Pharmaceutical technology

Sedimentation parameters

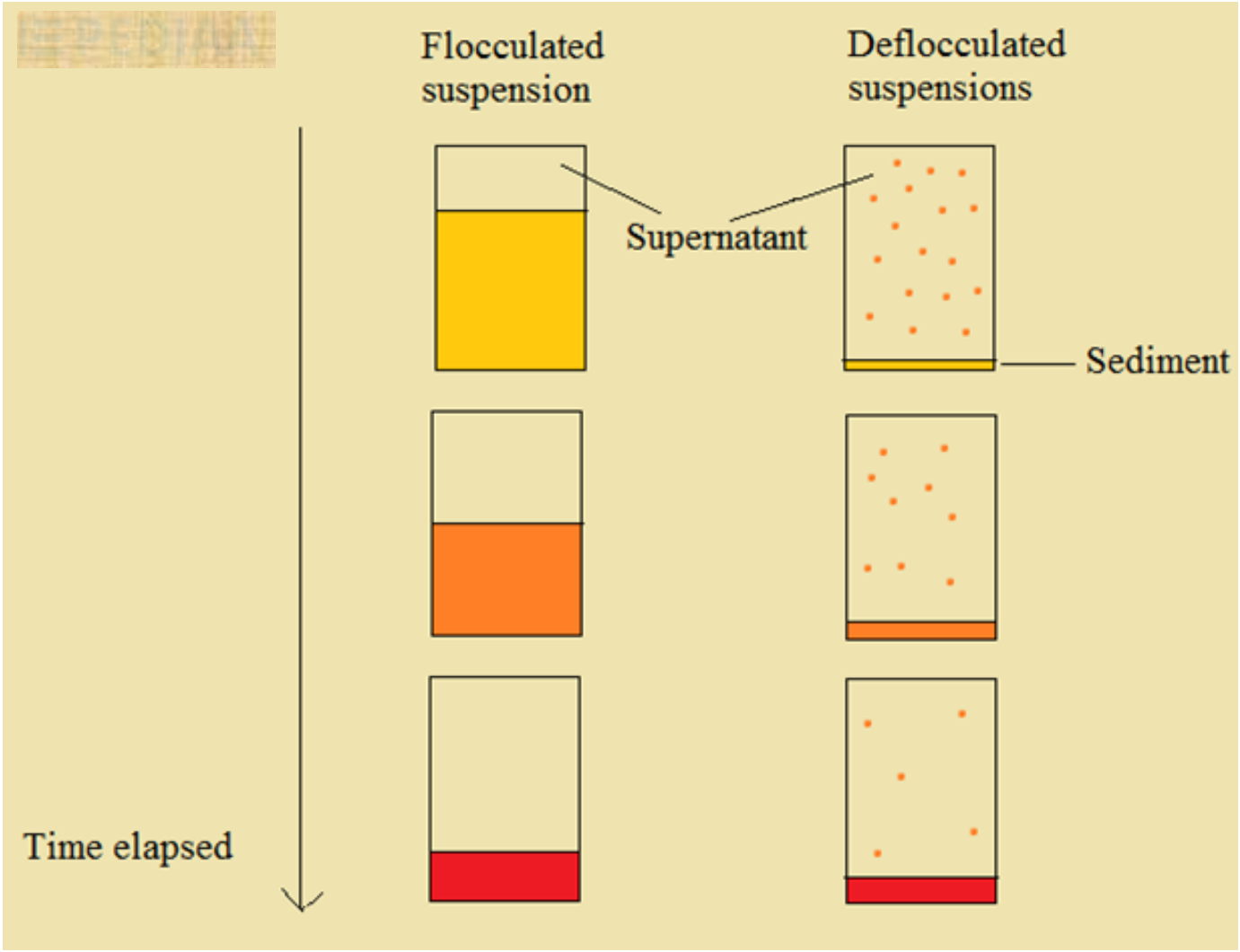
Sedimentation parameter
(Degree of flocculation)

- The second parameter is degree of flocculation(β). It is a better parameter for evaluating flocculation in a suspension, it describes the relationship between the sedimentation volume of the flocculated suspension (F) to the sedimentation volume of the same suspension when deflocculated (F_∞).
- The following equation is used to calculate β

$$\beta = \frac{F}{F_\infty} = \frac{v_u/v_0}{v_\infty/v_0} = \frac{v_u}{v_\infty}$$

