Pharmaceutical Compounding- Introduction

Complied by:Dr. Saja Hamed

The origin of the pharmacy profession

الأساس للصيدلاني

- Compounding of medicinal preparations from material of animal, vegetable and mineral sources has been practiced by Ancient Egypt, Greece, Rome and the Arabian culture
- Opium, myrrh, and liquorice ← بعض من الأشياء التي كانوا يستخدمونها بتحضير الأدوية

منبات — العصارة الطبيعية — مر — صمغ اللوز

- History of Pharmacy Profession (wikipedia)

* بدأت مهنة الصيدلة منذ العصور ... اشهر مصر هو العصر الفرعوني

* الأدوية ← صناعية ← مستخلصة مثل عنصر البنسيلينيوم
لما استخلصنا منه الـ Pencillen
واستخدمكي انتي بيوتك

Compounding

- **Extemporaneous compounding**
  - On-demand preparation of a drug product.
  - According to a physician's prescription.
  - Meets the unique needs of an individual patient.
- **Manufacturing**
  - The production or processing of a drug in a LARGE quantity by various mechanisms.

Definitions

- Chapter <1075> Good Compounding Practices in the USP-NF defines compounding as:

" the preparation, mixing, assembling, packaging, or labeling of a drug or device in accordance with a licensed practitioner's prescription under an initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice"

Compounding is NOT manufacturing in the legal sense

إنتاج الجرعات من الأدوية التي تمت الموافقة عليها من قبل الـ FDA

final product

- Manufacturing is the mass production of drug products that have been approved by the Food and Drug Administration (FDA). These products are sold to pharmacies, health care practitioners (ممارسين) or others authorized under state and federal law to resell them.

* هذه الأدوية تباع للصيدلية وممارسي الرعاية الصحية او غيرهم مصرح لهم بإعادة بيعها

- Manufacturing is defined in USP/NF as:

" the production, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction of the drug from substances of natural origin or by means of chemical or biological synthesis……."

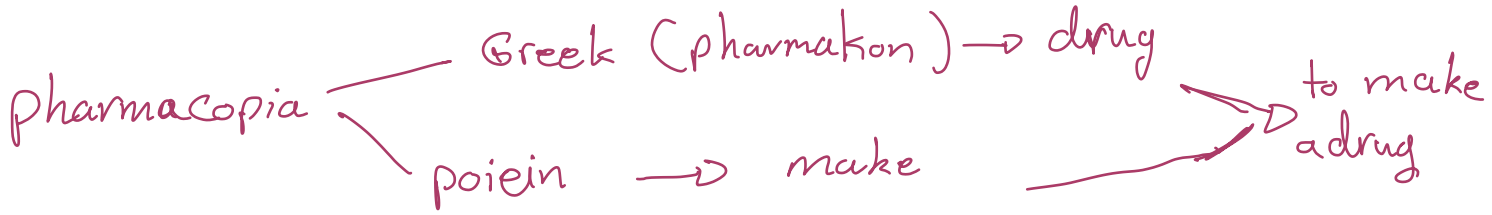
Compounding USP/NF

Manufacturing → FDA Approved

(United state pharmacopia)

USP

- The term (pharmacopeia) comes from the Greek *pharmakon, meaning drug, and poiein, meaning* make, and the combination indicates any recipe or formula or other standards required to make or prepare a drug.



USP :- United states pharmacopia

USP-NF :- The United states pharmacopia convention

USP

United state pharmacopia ← USP – NF → National formaly

- The **United States Pharmacopeia** (**USP**) is the official pharmacopeia of the United States, published dually with the National Formulary as the USP-NF. The **United States Pharmacopeial Convention** (usually also called the USP) is the nonprofit organization that owns the trademark and copyright to the USP-NF and publishes it every year.

غير ربحية

- Prescription and over–the–counter medicines and other health care products sold in the United States are required to follow the standards in the USP-NF. USP also sets standards for food ingredients and dietary supplements.

