API and Dosage Development

WITH DALTON

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[COMPANY VISION]

"To make the impossible possible. Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

[SERVICES]

- Contract Research
- Custom Synthesis
- Medicinal and Flow Chemistry
- API Process Development Formulation
- Development
- cGMP API Manufacturing
- cGMP Sterile Filling
- Analytical and Microbiology Services

FDA inspected, HC approved, & MRA with EMA

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API Form Development

API Definition

Active pharmaceutical ingredient (API) – the substance(s) in pharmaceutical drugs that is/are responsible for the beneficial health effects experienced by consumers. (1)

API Selection

Key factors that drive API selection (2):

Crystallinity:
Influences the dissolution rate and transport characteristics of the drug (3)

Solubility:
The ability of a solute to dissolve in solvent. Influences desired concentration and drug absorption (6)

Stability:
Influenced by moisture, excipients, temperature, pH, oxygen, light (7)

Density:
Influences flow properties and compressibility (5)

Polymorphism:
The ability of a drug substance to take on more than one form/ crystalline phase. Influences drug dissolution and drug stability (i.e., premature degradation) (4)

Density:
Influences flow properties and compressibility (5)

Particle size distribution:
Influences the ability of the drug to cross blood barriers, enter cells, and absorbed by the human body (2)

The development stage and needs

API & CTD

Note: In any clinical application or new drug submission the 1) description of manufacturing (including flowcharts) is required along with 2) physiochemical characteristics (melting point, boiling point, denaturation temperature, solubility) (2.3.S.2, 2.3.S.3 and 2.3.P.3) (4)

Once the API form is determined, the dosage form must be selected.

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Dosage Form Development

Preformulation | Formulation Development | Drug Product Manufacturing | Drug Product Release

Preformulation Studies

- Microscopic examination: Indicates particle size, size range, and crystal structure
- Heat of vaporization: Important for aerosol dosage forms and medication delivery systems
- Melting point depression: Helps determines purity
- The phase rule: Indicates the drugs pressure, volume, and temperature in thermodynamic equilibrium
- Particle size: Influences the dissolution rate, bioavailability, content uniformity, texture, and stability of your drug
- Polymorphism: Influences melting point, solubility, bioavailability, and stability
- Solubility: Required for therapeutic efficacy; Influenced by pH and particle size
- Dissolution: Determines the time it takes for your drug to dissolve at the absorption site; Influenced by the compaction of a drug. Compaction involves two distinct stages (4):
  - Compression: initial particle re-arrangement under relatively lower compaction pressure
  - Consolidation: material deformation at higher compaction pressure to form inter-particulate bonds leading to the formation of compact mass. Material deformation may be of three types – plastic, elastic and brittle fracture:
    - Plastic materials deform under pressure and do not regain their original state after removal of compaction pressure
    - Elastic materials regain their original form after removal of compaction pressure
    - Brittle materials break down into smaller particles under compaction pressure
- Membrane permeability: Influenced by particle size
- Partition coefficient: Determines the ratio of the concentration of the drug substance in one phase to the concentration in a second phase
- pka/ dissociation constants: Dissociation or ionization is influenced by the pH and influences the absorption, distribution, and elimination of your drug

Factors to consider when deciding your drug's dosage form (8)

- Functionality (absorption, bioavailability, stability)
- Suitability of ingredients (chemical, form, physical, pH, solubility)
- Availability of ingredients/excipients
- Costs
- Marketing preferences
- Target population (age, nature of disease or illness)
- Previous preclinical/ clinical data

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Dosage Form Development

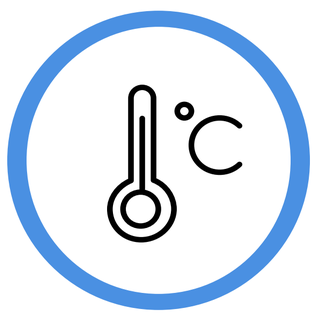
Formulation Development

Various formulations are developed and examined for desired features and critical quality attributes (CQA). According to ICH Q8 R2, a CQA is a “physical, chemical, microbiological or biological properties which should be required within the certain range or limit to confirm the predefined quality standard product.” (9) The formulation that best meets the target product profile is selected to be its master formula.

