جامعة الجزيرة الخاصة
ALJAZEERA PRIVATE UNIVERSITY

Disperse Systems
(النظم المبعثرة)

Chapter 14

Introduction

- Dispersed systems: they are liquid preparations containing undissolved or immiscible drug distributed throughout a vehicle.

- They are composed of:
  - Disperse phase (الطور المبعثر) : the distributed substance
  - Dispersing phase (dispersion medium وسط التبعثر): the vehicle

- Suspensions (المعلقات) :
  - Dispersed phase: particles of solid material that is insoluble in the dispersion medium

- Emulsions (المستحلبات) :
  - Dispersed phase: particles of a liquid that is neither soluble nor miscible with the liquid of the dispersion medium

- Aerosols (الضبوبات او الحلالات الهوائية) :
  - Dispersed phase: small air bubbles dispersed throughout the dispersion medium

- Question: what is the size of the dispersed phase particles?
- Answer: it varies widely

  - 10 – 50 μm: coarse dispersions (تبعثرات خشنة) , include suspensions and emulsions

  - 0.5 - 10 μm: fine dispersions (تبعثرات ناعمة) , include gels (الهلامات) and magmas (الصهارات)

  - 1 nm – 0.5 μm: colloidal dispersions (تبعثرات غروانية او غروية), such as milk

- Because of the greater particle size of coarse dispersions, they have the tendency to separate from the dispersion medium more often then fine dispersions.

  - Suspensions $\Rightarrow$ sedimentation (الترسب)
  - Emulsions $\Rightarrow$ coalescence (التجمع)

- In such products, moderate agitation (تحريك معتدل) of the container should be enough for complete and uniform distribution of the dispersed phase to ensure accurate administration of uniform doses (اعطاء مضبوط لجرعات متجانسة).

suspensions

- Definition: preparations containing finely divided drug particles (the suspensoid المستعلق) distributed somewhat uniformly throughout a vehicle in which the drug exhibit a minimum degree of solubility.

- Could come in
  - Ready-to-use form (جاهز للاستخدام): the drug is already distributed throughout the vehicle (السواغ) with/without stabilizers and additives.
  - Dry powder to be suspended (مسحوق جاف معد لتحضير معلق): it's a powder mixture of the drug and a suitable suspending and dispersing agents to be diluted and agitated with a specified quantity of vehicle (usually water)... Example: antibiotics that are not stable for extended periods in aqueous medium

- Reasons for suspension:
  - Certain drugs are unstable (غير ثابت) in solution but stable when suspended $\Rightarrow$ the suspension ensures chemical stability while permitting liquid therapy.
  - To overcome the disadvantage of disagreeable taste (المذاق او الطعم السيء غير المقبول) of certain drugs in solution $\Rightarrow$ by administration of undissolved particles of an oral suspension.

➢ Taste masking and suspension:

- Strategy: The chemical form of certain poor-tasting drugs can be specifically developed for their insolubility (i.e., making them insoluble) in a desired vehicle for the sole purpose pf preparing a palatable liquid dosage form.

- Example: Chloramphenicol palmitate.

  It is a water-insoluble ester of chloramphenicol that was developed to prepare a palatable (مستساغ) liquid dosage form of the drug ⇒ Chloramphenicol Palmitate Oral Suspension, USP.

Suspension with proper selection of flavorants

Taste Masking

- Features desired in pharmaceutical suspensions:

⇒ General features:

  - Therapeutic efficacy النجاعة العلاجية
  - Chemical stability of formulation components الثبات الكيميائي لمكونات التركيبة
  - Permanency of preparation دوام او ديمومة المستحضر
  - Esthetic appeal of the preparation الاغراء الجمالي للمستحضر

- Features desired in pharmaceutical suspensions:

⇒ Specific consideration

  - Should settle slowly (يترسب ببطء) and should be readily disperse upon gentle shaking (الرج/الخض اللطيف) of the container.
  - The particle size (حجم الجسيمات) of the suspensoid should remain fairly constant throughout long periods of undisturbed standing (البقاء لفترة طويلة دون تحريك) .
  - The suspension should pour readily and evenly (يسكب بسهولة و بالتساوي) from its container

- **Sedimentation rate (معدل الترسب) of he particles of a suspension:**

    1. Particle size: ↑ size ⇒ ↑ rate of descent (سقوط) of the particles
    2. Particle density (كثافة الجسيمات) : ↑ density ⇒ ↑ rate of descent of the particles
    3. Viscosity (اللزوجة) ↑ viscosity ⇒ ↓ rate of descent of the particles

- Too much viscosity is not desirable as the suspension might pour with difficulty (صعوبة السكب) and it will be equally difficult to re-disperse (اعادة بعثرة) the suspensoid.