وصفة طبية

ادوية بدون وصفة

مكملات غذائية

* في كثير دول عندهم own pharmacopia ، بس ممكن لدولة ما يكون إلها pharmacopia خاص فيها فتعتمد ع (USP)

(FDA) هيئات مثل بتستخدم standards هي *

USP

1) identity :- هل فعلاً هذه المادة مطلوبة

2) strength عادةً تورد دوا معين بيكون مكتوب : (الجرعة) انه جرعة مثلا (500g) فبيأخذوا صبة وحدة من هذا الدوا وبحللوا جرعتها عشان يتأكدوا انها 500

3) Quality :- جودة هذا الدواء وهل يتطابق مع ال standard الي عنا؟

4) purity نتأكد انه المادة نقية وما فيها شوائب

5) Consistancy :- الثبات

مثال الباراسيتامول :-

- The USP and NF adopt standards for:
  - drug substances, ← باراسيتامول
  - pharmaceutical ingredients, ← إضافات صيدلانية ويمكن تكون أهم من الدواء نفسه
  - and dosage forms

→ used by Regulatory agency manufactors

reflecting the best in the current practices of medicine and pharmacy and provide suitable tests and assay procedures for demonstrating compliance with these standards

- These standards are used by regulatory agencies and manufacturers to help to ensure that these products are of the appropriate identity, as well as strength, quality, purity, and consistency. التوام

chapters في pharmcopia بال

Chapters

- **Chapters <795>** - called **Pharmaceutical Compounding - Nonsterile Preparations**,
  - Published in 2000
  - Enforceable

oral, Nasal, Creams
شئ ضروري يكون عندي شروط معينة لتصنيعهم

- **Chapter <797>** - called **Pharmaceutical Compounding - Sterile Preparations,**
  - Became official in 2004.
- **Other Chapters**
  - Containers <661>
  - Good Compounding Practices <1075>
  - Pharmaceutical Stability <1150>
  - Pharmaceutical Dosage Forms <1151>

الشروط التي يلزم توفرها

لـ حجم العينات

١- الموقع الإلكتروني

ج- كتاب : يمكن الحصول بطريقتين USP

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Our Mission

USP's mission is to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.

Standards Updates

USP–NF | Reference Standards | Food Chemicals Codex

Review these updates to the USP–NF.

- Compounded Preparations Title Changes (29–Aug–2014)
- Two New Intent to Revise Notices (25–Jul–2014)
- Seven New Revision Bulletins (25–Jul–2014)
- Six New Interim Revision Announcements (25–Jul–2014)
- USP 38–NF 33 Revisions, Deferrals, and Cancellations & IRA Commentary (25–Jul–2014)

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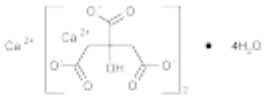
- Regulators


British Pharmacopoeia
2008
British Pharmacopoeia
2008
British Pharmacopoeia
2008

A sample of USP-NF monograph

إذا بدي ادور ع مركب او دواء بضافر بالكتاب بلاقي إله شرح مفصل

Calcium Citrate



$C_{12}H_{10}Ca_3O_{14} \cdot 4H_2O$ 570.49

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, calcium salt (2:3), tetrahydrate;
Calcium citrate (3:2), tetrahydrate [5785-44-4].

① **DEFINITION**

Calcium Citrate contains four molecules of water of hydration. When dried at 150° to constant weight, it contains NLT 97.5% and NMT 100.5% of $Ca_3(C_6H_5O_7)_2$.

② **IDENTIFICATION**

- **A.**

Analysis: Dissolve 0.5 g in a mixture of 10 mL of water and 2.5 mL of 2 N nitric acid. Add 1 mL of mercuric sulfate TS, heat to boiling, and add 1 mL of potassium permanganate TS.

Acceptance criteria: A white precipitate is formed.

- **B.**

Sample: 0.5 g of Calcium Citrate

Analysis: Ignite completely the *Sample* at as low a temperature as possible, cool, and dissolve the residue in dilute glacial acetic acid (1:10). Filter, and add 10 mL of ammonium oxalate TS to the filtrate.

Acceptance criteria: A voluminous white precipitate that is soluble in hydrochloric acid is formed.

③ how to

ASSAY

- **PROCEDURE**

Sample solution: Dissolve 350 mg of Calcium Citrate, previously dried at 150° to constant weight, in 12 mL of 0.5 M hydrochloric acid, and dilute with water to about 100 mL.

Analysis: While stirring the *Sample solution*, add 30 mL of 0.05 M edetate disodium VS from a 50-mL buret. Add 15 mL of 1 N sodium hydroxide and 300 mg of hydroxy naphthol blue, and continue the titration to a blue endpoint. Each mL of 0.05 M edetate disodium is equivalent to 8.307 mg of calcium citrate $(Ca_3(C_6H_5O_7)_2)$.

