Experimental Pharmaceutics

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EXPERIMENTAL PHARMACEUTICS

FOURTH EDITION

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PREFACE

Pharmaceutics quantitatively correlates physicochemical theories with the characterization, design, development, evaluation, and preparation of dosage forms. Specifically, the area of pharmaceutics is concerned with properties and means of classifying properties of drugs, absorption, dosage forms, extraction, chemical kinetics, solubility, polyphasic systems, preservation, formulation, patient acceptance, sterilization, packaging and stability, and the physiological availability of the medicinal substance from the dosage form.

It is a purpose of this manual to aid in establishing pharmacy on a more mathematical and scientific basis. With this underlying purpose, pharmaceutics will acquaint the student with the characteristics of pharmaceutical systems, will teach the student skills and techniques, will familiarize the student with equipment used in pharmaceutical processes, will acquaint the student with scientific and and technical terminology, will let the student know and apply scientific principles to solving pharmaceutical problems, will give the student judgement in evaluating pharmaceutical products and problems, and will aid in the development of logical and creative thinking.

Another purpose of this manual is to aid the beginning student to obtain an overall concept of a dosage form. He should appreciate a pharmaceutical product not only from the viewpoint of skills and techniques of preparation, packaging, and stability, but also from the viewpoint of patient utilization and physiological availability of the drug from the dosage form. The pharmacist uses his knowledge and appreciation of biological sciences to safeguard the public health by evaluation of the dose of a drug and its interactions with excipients and other medication.

The exercises on the compressed tablet can be used as an example of this philosophy and means of presentation. The section on the manufacture of a compressed tablet is arranged so that the student will prepare a compressed tablet, which he will in subsequent exercises evaluate and coat. The evaluation of the tablet includes not only traditional *in vitro* tests, but also a dissolution test and the urinary recovery technique by which the student determines the biological availability of the drug from his tablet. The tablet is then enteric coated, and the effectiveness of the coating is evaluated by *in vitro* tests and through a urinary recovery technique by a comparison of the biological availability of the drug from the tablet to that from the coated tablet. Thus, the student acquires a total appreciation of the most commonly prescribed dosage form, the compressed tablet. His comprehension includes: the skills and techniques of weighing, blending, milling, and granulation; the familiarization with the equipment used in tabletting; the specifications of tablets and their physical testing; and the *in vivo* evaluation of the bioavailability of the drug from his tablet as it will be used by the patient. By coating the tablets and by *in vitro* and *in vivo* evaluation of the effectiveness of the coating his overall comprehension of the tablet is further expanded.

Sufficient exercises are available so that selections may be made according to the requirements of the individual college. For example, the instructor may use the section on the manufacture of a compressed tablet and the section on suppositories to provide the student with experience in comparing oral and rectal absorption. Or if the instructor prefers, he may use the section on suppositories to demonstrate the effect of the vehicle or base on the release of the medication from a dosage form.

The use of this manual does not presuppose a background in calculus or physical chemistry. A logical outline of presentation is followed according to physical state: solids, solutions, polyphasic systems, and plastic systems. Preparations, as such, are not stressed; however, the traditional

pharmaceutical classes are given consideration within their classification by physical state to show their fundamental relationships and similarities.

Laboratory instructions are maintained at a minimum to permit the student to reason, experiment, and apply his theoretical knowledge. When feasible, each exercise has a practical formulation to be developed by the student applying facts or skills gained in previous exercises.

Experience has shown that mathematics are often forgotten by the time a student enters professional training. As an aid to the student, the appendix includes a concise review of the simpler mathematics utilized in the manual. Differentiation is discussed in the appendix with the hope that the concept of a rate of change of a function and limits will be gained by the student.

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E. L. P.
W. S.

CONTENTS

METROLOGY

1. CHARACTERISTICS OF THE PRESCRIPTION BALANCE

Although the mortar and pestle are commonly used as a symbol of pharmacy, the ever-present prescription balance could as appropriately represent pharmacy. As the prescription balance is used daily to weigh vital medicinals, it is imperative that the pharmacist completely understands its characteristics and correct usage.