  ⇒ viscosity should be increased only to the modest extent (مدى معتدل) to avoid such difficulties.

- The viscosity characteristics of a suspension can be altered (تعدل) by:
  - The vehicle used نوع السواغ المستخدم
  - The solid content محتوى المواد الصلبة : ↑ proportion (نسبة) of solid content ⇒ ↑ viscosity
  - Viscosity enhancing agents

- The physical stability of a suspension appears to be most appropriately adjusted (احكامه او تصحيحه بشكل اكثر ملائمة) by an alteration (تعديل) of the dispersed phase rather than through great changes in the dispersion medium. Such adjustments might include
  - Particle size
  - Uniformity of particle size تجانس او موحودية الحجم الجسيمي
  - Separation of particles انفصال الجسيمات : avoid aggregation (تجمع) and caking (كتلة صلبة)

- **Physical features (الملامح الفيزيائية) of the dispersed phase of a suspension:**

- The most important single consideration is the size of the particles

  for pharmaceutical suspensions: 1-50 μm

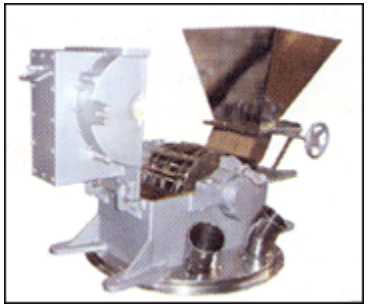
- How to reduce particle size اختزال و تخفيض حجم الجسيمات ?

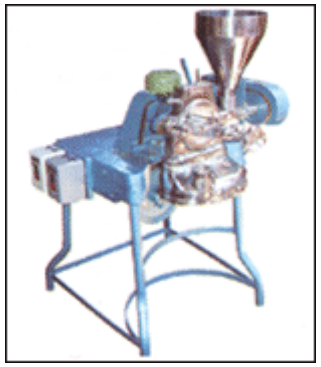
  1. Dry milling الطحن الجاف : it is method that is usually used for incorporation of the dispersed phase into the dispersion medium.

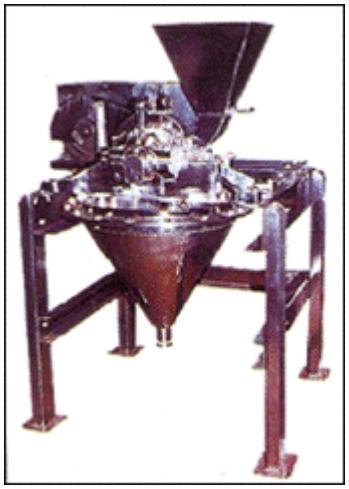
     Technique: micropulverization (السحق المكروي)

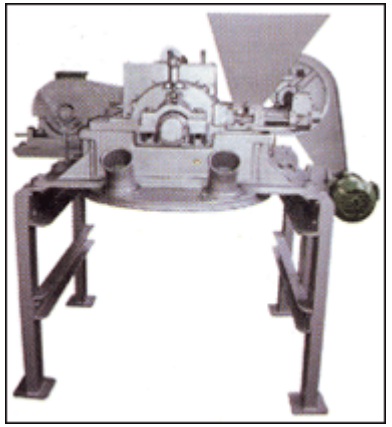
     Micropulverizers: high speed attrition (تاكل) or impact (تصادم) mills (مطاحن) that are efficient in reducing powders to the size acceptable for most oral suspensions.

     Particle size: 10-50 μm









- How to reduce particle size?

