3. Liquid Dosage Forms
Liquid dosage forms are designed to provide the maximum therapeutic response in a target population with difficulty swallowing tablets and capsules and/or to produce rapid therapeutic effects. The major ingredient in most liquid dosage forms is water.

Commercial liquid dosage forms reach large-scale production after being preformulated at the laboratory level followed by formulation at the small scale and then at the pilot plant scale. Due to the complexity of the manufacturing process, scale-up from pilot to commercial production is not a simple extrapolation. The approaches to the four levels of production are different. Most of the formulation ingredients are analyzed, studied, and selected at the laboratory scale. While small-scale production is more focused on the liquid preparation procedure with higher amounts of ingredients, the main issues at the pilot plant scale are the design of infrastructure and reduction of costs. Commercial production introduces problems that are not a major issue on a small scale, for instance, materials handling and storage, pulverizing, mixing, dissipation of the generated heat during production, time control, personnel administration, and bottle-filling capabilities. Furthermore, purified water is essential for the manufacturing of these products as well as on-site packing capabilities.
According to the FDA: “A dosage form is the physical form in which a drug is produced and dispensed. In determining dosage form, FDA examines such factors as (1) Elegance: physical appearance of the drug product, (2) Stability: physical form of the drug product prior to dispensing to the patient, (3) Acceptability: the way the product is administered, (4) Efficacy: frequency of dosing, and (5) Safety: how pharmacists and other health professionals might recognize and handle the product”
The physical form of a drug product that is pourable displays Newtonian or pseudoplastic flow behavior and conforms to its container at room temperature. In contrast, a semisolid is not pourable and does not flow at low shear stress or conform to its container at room temperature. According to its physical characteristics, liquid dosage forms may be dispersed systems or solutions.

Dispersed systems are dosage forms composed of two or more phases, where one phase is distributed in another. If a dispersed system is formed by liquid phases, then it is known as an “emulsion.” In contrast, the dispersed system is named a “suspension” when the liquid dosage form is accomplished by the distribution of a solid phase suspended in a liquid matrix. The solid phase of a suspension is usually the drug substance, which is insoluble or very poorly soluble in the matrix.
A solution refers two or more substances mixed homogeneously. Although solubility refers to the concentration of a solute in a saturated solution at a specific temperature, in pharmacy, solution liquid dosage forms are unsaturated to avoid crystallization of the drug by seeding of particles or changes of pH or Temperature. The precipitation of drug crystals is one of the most important physical instabilities of solutions that may affect its performance. Water is the most used solvent in solutions manufacturing; however, there are also some commercial nonaqueous solutions in the pharmaceutical market.
The manufacturing of liquid dosage forms with market-oriented planning includes the following stages with respect to special good manufacturing practice (GMP) requirements: planning of material requirements, liquid preparation, filling and packing, sales of drug products, vendor handling, and customer service.

A “batch” job or operation is defined as a unit of work. Raw materials, semifinished drug products (bulk), and finished drug products are handled in batches. Each different type of material used during the process, such as product packing, should be managed by batches. This applies also to process aids and operation facilities.
Advantages of liquid dosage forms

1. Used for patients who cannot swallow.
2. Has fast absorption rate.
3. Is more flexible in achieving the proper dosing.
4. Best choice for young children and elders.
Disadvantages of liquid dosage forms

1. Has short shelf life due to low stability.
2. Has less accuracy.
3. Needs special storage and transferring conditions.
4. Is easily infected by microorganisms.
5. Has special storage requirements
Types of liquid dosage forms

1. Solutions
2. Suspensions
3. Syrups
4. Lotions
5. Tinctures
6. Spirits
7. Elixirs
8. Fluid extracts
9. Liniments
10. Aromatic water
11. Decoctions
12. Collodion
Steps of Liquids Manufacturing Process

Planning of Material Requirements: Research and development of protocols and selection of materials; acquisition and analysis of raw materials; physical plant design, building, and installation; equipment selection and acquisition; personnel selection and initial training; and monitoring information system.

Liquid Preparation: Research and development of protocols concerning liquid compounding; scale-up of the bulk product compounding; physical plant control and maintenance; equipment maintenance and renovation; continuous training of personnel and personnel compensation plan; and supervision of system reports.
**Filling and Packing:** Research and development of protocols concerning filling and packing; scale-up of the finished drug product filling and packing; physical plant control and maintenance; equipment maintenance and renovation; continuous training of personnel and personnel compensation plan; and supervision of system reports.

