Experiment 1

Introduction:

Pharmaceutics principles and pharmaceutical calculations

Dispensing laboratory is one of the most useful labs for pharmacy student, where they learn how to prepare specific medicine in a desired form, to achieve therapeutic effect and patient satisfaction. This lab session will cover aspects you have to know before starting compounding formulation.

Definitions:

***Pharmacists** are experts on the action and uses of drugs, including their chemistry, the formulation of medicines and the way in which drugs are used to manage diseases.*

***Extemporaneous preparation** is defined as a drug that is compounded in a pharmacy according to a prescription and should only be used when manufactured medicines are not available.*

***Dosage forms** are the means by which drug molecules are delivered to sites of action within the body.*

There are three main types of dosage forms:

1. **Solid dosage forms**: e.g. tablets, granules, suppositories and lozenges
2. **Liquid dosage forms:** e.g. drops, gargles, mouthwashes and suspension
3. **Semisolid dosage forms**: e.g. emulsions, creams, gels, ointments and pastes

An Ingredient: is a chemical or material that is added to a formulation during the formulation process.

A. **Active Ingredients:** are those chemicals or materials that have therapeutic benefits

B. **Inactive ingredients (also called excipients, added substances)** are necessary for preparing dosage forms or for enhancing the stability of finished preparations. They do not give a therapeutic response (or, at least, are not intended to) if given alone in the concentration present in the dosage form.

Packaging

The pharmacist must dispense a compounded formulation in an appropriate package:

- The container should not react with the formulation
- The container should protect the formulation against factors that couldcause deterioration or destruction of dosage form such as humidity, light, airborne contamination, microorganism, ingredient loss and physical damage

Storage Temperature Requirements:

Descriptors of storage condition	Temperature
Freezer	-25C° to – 10C°
Cold	Not exceeding 8 C°
Refrigerator	2 C° to 8 C°
Cool	8 C° to 15 C°
Room	Prevailing temperature
Controlled room temperature	Thermostatically maintained 20 C° to 25 C°
Warm	30 C° to 40 C°
Excessive heat	Above 40 C°

Stability is defined as" the extent to which a dosage form retains, within specified limits,and throughout its period and use (i.e. its shelf life), the same properties and characteristics that it possessed at the time of its manufacture".

Expiration dates are required on commercially manufactured pharmaceutical dosage forms and are determined by extensive study of the product's stability. These studies are conducted with the entire pharmaceutical products-i.e., the active drug in its complete formulation, in its specific container, and under the environmental conditions expected in shipment, storage, and handling. Expiration date is usually in the order of years.

Beyond-use dates are used for compounded preparations only and are generally in the order of "days" or "months."

Assigning a Beyond-Use Date:

- **Nonaqueous liquids and solid formulations**
  - If the source of the active drug is a manufactured drug product, the beyond-use date is not later than 25% of the time remaining until the drug product's expiration date, or 6 months, whichever is earlier.
  - If the source of the active drug is a USP or NF substance, the beyond-use date is not later than 6 months.
- **Water containing formulations**
  - When prepared from ingredients in solid form, the beyond-use date should be not later than 14 days when stored at cold temperature.
- **For all other formulations**
  - The beyond-use date is not later than the intended duration of therapy or 30 days, whichever is earlier.

Freshly prepared is defined in the BP as prepared no more than 24 hrs beforeuse but there is no indication when it should be discarded

Recently prepared is defined in BP as discarded after 4 weeks

Observing Signs of instability:

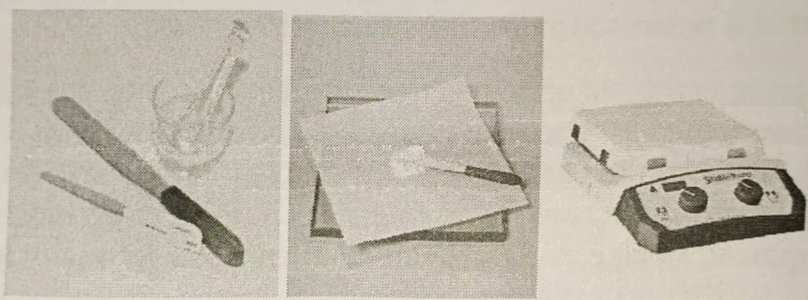
لو شفتي اي واحدة من هاي العلامات على ال formula لازم تتوخي

