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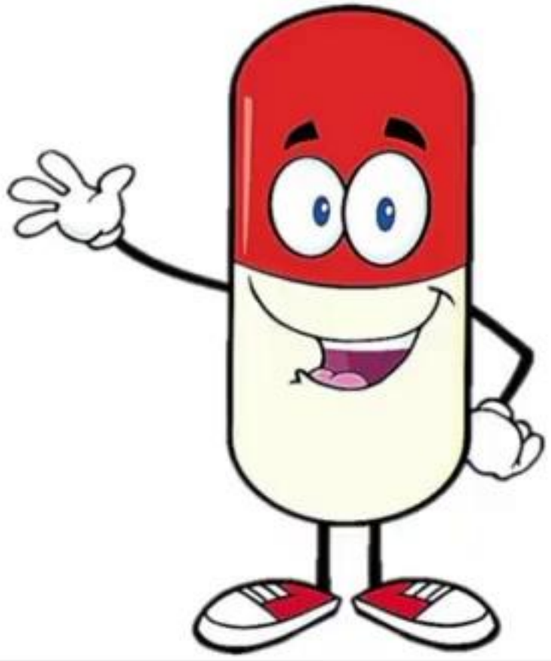
GPAT & NIPER 2025

Pharmaceutics

One Shot Series



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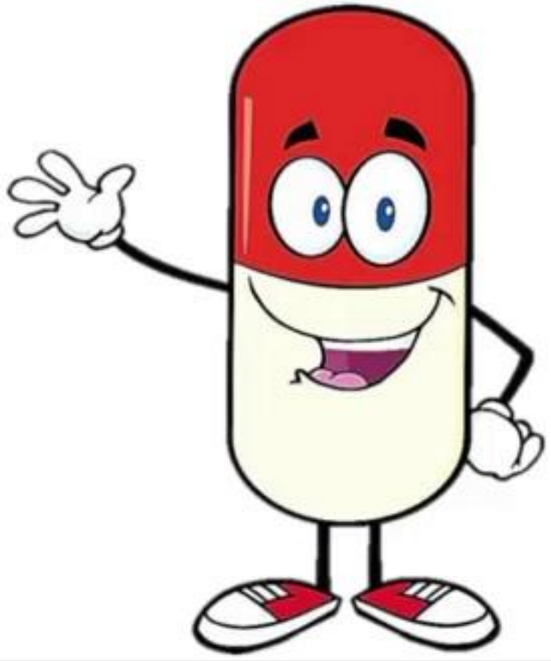

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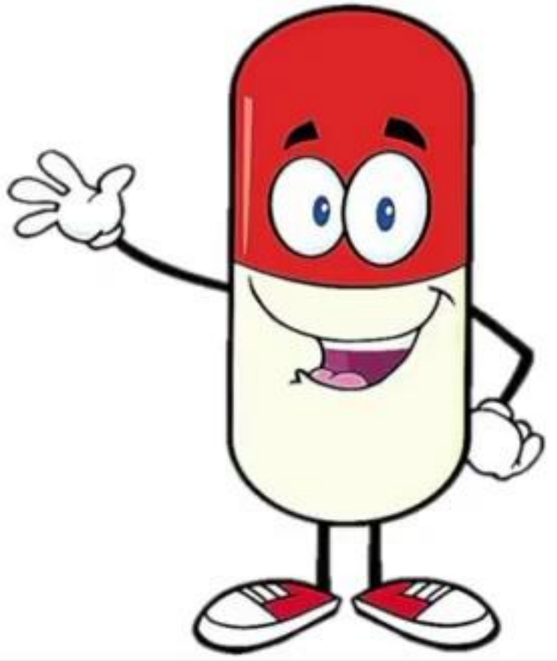

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PREFORMULATION

Preformulation commences when a newly synthesized drug shows sufficient pharmacologic promise in animal models.

I. Bulk Characterization

Crystallinity and Polymorphism
Hygroscopicity
Fine Particle Characterization
Bulk Density
Powder Flow Properties

II. Solubility Analysis

Ionisation Constant – pKa
pH Solubility Profile
Common Ion Effect – Ksp
Thermal Effects
Solubilization
Partition Coefficient
Dissolution

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III. Stability Analysis

Stability in Toxicology Formulations

Solution Stability

pH Rate Profile

Solid State Stability

Bulk Stability

Compatibility

Crystallinity

- Outer appearance (External structure) – "Habit"
- Inner appearance (Internal structure) – "Crystal"

Polymorphism

The state of a substance existing in more than one crystalline form is called Polymorphism"

Classification:

(i) **Enantiotropic** - one polymorph can be reversibly changed into another by varying temperature or pressure, e.g. sulphur.