Balances must meet standards set forth by the National Bureau of Standards. The Class A prescription balance has a sensitivity requirement of 6 mg with no load and with a load of 10 g on each pan. Most Class A balances have a capacity of 120 g and bear a statement to that effect. If no information is given, the nominal capacity of a Class A is assumed to be 15.5 g. The Class A balance should be used for all the weighing operations required in prescription compounding. In order to avoid errors of 5% or more which might be due to the limit of accuracy of the Class A prescription balance, no less than 120 mg of any substance should be weighed.

The Class B Balance has a sensitivity requirement of 30 mg. It is used for weighing larger amounts of drugs but nothing less than 648 mg.

Every prescription counter must have a Class A balance, but the Class B balance is optional and is becoming of less use to the modern practitioner.

PROCEDURE. The Class A prescription balance meets the four tests using metric weights described in the National Formulary, which require that set of analytical weights meet the National Bureau of Standards requirements. Test weights consist of two 20-g, two 10-g, one 1-g, one 500-mg, one 20-mg, one 10-mg, and one 6-mg weights.

Before weighing or testing the balance, level the balance by means of the thumbscrews and adjust the balance to obtain equal swings of the pointer to the right and left or up and down (depending on the type of indicator) or to obtain stoppage or rest with exact alignment of the double pointers. The rider on the graduated beam must be at its zero position at all times during operations, unless otherwise specified.

A. **SENSITIVITY REQUIREMENT.** The sensitivity requirement is the maximum change in load that will cause a specified change in the position of rest of the indicating element, or elements, of the balance. The smaller the weight required to move the indicator one division, the more sensitive is the balance. The National Formulary calls for a sensitivity requirement of 6 mg for a Class A prescription balance.

1. Level the balance and determine the rest point. The balance lid is to be closed to prevent drafts from affecting the oscillations.
2. Place a 6-mg weight on the right pan. The rest point should not shift less than one division on the indicator scale.
3. Level the balance and determine the rest point with a 10-g weight in the center of each pan.
4. Place a 6-mg weight on the right pan. The rest point should not be shifted less than one division.

Since few, if any, Class C sets of weights include a mass of less than 10 mg, the following practical procedure is suggested:

1. Record the number of scale divisions the index pointer is shifted by a 30-mg, a 20-mg, and a 10-mg weight.
2. Plot the weight against the number of scale divisions shifted by each weight.
3. Draw a straight line through the points, and from the straight line read the weight that will cause a shift of one scale division.
4. Repeat with a 10-g weight on each pan.

B. **ARM RATIO TEST.** The arm ratio test detects errors in the equality of length of the two arms of the balance.

1. Determine the rest point of the balance without any weights on the pans.
2. Place a 30-g weight in the center of each pan and determine the rest point.
3. If the two rest points are different, place a 20-mg weight on the lighter side. If the rest point does not move back to the original place on the index plate or farther, the arm lengths are incorrect and the balance should be repaired.

C. **SHIFT TEST.** The shift test reveals improper arm and lever components of a balance. This series of tests is particularly useful when there has been some abuse of the balance. A balance that does not pass this test should be factory repaired.

1. Determine the rest point without any weights on the pans.
2. Place a 10-g weight in the center of the left pan and another 10-g weight successively toward the right, left, front, and back of the right pan, noting the rest point in each case. If the rest point differs from the rest point without weights, add a 10-mg weight to the lighter side; this should cause the rest point to shift back to the rest point or farther.
3. Place a 10-g weight in the center of the right pan, and place a 10-g weight successively toward the right, left, front, and back of the left pan noting the rest point in each case. If the rest point differs from the rest point without weights, the difference should be overcome by the addition of the 10-mg weight to the lighter side.
4. Make several observations in which both weights are simultaneously shifted to off-center position on their pans, both toward the outside, both toward the inside, one toward the outside and the other toward the inside, both toward the back, and so on until all combinations have been checked. The addition of a 10-mg weight should correct any variation of the rest point from the rest point with no weights on the pan.

D. **RIDER AND GRADUATED BEAM TEST.** The rider and graduated beam test detects improper weighbeam graduations or an improper rider.