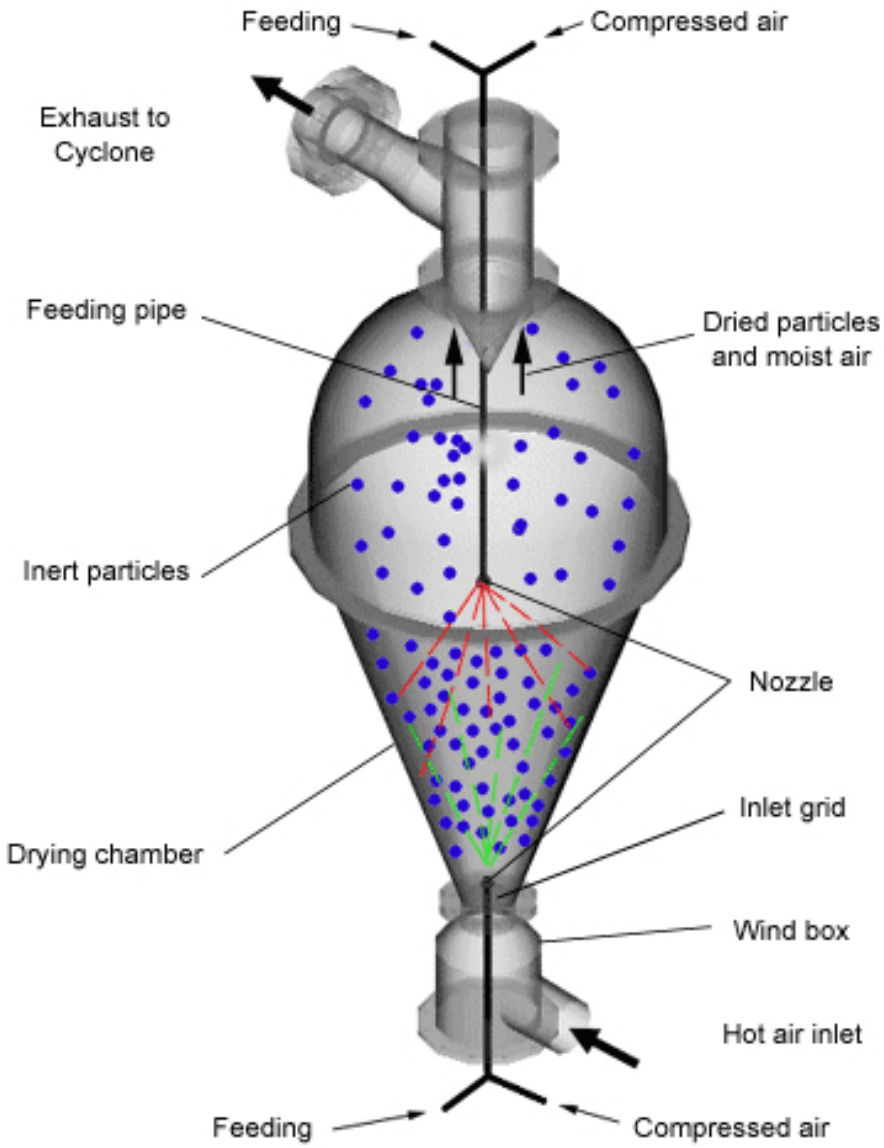
2. Fluid energy grinding الطحن بالطاقة السائلة also known as jet milling (السحق المتدفق) or micronization (المكرنة).

   To produce particles smaller than 10 μm.

   Mechanism: the shearing action (التأثير القاص) of high-velocity compressed airstreams (تيار هوائي مضغوط) of the particles in a confined place (مكان محدود) . The particles are accelerated to high velocities and collide with each other ⇒ fragmentation (تكسر) .

   Mainly for suspensions intended for parenteral (الحقن) or ophthalmic (العينية) use.

3. Spray drying التجفيف بالرذ : produces particles of extremely small dimensions.


Feeding
Compressed air
Exhaust to Cyclone
Feeding pipe
Dried particles and moist air
Inert particles
Nozzle
Drying chamber
Inlet grid
Wind box
Hot air inlet
Feeding
Compressed air


3 5 2006

➢ Particle size/shape and physical stability of suspensions:

- ↓ size ⇒ slow and uniform rate of settling.

- However, too much reduction in particle size ⇒ caking after settling in the bottom of the container.

  The cake will resist breakup (تقاوم التكسر) upon shaking and form rigid aggregates (تكدسات قاسية) that are larger and less suspendable than the original suspensoid.

- Particle shape شكل الجسيمات :

  Symmetrical متناسقة (e.g. barrel-shaped شكل البرميل) particles produces more stable suspensions that asymmetrical غير المتناسقة (e.g. needle shaped شكل الابرة) ones.

➢ How to prevent caking (تكون الكتلة و التكتل) ?

- Caking can be avoided by preventing agglomeration (تكوم) of particles into larger crystals (بلورات) or into masses (كتل).

- Solution: by intentional formation of less rigid (اقل قساوة) or loose aggregates (تكدسات اقل ثباتا او رخوة) of the particles held together by comparatively weak particle-to-particle bonds.

⇒ Such loose aggregation of particles is referred to as : a *floc (لبادة)* or a *floccule (ندفة)* .