Formulation	Potential sign of instability
Solutions	Crystal formation
Emulsions	Phase separation
Suspensions	Increased Sedimentation
Tablets	Cracking

Equipment and supplies for measuring, mixing, molding, and packaging:

- Spatulas
- The Mortar and pestle
- Ointment slabs (pill tiles)
- A stirring hotplate

وفي كمان ادوات مطلوبة بآخر المانيوال



Labeling of dispensed medicines

It is the pharmacist responsibility to provide the patient with all information necessary so that the medicine is used appropriately.

Labeling of dispensed medicines has two main functions:

1. To identify the patient with the contents of the container
2. To ensure that the patients have clear and concise information, which will enable them to use their medicine in the most effective way

Any label should contain the following: **(do not use any abbreviations- use full text)** → could mis undersant by patient

A. Main label:

(1) *Name of Patient* .... (Full name)
(2) *Name of preparation.*
(3) *Form.*
(4) *Strength.*
(5) *Manufacturing date.* → Don't Use Beyond
(6) *Use(s): for the whole product " why we use it "*
(7) *Storage conditions*

B. Auxiliary label:

(1) ***Direction of use:***
e.g., for external use, for rectal use, …etc

(2) *Warning:* تحذيرات
e.g. keep out of reach of children. Shake well before use" for suspensions and emulsions. "For external use only" for external liquid and semisolid preparations. "May cause drowsiness" for drugs that cause sedation as a side effect

(3) *Interaction with food, drinks or other medicines.* الدواء يتعارض مع نوعية من الغذاء او بعض الادوية الأخرى

Example of Auxiliary labels

-Swallow whole with a drought of water
-For external use only
-Shake the bottle
-For rectal use only
-Not to be swallowed
-Avoid application to broken skin
-For external use only
-For nasal use only

Pharmaceutics Lab	**Hashemite University** **School of Pharmacy**
Patient's Name's: *XY*	
R$_x$	*Ketoprofen gel 10%w/w, 10 ml*
Direction: *Apply twice daily to affected knee*	
Refill: *0*	
Storage requirements: *store at room temperature*	
Dispensed by: *ND*	
Manufacturing date: *1/1/2020*	**Do Not Use Beyond:** *1/2/2020*
For external use only & Avoid application to broken skin	

Calculations for compounding

Most of the calculations required for compounding and dispensing involve **relatively** simple arithmetic. The welfare of patients depends on the accuracy of **pharmaceutical** calculations and so *careless calculations cost lives.*

Working from a master formula

The master formula is obtained from reference sources such as British Pharmacopeias (BP), British National Formulary (BNF) and United States Pharmacopeias (USP). The master formula lists the ingredients for the total quantities greater than or less than the amount required to be prepared. The formula must therefore be scaled down or scaled up as appropriate.

- Pharmacopeias: Books contain information about drugs, their properties (physical / chemical), assay of drugs, and how to prepare a preparation. They are published by the authority of government, or medical or pharmaceutical society. We will use both USP (United States Pharmacopeia) and BP (BritishPharmacopeia).
- NF (National Formulary): is a manual containing a list of medicines that are approved for prescription throughout the country, includes information of the composition, description, selection, prescribing, dispensing and administration of medicines.