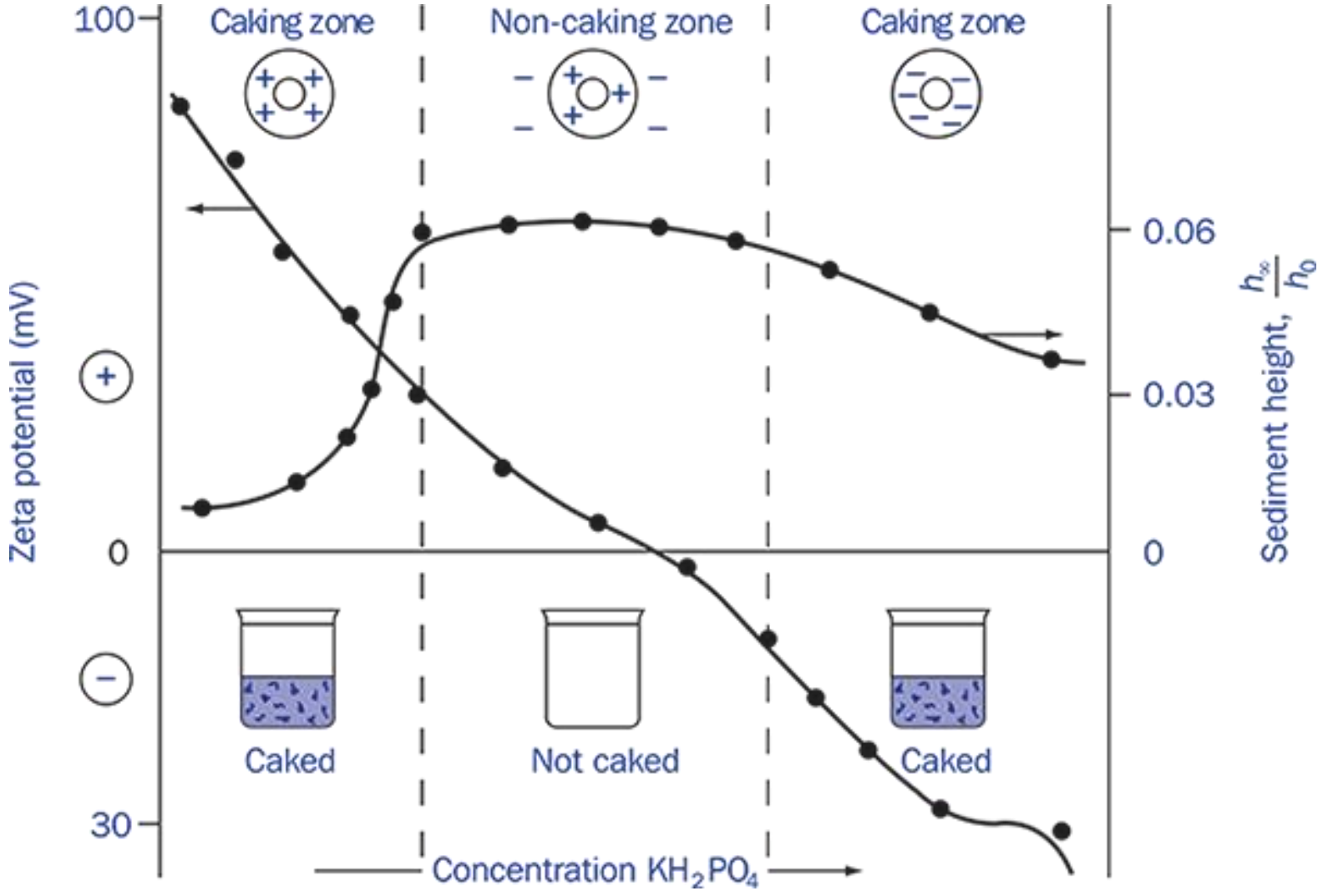
- Where,
  - v_u is the ultimate volume of flocculated suspension
  - v_∞ is the ultimate volume of deflocculated suspension

- A suspension consisting of floccules held together loosely will have large β, while suspension containing sediment has small β.
- The lower limit of β is equal to 1; which means there is no flocculation, i.e., $v_u = v_\infty$
- How can you induce flocculation?
- You can do that by use of flocculating agents, such as electrolytes, detergents and polymers.
- Flocculating agents are agents that are added to the medium to promote flocculation by counter acting the effect of protective layer the thus decrease zeta potential.