Formulation Testing

Stability studies to conduct when deciding dosage form (10)

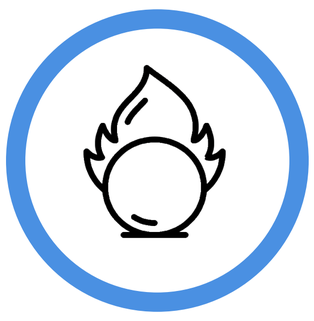
pH studies



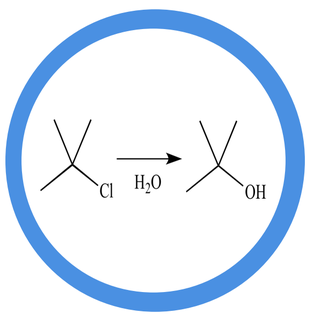
Elevated temperature studies

High humidity studies

Photolytic studies



Oxidation studies



Hydrolysis

Formulation Options

There are a variety of dosage forms to choose from. Dosage forms are classified based on the (10)

1) Physical state of the ingredient
   - Solid (tablets, capsules, powders, films, chewing gum, pellets, lozenges)
   - Liquid (syrups, injections, emulsion, solutions, suspensions, colloids, liposomes, ophthalmic, oral, nasal)
   - Semisolid (gels, creams, ointments, lotions)
   - Gas (aerosols, inhalers, nebulizers)
2) Or the route of administration (ROA)
   - Enteral (oral, buccal, sublingual and rectal)
   - Topical (transdermal, ophthalmic, gels, creams, ointments, lotions)
   - Parenteral (intravenous, and intramuscular, subcutaneous injectables)
   - Inhaled (oral, nasal)

Offered at Dalton

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Dosage Forms (11), (12), (13)

Solids *Tablets, Capsules*

Pros

- Formulated to give an exact dose
- High level of consumer acceptability/compliance/ convenience
- Generally masks taste and odor of ingredients
- Good physical and chemical stability
- Can be formulated for immediate or controlled release
- Economical to produce
- Can be coated. This protects the drug substance from degradation by atmospheric oxygen, humidity, or gastric acid
- Various form options for tablets: soft (chewable), effervescent, lozenge (pastille), multi-layered, and buccal/sublingual

Challenges

- Risk of choking and chewing
- Compatibility with food/drink
- May need taste masking requirements
- Difficult to adjust an exact dose
- Impossible for unconscious patients to consume

Topicals *Transdermal, Gels, Creams, Ointments, Lotions*

Pros

- Painless and easy administration
- Sustained drug delivery

Challenges

- Unintended systemic absorption/toxicity risk in neonate
- Local skin irritation
- Deliberate removal or patches (consumer noncompliance)

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Sterile Liquids *Solutions, Suspensions, Colloids, Liposomes*

Pros

- Allows for dose adjustments
- Easy to swallow
- Better bioavailability than solid dosage forms
- Acceptability from term birth
- Options for different doses and modified release

Solutions

- Provides clear liquid dosage forms of substances through a liquid preparation contains more than one chemical substance homogeneously dissolved in a liquid solvent or mixture of mutually miscible solvents (12)

Colloids

- Expand circulatory volume

Liposomes

- Permits a cell membrane drug delivery vehicle that protects drugs against chemical, enzyme, and immunological breakdown

Emulsions

- Allows for a mixture of two liquids that would not normally mix (immiscible liquids)

Challenges

- Difficult to mask bad taste or odors of ingredients
- May require a preservative system to prevent microbial growth and improve stability
- Potential for dosage inaccuracy
- Inconvenient to travel with
- Potential sensitivity to oxygen or light
- May be insoluble or chemically unsuitable in the presence of water
- Suspensions require shaking or stirring of the liquid preparation because it is not completely dissolved in the desired vehicle

Sterile Liquid *Ophthalmic, oral, nasal*

Pros

- Good nasal transmucosal bioavailability
- Avoidance of hepatic first pass metabolism

Challenges

- Irritation of the mucous-
- Ineffective in abundant secretion
- Increased deposition in upper/central airways