(ii) **Monotropic** - in which one polymorphic form is unstable at all temperatures and pressures. It is irreversible, e.g. glyceryl stearates.

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- Transition temperature is obtained by extrapolation of **Van't Hoff plots.**
- **Van't Hoff plot** is a graph of Log Molar Solubility vs. Temperature
- **Bridging solvent** – Helps in the conversion of one polymorph to another.

Microscopy

- Single refractive index – **Isotropic**
- More than one refractive index – **Anisotropic**

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→ Solid state NMR

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Anisotropic: (i) Uniaxial (two refractive indices)

(ii) Biaxial (three refractive indices)

Moisture Content:

- TGA (Thermogravimetric analysis)
- Karl Fischer
- Gas Chromatography
- Gravimetry

Fine Particle Characterization:

1. **Particle Size:**

- Single refractive index — **Isotropic**
- More than one refr… **…isotropic**

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1. **Particle Size:**
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   - HIAC (stream counting device)
   - Optical microscopy

2. **Surface Area:**
   - Brunauer-Emmett-Teller BET adsorption

   Temperature: -196°C

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     Temperature: -196°C
     Each nitrogen molecule (N_2) occupies an area of $16A^2$
   - Gas adsorption
     No. of moles = Wt. in gram / molecular weight

Note: Effective S.A exposed to dissolution media

Morphology:

- Scanning Electron Microscope (SEM)
- Gold coating (to make surface superconductive)

- Karl Fischer
- Gas Chromatography
- Gravimetry

Fine Particle Characterization:

0.5-500µm

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   - Optical microscopy

1µm

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Adsorption
Air Power
ability
Poiseuille
Kozeny
Carman

Henderson-Hasselbach equation provides an estimate of the ionized and un-ionized drug concentration at a particular pH.

For acidic compounds:

$$pH = pK_a + \log [\text{ionized drug}] / [\text{unionized drug}]$$

For basic compounds:

$$pH = pK_a + \log [\text{unionized drug}] / [\text{ionized drug}]$$

pKa determination: (i) Spectral shift in UV (ii) Potentiometry

Partition Coefficient:

- $K_{o/w} = C_o / C_w$
- Higher the partition coefficient, more is the lipophilicity.

Dissolution

- Expressed in mg/min

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$$dc / dt = DA / hV (C_s - C)$$

Where,

D = the diffusion coefficient

h = the thickness of the diffusion layer

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A = the surface area

V = the volume of media

Cs = the conc. of a saturated solution of the solute in the dissolution medium

C = the concentration of drug in solution at time, t

Intrinsic dissolution rate (IDR)

- **Unit:** mg cm^{-2} min^{-1}

Ionic strength of isotonic 0.9% w/w NaCl is 0.15

Surface discoloration study (Mottling):

- Tristimulus reflectance spectroscopy
- Diffuse reflectance spectroscopy
- Microreflectance photometry

Stability indicating assay method: HPLC

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Very soluble	Less than 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble	More than 10,000

Glass transition temperature:

Temperature at which glassy state is converted to rubbery state, during the amorphous phase.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

Class	Solubility / Permeability

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4°c → Physical Stability
37°c → Biopharmaceutics Evalu

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I	High / High
II	Low / High
III	High / Low
IV	Low / Low

Compressibility and Flowability of Pharmaceutical Excipients

% Compressibility	Flowability
5-15	Excellent
12-16	Good

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Insulin, Met

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Furosemide

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< 40	Very, very poor

$$\left(\frac{TD - BD}{Tap.}\right) \times 100$$

How to get Crystal Purity?

- **DSC (Differential Scanning Calorimetry)** – Drug Excipient compatibility study
- **XRD (X-ray diffraction)** – Study of polymorphism

X-ray diffraction

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X-ray diffraction

$$n\lambda = 2d \sin \theta$$

Where,

θ = the angle of diffraction
n = the integer
λ = the wavelength
d = the distance between crystals

- **Sharp peak:** Crystalline

Halo Pattern

- **No peak:** Amorphous

Analytical Methods for Characterization of Solid Forms

- Hot Stage Microscopy (melting point)
- Differential Scanning Calorimetry (DSC)

Solvent Power

Solvent	Solvent Power
Glycerol	0.5
Propylene glycol	1
Ethanol	2
DMF / DMA	4

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DMF / DMA	4

Equations:

Equations	Determination of
Noyes-Whitney	Dissolution
BET	Surface area
Stokes	Sedimentation
Higuchi	Release of drug from granular matrix
Handersson-Hasselbach	pH
Yong's	Properties of surfactant
Arrhenius	Stability of drug / product at R.T at accelerated temperature

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TABLETS

- Crown thickness measured using a sliding calliper scale.
- Tablet thickness controlled within a ±5% variation.

