Liquid Dosage Form

Reference: A. J. Hickey & D. Ganderton,
Pharmaceutical Process Engineering, Chapter 14, 2nd edition, Informa Healthcare. 2010

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Liquid Dosage Form

- **Dosage forms:**
  are essentially pharmaceutical products in the form which involves a mixture of active drug components and nondrug components (excipients).
- **Liquid Dose Form of a Drug** used as a drug or medication intended for administration or consumption.

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Liquid Dosage Form

- **Liquid Dosage Forms** are prepared by:
  - Dissolving the active drug substance in an aqueous or non- aqueous (e.g. alcohol, ether, glycerin) solvent
  - Suspending the drug in appropriate medium
  - Incorporating the drug substance into an oil or water phases

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Liquid Dosage Form

Advantages

- Better patient compliance for those with swallowing difficulties, like the elderly and the young children
- Better dosage control versus a fixed tablet dose
  - More flexibility in achieving the proper dosage of medication
- No dissolution time and rapid absorption from the stomach/intestines compared to tablets
  - an important factor for pain-relieving drugs
- May contain flavors that make them *palatable* and help to *disguise* the awful taste of the actual medicine

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Liquid Dosage Form

Disadvantages

- Less stable and have a shorter shelf life than other dosage form
- Their storage requirements are typically more narrow
- More susceptible to bacterial microorganisms
- More complex to administer and need to be measured each time a dose is taken
- The risk of reaching peak plasma levels too fast, which could be harmful

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Liquid Dosage Form

Administration

- Liquid dosage forms can be administered:
  - Topically - lotions or suspension applied to the skin, nasal drops, ear drops, eye solutions
  - Orally – oral suspension (syrup), emulsion and solution
  - Parenterally
    - subcutaneous injection (S.C.)
    - intramuscular injection (I.M.)
    - intravenous administration (I.V.)

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Liquid Dosage Form

Syrups

- Syrups are concentrated aqueous preparations of a **sugar or sugar substitute**, with or without **flavoring agents**, and **active drug ingredients**.
- Types of syrup:
  - **Medicated syrups:**
    Syrups containing flavoring agents with medicinal substances.
  - **Flavored Syrups:**
    Used as vehicles for unpleasant tasting medications; the result is medicated syrup.

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Liquid Dosage Form

Syrups Advantages

- Ability to disguise bad taste of medication.
- Thick character of syrup has soothing effect on irritated tissues of throat.
- Contain little or no alcohol.
- Easy to adjust the dose for a child's weight.

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Syrups Disadvantages

- Delayed onset of action because absorption takes time.
- Not suitable for emergency cases or for unconscious patients.
- Not convenient for patients with GI disorder (diarrhea, constipation, ulceration, etc.)
- Cannot avoid first pass metabolism.

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Liquid Dosage Form

Syrups Components

- In addition to purified water and API, most syrups contain:
  - Sweetening agent: sugar (sucrose) / sugar substitute
  - Antimicrobial preservative
  - Viscosity modifier
  - Flavoring Agents
  - Colorants

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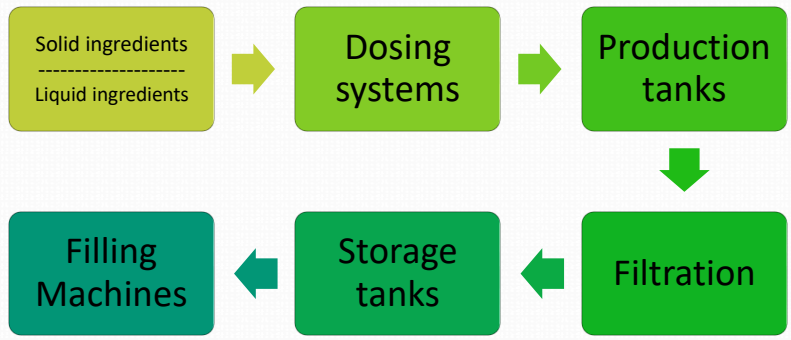
Preparation of Syrup

- Pharmaceutical syrups are produced by mixing purified water, sweeteners, active ingredients (API), aromas, flavors and other ingredients (thickeners, etc).