Flocculated suspension
Deflocculated suspensions
Supernatant
Sediment
Time elapsed

1. Electrolytes: they are used to obtain a product of large sedimentation volume. The ions will reduce the electrical barrier between the particles and link them together by forming a bridge between the particles, so the particles are held loosely in the suspension, but these large aggregates although settles rapidly they are easily redispersed by agitation.

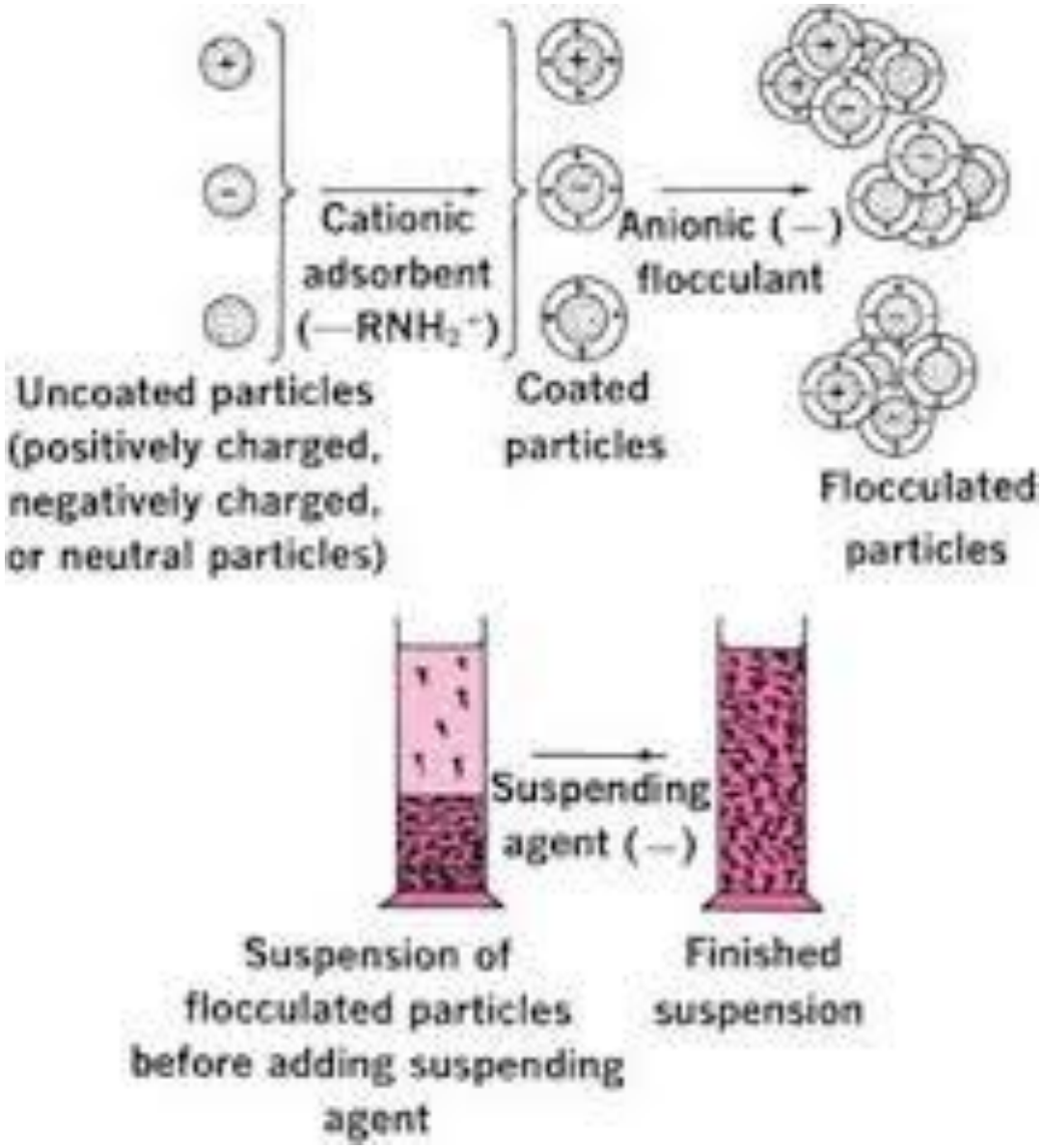
- The addition of electrolytes may be illustrated by the addition of monobasic potassium phosphate (KH_2PO_4) as a negative flocculating agent to a suspension of bismuth subnitrate (the particles of which are positively charged).