1. Determine the rest point for the balance with no weight on the pans.
2. Place a 500-mg weight on the left pan and move the rider to the 500-mg mark. Determine the rest point. If this rest point is different than the rest point with no weights, a 6-mg weight added to the lighter side should bring the rest point back to its original position or farther.
3. Place a 1-g weight on the left pan and move the rider to the 1-g position. If the rest point is different than the rest point with no weights on the pan, it should be brought back to at least zero rest point by the addition of a 6-mg weight to the lighter pan.

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Characteristics of the Prescription Balance

Data and Conclusions Balance No.____

1. Sensitivity Requirement.

   How many divisions is the rest point shifted by 6 mg with no load?
   How many divisions is the rest point shifted by 6 mg with a 10 g load?
   What is the sensitivity requirement of the balance?
   If the alternative procedure was followed, do the two curves coincide?

2. Arm Ratio Test.

   Does 20 mg overcome the rest point difference?

3. Shift Test.

   Does 10 mg overcome the rest point difference when:
   a. the right weight is shifted?
   b. the left weight is shifted?
   c. both weights are shifted?

4. Rider and Weighbeam Test.

   Does 6 mg overcome the rest point difference with:
   a. 500 mg?
   b. 1 g?

2. USE OF THE PRESCRIPTION BALANCE

The pharmacist must not only maintain a proper prescription balance, but he must employ the correct weighing technique and be conscious of the limitations of the balance for the particular quantity of drug to be weighed.

Medicinal substances are weighed on powder papers. The paper protects the pans from chemical action and eliminates the need for repeated washing of the pans. A new paper for each item prevents contamination. Another advantage to utilizing a paper is that it serves as a transfer funnel.

Weighing papers should have a glazed surface so that no appreciable amount of the drug will adhere to the paper. This is especially important when small quantities are to be weighed. A paper should be chosen so it is of reasonable size giving a maximum weighing area without touching any part of the balance except the pan. The papers should be creased diagonally from each corner to the opposite corner and then flattened before placing on the pans. If desired, tared watch glasses may be used on the balance pans instead of papers.

WEIGHING TECHNIQUE. Place the creased papers on the balance pans and adjust the balance by means of the leveling screws so the index pointer is at zero. It is an inviolable rule that before compounding any prescription the balance must be adjusted in this manner. Powder papers taken from the same box can vary in weight by as much as 65 mg. If equilibrium is not established after the papers are placed on the pans, an error of more than 30% can result in weighing 200 mg of material.

With the balance arrested, open the balance lid and place the desired weights on the right pan and/or the weighbeam. Place the material to be weighed on the left pan, then unlock the balance to observe if too little or too much material was deposited. Using a spatula, remove or add material, arresting the balance each time a transfer is made. When equilibrium is established, the balance should be arrested, the lid closed, and the arrest released to check the equilibrium. The arresting knob is most conveniently operated by the left hand.

When a substance is stated to have weighed a certain quantity, this includes not only the true weight but also the possible excessive or deficient weight by virtue of the sensitivity of the balance. Knowing the sensitivity of the balance, one may calculate the percent of possible error for a given amount to be weighed.

Assuming 5 mg produce a change of one index plate division in the rest point and 200 mg of drug is to be weighed, the actual weight could be between 195-205 mg. The percentage of possible error is calculated by the ratio

$$\frac{5 \text{ mg}}{200 \text{ mg}} = \frac{x\%}{100\%}$$

$$x = 2.5\%$$

Thus, the inherent percentage of error for any given situation may be expressed

$$\text{Percentage of Error} = \frac{\text{Sensitivity Requirement} \times 100}{\text{Quantity Desired}}$$

The same relationship may be used to calculate the smallest amount that can be weighed within a particular permissible percentage of error. Assuming the sensitivity requirement of a balance is 5 mg and the permissible percentage of error is 5%, one may calculate the smallest quantity that can be weighed within this limit of error. A ratio is set up as before

$$\frac{5 \text{ mg}}{x \text{ mg}} = \frac{5\%}{100\%}$$

$$x = 100 \text{ mg}$$

Thus, the smallest amount that can be weighed with a certain permissible percent of error may be expressed

$$\text{Smallest Quantity to be Weighed} = \frac{\text{Sensitivity Requirement} \times 100}{\text{Permissible Percent of Error}}$$

In order to achieve 99% accuracy, that is, to permit a 1% error, the amount weighed must be at least 100 times as great as the sensitivity requirement of the balance: To achieve 90% accuracy or to allow a 10% error, one must weigh at least 10 times as much as the sensitivity requirement of the balance.