**Sales of Drug Products:** Research and development of protocols concerning product storage; distribution process; continuous training of personnel and personnel compensation plan; and supervision of system reports.

**Vendor Handling:** Research and development protocols concerning precautions to maintain product stability; control of vendor stock; and sales system reports.

**Customer Service:** Research and development of protocols concerning home storage and handling to maintain product stability; relations with health insurance companies and health care professionals; educational materials for patient counseling; and customer service system reports.
Raw materials → Weighing & Measuring → Mixing → Filling → Packing → Distilled water → Finished Product storage → Quality Assurance

Pilot Plant Scale-Up Techniques for liquid orals
TYPES OF ORAL LIQUIDS

SOLUTIONS
EMULSION
SUSPENSION
<table>
<thead>
<tr>
<th>Purpose</th>
<th>Agent</th>
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<tbody>
<tr>
<td>Protecting the active product</td>
<td>- Buffers</td>
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<td>ingredients</td>
<td>- Antioxidants</td>
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<td>- Preservatives</td>
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<td>Maintaining the appearance</td>
<td>- Colorings</td>
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<td>- Antimicrobial preservatives</td>
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<td>Taste/Small Masking</td>
<td>- Electrolytes</td>
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<td>- Sweeteners</td>
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<td>- Flavorings</td>
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<td>Purpose</td>
<td>Agent</td>
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<tr>
<td>Facilitating the connection between Active Product Ingredient and vehicle</td>
<td>Wetting agents particle size (&gt;0.1 μm)</td>
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<td>Salt formation ingredients</td>
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<td>Sugars</td>
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<tr>
<td>Protecting the Active Product Ingredients</td>
<td>Buffering–systems</td>
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<td></td>
<td>Polymers</td>
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<td></td>
<td>Antioxidants</td>
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<td>Poorly soluble drugs</td>
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<tr>
<td>Maintaining the suspension appearance</td>
<td>Colorings</td>
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<td></td>
<td>Suspending agent</td>
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<tr>
<td></td>
<td>Flocculating agent</td>
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<tr>
<td></td>
<td>Antimicrobial preservatives</td>
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<td>Electrolytes</td>
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<tr>
<td>Masking the unpleasant taste/smell</td>
<td>Sweeteners</td>
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<td>Flavorings</td>
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<td></td>
<td>Poorly soluble Active Product Ingredient</td>
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<td>Purpose</td>
<td>Agent</td>
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<tr>
<td>Particle Size</td>
<td>- Solid particles (10 nanometers to 5 micrometers size)</td>
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<td></td>
<td>- Droplet particles (0.1–1.0 micrometers size)</td>
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<tr>
<td>Protecting the Active Product</td>
<td>- Buffering-Systems</td>
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<tr>
<td>Ingredients</td>
<td>- Polymers</td>
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<td></td>
<td>- Antioxidants</td>
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<td>- Distribution pattern (O/W, W/O)</td>
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<td>Maintaining the appearance</td>
<td>- Colorings</td>
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<td>- Emulsifying agents</td>
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<td>- Penetration enhancers</td>
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<td>- Gelling agents</td>
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<td>- Stabilizers</td>
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<td>Taste/smell Masking</td>
<td>- Antimicrobial preservatives</td>
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<td>- Flavorings</td>
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<td></td>
<td>- Relation oil vs. water</td>
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Formulation consideration:

- Solvents
- Preservatives
- Antioxidants
- Solubilizers
- Organoleptic agents etc.
SOLVENTS

- Water
- Alcohol
- Glycerol
- Polyethylene glycol
- Propylene glycol.
Compared to ordinary drinking water, purified water USP is more free of solid impurities.

When evaporated to dryness, it must not yield greater than 0.001% of residue.

Purified water is obtained by distillation, ion-exchange treatment, reverse osmosis and other relevant method.
Preservatives are added to prevent the microbial growth

Preservative are necessary due to chances of microbial growth

Raw material, processing containers & equipments, the manufacturing environment, operators, packing materials & the user.

Phenol, chlorocresol, benzoic acid, etc.
Antioxidants: ascorbic acid, sodium thiosulphate, sodium metabisulphate.