- The flocculated particles tends to settle down more rapidly than fine (ناعمة), individual particles. Nevertheless, they form a lattice (بنية شعرية او شبكة) that resist complete settling and thus less prone to compaction (اقل عرضة للتراص) than unflocculated particles.

The loose structure of the flocculated particles permits the aggregates to break up easily and distribute readily with small amount of agitation.

- Preparing flocculating suspensions معلقات متندفة :
  - Clays الغضارات او الطين الصلصالي: diluted bentonite magma is a common flocculating agent in oral suspensions, but unsuitable for parenteral suspensions.
  - Alteration of the pH of the preparation: generally to the region of minimum drug solubility.
  - Electrolytes الكهارل : reducing electrical barrier تخفيض) (الحاجز الكهربائي between the particles of the suspensoid.
  - Surfactants العوامل الفاعلة سطحيا : nonionic and ionic surface active agents can induce flocculation in suspension.

Dispersion Medium

- In commercial suspensions, suspending agents (العوامل المعلقة) are usually added to the dispersion medium to lend it structure (اعطائه بنية او قوام) . These agents thicken (ترفع لزوجة) the suspension and help suspend the suspensoid. Such agents include:
  - Carboxymethylcellulose
  - Methylcellulose
  - Microcrystalline cellulose
  - Polyvinyl pyrrolidone
  - Xanthan gum (صمغ الكزانتان)
  - Bentonite

- The solid content (المحتوى الصلب) of the drug depends on:
  - The dose (الجرعة) of the drug to be administered.
  - The volume (الحجم) of product to be administered.
  - The ability of the medium to support the concentration of the drug while maintaining (دعم) desirable features (الملامح المرغوبة) of viscosity and flow (اللزوجة و الجريان).

- The usual adult dose: 5 ml or one teaspoonful
- Pediatric (الاطفال) suspension comes sometimes with a calibrated dropper (قطارة معايرة) or built-in dropper for administering a dose-calibrated number of drops.
- The drops might be placed directly into the infant mouth or mixed with small portion of food.

Preparation of Suspension

- In the preparation of suspensions, the pharmacist must be acquainted (مطلع على) with the characteristics of both, the dispersed phase and the dispersion medium.
  - some dispersed phases has affinity(الفة او تجاذب) for the dispersion phase and can be easily wetted (يبلل او يرطب) by it.
  - Other drugs are not easily penetrated by the vehicle and have a tendency to clump (ميل للتكتل) together or to float (يطفو) on the vehicle.

- In the later case (في الحالة الاخيرة) , a wetting agent (عامل مرطب) has to be employed to make the drug more penetrable (اكثر قابلية للاختراق) by the dispersion medium.

- In the case of aqueous vehicle, the following wetting agents can be used:
  - Alcohol
  - Glycerin
  - Propylene glycol

- They function by replacing the air in the crevices (فلعات او شقوق) of the particles.

  - In large scale preparation (التحضير على نطاق واسع) of suspension: the wetting agent is mixed with the particles in an apparatus such as a colloidal mill (مطحنة غروية) or a homogenizer (ممازج) .

  - In a small scale in pharmacy: they are mixed with a mortar and pestle (الهاون و المدقة) .

- The dispersion medium is prepared. All the soluble formulative components such as colorants, flavorants and preservatives are added to the dispersion medium

- After wetting, the dispersion medium is added in portions to the powder.

- A portion of the vehicle will be used to rinse (غسل) the mixing equipment free of suspensoid. This portion will be used to bring the suspension to its final volume and insure that the suspension contains the desired concentration of the solid matter.

- The final product will be then passed through a colloidal mill or any other blender (خلاط) or mixing device to ensure uniformity.

Sustained-release Suspensions

المعلقات ذات الاطلاق المستديم

- Limited success (نجاح محدود) due to the difficulty of maintaining (صعوبة الحفاظ) the stability of sustained-release particles in liquid dispersed systems.

- Product Development Research (بحوث التطوير) focused(ركزت) on the technologies used in preparing sustained-release tablets and capsules such as:
  - Coated beads الخرزات الملبسة
  - Drug-impregnated wax matrix مطرس شمعي مشبع بالدواء
  - Microencapsulation التمحفظ المكروي
  - Ion exchange resins الراتينات المبادلة للايونات

- The only successful attempt so far is based on using a combination of ion exchange resin complex and particle coating.