100
Caking zone
Non-caking zone
Caking zone
Zeta potential (mV)
+
0
−
30
0.06
0.03
0
Sediment height, $\frac{h_\infty}{h_0}$
Caked
Not caked
Caked
Concentration KH_2PO_4

- Initially, the bismuth subnitrate particles have a large positive charge with the addition of (KH_2PO_4) the apparent zeta potential will decrease to a point where the system have maximal flocculating.
- sedimentation study on bismuth subnitrate with increasing concentrations of flocculating agent have shown that:

1. The sedimentation volume is low initially, a condition that suggests a close-packed sediment of bismuth subnitrate particles.
2. Flocculation by KH_2PO_4 will increase the sediment volume relative to the initial value; until it reaches a maximum value. This is known as noncaking zone.
3. Additional flocculating agent will neutralize the charge on the particles and finely it will reverse the charge from +ve to –ve and again we get a caked suspension.

- The bridging action of the flocculated agent is more important than the neutralization of surface charge on the particles.

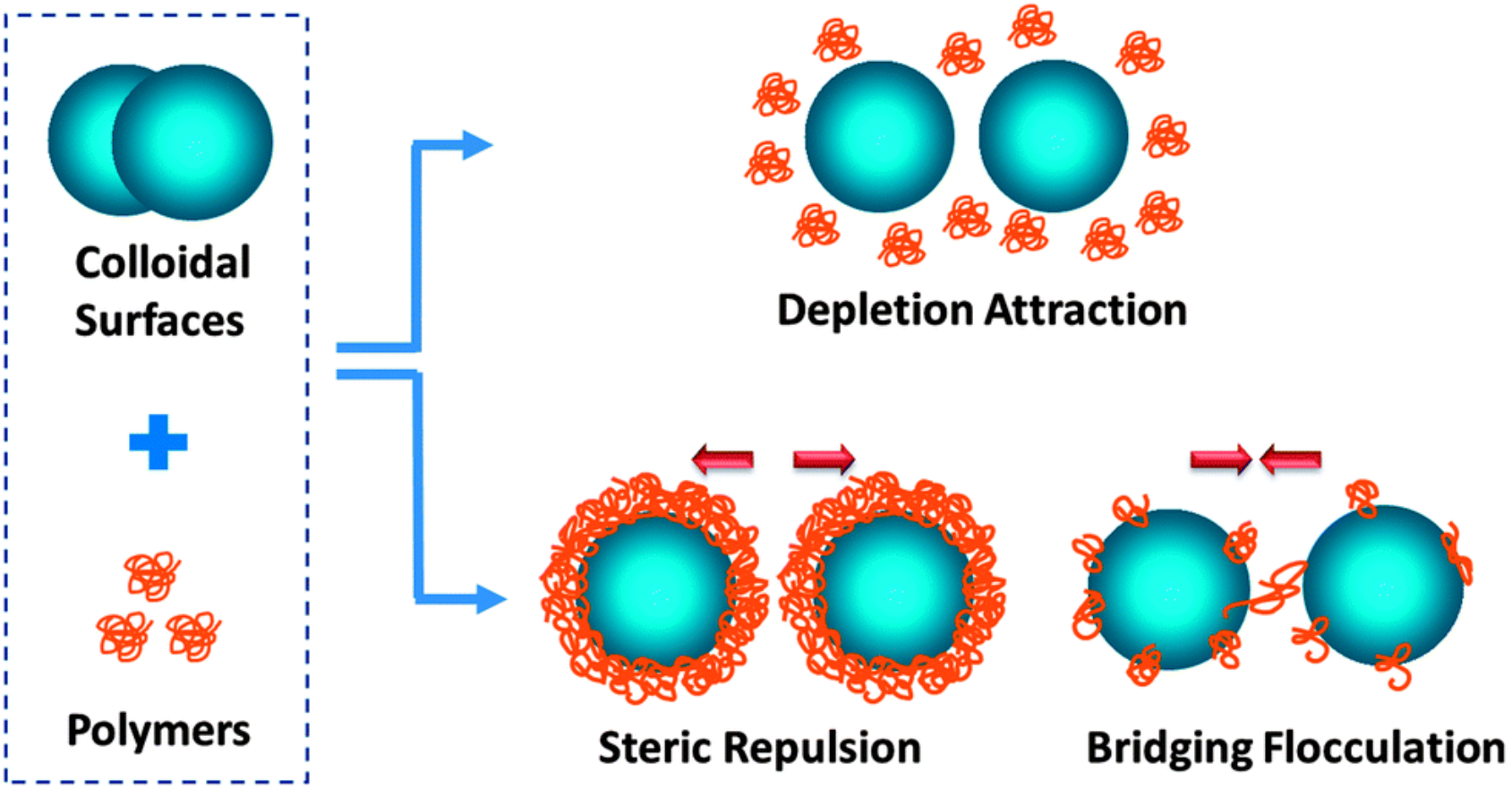

Cationic adsorbent (—RNH$_2$$^+$)
Anionic (—) flocculant
Uncoated particles (positively charged, negatively charged, or neutral particles)
Coated particles
Flocculated particles
Suspending agent (—)
Suspension of flocculated particles before adding suspending agent
Finished suspension

2. Detergent: ionic and non-ionic surfactant are used to bring about flocculation of suspended particles.

- Ionic surfactant increases sedimentation volume, while non-ionic surfactant may be adsorbed onto suspended particles and produce flocculated system at certain concentration.

3. Polymers: lyophilic polymers are commonly used as suspending agent.

- The polymer molecules contain active groups spaced along molecules may be adsorbed on the particles, leaving extended segments projecting out from the particle for bridging across to adjacent particles and thus producing flocculated system.


Colloidal Surfaces
Polymers
Depletion Attraction
Steric Repulsion
Bridging Flocculation

- A number of hydrocolloids are polyelectrolytes, their flocculating action is dependent on the pH of the medium and the ionic strength, and there is an optimum pH for sedimentation.
- For example, gelatin, which is a natural hydrocolloid may be used to bring about flocculation and prevent caking.

- In the preparation of suspension, the suspending agent act both as protective colloid to keep a settled particles from caking and as flocculating agent to produce loose cell-like structure in the liquid medium; through its rheological properties the suspending agent may provide certain consistency for supporting the particles.