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Preparation of Syrup

- The ingredients are added by means of metering or dosing systems like flow meters and load cells to one or more reactors
- The order and quantity of the ingredients to be added is specified in the recipe.
- Usually, preparations are heated before finishing the addition of components.
- Solid products are added by means of solid-liquid blenders or vacuum systems.
- When the process is finished, the end product is filtered (if required) and sent to a storage tank.
- The product is transferred from the storage tanks to the filling machines by pumps.

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Preparation of Syrup

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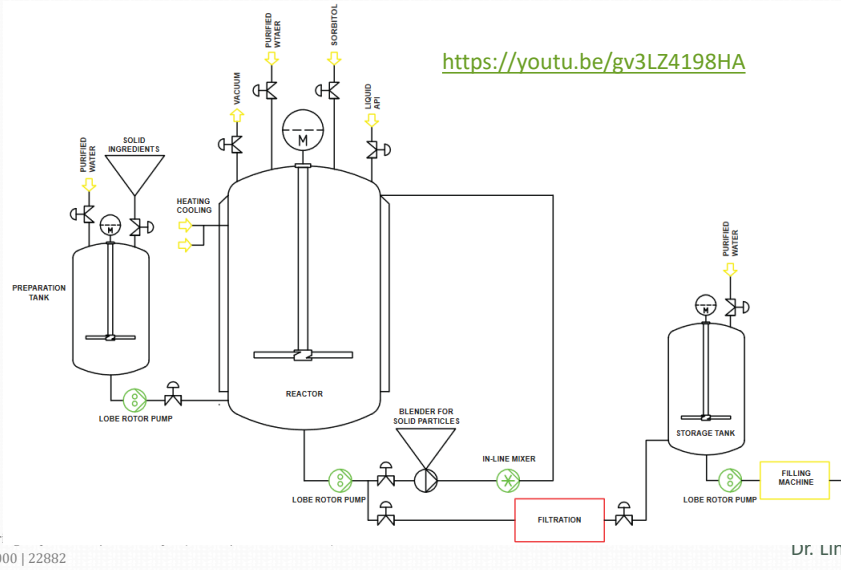

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Liquid Dosage Form

Preparation of Syrup

- There are four methods of syrup preparation:
  1. **Solution with heat**
  2. **Agitation without heat**
  3. **Addition of sucrose to liquid medicament**
  4. **Percolation method**
- The choice of the method is based on the physical and chemical properties of the ingredients.

Preparation of Syrup

1. Solution with Heat

Temperature of purified water is increased to 80 to 85 ºC

Taken off from the heat source

↓

Add sucrose and shake it thoroughly

↓

Heat sensitive substances and volatile agents are added after the solution attain the room temperature

↓

During heating, the sucrose gets hydrolyzed, results in the formation of dextrose and fructose

↓

These two sugars together called as invert sugar and the process is known as inversion

↓

Inversion leads to darkening of the solution

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Preparation of Syrup

2. Agitation without Heat

Vessel is taken generally made up of stainless steel or glass

↓

The vessel should be larger than the desired volume of syrup required

↓

The ingredients according to the formulation are added to water and mixed

It is better to dissolve solid ingredients in the water first and then to add them to syrup

↓

This results in easy mixing as sugar solution generally retards mixing

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Preparation of Syrup

4. Percolation Method

The principle of percolation is used

↓

A sucrose bed is prepared and then water or vehicle containing therapeutic agent is passed

↓

Here the sucrose bed should be coarse and shape of percolator must be cylindrical or cone shaped

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Liquid Dosage Form

Elixir

- Elixir is clear, sweetened hydro-alcoholic solution.
- Intended for oral use and are usually flavored to enhance palatability.
- Usually less sweet and less viscous than syrups.
- Classified into two classes:
  - **Non medicated elixirs** – vehicles
  - **Medicated elixir** – used for therapeutic effects

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Liquid Dosage Form

Elixir

- **The alcohol is mainly used to:**
  - Solubilize the active ingredient(s) and some excipients
  - Retard the crystallization of sugar
  - Preserve the finished product
  - Provide a sharpness to the taste
  - Aid in masking the unpleasant taste of the active ingredient(s)
  - Enhance the flavor

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Liquid Dosage Form

Elixir Advantages

- Better ability to maintain both water-soluble and alcohol-soluble components in solution
- Has stable characteristics
- Easily prepared by simple solution

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Liquid Dosage Form

Elixir Disadvantages

- Less effective than syrups in masking taste of medicated substances
- Contains alcohol, accentuates saline taste of bromides.