Acceptance criteria: 97.5%–100.5% on the dried basis

IMPURITIES

and 10 mL of 0.2 M edetate disodium. If necessary, adjust with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 5.5. Transfer to a 100-mL volumetric flask, and dilute with water to volume. This solution contains 0.05 µg/mL of fluoride.

Linearity solution B: Transfer 5.0 mL of the *Standard solution* to a 250-mL plastic beaker, and proceed as directed for *Linearity solution A* beginning with "Add 50 mL of water,". This solution contains 0.25 µg/mL of fluoride.

Linearity solution C: Transfer 10.0 mL of the *Standard solution* to a 250-mL plastic beaker, and proceed as directed for *Linearity solution A* beginning with "Add 50 mL of water,". This solution contains 0.50 µg/mL of fluoride.

Sample solution: Transfer 1.0 g of Calcium Citrate to a 100-mL beaker. Add 10 mL of water and, while stirring, 10 mL of 1 N hydrochloric acid. When dissolved, boil rapidly for 1 min, transfer the solution to a 250-mL plastic beaker, and cool in ice water. Add 15 mL of 1.0 M sodium citrate and 10 mL of 0.2 M edetate disodium, and adjust with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 5.5. Transfer this solution to a 100-mL volumetric flask, and dilute with water to volume.

Electrode system: Use a fluoride-specific, ion-indicating electrode and a silver–silver chloride reference electrode connected to a pH meter capable of measuring potentials with a minimum reproducibility of ±0.2 mV (see *pH* ⟨791⟩).

Analysis

Samples: *Linearity solution A, Linearity solution B, Linearity solution C,* and *Sample solution*

Transfer 50 mL of each *Linearity solution A, Linearity solution B,* and *Linearity solution C* to separate 250-mL plastic beakers, and measure the potential of each solution with the *Electrode system*. Between each reading wash the electrodes with water, and absorb any residual water by blotting the electrodes dry. Plot the logarithms of the fluoride concentrations (0.05, 0.25, and 0.50 µg/mL, respectively) versus potential to obtain a Standard response line.

Transfer 50 mL of the *Sample solution* to a 250-mL plastic beaker, and measure the potential with the *Electrode system*. From the measured potential and the Standard response line determine the concentration, *C*, in µg/mL, of fluoride ion in the *Sample solution*. Calculate the percentage of fluoride in the specimen taken by multiplying *C* by 0.01.

Acceptance criteria: NMT 0.003%

④ **LIMIT OF ACID-INSOLUBLE SUBSTANCES**

Sample solution: Dissolve 5 g of Calcium Citrate by heating with a mixture of hydrochloric acid and water (10:50) for 30 min

EP :- European pharmacopia

BP. ph :- British pharmacopia

US → united states

* الإختصارات معناها

- Over the years, (ex: a number of countries have published their own pharmacopeias,)
- Including the United Kingdom, France, Italy, Japan, India, Mexico, Norway, and the former Union of Soviet Socialist Republics.
- These pharmacopeias and the *European Pharmacopeia (EP or Ph Eur)* *are used* within their legal jurisdictions and by multinational pharmaceutical companies that develop and market products internationally.
- Countries not having a national pharmacopeia frequently adopt one of another country for use in setting and regulating drug standards.
- For example, Canada, which does not have its own national pharmacopeia, has traditionally used USP–NF standards

* بإختصار إي ماعندهم pharmacopia بيتضبطوا بالـ (USP – NF) (standard)

USP/NF

- The point of origin for many regulations
- Its guidelines can be legally enforced by the Food and Drug Administration (FDA)
- Established in 1820 to set uniform standards for the medications prescribed by physicians and to publish compendia of these standards
- NF was first published in 1888 by APA listing standardized formulas including the ingredients and their quantities required for compounding
- In 1975 the USP purchased the NF
- Today the USP/NF is an independent organization

Official compounded formulations

- USP contains monograph of most commonly compounded preparations used in pharmacy practice that has the advantage of:

- USP testing
- Quality assurance
- "beyond use date" assignment
  - ↳ for compounded
  - Expiry date → for manufacturing

