matogram of each of these mixtures possessed the small extraneous peak at 9.3 min.

The average amount of IV in the formulations (Table IV) was estimated, by difference, to be 10.5%. The UV analyses (mean = 126.1%) indicated an average "overfill" of 26.1%; therefore, the average amount of IV in the formulation is equivalent to 8.3% of the total tetracyclines, expressed as I. This value is comparable to the 7.4% found in the particular sample of I-nitrate bulk drug substance used in this study. Close correlation was also obtained between the results of the microbiological analyses and the total amount of I and II determined by the HSLC procedure. This finding is consistant with the fact that III, which would be formed by the hydrolysis of IV, is less microbiologically active than II (6).

In conclusion, the HSLC procedure provides a rapid, precise method for the simultaneous qualitative and quantitative analysis of rolitetracycline and its hydrolysis product, tetracycline, in both rolitetracycline and rolitetracycline nitrate formulations. A third component found in rolitetracycline nitrate formulations has not been identified conclusively, but UV and microbiological assays indicate that this compound is present at levels as high as 10% of total tetracyclines, contains a tetracycline moiety, and is comparatively inactive microbiologically. A tentative identification as 4-epirolitetracycline is suggested.

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PHARMACEUTICAL TECHNOLOGY

Versatile Unit for Filling Gelatin Capsules with Drugs or Chemicals

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Abstract □ A new, inexpensive device was developed for making individually prepared capsules that can be administered to experimental animals. The device was designed for accurate and rapid production of large numbers of various capsule sizes and drug dosages. During 12 months of usage, 21 capsules were prepared weekly for each of 44 dogs (924 total capsules) in approximately 2.5 workhours/week. Each capsule contained a precise amount of drug to administer a specific dosage to each individual dog. No difficulties were encountered in the manufacture or utilization of this device, and it can be operated by untrained personnel.

Keyphrases □ Capsules—device for making individually prepared capsules, design and application □ Gelatin capsules—rapid production of various capsule sizes and drug dosages, device described □ Equipment—rapid production of various capsules and drug dosages, design and application

Drugs and chemicals intended for human consumption or exposure must first be evaluated for toxicity in laboratory animals. The Food and Drug Administration and other governmental regulatory agencies recommend that the route of administration in animals corresponds to the route for proposed human usage (1). For subacute or chronic oral administration of food additives, pesticides, or other materials to rodents, the compounds can be incorporated into the diet. Dogs and monkeys can receive daily *per os* administration of drugs or other orally consumed chemicals by administration of the materials as tablets, in capsules, or by intubation of solutions or suspensions. Each of these three alternatives for drug administration involves significant shortcomings with large numbers of animals for long periods.

Manual production of tablets or capsules requires considerable effort and adds unduly to the cost of an experiment[1]. Preparation of tablets or capsules with commercial units decreases time and cost but sacrifices accuracy in dosage due to unit-to-unit variation (2, 3) and loss of the ability to adjust *precisely* for

[1] Manual preparation of 924 capsules/week for 44 dogs in a 1-year toxicity study could cost more than $15,800.

Table I—Softening Times of No. 13 Gelatin Capsules

Capsule Contents	Storage Temperature	Softening Time (min)[a], $\bar{x} \pm SD$
1.0 ml of water	22.8°	12.54 ± 1.67
1.0 ml of water	9.0°	18.50 ± 2.21
1.0 ml of water	−9.0°	20.04 ± 2.25
0.82 g of gelatin powder + 1.0 ml of water	22.8°	25.20 ± 2.27
0.82 g of gelatin powder + 1.0 ml of water	9.0°	>120[b]
0.82 g of gelatin powder + 1.0 ml of water	−9.0°	>120[c]

[a] Mean values for five individual capsules per group. The softening time was defined as the elapsed time from instillation of the water until the capsules became too soft for administration to animals. [b] These five capsules were slightly soft within 20 min, but they were never judged too soft for administration; they were only "rubbery" instead of "collapsible." [c] These five capsules never became soft and they were frozen within a few hours.

short-term changes in body weights of the animals. This last deficiency can be partially rectified by preparing several units with different dosages and administering multiple units to approximate the desired dose. However, considerable accuracy in dosage can still be lost, and substantial time and effort are required to total manually the units for dosing each animal. In addition, commercial production of tablets or capsules offers cost savings only if thousands of units are prepared simultaneously; the units must, therefore, be handled and stored so that problems with physical instability are avoided (4).