Solubilizers: co-solvents and surface active agents

Organoleptic agents etc: colour, flavor, sweetening agents
Stages of operations:  
1. Tank selection

Material of the tank must not be additive to the product

The shape and size of equipment must be selected according to the batch size

The tanks are usually constructed of polished stainless steel of different grades

Teflon and glass lined tank.

Adequate clean-up procedures developed.
2. Mixing

Simple mixing is essential to increase flow of liquids.

If the liquid is of high viscosity, high electrical stirrer may be used.

Addition of ingredients in proper order have vital important.

At high viscosity the chance of air entrapment.
By reducing agitator speed

By caring out the mixing procedure in enclosed tank under vacuum

The alternative procedure to the all is versator

Air entrapment Minimize:-
Versator
3. Dispersion

Suspensions and emulsions require considerably greater shear forces

Laboratory formulation is difficult to duplicate at large scale

Dispersion produced by colloidal mill or an immersion homogenizer

Variety of equipment should be evaluated for better results.
4. Filtration and clarification—

Filtration procedure, requires careful evaluation to ensure that pilot scale-ups will exhibit the same degree of clarity as their laboratory counterparts.

During the pilot run the clarity of the filtrate should be checked periodically, in order to establish schedule for changing pads, cake, or cartridges, depending on the type of filtration employed.

In filtration, filter pads are used which is made up of asbestos and cellulose.

**Selection of filtration depends on**

- The product viscosity
- Volumes
- Rate requirement
5. Transfer and filling

Filling – important parameter in the transfer of liquids from tank to tank and into containers.

New batches should not be started until the previous batches are completely filled and the tanks are emptied.

Bins and Piping
Methods for filling of liquids:

The selection of equipment depends on characteristic of liquid such as, viscosity, type of packaging, surface tension.

- Gravimetric (specific weight)
- Volumetric (specific volume)
- Constant volume filling
Containers and closures:

Glass

Plastic

It is more important to store the final product in container until its expiration.

Most oral liquids are packed in either amber or flint glass containers with plastic or metal caps.
GMP considerations:

- A check list of GMP items
- Equipment qualification
- Process validation

- Regular process review and revalidation
- Relevant written SOP
- Adequate provision for training of personnel

- A well defined technology transfer system
- An orderly arrangement of equipments
During the scale up new product the analytic test methods transferred to the quality department.

The quality assurance staff should review the process to make sure that the proper analysis instrumentation is available and that personnel are trained to perform tests.

Transfer of analytic method to quality assurance:
Viscosity

It is the internal resistance (or) friction to the movement of molecules to “FLOW”.

Agents which control viscosity

E.g. Polyvinylpyrrolidone, alginates, carbomers, and various cellulose derivatives.
Purpose to control Viscosity -

1. Improve pour ability.
2. Improve acceptability.
3. Improve palatability.
Equipments to analyse Viscosity -

FALLING SPHERE VISCOMETER

OSTWALD VISCOMETER
Preservative evaluation – should be done in addition to physical and chemical tests.

Bacteriological testing should be done, to know if the concentration of preservative is to be increased in the formulation.

Depending on the nature of the product and degree of protection required the surface of the product can be over lapped during filling or holding stages with carbon dioxide or nitrogen.
Stability studies:-

**Physical:** Physical instability of liquid formulations involves the formation of precipitates, less-soluble polymorphs, and adsorption of the drug substances onto container surfaces, changes in product appearance.

**Chemical:** Chemical instability of liquid formulation is mainly due to interaction between additives, oxidation or some due to interaction with containers.

**Microbiological:** It is the most favorable condition for the growth of microorganism. So studies must me conducted for different microbiological test. Different preservatives are used to make product more stable.
Notes:

1. A liquid is pourable; it flows and conforms to its container at room temperature. It displays Newtonian or pseudoplastic flow behavior.

2. Previously the definition of a lotion was “The term lotion has been used to categorize many topical suspensions, solutions, and emulsions intended for application to the skin.” The current definition of a lotion is restricted to an emulsion.

3. A semisolid is not pourable; it does not flow or conform to its container at room temperature. It does not flow at low shear stress and generally exhibits plastic flow behavior.

4. A colloidal dispersion is a system in which particles of colloidal dimension (i.e., typically between 1 nm and 1 μm) are distributed uniformly throughout a liquid.