- In many commercial suspensions, suspending agents are added to the dispersion medium to lend it structure.

1. Carboxymethylcellulose (CMC), methylcellulose,
2. microcrystalline cellulose,
3. polyvinylpyrrolidone,
4. xanthan gum, and
5. bentonite are a few of the agents employed to thicken the dispersion medium and help suspend the suspensoid.

- When polymeric substances and hydrophilic colloids are used as suspending agents, appropriate tests must be performed to show that the agent does not interfere with availability of the drug.
- These materials can bind certain medicinal agents, rendering them unavailable or only slowly available for therapeutic function.
- Also, the amount of the suspending agent must not be such to render the suspension too viscous to agitate (to distribute the suspensoid) or to pour.

- Frequently, the usual adult oral suspension is designed to supply the dose of the particular drug in a convenient measure of 5 mL or 1 teaspoonful. Pediatric suspensions are formulated to deliver the appropriate dose of drug by administering a dose-calibrated number of drops or with the use of a teaspoon. The following Figure shows commonly packaged oral suspensions administered as pediatric drops.

- Some are accompanied by a calibrated dropper, whereas other packages have the drop capability built into the container.
- On administration, the drops may be placed directly in the infant's mouth or mixed with a small portion of food.
- Because many of the suspensions of antibiotic drugs intended for pediatric use are prepared in a highly flavored, sweetened, colored base, they are frequently referred to by their manufacturers and also popularly as syrups, even though in fact they are suspensions.

FIGURE 14.4 Oral pediatric suspensions showing package designs of a built-in dropper device and a calibrated dropper accompanying the medication container.

Preparation of suspensions

- In the preparation of a suspension, the pharmacist must be familiar with the characteristics of both the intended dispersed phase and the dispersion medium.
- In some instances, the dispersed phase has an affinity for the vehicle to be employed and is readily wetted by it. Other drugs are not penetrated easily by the vehicle and have a tendency to clump together or to float on the vehicle.
- In the latter case, the powder must first be wetted to make it more penetrable by the dispersion medium. Alcohol, glycerin, propylene glycol, and other hygroscopic liquids are employed as wetting agents when an aqueous vehicle is to be used as the dispersion phase.