Gastric intubation of solutions or suspensions to dogs and monkeys provides an accurate dosage and is relatively inexpensive. However, daily intubation for protracted periods can produce aspiration pneumonitis (5, 6) as well as a low incidence of intubation accidents.

DISCUSSION

Solutions or suspensions can be accurately formulated for administration to animals; but when these formulations are placed in gelatin capsules, dissolution of the capsule is an undesirable effect. Capsule dissolution can be significantly retarded by cooling filled capsules, adding powdered gelatin to the capsule prior to addition of a liquid formulation, or by a combination of these two techniques (Table I).

Cooled No. 13 capsules filled with 1.0 ml of water became too soft to handle within a mean time of 18.5 min when refrigerated at 9.0° and within 20.0 min when stored at −9.0°. Similar capsules stored at ambient temperature (22.8°) softened in an average of 12.5 min. Addition of an average of 0.82 g of powdered gelatin prior to 1.0 ml of water resulted in a mean softening time of 25.2 min at ambient temperature; similarly filled capsules stored at 9° were slightly soft in approximately 15–20 min, but these capsules were never too soft to handle. Capsules with powdered gelatin and water stored at −9° never became soft and were frozen within a few hours. Therefore, the device was designed to add a consistent amount of powdered gelatin to each capsule just prior to addition of the drug solution. The capsules were then quickly frozen until needed during the next week. The drug used in these studies was stable in frozen capsules for more than 6 weeks.

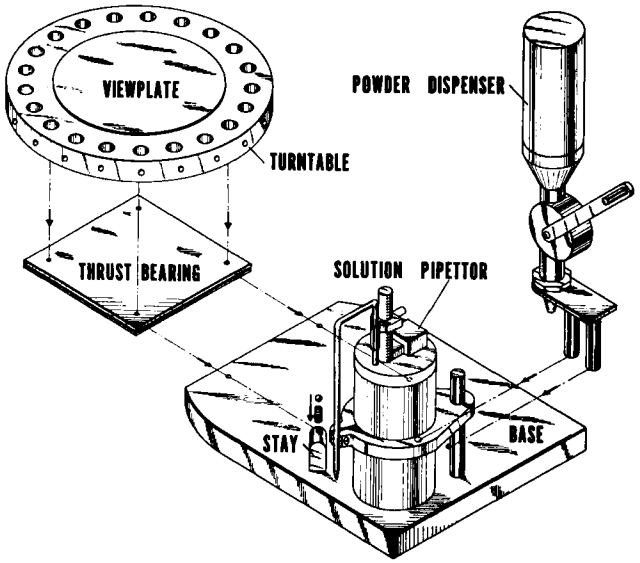

Figure 1—*Schematic presentation of the unit assemblage. The base of the unit measured 25.4 × 30.4 cm (10 × 12 in.), and the thrust bearing was 10.2 × 10.2 cm (4 × 4 in.). The diameter of the turntable was 24.76 cm (9.75 in.)*

EXPERIMENTAL

The details of the design and construction of the capsule-filling unit are illustrated in Fig. 1. The base and turntable were cut from scrap pieces of 2.54-cm (1-in.) oak and varnished to seal the wood for protection against spilled solutions and powders. Sufficient holes for a 1-week/animal supply of capsules were drilled into the turntable, and the hole diameters in various turntables were varied to accommodate different capsule sizes (Table II). The edge of the turntable was pitted perpendicular to each capsule hole, and these pits served as sites for engaging the stay. The white formica view-