- In this technique, ionic drugs are complexed with ion exchange resin and the drug-resin complex particles are coated with ethyl cellulose.
  - The drug will be slowly released by the ion exchange process in the GIT.

Extemporaneous Compounding of Suspensions

- Not all medications are available in a convenient (ملائم) easy-to-take liquid dosage forms $\Rightarrow$ the pharmacist may have to use a solid dosage form of the drug and extemporaneously compound a liquid product.

- Preparation:
  - Empty the content of capsule into a mortar or crush (اسحق) the tablet by a mortar and pestle.
  - Add a small portion of the vehicle (e.g. syrup) to wet the particles
  - Add portions of the vehicle, mix and transfer to the bottle.
  - Rinse the mortar with the vehicle and qs (اكمل الحجم) to the desired volume.

- A liquid suspension for neonates (حديثي الولادة) should not include preservatives, colorants, flavorants, or alcohol. Such agents may cause acute (حاد) or long term (طويلة الامد) adverse effects (تأثيرات جانبية ضارة) .
  - Alcohol may can alter liver function (وظائف الكبد) , cause gastric irritation (تهيج في المعدة), and neurologic depression (خمود عصبي).
  - Preservatives have been implicated in adverse effects in preterm infants (الرضع الذين ولدوا قبل الاوان الطبيعي) . Benzyl alcohol can cause gasping syndrome (متلازمة اللهاث) characterized by a deterioration (تردي) of multiple organ systems and eventually death.
  - Propylene glycol has been implicated (تم اتهامه) in problems such as seizures (نوبات صرع) and stupor (الذهول) in some preterm infants

The formulation for neonates should be kept simple and not compounded to supply more than few days of medicine

- Extemporaneous Compounding of Suspensions

- Problem: no information on stability of the drug in a liquid vehicle. To minimize stability problems of the extemporaneous product:
  - Place it in an air-tight (محكمة الاغلاق), light resistant container (مقاومة للضوء) .
  - The product should be refrigerated (يحفظ في البراد).

➢ Packaging and storage of suspensions:

- All suspensions should be packaged in wide-mouth containers (حاويات واسعة الفم) having adequate airspace (غراغ هوائي كافي) above the liquid to permit thorough mixing by shaking and ease of pouring.
- Do not freeze: ممنوع التجميد
- Avoid excessive (زائد) heat and light
- Shake well before use to ensure a uniform distribution of solid in the vehicle and thereby, uniform and proper dosage.

Oral suspensions

- **Antacid (مضادات الحموضة) oral suspension**:
  - Uses الاستخدامات:
    - To counteract (لمواجهة) the effects of gastric hyperacidity (فرط الحموضة المعدية) ⇒ taken by peptic ulcer (القرحة الهضمية) patients to reduce the level of acidity in the stomach.
    - As OTC (بدون وصفة) for patients with acid indigestion (عسر هضم حمضي), heartburn (الحرقة) and sour stomach (المعدة الحامضة).
    - For patients who have acid reflux جريان حمضي (رجوعي from the stomach to the esophagus.

- **<u>Antacid oral suspension</u>**:
- General composition: antacid are composed of either:
  - Water-insoluble materials that act within the GIT to counteract the acid and/or sooth (تسكين) the irritated (المتهيجة) or inflamed (الملتهبة) linings (التبطينات) of the GIT: aluminum hydroxide, aluminum phosphate, dihydroxyaluminum aminoacetate, calcium carbonate, calcium phosphate, magnesium carbonate, magnesium oxide, magnesium hydroxide as well as simethicone and sodium alginate.
  - Water soluble agents: sodium carbonate.

➢ Criteria for selecting an antacid:

1. The ability of these chemical agents to neutralize gastric acid varies:
   - Effective and fast acting (فعال و سريع): sodium bicarbonate, calcium carbonate and magnesium hydroxide.
   - Less effective and slow (اقل فعالية و بطيء): aluminum hydroxide and magnesium trislicate.

2. Side effects of the chemical agent:
   - Sodium bicarbonate: sodium overload (التحميل القلونة الجهازية و هي and systemic alkalosis المفرط) (رفع درجةحموضة الدم او حعله اكثر قاعدية.

- Magnesium-containing agents: diarrhea (الاسهال). Avoid in patients with diminished (منخفض) renal function(وظائف الكلى) who don't have the ability to excrete (طرح) all the magnesium that may be absorbed.

  Magnesium hydroxide converts (يتحول) to magnesium chloride in the stomach. The latter (الاخير) is water soluble and partially absorbed.