- In large-scale preparation of suspensions, wetting agents are mixed with the particles by an apparatus such as a colloid mill; on a small scale in the pharmacy, they are mixed with a mortar and pestle.
- Once the powder is wetted, the dispersion medium (to which have been added all of the formulation's soluble components, such as colorants, flavorants, and preservatives) is added in portions to the powder, and the mixture is thoroughly blended before subsequent additions of vehicle.
- A portion of the vehicle is used to wash the mixing equipment free of suspensoid, and this portion is used to bring the suspension to final volume and ensure that the suspension contains the desired concentration of solid matter.
- The final product is then passed through a colloid mill or other blender or mixing device to ensure uniformity.

- Whenever appropriate, suitable preservatives should be included in the formulation of suspensions to preserve against bacterial and mold contamination.
- An example formula for an oral suspension is the antacid aluminum hydroxide, the preservatives are methylparaben and propylparaben, and syrup and sorbitol solution provide the viscosity and sweetness.
- Aluminum hydroxide compressed gel 326.8 g
- Sorbitol solution 282.0 mL
- Syrup 93.0 mL
- Glycerin 25.0 mL
- Methylparaben 0.9 g
- Propylparaben 0.3 g
- Flavor qs
- Purified water, to make 1,000.0 mL

Sustained-Release Suspensions

- The formulation of liquid oral suspensions having sustained-release capabilities has had only limited success because of the difficulty of maintaining the stability of sustained release particles in liquid disperse systems.
- Product development research has centered on the same types of technologies used in preparing sustained-release tablets and capsules (e.g., coated beads, drug-impregnated wax matrix, microencapsulation, ion exchange resins).
- The use of a combination of ion exchange resin complex and particle coating has resulted in product success via the so-called Pennkinetic system.

- By this technique, ionic drugs are complexed with ion exchange resins, and the drug–resin complex particles coated with ethylcellulose.
- In liquid formulations (suspensions) of the coated particles, the drug remains adsorbed onto the resin but is slowly released by the ion exchange process in the gastrointestinal tract.
- An example of this product type is hydrocodone polistirex (Tussionex Pennkinetic Extended-Release Suspension, CellTech).

Extemporaneous compounding of suspensions

- Unfortunately, not all medicines are available in a convenient, easy-to-take liquid dosage form. Consequently, patients who are not able to swallow solid medicines, such as infants and the elderly, may present a special need. Thus, the pharmacist may have to use a solid dosage form of the drug and extemporaneously compound a liquid product.
- A difficulty that confronts the pharmacist is a lack of ready information on stability of a drug in a liquid vehicle. It is known that drugs in liquid form have faster decomposition rates than in solid form and some are affected by the pH of the medium.
- Leucovorin calcium when compounded from crushed tablets or the injectable form is most stable in milk or antacid and is unstable in acidic solutions.

- Typically, in formation of an extemporaneous suspension, the contents of a capsule are emptied into a mortar or tablets crushed in a mortar with a pestle.
- The selected vehicle is slowly added to and mixed with the powder to create a paste and then diluted to the desired volume.
- A liquid suspension for a neonate should not include preservatives, colorings, flavorings, or alcohol because of the potential for each of these to cause either acute or long-term adverse effects.

- In the neonate, alcohol can alter liver function, cause gastric irritation, and effect neurologic depression. So unless it is absolutely necessary, it should be omitted from an extemporaneous formulation.
- Pharmacists must be cautious because some vehicles, such as Aromatic Elixir, NF, contain a significant amount of alcohol, 21% to 23%, and are not suitable for use in these patients.
- The same problem holds for liquid formulations for the elderly or any patient who may be receiving another medication that depresses the central nervous system or would cause the patient to get violently ill, for example, metronidazole (Flagyl) and disulfiram (Antabuse).

- Preservatives have been implicated in adverse effects in preterm infants.
- Benzyl alcohol should be omitted from neonate formulations because this agent can cause a gasping syndrome characterized by a deterioration of multiple organ systems and eventually death.
- Propylene glycol has also been implicated in problems such as seizures and stupor in some preterm infants.
- Thus, formulations for neonates should be kept simple and not compounded to supply more than a few days of medicine.