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Liquid Dosage Form

Suspension

- A heterogeneous mixture containing solid particles that are sufficiently large for sedimentation.
- Consists of a dispersion of relatively coarse particles, usually in aqueous vehicle.
- Suspensions may be used for oral and topical administration.
- Like solutions, oral suspensions are useful in children and patients who cannot tolerate a solid dosage form.

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Liquid Dosage Form

Emulsion

- A mixture of two or more liquids that are normally immiscible.
- Emulsions are two-phase systems consist of liquid drug substances.
- They are classified as:
  - oil-in-water emulsion (O/W)
  - water- in-oil emulsion (W/O)
- Emulsions can be administered
  - Topically
  - Orally
  - I.M.

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Exercise

- Drug X degrades by a zero-order process with a rate constant of 0.05 mg /(ml . year) at room temperature.

  If a 1% weight/volume (w/v) solution is prepared and stored at room temperature:

  1. What concentration will remain after 18 months?
  2. What is the half-life of the drug?

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Liquid Dosage Form

Formulations Of Liquids

- Oral liquids are formulated as solutions, syrups, suspensions and emulsions depending on **the nature of the active ingredient** particularly *solubility* and *stability*.
- Liquid formulation needs various **excipients** including

vehicle (base)	solubilizer	stabilizer	color
preservative	sweeteners	viscosity builder	flavor

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Formulations Of Liquids

Selection of Excipients

- The selection of the excipients is of major concern to design *stable*, *effective* and *palatable* oral liquid formulation.
- *Characteristics of active drug* are of major concern in developing an oral liquid dosage formulation.
- The major challenges in developing oral liquid dosage forms are
  - The stability of a drug in solution
  - The solubility of a drug at the required level
  - An acceptable taste

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Formulations Of Liquids

Selection of Excipients

- An excipient's compatibility with a drug in the solid state cannot infer the same compatibility in solution.
- If the mechanism of degradation of the drug is understood, the process of selecting suitable excipients to use in a solution will be much easier.
- Some knowledge of the drug's physical and chemical characteristics such as the *solubility*, *pH stability*, and *pKa value*(s) of reactive functional groups is essential in order to choose the proper excipients effectively.

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Formulations Of Liquids

Syrup vs. Suspension

- Ideally, the pH at which the drug is most stable would also be close enough to the solubility for delivering the desired dose in a tea spoon (approximately 5 mL).
- Requiring patients to take more than two tea spoon full at a time may not be advisable because of lower patient compliance.
- If the pH at which the drug is most stable is
  - one at which there is enough solubility, a simple oral **solution or syrup** formulation may be developed.
  - **NOT** one at which there is enough solubility, a **suspension** formulation may be required.

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Formulations Of Liquids

Selection of Excipients

- The decision to develop a solution, syrup or a suspension of a drug is influenced by many factors like
  - solubility
  - the desired release profile of the drug
  - properties of the base vehicle like surface tension, viscosity, boiling point, and specific heat of solution

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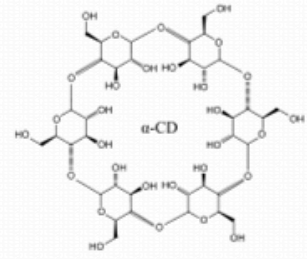
Formulations Of Liquids

Selection of Excipients

- In case of clear liquids, lack of solubility of the drug in the base vehicle may demand the need for miscible co-solvents.
- A miscible solvent may also be needed to *decrease the solubility* of the drug in a primary vehicle in formulating a *suspension*.
- Other approaches to *increasing the solubility* of a drug in solution is to use
  - a complexing agent such as a cyclodextrin.
  - Surfactants



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Oral Liquid Formulations

Excipients

- Oral liquid formulation needs a meticulous blend of ingredients to perform various functions like *wetting and solubilisation*, *stabilization,* and to impart suitable *color, taste and viscosity*.
- The **blend** should be compatible, non reactive and stable.

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Oral Liquid Formulations

Excipients

- The common excipients generally required for any liquid formulation are

vehicle (base)	preservative	stabilizer	color
sweeteners	viscosity builder		flavor

- In addition,
  - solubilizers are required in case of clear liquids
  - suspending agents are needed for suspension
  - emulsifying agents for emulsions.

