 minutes at 90°.

The positions of the estrogens on the chromatogram are located by employing the guide strip technique. The strip corresponding to the No. 1 spot on each chromatogram is cut out, dipped into the diluted phenol reagent, and then exposed to

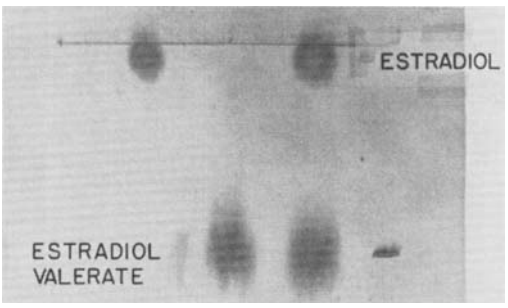

Fig. 1.—Chromatogram showing the separation achieved between estradiol valerate and estradiol in the solvent system methylcyclohexane saturated with Carbitol. Folin-Ciocalteau phenol reagent was used as the color reagent.

[1] Marketed as Gestest by E. R. Squibb & Sons.

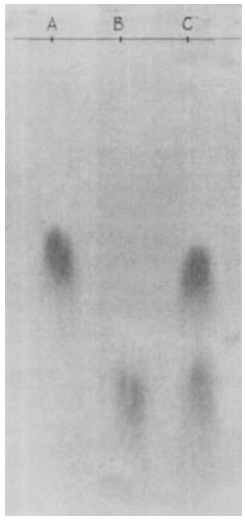

Fig. 2.—Chromatogram showing the separation achieved between ethinyl estradiol and estradiol in the solvent system toluene saturated with propylene glycol. Folin-Ciocalteau phenol reagent was used as the color reagent. A = estradiol, B = ethinyl estradiol, and C = mixture of the two.

ammonia vapors for 5 minutes by placing them into a chamber containing concentrated ammonium hydroxide. Estrogens appear on the chromatogram as blue spots against a light gray background (Figs. 1 and 2). This color development procedure is a slight modification of the procedure for the detection of estrogens on chromatograms described by Mitchell (6).

The color developed guide strip is air dried and then realigned with the untreated portion of the chromatogram. The positions of the estrogens are marked off with a solder pencil, cut out and folded, and placed in 50 ml. Erlenmeyer flasks. A paper blank, equal in area to the standard and sample segments, is included for each chromatogram. Ten milliliters of 95% ethanol are added to each flask and the estrogens are eluted off the filter paper segment by shaking on a reciprocating shaker for 30 minutes (1).

The amount of estrogens present in the eluates is determined by spectrophotofluorometry. An Aminco-Bowman spectrophotofluorometer (Cat. No. 4-8100) is used under the following conditions: clear silica cells, 10 mm. light path; 1P28 photomultiplier tube; No. 3 slit arrangement; and activation at 280 mμ and measurement of the resulting fluorescence at 310 mμ for estradiol valerate and 305 mμ for ethinyl estradiol.

The instrument is adjusted to a scale reading (on the photomultiplier-microphotometer) of 90–95, using the maximum standard eluate. The intensity of fluorescence is measured on an arbitrary 0–100 scale, using the photometer.

Calculation of Estradiol Valerate in Castor Oil Formulations.—The photometer readings are recorded on a data sheet which contains all the information necessary to calculate the concentration of estradiol valerate in the sample. Table II gives the data obtained in typical analyses.

For each of the two chromatograms, readings are obtained for the standard at two levels and for the sample at one level in duplicate. The readings of the two standards for each of the chromatograms are converted to the equivalent reading for the 0.1 ml. standard concentration and averaged. The two photometer readings of the sample are converted to 0.1 ml. readings and averaged.

The concentration of estradiol valerate in the sample is calculated from the following equation

$$\text{mg. estradiol valerate per ml. formulation} = \frac{A \times B \times C \times D}{E \times F \times G}$$

where: A = average photometer reading of 10 ml. eluate of 0.1 ml. chromatographed sample; B = weight in mg. of chromotographed 0.1 ml. standard; C = volume in ml. of sample dilution; D = specific gravity of formulation; E = average photometer reading of 10 ml. eluate of 0.1 ml. chromatographed standard; F = weight in Gm. of sample; and G = volume (0.1 ml.) of chromatographed sample.

The final concentration of estradiol valerate in the sample is obtained by averaging the values obtained for each of the two chromatograms.