- To minimize stability problems of the extemporaneous product, it should be placed in an airtight, light-resistant container by the pharmacist and stored in the refrigerator by the patient.
- Because it is a suspension, the patient should be instructed to shake it well prior to use and watch for any color change or consistency change that might indicate a stability problem.

Package and storage of suspensions

- All suspensions should be packaged in wide mouth containers having adequate airspace above the liquid to permit adequate shaking and ease of pouring.
- Most suspensions should be stored in tight containers protected from freezing, excessive heat, and light.
- It is important that suspensions be shaken before each use to ensure a uniform distribution of solid in the vehicle and thereby uniform and proper dosage.

Example of oral suspensions

1. Antacid suspension e.g., Aluminum, Magnesium and simethicone oral suspension.

- Antacids are intended to counteract the effects of gastric hyperacidity and, as such, are employed by persons, such as peptic ulcer patients, who must reduce the level of acidity in the stomach. They are also widely employed and sold over the counter (OTC) to patients with acid indigestion and heartburn.
- Many patients belch or otherwise reflux acid from the stomach to the esophagus and take antacids to counter the acid in the esophagus and throat.

- Most antacid preparations are composed of water-insoluble materials that act within the gastrointestinal tract to counteract the acid and/or soothe the irritated or inflamed linings of the gastrointestinal tract.
- A few water-soluble agents are employed, including sodium bicarbonate, but for the most part, water-insoluble salts of aluminum, calcium, and magnesium are employed; these include aluminum hydroxide, aluminum phosphate, dihydroxyaluminum aminoacetate, calcium carbonate, calcium phosphate, magaldrate, magnesium carbonate, magnesium oxide, and magnesium hydroxide.

- The ability of each of these to neutralize gastric acid varies with the chemical agent.
- For instance, sodium bicarbonate, calcium carbonate, and magnesium hydroxide neutralize acid effectively, whereas magnesium trisilicate and aluminum hydroxide do so less effectively and much more slowly.
- In selecting an antacid, it is also important to consider the possible adverse effects of each agent in relation to the individual patient. Each agent has its own peculiar potential for adverse effects.

- For instance, sodium bicarbonate can produce sodium overload and systemic alkalosis, a hazard to patients on sodium-restricted diets.
- Magnesium preparations may lead to diarrhea and are dangerous to patients with diminished renal function because of those patients' inability to excrete all of the magnesium ion that may be absorbed; the gastric acid converts insoluble magnesium hydroxide to magnesium chloride, which is water soluble and is partially absorbed.
- Calcium carbonate carries the potential to induce hypercalcemia and stimulation of gastric secretion and acid production, the latter effect known as acid rebound.
- Excessive use of aluminum hydroxide may lead to constipation and phosphate depletion with consequent muscle weakness, bone resorption, and hypercalciuria.

- Thus, in the treatment of ulcerative conditions, a combination of magnesium hydroxide and aluminum hydroxide is frequently used because the latter agent has some constipating effects that counter the diarrhea effects of the magnesium hydroxide.

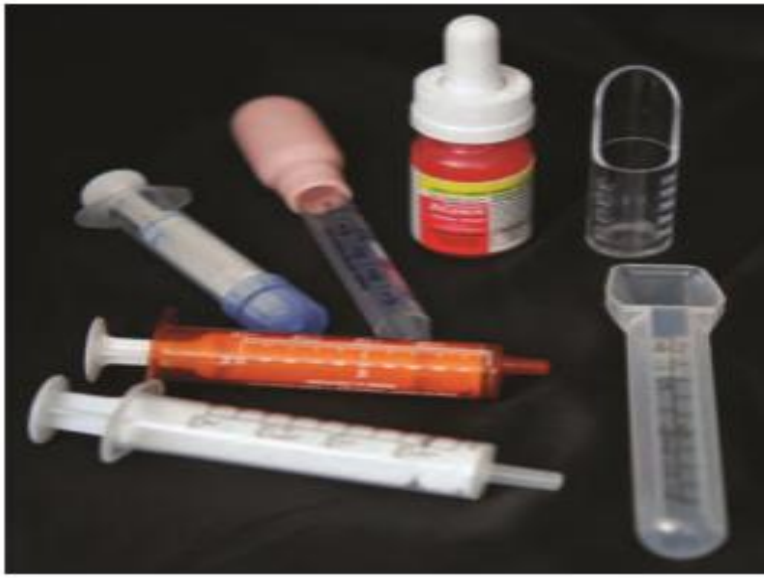
- When frequent dosage administration is required and when gastroesophageal reflux is being treated, liquid antacids generally are preferred to tablet forms. For one thing, the liquid suspensions assert more immediate action, because they do not require time to disintegrate.
- It is important that an antacid have a reasonably fast onset of action, because gastric emptying may not allow it much time in the stomach.
- Endoscopic studies have shown that very little antacid remains in the fasting stomach 1 hour after administration. Therefore, the U.S. Food and Drug Administration (FDA) requires that antacid tablets not intended to be chewed must disintegrate within 10 minutes in simulated gastric conditions. Generally, frequent food snacks prolong the time an antacid remains in the stomach and can prolong its action.