- Calcium carbonate: hypercalcemia (فرط كالسيوم الدم) and stimulation (تنبيه) of gastric acid production(الافراز المعدي و انتاج الحمض) ⇒ *acid rebound (الارتداد الحمضي)*

- Aluminum hydroxide: constipation (الامساك) and phosphate depletion (نفاد) with consequent (لاحق او تالي) muscle weakness (الضعف العضلي), bone resorption(ارتشاف عظمي) and hypercalciurea (فرط كالسيوم البول).

- Note: these side effects may be induced upon excessive administration (فرط اخذ الدواء) of the aforementioned agents (الادوية السابق ذكرها) .

- Treatment of acute peptic ulcer or duodenal ulcer requires frequent administration of antacids:
  - A combination of magnesium hydroxide and aluminum hydroxide is usually used because the aluminum hydroxide has some constipating effect that counter the diarrhea effects of magnesium hydroxide.

  - Liquid antacid are preferred over tablet forms $\Rightarrow$ the liquid form has a faster onset of action as it requires no disintegration (تفتت). This is important since the gastric emptying (تفريغ المعدة) time is short (1 hour) and might not allow much time for the antacid in the stomach.

- **<u>Special considerations</u>**:
  - Aluminum and calcium containing products might interfere (تتداخل) with the absorption (امتصاص) of some drugs, e.g. tetracycline antibiotics, so the pharmacist must caution patients about taking such drugs concomitantly (من وقت الى وقت).

  - As oral dosage form, antacid suspensions are usually flavored to enhance their palatability (مستساغ) and patient appeal (قبول المريض).

  - They contain a high solid content $\Rightarrow$ must be shaken vigorously (ترج او تخض بشكل عنيف) to redistribute the antacid prior to administration.

- Commercial preparations:
  - Mylanta®: each 5 ml contains 200 mg $Al(OH)_3$; 200 mg $Mg(OH)_2$; and 20 mg simethicone.
  - Maalox®: each 5 ml contains 225 mg $Al(OH)_3$; 200 mg $Mg(OH)_2$.
  - Gaviscon®: each 15 ml contains 95 mg $Al(OH)_3$; 358 mg $Mg(OH)_2$; and sodium alginate.

Antibacterial Oral Suspensions

- Many antibiotics are unstable when maintained in solution for appreciable length of time. From a stability point of view, these materials are prepared as:
  - Insoluble form of the drug substance in aqueous suspension (chloramphenical palmitate)
  - Dry powder for reconstitution مساحق جافة للاستنشاء او الحل.

➢ Dry powder for oral suspensions:

- Intended to be suspended in water or some other vehicle prior to oral administration.

- the dry powder contains:
  - The drug: antibiotic
  - Colorants
  - Flavorants
  - Sweeteners
  - Stabilizing agent
  - Suspending agent
  - preservatives

- Method of preparation:
  - Loosen the powder at the bottomof the container (حرر المسحوق في قاع العلبة) by lightly tapping (ضرب خفيف) it against a hard surface (سطح صلب).
  - Add the label-designated amount of purified water (اضافة الكمية الموصوفة من الماء المنقى): usually done in portions (على مراحل او اجزاء)
  - Shake until all of the dry powder is suspended.

- Special considerations:
  - Use purified water rather than tap water to avoid the possibility of adding impurities that could adversely affect the stability of the preparation.
  - Manufacturers usually provide the dry powder or granules (الحثيرات) in a slightly oversized containers to permit adequate shaking of the suspensions after the entire amount of purified water is added $\Rightarrow$ add the exact amount of required purified water.

- Official antibiotic drugs for oral suspension:
  - Amoxicillin for oral suspension, USP.
  - Ampicillin for oral suspension, USP.
  - Cefaclor for oral suspension, USP.
  - Cefixime for oral suspension, USP.
  - Cephradine for oral suspension, USP.
  - Cephalexin for oral suspension, USP.
  - Dicloxacillin for oral suspension, USP.
  - Doxycycline for oral suspension, USP.
  - Erythromycin ethylsuccinate for oral suspension, USP.

- In addition, there are several official preparations (تحضيرات دستورية) of antibiotic combined with other drugs, such as:
  - Erythromycin ethylsuccinate & acetyl sulfisoxasole
  - Probenecid and ampicillin.

- Other official non-antibiotic dry powder mixtures for reconstitution to oral suspensions:
  - Cholestyramine
  - Barium sulfate: non soluble and therefore, non toxic. Should not be confused with soluble and toxic barium sulfide and barium sulfite.