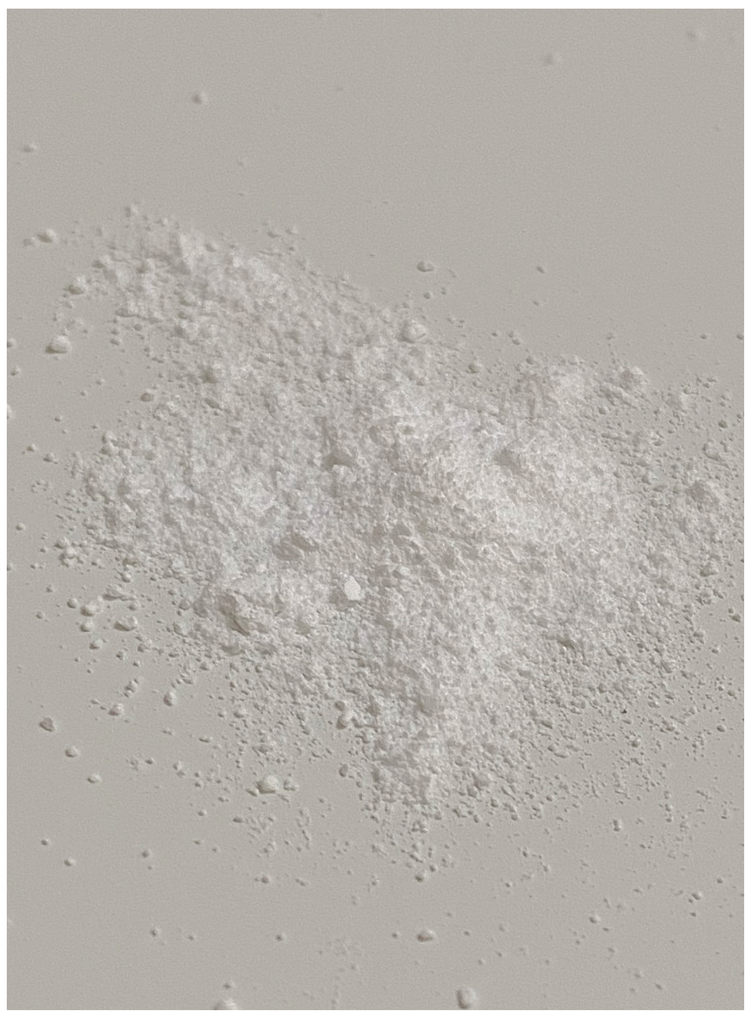
Powders *Sterile and non-sterile powder filling*

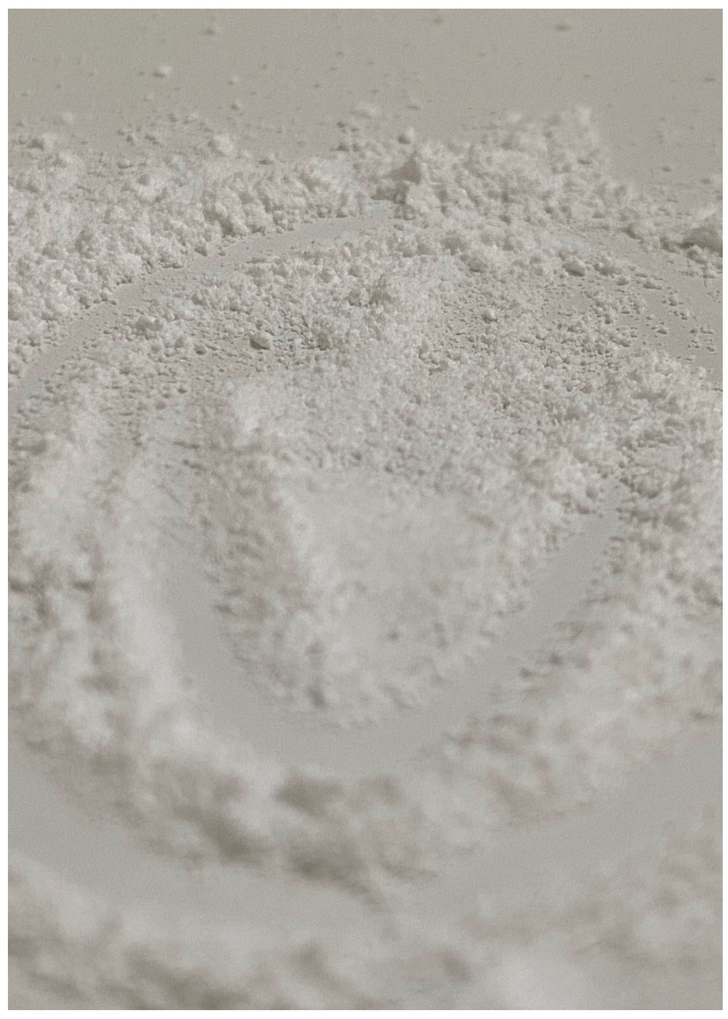
Pros

- Allows for dose adjustments
- Easier to swallow
- Better bioavailability than solid dosage forms
- Can handle large dosing of materials
- Economical to produce
- Allows for multi-dose preparations consisting of solid, loose, dry particles of varying degrees of fineness

Challenges

- Must be mixed with a liquid-
- Difficult to mask bad taste or odors of ingredients
- Not compatible with hygroscopic, oxidizing, and deliquescent materials
- Potential for dosage inaccuracy
- Inconvenient to travel with