ALIQUOT METHOD. An aliquot part may be defined as any part that is contained a whole number of times in a quantity; e.g., 2 is an aliquot part of 10. When the amount of drug is too small to be weighed directly on the balance, the aliquot method of weighing is used. The aliquot method consists of weighing a multiple of the amount desired, of diluting the multiple amount, and of weighing an aliquot of the dilution.

Using a balance with a sensitivity requirement of 5 mg to weigh 15 mg of atropine sulfate with 95% accuracy with lactose as a diluent, one would first select the multiple quantity. Calculate the smallest quantity of the substance that can be weighed with the required accuracy. To ensure an error no greater than 5%, an amount at least 20 times the sensitivity of the balance must be weighed.

$$5 \text{ mg} \times 20 = 100 \text{ mg}$$

This amount is not convenient since 100 divided by 15 is not a whole number; therefore, 14 is arbitrarily chosen as a multiple for convenience and to aid in lowering the total error

$$15 \text{ mg} \times 14 = 210 \text{ mg}$$

Thus, an amount 42 times the sensitivity requirement of the balance is to be weighed. The size of this multiple quantity is determined by the accuracy desired, the convenience of the multiple, the availability of weights, and the cost of the substance.

The amount of inert diluent to be added must be a quantity large enough to be weighed within the desired limit of error. The weight of the aliquot must be at least as much as the multiple quantity, and to reduce the error its weight should usually be somewhat greater. Here the multiple quantity weighs 210 mg, so the aliquot must weigh at least 210 mg. If 500 mg is selected as the aliquot, it is multiplied by the multiple quantity

$$500 \text{ mg} \times 14 = 7{,}000 \text{ mg}$$

Knowing that the total dilution of 7,000 mg will contain 210 mg of atropine sulfate, one can calculate that 6,790 mg of lactose must be added to form the dilution.

Since the total trituration weighing 7,000 mg contains 210 mg of atropine sulfate, a 500-mg aliquot will contain the desired weight of atropine sulfate

$$\frac{210 \text{ mg of atropine sulfate}}{7{,}000 \text{ mg of trituration}} = \frac{x \text{ mg of atropine sulfate}}{500 \text{ mg of trituration}}$$

$$x = 15 \text{ mg}$$

PROCEDURE. When mixing a small amount of a drug with a large amount of a second ingredient, the drug present in the smaller amount is placed in the mortar with an equal bulk of the other ingredient. The two ingredients are triturated until intimately mixed. Then, an equal bulk of the second ingredient is added to the mixture, and the powders are triturated until intimately mixed. This procedure is repeated until all of the powders have been added and thoroughly mixed. Using this procedure, prepare in a glass mortar and submit to the instructor the following triturations:

A. Five grams of a trituration containing 25 mg of charcoal prepared with 95% accuracy. Charcoal has been selected to give visual appreciation of the accuracy of weighing and mixing. Lactose is to be used as a diluent.

B. Weigh 6 mg of amaranth or another colorant assigned by the instructor, using lactose as a diluent so that a 90% accuracy is maintained. Add sufficient lactose so that the final trituration will weigh 6 g.

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Use of the Prescription Balance

Data and Conclusions

1. Show the calculations made in preparing the charcoal trituration.

2. Show calculations for B.

3. Why is lactose the most commonly used diluent in aliquots, divided powders, and capsules?

4. Why is the balance arrested at each transfer during the process of weighing?

5. Why was a glass mortar and pestle used in A?

6. To achieve 95% accuracy the amount to be weighed must be how many times as great as the sensitivity requirement of the balance?

7. Is the aliquot method used only with dry ingredients?

8. What is the smallest quantity that can be weighed with a potential error of not more than 4% on a balance with a sensitivity requirement of 2 mg?