Sample Calculation.—In Table II, chromatogram No. 1:

Table II.—Data Sheet for Estradiol Valerate Assay[a]

Chrom.	Flask No.	Cell No.	Spot	Photometer Reading: Uncorrected	Corrected For Blank	Converted St. = 0.10 ml. Sa. = 0.10 ml.	Average St. = 20 γ Sa. = 0.1 ml.	Conc.[b] mg./ml. Formulation
1	1	1	St. = 0.05 ml.	70	30	60	57.75	40.5
1	2	2	St. = 0.10 ml.	95.5	55.5	55.5		
1	3	3	Sa. = 0.05 ml.	66	26	52	54	
1	4	4	Sa. = 0.05 ml.	68	28	56		
1	5	5	Paper Blank	40	...			
2	6	1	St. = 0.05 ml.	63	28	56	56.75	40.3
2	7	2	St. = 0.10 ml.	92.5	57.5	57.5		
2	8	3	Sa. = 0.10 ml.	89	54	54	53	
2	9	4	Sa. = 0.10 ml.	87	52	52		
2	10	5	Paper Blank	35	..	..		

[a] Project Hv. 45–53; sample Es. 31–35/15A–1 initial; assay, estradiol valerate; sample weight, 1.1900 Gm./250 ml.; sp. gr. sa., 1.0295; weight standard, 20.0 mg./100 ml.; filter paper, ethanol-washed finger strips impregnated with Carbitol (20% in chloroform); developing solvent, methylcyclohexane saturated with Carbitol; developing time, 3 hours; drying condition, 20 minutes at 90°C; eluting solution, 10 ml. of 95% EtOH; eluting time, 30 minutes. Spectrophotofluorometer specifications: Aminco-Bowman instrument, Cat. No. 4-8100; 10 mm. silica cells; 1P28 tube; No. 3 slit; activate, 280 mμ; fluorescence, 310 mμ. [b] Average: 40.4.

TABLE III.—DATA SHEET FOR ETHINYL ESTRADIOL ASSAY[a]

Chrom.	Flask No.	Cell No.	Spot	Photometer Reading: Uncorrected	Corrected for blank	Converted St. = 0.05 ml. Sa. = 0.20 ml.	Average St. = 10.1 γ Sa. = 0.20 ml.	Conc.[b] mg./Tablet
1	1	1	St. = 0.05 ml.	41	33	33	32.5	0.052
1	2	2	St. = 0.10 ml.	72	64	32		
1	3	3	Sa. = 0.20 ml.	41	33	33	33	
1	4	4	Sa. = 0.20 ml.	41	33	33		
1	5	5	Paper Blank	8	..	...		
2	6	1	St. = 0.05 ml.	41	34	34	32.75	0.050
2	7	2	St. = 0.10 ml.	70	63	31.5		
2	8	3	Sa. = 0.20 ml.	40	33	33	32.5	
2	9	4	Sa. = 0.20 ml.	39	32	32		
2	10	5	Paper Blank	7	..	...		

[a] Project Es.402a-11; sample Es.402a-11-C-1, 4 months at 22°C.; assay, ethinyl estradiol; sample weight, 499.5 mg./5 ml.; theoretical tablet weight, 100 mg.; weight standard, 20.3 mg./100 ml.; filter paper, ethanol-washed finger strips impregnated with propylene glycol (25% in chloroform); developing solvent, toluene saturated with propylene glycol; developing time, 16 hours; drying condition, 20 minutes at 90°C.; eluting solution, 10 ml. of 95% EtOH; eluting time, 30 min. Spectrophotofluorometer specifications: Aminco-Bowman instrument, Cat. No. 4-8100; 10 mm. silica cells; 1P28 tube: No. 3 slit; activate, 280 mμ; fluorescence, 305 mμ. [b] Average: 0.051.

mg. estradiol valerate per ml. =

$$\frac{54.0 \times 0.020 \times 250 \times 1.0295}{57.75 \times 1.190 \times 0.1} = 40.5$$

Calculation of Ethinyl Estradiol in Gestest Tablets.—For each of the two chromatograms, photometer readings are obtained for the standard at two levels and for the sample at one level in duplicate. The readings of the two standards for each of the chromatograms are converted to the equivalent reading for the 0.05 ml. (or 10 γ) standard concentration and averaged. The two readings of the sample are also averaged.

The concentration of ethinyl estradiol per tablet is calculated from the following equation

$$\text{mg. ethinyl estradiol/tablet} = \frac{A \times B \times C \times D}{E \times F \times G}$$

where: A = average photometer reading of 10 ml. eluate of 0.2 ml. chromatographed sample extract; B = weight in mg. of chromatographed 0.05 ml. standard; C = theoretical weight in mg. of 1 tablet; D = volume in ml. of sample extract; E = average photometer reading of 10 ml. eluate of 0.05 ml. chromatographed standard; F = weight in mg. of sample; and G = volume (0.2 ml.) of chromatographed sample extract.

The final concentration of ethinyl estradiol per tablet is obtained by averaging the values obtained for each of the two chromatograms.