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Excipients for Oral Liquid Formulations

1- Vehicles

- Vehicles, in pharmaceutical formulations, are the liquid bases that carry drugs and other excipients in dissolved or dispersed state.
- Pharmaceutical vehicles can be classified as:
  - **Aqueous vehicles:** Water, hydro-alcoholic, polyhydric alcohols and buffers.
    - These may be thin liquids, thick syrupy liquids, or hydrocolloidal bases.
  - **Oily vehicles:** Vegetable oils, mineral oils, organic oily bases or emulsified bases.

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Water

- Natural water contains large number of dissolved and suspended impurities.
  - The dissolved impurities include ***inorganic impurities*** like salts of sodium, potassium, calcium, magnesium, and iron as chlorides, sulfates and bicarbonates.
  - ***Organic impurities*** present in purified water are either in soluble or insoluble state.
  - ***Micro-organisms*** are the other impurities and the load of micro-organism in natural substances including water is called ***bio-burden***.

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Water

- Drinking (potable) water contains less than 0.1% of total solid.
- Acceptable drinking water should be clear, odorless, colorless and neutral with slight deviation in pH (due to dissolved solids and gasses).
- Drinking water **is not usable in pharmaceutical formulation**, obviously due to the possible incompatibility of formulation components with dissolved impurities in water.

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Water

- ***Purified water USP*** is allowed for usage as vehicle or as a component of vehicle for aqueous liquid formulations *except for those intended for parenteral administration* (injections).
- It is obtained by distillation, ion exchange treatment, reverse osmosis or any other suitable process.

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Water

- USP criteria for purified water (PW) compared with USP Water for Injection (WFI)

Parameter	USP Purified Water (PW)	USP Water for Injection (WFI)
pH	5.0 – 7.0	5.0 – 7.0
TOC (Total organic carbon)	< 500 ppb	<500 ppb
Total bacteria count	10 colony forming units (cfu) /mL, pathogen free	10 colony forming units (cfu) / 100 mL, pathogen free
Endotoxin	Not specified	0.25 EU/mL
Feed water	Potable water	Not specified, but Health. Canada regulations demand that PW be used

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Alcohol (Ethyl Alcohol)

- Next to water, alcohol is the most useful solvent in pharmacy.
- It is invariably used as hydro-alcoholic mixture that dissolves both water soluble and alcohol soluble drugs and excipients.
- Diluted alcohol, prepared by mixing equal volumes of Alcohol USP and purified water USP, is a useful solvent in various pharmaceutical processes and formulations.

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Glycerol

- Glycerol (or Glycerin) is a clear, colorless liquid, with thick, syrupy consistence, oily to the touch, odorless, and very sweet to the taste.
- When exposed to the air, it slowly abstracts moisture.
- Obtained by the decomposition of vegetable or animal fats or fixed oils and containing not less than 95% of absolute Glycerin.
- Soluble in all proportions, in Water or Alcohol; also soluble in a mixture of 3 parts of Alcohol and 1 part of Ether, but insoluble in Ether, Chloroform, Carbon Disulphide, Benzin, Benzol, and fixed or volatile oils.

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Glycerol

- Glycerin is used as vehicle in various pharmaceutical products like Elixir of Phosphoric acid, Solution of Ferric Ammonium Acetate, Glycerin of Boric Acid, Glycerin of Tannic Acid, and in many Extracts, Fluid Extracts, Syrups and Tinctures.
- As glycerin is an excellent solvent for numerous substances, such as iodine, bromine, alkalies, tannic acid, many neutral salts, alkaloids, salicin, etc., it is a good vehicle for applying these substances to the skin and to sores.

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Glycerol

- It does not evaporate nor turn rancid, and is powerfully hygroscopic.
- As glycerin is sweet, it is an excellent flavoring agent.
- It is demulcent, and is used as a vehicle for applying substances, such as tannic acid, to the throat.
- In oral liquid formulations, glycerin is used as co-solvent to increase solubility of drugs that show low solubility in water.
- It is also used to improve viscosity, taste and flavor.
- In external applications it is used as humectants.