Dealing with strength expressions:

1. **Percentage Strength:**

- % w/w or percentage weight in weight: this expresses the amount in grams of solute in 100 g of product
- %w/v or percentage weight in volume: this expresses the amount in grams of solute in 100 ml of product
- %v/v or percentage volume in volume: this expresses the number of milliliters of solute in 100 mL of product
- %v/w or percentage volume in weight: this expresses the number of milliliters of solute in 100g of product

2. Other strength expression: strength may be written for the amount of active ingredient(s) in unit dose (e.g. capsules or tablets), so here we write the amount per unit dose; e.g. 10 mg Phenobarbital per capsule.

3. Millimoles: To calculate the number of millimoles of an ingredient in a medicinal product, you will first need to know the molecular weight of an ingredient (listed in pharmacopeias, Martindale…etc). The number of moles of ingredient is the mass of ingredient divided by the molecular mass:

$$\text{Number of moles} = \text{Mass in grams} / \text{Molecular mass}$$

Example I

Example: How much sodium Chloride BP is required to prepare 100 ml of sodium Chloride BP solution containing 1.5 mmol sodium chloride per ml? Mwt= 58.4

1.5 mmol → 1 ml

?? → 100 ml

150 mmol

$$Mol = \frac{wt}{Mwt}$$

= 0.15 * 58.4

= 8.76 g

100ml of the final solution of 1.5mmol per ml will contain 150 mmol (0.15mol).

Number of moles (moles)= weight (g)/molecular weight(g/mol)

0.15 =weight/58.44

Weight=0.15*58.44=8.766g of Sodium Chloride BP

Example 2 → Scaling down هاد المثال عملنا → صغرنا

Calculate the amounts of the ingredients for 200 ml Turpentine liniment BP1988.

Ratio ←

$\frac{200}{1000} = 0.2$ بنضربها بكل قيم الـ master formula

Ingredients	Master formula BP	Scaled quantities
Soft soap	75 g	15 g
Camphor	50 g	10 g
Turpentine oil	650 ml	130 ml
Water	Up to 1000 ml	Up to 200 ml

In this example the volume of water can't be calculated because a **combination of** weights and volumes are present in this formula.

Example 3 → Scaling up → كبرنا

Calculate the amounts of the ingredients for 60 g of Zinc oxide and **calamine** paste BP 1988

Ratio ←

$\frac{60}{30} = 2$

Ingredients	Master formula BP	Scaled quantities
Zinc oxide	3.75 g	7.5 g
Calamine	15%w/w	9 g
Wool fat	7.5 g	15 g
White soft paraffin	Up to 30 g	Up to 60 g

Dilutions: التخفيف

There are two main methods for expressing dilutions. It is important that the two are not mixed up as there is a key difference between them:

a) 1 in x – 1 part of solute in x parts of final solution. For example 1 in 10 means that there is one part of concentrate in 10 parts of final solution

b) 1: x (or 1 to x)- 1 part of solute to x parts of solvent. For example 1:10 means that there is one part of concentrate to 10 parts of solvent (or 1 in 11) (e.g. 1 ml of concentrate and 10 ml vehicle with a final volume of 11 ml)

Example I:

Prepare 500 ml of a 0.1% w/v solution using a 20% w/v concentrated stock solution? $C_1V_1 = C_2V_2$

First, you need to calculate the total amount of active ingredient required in the final solution:

0.1% w/v solution= 0.1g in 100 ml

Therefore, there is 0.5g in 500 ml. Next, you need to calculate the quantity of the concentrated solution that contains the same amount of active ingredient:

20% w/v solution = 20g in 100 ml

So there are 2 g in 10 ml, 1g in 5ml and 0.5g in 2.5 ml. Therefore 2.5 ml of 20% w/v solution would be required to make 500ml of a 0.1% w/v solution.

Example 2

How much solute is required to produce 5 liters of a 0.9% w/v solution?

0.9%= 0.9g in 100 ml

Therefore there are 9 g in 1000 ml and you would need 45g in 5000 ml

Example 3

What quantity of a 40% w/v solution would be required to produce 1 liter of a 1 in 1000 solution?