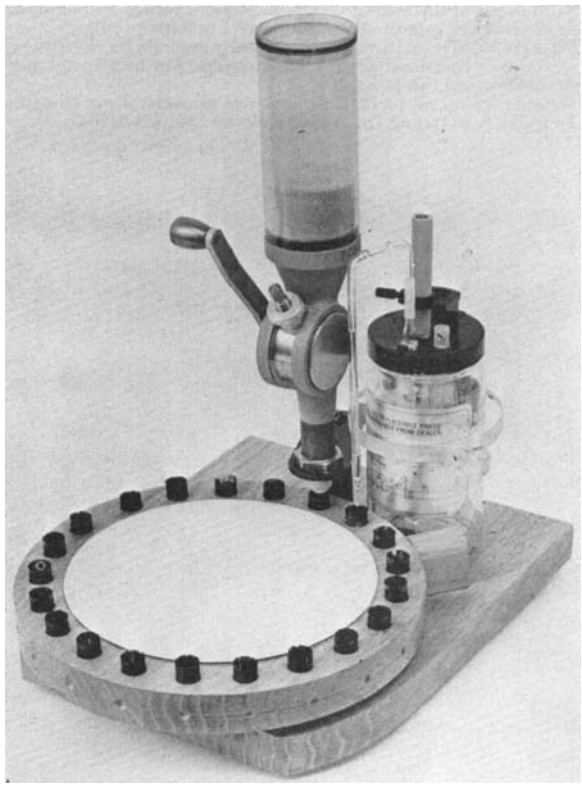

Figure 2—*View of the assembled unit.*

Table II—Physical Dimensions of Gelatin Capsules

Capsule No.	Length, cm	Diameter, cm	Maximum Volume[a], ml
13[b]	2.966	1.460	2.63
00[c]	2.324	0.840	0.93
0[d]	2.128	0.741	0.67
1[d]	1.905	0.675	0.49
2[d]	1.800	0.622	0.38
3[c]	1.617	0.571	0.28
4[d]	1.332	0.523	0.21

[a] Maximum volume of water that could be placed in the bottom half of the capsule. Capsules 00–4, containing their maximum volumes of water, were too soft to handle within 1–2 min; No. 13 capsules were too soft to handle within approximately 12.5 min. [b] Michigan Capsule Co. [c] Eli Lilly. [d] Parke-Davis.

plate offered an easily cleaned surface for checking the integrity of capsules before and after filling.

The thrust bearing and wooden stay were utilized to allow easy and reproducible alignment of each capsule under the powder dispenser[2] and/or the pipet[3]. The powder dispenser and solution pipet were positioned so that they simultaneously centered over capsules. When capsules smaller than the No. 13 were utilized, a special funnel had to be attached to the bottom of the powder dispenser. An extension of glass tubing was attached to the pipet to minimize the distance between the delivery tip and the capsule. The assembled unit is shown in Fig. 2.

Volumes of formulation to be dispensed into each capsule for an individual animal were calculated from the weekly body weight of the animal, the dose to be administered, and the solution concentration. The formulation was placed in the pipet, which had been adjusted for the desired volume for each capsule, and the gelatin powder was placed in the reservoir of the dispenser. All holes in the turntable were then filled with the bottom half of the appropriate size of capsule. The first two capsules were filled with gelatin powder; but while the second capsule was filled with the powder, the first capsule was filled with the proper formulation volume from the pipet. Therefore, as the turntable was rotated, two capsules were filled simultaneously—one with gelatin powder and one with drug solution onto gelatin powder. As soon as the turntable completed one revolution, all capsules were capped and stored in a freezer. Following this procedure, 21 capsules could be filled with gelatin powder and formulation in less than 1 min.

[2] Uniflow model II powder measure, available commercially or from RCBS Inc., Oroville, CA 95965. This particular powder dispenser has been found to be extremely accurate. Ten samples at a setting for approximately 0.82 g of powdered gelatin varied from 0.8071 to 0.8282 g with an $\bar{x} \pm SD$ of 0.8202 ± 0.0055. This unit may be sufficiently accurate for dispensing powdered drugs or chemicals directly into capsules, but no attempt has been made to investigate this possibility.

[3] Oxford Pipettor model P5058-2, available through various scientific supply houses or from Oxford Laboratories, Foster City, CA 94404

SUMMARY

This device circumvents or minimizes essentially all problems of dosage accuracy, physical instability of dosage units, labor costs, and incidental pathology. Costs for materials in this unit were less than $70.00, and only 10 hr was required for its construction. The unit can be operated efficiently by untrained personnel with little chance for technical error. Care and maintenance of this device are extremely easy, since all contaminated units or surfaces are either removable or openly exposed for cleaning.

During 12 months of usage, 924 capsules were prepared weekly for 44 dogs, and each capsule contained a precise amount of drug to administer a specific dosage (on the basis of milligrams per kilogram) to each individual animal. Dosages were easily adjusted each week for changes in body weights of the individual dogs by adjusting the volume of drug solution pipetted into each capsule.

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