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Propylene Glycol USP

- Pharmaceutical grade of Propylene Glycol is monopropylene glycol (PG or MPG) with a specified purity greater than 99.8%.
- An outstanding solvent for many organic compounds.
- Colorless and odorless and has a very slight characteristic taste which is not objectionable.
- *These properties make propylene glycol particularly suitable as a solvent for flavorings and dyes in cosmetics, toothpastes, shampoos, and mouthwashes.*

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Propylene Glycol USP

- PG is an important ingredient for a multitude of uses, including:
  - **Solvent** for aromatics in the flavor-concentrate industry
  - **Wetting agent** for natural gums
  - Ingredient in the compounding of citrus and other emulsified flavors
  - **Solvent** in elixirs and pharmaceutical preparations
  - Solvent and **coupling agent** in the formulation lotion, shampoos, creams and other similar products
  - **Emulsifier** in cosmetic and pharmaceutical creams
  - Very effective **humectants**, **preservative** and **stabilizer**

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Excipients for Oral Liquid Formulations

1.a Aqueous Vehicles

Propylene Glycol USP

- Propylene glycol is non-allergenic and may be used in cosmetics and other toilet goods specifically formulated for sensitive skin.
- Propylene glycol is a general solvent and antimicrobial preservative used in a wide range of pharmaceutical preparations including oral liquid, topical and parenteral preparations.
- The toxicity of propylene glycol is quite less in comparison to many other co-solvents generally used.

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Excipients for Oral Liquid Formulations

1- Vehicles

Lipid-Based Delivery Vehicles

- A large number of new drugs being developed show low water solubility.
- To overcome low solubility and low bioavailability there has been a growing interest in developing novel oral delivery strategies using lipid-based formulations.
- While oral liquid emulsions have been used for many years, self-emulsifying drug delivery systems, which utilize a lipid/surfactant-based vehicle, are becoming a more widely used approach to solubilize water-insoluble drugs.

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Excipients for Oral Liquid Formulations

1- Vehicles

Lipid-Based Delivery Vehicles

- Benefits of these types of formulations are that lipids that keep a hydrophobic drug in solution may facilitate the dissolution and absorption of the drug as the lipid vehicle is metabolized in the GI tract.
- The erratic bioavailability of some drugs may be overcome by formulation into a microemulsion, which includes oil.

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Excipients for Oral Liquid Formulations

2- Solubilizers

Wetting Agents and Surfactants

- Wetting agents are routinely used in pharmaceutical formulations, especially in liquid dosage forms to create a homogeneous dispersion of solid particles in a liquid vehicle.
- This process can be challenging due to a layer of adsorbed air on the particle's surface. Hence, even particles with a high density may float on the surface of the liquid until the air phase is displaced completely.
- The use of a wetting agent allows removal of adsorbed air and easy penetration of the liquid vehicle into pores of the particle in a short period of time.

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Excipients for Oral Liquid Formulations

2- Solubilizers

Wetting Agents and Surfactants

- For an aqueous vehicle, **alcohol**, **glycerin**, and **PG** are frequently used to facilitate the removal of adsorbed air from the surface of particles.
- Whereas for a non-aqueous liquid vehicle, **mineral oil** is commonly used as a wetting agent.
- Typically, hydrophobic API particles are not easily wetted even after the removal of adsorbed air. Hence, it is necessary to reduce the interfacial tension between the particles and the liquid vehicle by using a surface-active agent.

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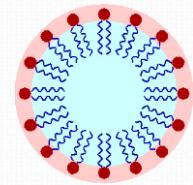
Excipients for Oral Liquid Formulations

2- Solubilizers



Wetting Agents and Surfactants

- Structurally, wetting agents comprise branched hydrophobic chains with central hydrophilic groups or short hydrophobic chains with hydrophilic end groups.
- Sodium lauryl sulfate is one of the most commonly used surface-active agents.
  - Such surfactants, when dissolved in water, lower the *contact angle* of water and aid in spreadability of water on the particles surface to displace the air layer at the surface and replace it with the liquid phase.

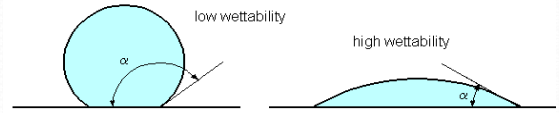


Figure 10 - The contact angle of a liquid with a solid is used as wettability index. For $\alpha < 90°$ the liquid wet the wall (eg: water on glass), for $\alpha > 90°$ the liquid does not wet the wall (eg: mercury on glass). If $\alpha = 0°$ the liquid perfectly wet the wall.