1 in 1000= 1 g in 1000ml

What volume of a 40% w/v solution contains 1g?

40% w/v = 40g in 100 ml.

There are 4g in 10 ml, therefore 1 g in 2.5ml. Therefore, 2.5 ml of a 40% solution would be required to produce 1 Liter of a 1 in 1000.

Appendix I

Weighing and Measuring

Objectives

Upon completion of this exercise, you should be able to:

- Define percentage error and state the percentage error tolerated in most prescription formulas.
- Calculate the potential percentage error for weighing a stated amount of a substance given the sensitivity of the balance.
- Define least weighable quantity.
- Calculate the least weighable quantity for any balance, given the allowed percentage error and the sensitivity of the balance.
- Describe and/or demonstrate the proper techniques for using the balance to measure solid or liquid substances with an error of measurement not to exceed ± 5%.
- Differentiate between volumetric/non-volumetric glassware and devices.
- Select glassware/liquid measurement devices which are appropriate for a particular measurement operation.
- Describe and/or demonstrate the proper techniques for using pipettes, syringes, and graduates for measuring and delivering liquids.

❖ Measurement Systems:

Accurate calculation and **measurement** are two of the most crucial steps in compounding any pharmaceutical product; the pharmacist must have a working knowledge of three systems of measurement:

1. Metric system (SI)
2. Avoirdupois system
3. Apothecary system

I. The Metric System

The metric system is the preferred and most frequently used system of measurement in pharmacy. Since it is a decimal system, other denominations of measure in the system are easily and quickly generated as a 10nth multiple at the basic unit. To convert from larger to smaller units, one need only move the decimal the appropriate number of places to the right. The decimal is moved to the left to convert from smaller to larger units.

The three basic units of measurement are the gram (weight), liter (volume), and meter (length). The nomenclature to indicate multiples of 10 is deca-, hecto-, and kilo-, and fractions of 10 are expressed as deci-, centi-, milli-, and micro.

III. The Apothecary System:

In the past, pharmacists and physicians commonly used this system for prescribing and dispensing medications. Nowadays it has been largely replaced by the metric system.

Table 3. Unit of Measure in the Apothecary System.

Unit	Symbol	Conversions
Gallon	gal	1 gal = 4 qt
Quart	qt	1 qt = 2 pt
Pint	pt	1 pt = 16 floz
Ounce	floz	1 floz = 8 fldr
Fluid drachm	fldr	1 fldr = 60 min
Minim	min	

❖ ***Conversions between systems of measurement***

Table 4. Common Conversions between systems of Measurement

1 L = 33.8 floz	1 lb = 453.59 g
1 pt = 473.17 ml	1 oz = 28.35 g
1 floz = 29.57 ml	1 g = 15.43 gr
1 kg = 2.2 lb	1 gr = 64.8 mg
1 g = 1000 mg	1 kg = 1000 g
0.12 mg = 1/500 gr	1 mg = 1000 mcg
0.2 mg = 1/300 gr	0.15 mg = 1/400 gr
0.1 mg = 1/600 grain (gr)	0.3 mg = 1/200 gr
1 pint (pt) = 473.2 mL	1 quart (qt) = 946.4 mL
1 kg = 2.2 lb	1 fluid oz (floz) = 29.57 mL
1 oz = 28.35 g	1 lb = 453.6 g (0.4536 kg)
1 mL = 16.23 minims	1 Minim = 0.06 mL
1 g = 15.43 grains	1 grain = 64.8 mg

❖ **Balances:**

- ***Accuracy:*** *is a measure of the capability of a balance to approach a true or absolute value.* القراءة الأقرب للقيمة الحقيقية ← الدقة
- ***Precision:*** *is the relative degree of repeatability, i.e. how closely the values within a series of replicate measurements agree*
- ***Tolerance:*** *or 'limits of permissible errors' are the extreme value of an error permitted by specifications for a measuring instrument.* الحد المسموح لل error

Accuracy refers to the closeness of a measured value to a standard or known value. For example, if in lab you obtain a weight measurement of 5.2 kg for a given substance, but the actual or known weight is 9 kg, then your measurement is not accurate. In this case, your measurement is not close to the known value.