Elixir sulfanilamide

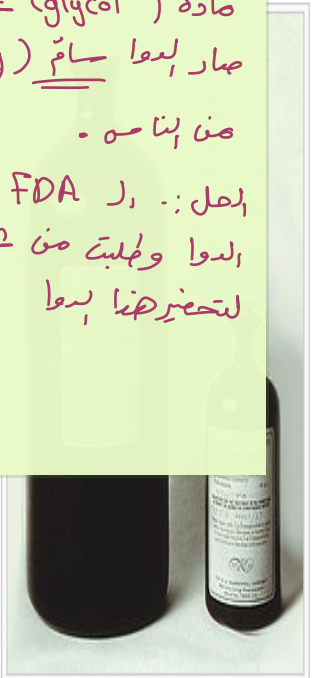
From Wikipedia, the free encyclopedia

Elixir sulfanilamide was an improperly prepared sulfanilamide medicine that caused mass poisoning in the United States in 1937 people. The public outcry caused by this incident and other similar disasters led to the passing of the 1938 Federal Food, Drug, ar

History [edit]

Aside from the Pure Food and Drug Act of 1906 and the Harrison Act of 1914 banning the sale of some narcotic drugs, there was States of America ensuring the safety of new drugs until Congress enacted the 1938 Food, Drug, and Cosmetic Act in response to

In 1937, S. E. Massengill Company, a pharmaceutical manufacturer, created a preparation of sulfanilamide using diethylene glyco preparation "Elixir Sulfanilamide".[3] DEG is poisonous to humans and other mammals, but Harold Watkins, the company's chief ph (Though the first case of a fatality from ethylene glycol occurred in 1930 and studies had been published in medical journals statin its toxicity was not widely known prior to the incident.)[1][4] Watkins simply added raspberry flavoring to the sulfa drug which he had dissolved in DEG and the company then marketed the product. Although animal testing should have been routine in most drug company operations, Massengill performed none and there were no regulations requiring premarket safety testing of new drugs.



Bottles of Elixir Sulfanilamide

The company started selling and distributing the medication in September 1937. By October 11, the American Medical Association received a report of several deaths caused by the medication. The Food and Drug Administration was notified, and an extensive search was conducted to recover the distributed medicine.[5] Frances Oldham Kelsey assisted on a research project that verified that the excipient DEG was responsible for the fatal adverse effects. At least 100 deaths were blamed on the medication.

The owner of the company, when pressed to admit some measure of culpability, infamously answered, "We have been supplying a legitimate professional demand and not once could have foreseen the unlooked-for results. I do not feel that there was any responsibility on our part."[6] Watkins, the chemist, committed suicide while awaiting trial.[6]

A woman wrote to U.S. President Roosevelt and described the death of her daughter: "The first time I ever had occasion to call in a doctor for [Joan] and she was given Elixir of Sulfanilamide. All that is left to us is the caring for her little grave. Even the memory of her is mixed with sorrow for we can see her little body tossing to and fro and hear that little voice screaming with pain and it seems as though it would drive me insane. ... It is my plea that you will take steps to prevent such sales of drugs that will take little lives and leave such suffering behind and such a bleak outlook on the future as I have tonight."

Congress responded to public outrage by passing the 1938 Food, Drug, and Cosmetic Act, which required companies to perform animal safety tests on their proposed new drugs and submit the data to the FDA before being allowed to market their products. The Massengill Company paid a minimum fine under provisions of the 1906 Pure Food and Drugs Act, which prohibited labeling the preparation an "elixir" if it had no alcohol in it.

Sulfanilamide:-

في عام 1914 هذا الدواء كان يحضر بشكل طبيعي بس اجت شركة اسمها (Massengill) اضافت مادة (glycol) عشان الـ flavor ، وهاد ضافوها صار الدوا سامّ (toxicity) ومات عدد كبير من الناس .

الحل :- الـ FDA الأمريكية اصدرت قانون يمنع الدوا وطلبت من شركات معينة باتباع rules معينة لتحضير هذا الدوا

مؤسسة الغذاء والدواء

FDA

- Congress responded with passage of the Federal Food, Drug, and Cosmetic Act of 1938 and the creation of the FDA to administer and enforce it.
- The 1938 act prohibits the distribution and use of any new drug or drug product without the prior filing of a new drug application (NDA) and approval of the FDA
- It became the responsibility of the FDA to either grant or deny permission to manufacture and distribute a new product after reviewing the applicant's filed data on the product's ingredients, methods of assay and quality standards, formulation and manufacturing processes, preclinical (animal, tissue, or cell culture) studies including pharmacology and toxicology, and clinical trials on human subjects.

ال FDA تسمح او ترفض تصنيع دواء سواء كان موجود او لا فبنقدم تقرير عشان يقبلوا يصنعوه بكون فيه (اي معلم بالأزرق)