Injectables *Intravenous, intramuscular, subcutaneous injectables*

Pros

- Main route for neonates and emergency cases
- Sustained release preparation
- Provides placement of a drug directly in the bloodstream or body tissues

Challenges

- Potential for infection
- Electrolyte imbalance
- Inappropriate dilutants
- Lag-volume effects in IV line-
- Needle puncture pain/phobia
- Potential for plastic migration into drug

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Lyophilized formulations

Pros

- Reduces biological and chemical reactions at the designated storage temperature through sublimation and desorption while in the frozen state

Challenges

- Costly equipment
- Increases handling and processing time

Inhalants

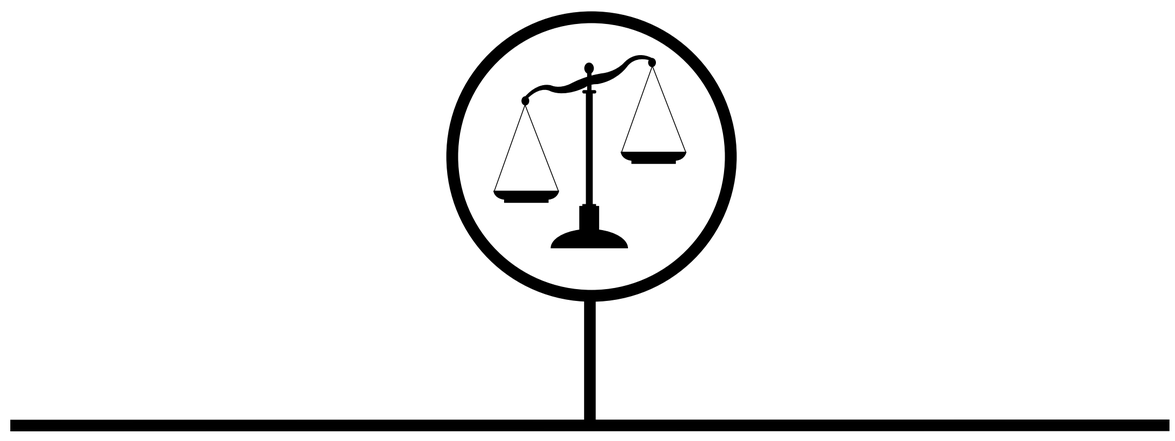
Pros

- Provides optimal drug action through inhalation therapy

Challenges

- Irritant effects on airways
- Additional work for delivery system

Regulatory



Australia

- Drugs that meet the orphan criteria are eligible for orphan drug designations (regulation 16J of the Therapeutic Goods Regulations 1990).
- In addition to standard orphan drug designation, drugs can seek a pathway for orphan designation for new dosage form. Eligibility for new dosage form medicines is intended to provide an incentive to sponsors to register medicines on the Australian Register of Therapeutic Goods (ARTG) that introduce a new dosage form that would not be financially viable in the absence of a TGA fee waiver.

Europe

- The pediatric program offers incentives for drug formulations that aim to achieve dosage forms that are more suitable than existing formulations for children. Read more here.
- Guideline on Manufacture of The Finished Dosage Form

Canada

- The recommended single and daily dosage of a drug
  (a) intended to be burned and the smoke inhaled may be increased to 10 times the oral dose, and
  (b) intended for use as suppositories may be increased to 33 1/3 per cent in excess of the oral dose.
- Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)

US

- Dosage Form Drug Manufacturers cGMPs (10/93)
- Oral Solid Dosage Forms Pre/Post Approval Issues (1/94)

DALTON Pharma Services

Dalton's Services

Dalton has specialized in the development, manufacture and sterile fill/finish of pharmaceutical and biotechnology products for over 15 years. We offer aseptic filling and terminally sterilized products in a variety of finished dosage forms. Dalton can support your needs for clinical development, through to small scale commercial batches.

Formulation Development

- Oral Immediate Release
- Oral Controlled Release
- Topical and Transdermals
- Sterile Liquids
- Powders
- Sterile liquid dosage formulations
- Injectable drugs
- Lyophilized formulations

Formulation Services and Capabilities

- Formulation development for new chemical entities
- Optimization of existing formulations
- Product/Process Optimization
- Novel formulations for improved delivery of existing dosage forms
- Controlled release and sustained release formulations
- Self-emulsifying drug delivery systems
- Colloidal drug delivery systems
- Sub-micron and nano-emulsions
- Feasibility Studies
- Excipient Compatibility selection and optimization
- Physico-Chemical Testing
- Process Scale-Up
- Technology Transfers
- Batch manufacture

For more on our formulation development services, click here.

For our API process development services, click here.

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