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Excipients for Oral Liquid Formulations

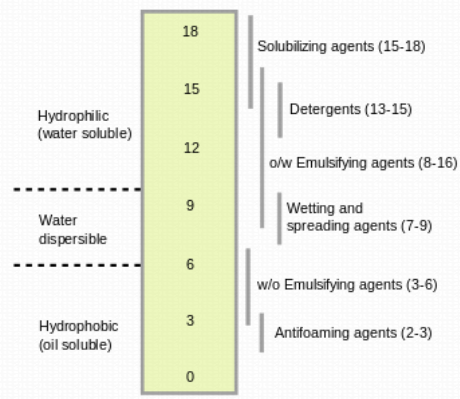
2- Solubilizers

Wetting Agents and Surfactants

- Wetting agents have a hydrophilic-lipophilic balance (HLB) value between 7 and 9.

$$HLB = 20 * M_h/M$$

- M_h = molecular mass of the hydrophilic portion of the molecule
- M = molecular mass of the whole molecule
- HLB ranges from 0 to 20
- HLB value of 0 corresponds to a completely lipophilic/hydrophobic molecule
- HLB value of 20 corresponds to a completely hydrophilic/lipophobic molecule.



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Topic 5 - Liquid Dosage Forms

Excipients for Oral Liquid Formulations

2- Solubilizers

Wetting Agents and Surfactants

- The following properties must be considered in the assessment of wetting agents:
  - The minimum surface tension that can be attained, regardless of the amount of agent required.
  - The depression of surface tension achieved with a specified concentration of agent.
  - The time required for an agent to achieve equilibrium.

A good wetting agent permits the depression of surface tension in water by up to 2.5 mN/m in 15 seconds

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Wetting Agents and Surfactants

- Careful consideration must be given to the potential changes in *activity* and *bioavailability* of the API and/or excipients when a surfactant is used.
- Dramatic changes in the *bactericidal activity* of certain excipients take place when they are solubilized by surfactants, and the stability of excipients against oxidation and hydrolysis may be modified by solubilization.

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Wetting Agents and Surfactants

- Additionally, many nonionic surfactants (at high concentrations) exhibit a characteristic temperature above which the solution becomes *cloudy*.
- This cloudiness is due to the formation of very large lamellar micelles, which results from the dehydration of the polyoxyethylene chains.
- For these types of surfactants, it is essential to consider the risk of exceeding the cloud point.

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Wetting Agents and Surfactants

- In addition to the concentration of surfactant, the location of the API or excipient in the micelle structure can influence its stability.
- Surrounding the positive surface of the cationic micelle will be a relatively higher concentration of hydroxyl ions from the surrounding solution.
- If the drug or excipient is more susceptible to base-catalyzed hydrolysis and exposed to the concentrated hydroxyl area near the surface of the micelle, then the result would likely be more degradation (hydrolysis).

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Wetting Agents and Surfactants

- However, if it is more stable under alkaline conditions, then there may be less degradation (hydrolysis).
- Therefore, if a correlation between the location of the drug or excipient in the micelle and its pH-dependent stability can be determined, a formulator may be able to optimize the choice of surfactant to prevent degradation.

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pH Modifiers and Buffering Agents

- The pH of an oral liquid formulation is a key point in many regards.
- Control of the formulation pH, could prevent large changes during torage.
- Therefore, most formulations utilize a buffer to control potential changes in the solution pH.
- The amount of buffer capacity needed is generally between 0.01 and 0.1 M, and a concentration between 0.05 and 0.5 M is usually sufficient.

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pH Modifiers and Buffering Agents

- The selection of a suitable buffer should be based on
  I. Whether the acid-base forms ***are listed*** for use in oral liquids.
  II. The ***stability*** of the drug and excipients in the buffer.
  III. The ***compatibility*** between the buffer and container.

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pH Modifiers and Buffering Agents

- A combination of buffers can also be used to gain a wider range of pH compared to the individual buffer alone. However, *not all buffers are suitable for use in oral liquids*.
  - For example, a boric acid buffer may be used for optical and IV delivery but not in oral liquids because of its toxicity.

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pH Modifiers and Buffering Agents

- Stability of formulation containing non-ionizable API may also depends on pH.
  - For example, a specific functional group or a particular resonance structure that is stabilized in a specific pH range may facilitate a reaction between the excipient and the drug.

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pH Modifiers and Buffering Agents

- The buffer may negatively influence the *solubility* of the drug and other excipients.
- This effect depends on both the **polarity of the solute and of the salt**.
  - Non-polar solutes are solubilized (salted in) by less polar organic salts and are desolubilized (salted out) by polar salts.
  - Conversely, polar solutes are salted in by polar salts and salted out by organic salts.