Sample Calculation.—In Table III, chromatogram No. 1

mg. ethinyl estradiol per tablet =

$$\frac{33 \times 0.0101 \times 100 \times 5}{32.5 \times 499.5 \times 0.2} = 0.052$$

The reported value, 0.051 mg. per tablet (see Table III), is the average of the values obtained for each of the chromatograms.

RESULTS AND DISCUSSION

In general, the fluorescent peak-height, as measured on the microphotometer, will be a linear function of concentration. This is true for the range of concentrations employed in the assays described here. This was demonstrated by preparing two chromatograms, each containing 10, 20, 30, 40, and 50 mcg. of ethinyl estradiol, and carrying them through the complete assay procedure. The two corrected readings were averaged for each concentration and plotted against the concentration, yielding the resulting straight line, as seen in Fig. 3.

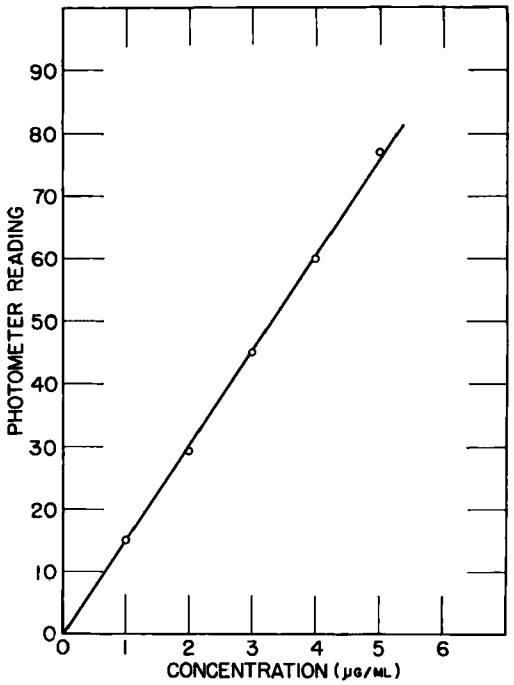

Fig. 3.—Variation of fluorescence with concentration. Ninety-five per cent ethanol eluates of chromatographed ethinyl estradiol.

The activation and fluorescence wavelengths

TABLE IV.—PAPER CHROMATOGRAPHIC ANALYSIS OF KNOWN ESTRADIOL VALERATE SOLUTIONS

Theoretical, mg.	Chromatogram, mg. found 1	2	Average, mg.	Dev. from Theory, %
25.2	24.6	24.7	24.65	−2.2
22.5	22.5	23.0	22.75	+1.1

TABLE V.—PAPER CHROMATOGRAPHIC ANALYSES OF ESTRADIOL VALERATE IN CASTOR OIL UNDERGOING STABILITY STUDIES

Sample No.	Theoretical Conc., mg./ml.	Time, Months	Temperature, °C. 5	22	40	50
			Found, mg./ml.			
1	5	6	5.1	5.3	5.3	5.0
2	5	12	...	4.8	4.8	5.0
3	5	6	...	5.0	5.2	5.1
4	16	6	...	16.9	16.5	15.8
5	20	8	...	20.2	20.5	20.8
6	20	6	20.9	20.7	20.6	20.4
7	20	6	20.7	21.0	20.0	20.4
8	40	6	...	40.6	39.3	38.6
9	40	6	41.7	41.3	38.1	40.0
10	40	12	...	40.1	39.9	40.4

(280–310 mμ for estradiol valerate and 280–305 mμ for ethinyl estradiol) are only apparent wavelengths. No corrections (7) have been made to provide true activation and fluorescence spectra. The apparent activation and fluorescence maxima may, therefore, vary slightly from instrument to instrument and should be determined by each investigator for his instrument.

The sensitivity of fluorescent measurement results in accurate analysis at eluate concentration ranges of 1 and 2 mcg. per ml. This, in turn, eliminates the need of any elaborate extraction procedure and permits the dilution of the oil formulation and the subsequent chromatography and resolution of estradiol valerate without interference from the oil base (which occurs at higher applications of diluted formulations to the filter paper).

While estradiol valerate in castor oil formulations is chromatographed at 10 and 20 mcg. levels, the sample extracts of ethinyl estradiol are chromatographed only at 10 mcg. levels. Ethinyl estradiol is present in Gestest at a concentration of 50 mcg. per tablet. Five hundred milligrams of powdered tablet (equivalent to 5 tablets) extracted with 5 ml. of solvent yields 50 mcg. of ethinyl estradiol per ml. of extract. Therefore, in order to chromatograph 10 mcg. of steroid, 200 μl. are spotted. To spot 20 mcg. would require 400 μl. of solution to be spotted. For this reason, the sample extract is spotted in duplicate at the 10 mcg. level.

As discussed previously (1), recoveries in excess of 95% must be obtained if any analytical method is to serve as an effective stability assay. The assay procedure described here yields results having an error less than ±5% and can accurately differentiate between preparations differing by 10%.