Precision refers to the closeness of two or more measurements to each other. Using the example above, if you weigh a given substance five times, and get 5.2 kg each time, then your measurement is very precise. Precision is independent of accuracy. You can be very precise but inaccurate, as described above. You can also be accurate but imprecise. For example, if on average, your measurements for a given substance are close to the known value, but the measurements are far from each other, then you have accuracy without precision.

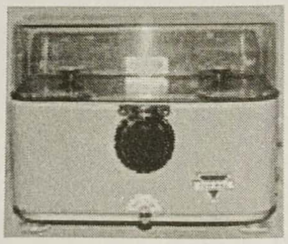
(Ref:https://www.ncsu.edu/labwrite/Experimental%20Design/accuracyprecision.htm)

Date	Initials	Class 1 Weight	Measured Weight	Acceptable Range	Pass/Fail?	Corrective Action
7/5/01	RM	50 mg	49 mg	45-55 mg	Pass	
7/5/01	RM	1 gm	0.9994 gm	0.9995-1.0005 gm	Fail	Re-calibrated balance & repeated test below.
7/5/01	RM	1 gm	0.9997 gm	0.9995-1.0005 gm	Pass	Repeat OK
7/5/01	RM	20 gm	19.9985 gm	19.9980-20.0010 gm	Pass	

(Ref:http://dnr.wi.gov/regulations/labcert/documents/training/BalanceVer2002.pdf)

Types of balances:

1. Class A Balances:



2. **Electronic Balances:**

They have digital displays, and many have internal calibration capabilities.

A. The Top-Loading Balance

The top-loading balance digitally displays a mass reading, in grams, to 2 decimal places. The uncertainty in a single reading on the top -loading balance is ±0.05 g.

B. The Analytical Balance

The analytical balance is more accurate than the top-loading balance. Its digital display gives mass, in grams, to 4 places after the decimal. The uncertainty in a single reading is ±0.0002 g.

Readability *(also Resolution, Scale Division, Scale Interval, Increment, Digit, d):*

is the smallest change in mass that corresponds to a change in displayed value. In other words, this is the amount that the scale will increment by as weight is added or removed.

Example:

- ✓ 152.358g is weighed on a scale with 0.001g readability
  The display will read "152.358g".
- ✓ 152.358g is weighed on a scale with 0.01g readability
  The display will read "152.36g"
- ✓ Normal rounding instrument with d=0.1 will indicate:
  1.0 if the load is 0.96 to 1.04, and
  1.1 if the load is 1.06 to 1.14.

Readability should not be confused with accuracy which is a separate concept. When properly calibrated and adjusted, most scales will be accurate to within plus or minus two scale divisions (+/-2d), though this can vary depending on individual specifications.

Maximum Capacity (also Max Capacity, Max, Rated Capacity) - *This is the maximum weight that can be measured using a particular scale.* أكبر وزن ممكن يقيسه الميزان

Weighing:

It is generally agreed that pharmaceutical products should be prepared with a *low percentage of error.*

Most pharmaceutical products allow for a tolerance of only **5% error**, where

$$\% \ error = \frac{error\ of\ measurement}{quantity\ desired} \times 100\%$$

If we know the sensitivity of the balance (i.e. the potential error) we can calculate the percentage of possible error when any amount of the substance is weighed.

$$\% \ error = \frac{sensitivity}{quantity\ desired} \times 100\%$$

E.g. The Class A prescription balance has a sensitivity of 6 mg (meaning that as much as 6 mg can be added to or removed from the pan before the pointer on the balance marker plate will move one division). What % of error would result in weighing 50 mg of a drug on the balance?

$$\% \ error = \frac{6\ mg}{50\ mg} \times 100\% = 12\%$$