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pH Modifiers and Buffering Agents

- The stabilizing effect of buffers that have *multiple charged species in solution* could also determine the potential reaction between excipients and API.
  - For example, buffers that use carbonates, citrate, tartrate, and various phosphate salts may precipitate with calcium ions by forming sparingly soluble salts.
  - However, this precipitation is dependent upon the solution pH. The activity of phosphate ions may be lowered due to interactions with other solution components.

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pH Modifiers and Buffering Agents

- There are a number of factors that may also affect the solution pH such as temperature, ionic strength, dilution, and the amount and type of co-solvents present.
  - For example, the pH of acetate buffers is known to increase with temperature, whereas the pH of boric acid buffers decreases with temperature.
- Finally, the drug in solution may itself act as a buffer.
- If the drug is a weak electrolyte, such as salicylic acid or ephedrine, the addition of base or acid, respectively, will create a system in which the drug can act as a buffer.

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Solubility and pH - Example

- A pharmacist prepares a 3.0% solution of an antibiotic as an ophthalmic solution and dispenses it to a patient. A few days later the patient returns the eye drops to the pharmacist because the product contains a precipitate. The pharmacist, checking the pH of the solution and finding it to be 6.0, reasons that the problem may be pH related. The physicochemical information of interest on the antibiotic includes the following:

Show that the problem is pH related, and find the pH at which the drug will remain in solution?

Molecular weight	285 (salt) 263 (free acid)
3.0% solution of the drug	0.1053 M solution
Acid form solubility (S_a)	3.1 mg/mL (0.0118 M)
K_a	5.86×10^{-6}

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Solubility and pH - Example

- To calculate the total quantity of drug that can be maintained in solution at a selected pH (S_T), the following equation can be used

$$S_T = S_a \left(1 + \frac{K_a}{[H^+]}\right)$$

$$where\ S_a = \text{Acid form solubility}$$

Molecular weight	285 (salt) 263 (free acid)
3.0% solution of the drug	0.1053 M solution
Acid form solubility (S_a)	3.1 mg/mL (0.0118 M)
K_a	5.86×10^{-6}

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$$S_T = 0.0118[1+] = 0.0809 \text{ molar}$$

$$0.1053 = 0.0118\left[1+\frac{5.86\times10^{-6}}{[H^+]}\right]$$

$$[H^+] = 7.333\times10^{-7}, \text{ or a pH of } 6.135$$

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2- Solubilizers

Suspending Agents and Viscosity-modifying Agents

- One of the most crucial factors involved in formulating a pharmaceutical suspension is the selection of an appropriate suspending agent.
- Suspending agents impart viscosity, and thus retard particle sedimentation.
- Factors considered in the selection of the appropriate agent include desired rheological property, suspending ability in the system, chemical compatibility with other excipients, pH stability, length of time to hydrate, batch-to-batch reproducibility, and cost.

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Suspending Agents and Viscosity-modifying Agents

- Suspending agents can be classified into:
  - Cellulose derivatives
  - Clays
  - Natural gums
  - Synthetic gums
- In many cases, these excipients are used in combination.

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Preservatives

- Microbiological contamination presents a significant health hazard in oral liquids.
- Therefore, the use of preservatives become inevitable to prevent the growth of microorganisms during the product's manufacture and shelf life, although it may be most desirable to develop a "preservative-free" formulation to address the increasing concerns about the biological activity of these compounds.

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2- Solubilizers

Preservatives

- Most formulations require some kind of preservative to ensure no microbial growth.
- The majority of preservatives are *bacteriostatic* rather than *bacteriocidal*, and consists of both acid and nonacid types.
- Among the acidic types are phenol, chloro-cresol, 9-phenyl phenol, alkyl esters of para-hydroxybenzoic acid, benzoic acid, boric acid, and sorbic acid, and their respective salts.

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Preservatives

- The pH of solution, and the pKa of the preservative need to be carefully evaluated prior to selecting a preservative for a formulation.
- Neutral preservatives include chlorobutanol, benzyl alcohol, and beta-phenylethyl alcohol.
- Under alkaline conditions, it is generally regarded that microbial growth is insignificant and at these pH values, the need for a preservative is not generally recommended.