This was demonstrated by preparing two known estradiol valerate solutions, one at 25.2 mg./ml. and the other, 10% less, at 22.5 mg./ml. The analysis of the first solution, Table IV, gave a result of 24.65 mg. of estradiol valerate, a deviation of 2.2% from the theoretical concentration of 25.2 mg. The second solution assayed 22.75 mg. or 1.1% deviation from the theoretical concentration of 22.5 mg.

Accuracies of this magnitude are obtained since the standards and sample are run on the same chromatogram in replicate and both are exposed simultaneously to the same chromatographic and assay conditions. Table V contains additional data indicating that assays with recoveries in excess of 95% are obtained with consistency. The data also show that estradiol valerate in castor oil formulations at various concentrations is extremely stable and no breakdowns have been observed upon prolonged storage at elevated temperatures.

The stability of ethinyl estradiol in Gestest tablets plus the sensitivity and accuracy of the technique is illustrated in the data presented in Table VI. The reliability of the assay is assured when 50 mcg. of ethinyl estradiol can be measured with an accuracy of ±5% or ±2.5 mcg.

TABLE VI.—PAPER CHROMATOGRAPHIC ANALYSES OF ETHINYL ESTRADIOL IN TABLETS UNDERGOING STABILITY STUDIES

Sample No.	Initial Assay (mg./Tablet)	Time, Months	Temperature, °C. 22	40
			mg./Tablet	
1	0.049	4	0.051	0.051
2	0.049	4	0.050	0.050
3	0.051	5	0.048	0.049
4	0.049	6	0.048	0.050
5	0.049	12	0.050	0.049
6	0.049	12	0.051	0.048

Not only does the procedure provide for an accurate analysis of ethinyl estradiol in tablets, but it achieves this without the need of any elaborate extraction. The extraction with N,N-dimethylformamide followed by dilution with methyl isobutyl ketone is all the sample preparation required.

The spectrophotofluorometric procedure for the assay of estrogenic hormones has not been applicable to those preparations which contain sesame oil. Some component or components present in the oil interfere in the spectrophotofluorometric measurement, resulting in assay figures greatly in excess of theory.

SUMMARY

1. A quantitative paper chromatographic spectrophotofluorometric procedure has been developed for the assay of estrogenic hormones.

2. The procedure is used routinely to measure the stability of a number of estrogenic hormones in castor oil and tablet formulations. The assay of estradiol valerate in castor oil and ethinyl estradiol in tablets are described in detail.

3. No extraction of the estrogenic hormones

in castor oil is required. A simple dilution with methyl isobutyl ketone is the only sample preparation required.

4. Estrogenic hormones in tablets are extracted simply with N,N-dimethylformamide followed by dilution with methyl isobutyl ketone and filtration.

5. Accuracies in excess of 95% are obtained by simultaneously chromatographing replicates of standard and sample solutions on the same chromatogram.

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Technical Articles

Adaptation of Commercial Viscometers for Special Applications in Pharmaceutical Rheology II

Severs Extrusion Rheometer

By JOHN H. WOOD, GREGORY CATACALOS, and S. V. LIEBERMAN†

The Severs rheometer has been slightly modified to provide greater flexibility of use. Besides its normal use as a rheometer, it may be used to accept samples in collapsible tubes. Such samples undergo no change in thixotropic set before actual measurement. The apparatus can also be used to shear samples of up to 700-ml. volume in a manner comparable to a high-speed filler. The method of calibrating the filler shears is outlined. Commercial fillers show shears from slightly in excess of 10,000 seconds^{-1} to 100,000 seconds^{-1}. It is demonstrated that the combination of nozzle, piston, and filler geometry is such that each can become the point of critical shear, depending on the relative dimensions of the other parts.

IN THE pharmaceutical field, couette-type instrument rheology has been largely the standard of usage because any instrument with either a range of cups and/or bobs or of springs could be adapted to take the wide range of consistencies so characteristic of this discipline. The engineering profession and the polymer, plastics, and petroleum industries tended to adapt the classical Poiseuille capillary to their special needs by increasing the radius to tubes, and even pipes, and by using pressure to increase the driving force over that of gravity alone. Such an instrument, designed by Severs (1), is commercially available. Its use with pressurized dentifrice has been described elsewhere (2). This paper is intended to show some other possible adaptations for this useful and relatively inexpensive instrument.

As a rheometer alone it is flexible and covers a wide shear-rate range but this alone does not justify special note. It is, however, readily adaptable to give useful information in two fields where the couette instrument is not directly utilizable. The first of these is the study of thixotropic systems of slow recovery in which the mere process of loading the instrument with sample partially destroys the set. Many creams, pastes, and other semisolid systems fall into this category. Two types of measurement on such

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† Present address: 33 Grand Street, Clark, N. J.