- Because many antacids, especially aluminum- and calcium-containing products, interfere with absorption of other drugs, especially the fluoroquinolone and tetracycline antibiotics and iron salts, pharmacists must caution their patients against taking such drugs concomitantly.

2. The antibacterial oral suspensions: include preparations of antibiotic substances (e.g., erythromycin derivatives and tetracycline and its derivatives), sulfonamides (e.g., sulfamethoxazole and sulfisoxazole acetyl), other anti-infective agents (e.g., methenamine mandelate and nitrofurantoin), or combinations of these (e.g., sulfamethoxazole–trimethoprim).

- Many antibiotic materials are unstable when maintained in solution for an appreciable length of time, and therefore, from a stability standpoint, insoluble forms of the drug substances in aqueous suspension or as dry powder for reconstitution are attractive to manufacturers.

- Many of the oral suspensions that are intended primarily for infants are packaged with a calibrated dropper to assist in the delivery of the prescribed dose. Some commercial pediatric antibiotic oral suspensions are pictured in the following Figure.



- The dispersing phase of antibiotic suspensions is aqueous and usually colored, sweetened, and flavored to render the liquid more appealing and palatable.
- The palmitate form of chloramphenicol was selected for the suspension dosage form not only because of its water insolubility but also because it is flavorless, which eliminates the necessity to mask the otherwise bitter taste of the chloramphenicol base.

- Dry Powders for oral suspension

  A number of official and commercial preparations consist of dry powder mixtures or granules that are intended to be suspended in distilled water or some other vehicle prior to oral administration.
- As indicated previously, these official preparations have “for Oral Suspension” in their official title to distinguish them from prepared suspensions.
- Most drugs prepared as a dry mix for oral suspension are antibiotics.
- The dry products are prepared commercially to contain the antibiotic drug, colorants (FD&C dyes), flavorants, sweeteners (e.g., sucrose or sodium saccharin), stabilizing agents (e.g., citric acid, sodium citrate), suspending agents (e.g., guar gum, xanthan gum, methylcellulose), and preserving agents (e.g., methylparaben, sodium benzoate) that may be needed to enhance the stability of the dry powder or granule mixture or the liquid suspension.

- When called on to reconstitute and dispense one of these products, the pharmacist loosens the powder at the bottom of the container by lightly tapping it against a hard surface and then adds the label-designated amount of purified water, usually in portions, and shakes the slurry until all of the dry powder has been suspended .
- It is important to add precisely the prescribed amount of purified water to the dry mixture if the proper drug concentration per dosage unit is to be achieved

- Also, the use of purified water rather than tap water is needed to avoid the possibility of adding impurities that could adversely affect the stability of the resulting preparation.
- Generally, manufacturers provide the dry powder or granule mixture in a slightly oversized container to permit adequate shaking of the contents after the entire amount of purified water has been added.

3. Anthelmintics: e.g., Albenzadol oral suspension
4. Antifungals:e.g., Nystatin oral suspension

Examples of other suspensions

1. Otic suspensions: for example combination of polymyxin B sulfate, neomycin sulfate and hydrocortisone otic suspension.
2. Ophthalmic suspension: Hydrocortisone eye drop suspension
3. Rectal suspensions: for example Barium sulfate for suspension may be employed orally or rectally for the diagnostic visualization.

- Commercially, barium sulfate for diagnostic use is available as a bulk powder containing the required suspending agents for effective reconstitution to an oral suspension or enema prior to administration.
- Enema units, which contain prepared suspension in a ready-to-use and disposable bag, are also available.