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2- Solubilizers

Preservatives

- Many preservatives are not recommended for use in oral liquids and hence the choice of an acceptable preservative for an oral liquid formulation is limited.
- In addition, the solubility of many preservatives in aqueous system may not be high enough for effective antimicrobial activity.
- Also, it is essential to understand that bacteriostatic agents like para hydroxyl benzoic acids can partition between organic and aqueous phases in a heterogeneous liquid formulations in such a way that their activity is significantly reduced.

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Excipients for Oral Liquid Formulations

2- Solubilizers

Preservatives

- Typical preservatives used in oral liquid dosage forms include:
  - Alcohol
  - Benzyl alcohol, Bronopol
  - Chlorbutol, Chlorocresol
  - Butylparaben, Methylparaben, Propylparaben
  - Phenol
  - Phenylethanol Sodium benzoate
  - Antimicrobial solvents like propylene glycol, chloroform etc.

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2- Solubilizers

Preservatives

- In addition, some formulation ingredients prevent microbial growth.
- These ingredients include
  - nonionic surfactants
  - quaternary ammonium compounds
  - Gelatin
  - ferric salts
  - calcium salts
  - salts of heavy metals including silver, lead, and mercury

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Preservatives

- Preservatives often contain reactive functional groups, which are responsible for their antimicrobial activity but lead to unwanted reactions.
- Therefore, in addition to the excipient's antimicrobial activity, other parameters should be evaluated during the formulation development for its *compatibility* with the API, other excipients, and the container system.

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Excipients for Oral Liquid Formulations

2- Solubilizers

Stabilizers - Antioxidants

- The oxidation of an API in an oral liquid formulation is difficult to control due to low activation energies (2-12 kcal/mol) for oxidation and photolysis compared to solvolysis, dehydration, and polymorphic transformations (10-56 kcal/mol).
- Trace amounts of impurities, which are invariably present in the API or excipient catalyzes the oxidation reaction.

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Stabilizers - Antioxidants

- Most drugs exist in a reduced form, show increased instability when the solution is consistently introduced into an atmosphere of 20% oxygen.
- The pH of the solution may effect the oxidation of phenolic and sulfhydryl group containing drugs because it is principally the ionized form of these drugs that participate in the oxidation.
  - For example, epinephrine is only slowly oxidized at pH < 4 but rapidly degrades under alkaline pH conditions.

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2- Solubilizers

Stabilizers - Antioxidants

- Antioxidants can be compounds that can *reduce a drug that has been oxidized*, or compounds that are *more readily oxidized than the agents they are to protect* (oxygen scavengers).
  - Many of the lipid-soluble antioxidants act as scavengers.
- Antioxidants can also act as *chain terminators*, reacting with free radicals in solution to stop the free-radical propagation cycle.

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Stabilizers - Antioxidants

- Mixtures of chelating agents and antioxidants are often used because there appears to be a synergistic effect. This occurs because many of the agents act at differing steps in the oxidative process.
- Some substances prone to oxidation include *unsaturated oils/fats*, *compounds with aldehyde or phenolic groups*, *colors*, *flavors*, *sweeteners*, *plastics and rubbers (*used in containers for products).

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Stabilizers - Antioxidants

- Oxidation may manifest as products with an unpleasant odor, taste, appearance, precipitation, discoloration or even a slight loss of activity.
- The term **rancidity** refers to many typical off-flavors that result from autoxidation of unsaturated fatty acids that are present in oils and fats, and it affects many oils and fats.
- The distinct *rancid odor* may result from short-chain, volatile monomers resulting from the *cleavage* of the longer chain, less volatile oils and fats.

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Stabilizers - Antioxidants

- Anti-oxidants generally used in liquid formulations include:

Oil Soluble	*Slightly Water Soluble*	*Water Soluble*
α-Tocopherol acetate	Acetone sodium bisulfite	Acetylcysteine
Ascorbic acid	Ascorbyl palmitate	Butylated hydroxyanisole (BHA)
Butylated hydroxytoluene (BHT)	Cysteine	Cysteine hydrochloride
d α-Tocopherol natural	*d*-α-tocopherol synthetic	Dithiothreitol
Monothioglycerol	Nordihydroguaiaretic acid	Propyl gallate
Sodium bisulfite	Sodium formaldehyde sulfoxylate	Sodium metabisulfite
Sodium sulfite	Sodium thiosulfate	Thiourea

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