Color evaluations:

(i) Reflectance spectrophotometry
(ii) Tristimulus colorimetry
(iii) Microreflectance photometry

- Odor of acetic acid in degrading aspirin tablets.

Hardness / Tablet crushing strength:

Hardness tester	Material/Mechanism
Monsanto	Plungers
Pfizer	Pliers
Strong-Cobb	Hydraulic pressure
Erweka	Operates in a vertical position
Schleuniger	Operates in a horizontal position

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Friability:

Name of the apparatus:	Roche friabilator
Revolutions:	25 rpm
Total revolutions:	100
Time required:	4 minutes
Distance of dropping the tablets:	6 inches

- When concave and especially deep concave punches are used and when the punches are in poor condition, or worn at their surface edges, it results in 'whiskering' at the tablet edge.

Rough handling tests include:

- Vibration test
- Drop test

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Rough handling tests include:

Tap Again to Exit

- Vibration test
- Drop test

- Incline plane impact test

Weight variation tolerances for uncoated tablets

Average weight of tablets (mg) USP	Average weight of tablets (mg) IP	Maximum percentage difference allowed (IP)
130 or less	80 or less	10
130-324	80-250	7.5
More than 324	More than 250	5

Disintegration

- 6 glass tubes (3 inches long)
- 10 mesh screen (2000 µm / 2 cm)
- 1L beaker of water, simulated gastric fluid, or simulated intestinal fluid
- Temperature- 37 ± 2°C
- Tablets remain 2.5 cm below the surface of liquid.
- Distance of 5-6 cm at frequency of 28 to 32 cycles per minute.

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130 or less	80 or less	10
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More than 324	More than 250	5

Disintegration

- 6 glass tubes (3 inches long)
- 10 mesh screen (2000 µm / 2 cm)
- 1L beaker of water, simulated gastric fluid, or simulated intestinal fluid
- Temperature- 37 ± 2°C
- Tablets remain 2.5 cm below the surface of liquid.
- Distance of 5-6 cm at frequency of 28 to 32 cycles per minute.

Dissolution

- 900 ml of dissolution media
- Paddle speed - 50 rpm
- Temperature-
  Apparatus (1) to (4) = 37 ± 0.5°C
  Apparatus (5) to (7) = 32 ± 0.5°C

- When concave and especially deep concave punches are used and when the punches are in poor condition, or worn at their surface edges, it results in 'whiskering' at the tablet edge.

Rough handling tests include:

- Vibration test
- Drop test

Uncoated → 300 rpm
sugar. → 60

- Incline plane impact test

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Average weight of tablets (mg) USP	Average weight of tablets (mg) IP	Maximum percentage difference allowed (IP)

- 10 mesh screen (2000 µm / 2 cm)
- 1L beaker of water, simulated gastric fluid, or simulated intestinal fluid
- Temperature- 37 ± 2°C
- Tablets remain 2.5 cm below the surface of liquid.
- Distance of 5-6 cm at frequency of 28 to 32 cycles per minute.

Dissolution

- 900 ml of dissolution media
- Paddle speed - 50 rpm
- Temperature-
  Apparatus (1) to (4) = 37 ± 0.5°C
  Apparatus (5) to (7) = 32 ± 0.5°C
- Basket coated with Gold. Gold-coating is done to avoid corrosion (Thickness: 0.0001 µm)
- Apparatus (3) – Flat bottom (Rest all hemispherical)
- Dissolution apparatus
  Length – 168-176 mm
  Width – 98-106 mm
- Distance b/w paddle and inside bottom: 25 ± 2 mm / 25 ± 0.2 cm

Stage 1 (S1) – 6 tablets are tested (Tolerance limit Q + 5%)

Stage 2 (S2) – If the tablets fail S1, additional 6 tablets are tested (Tolerance Q – 15%)

- Paddle speed - 50 rpm
- Temperature-
  Apparatus (1) to (4) = 37 ± 0.5°C
  Apparatus (5) to (7) = 32 ± 0.5°C
- Basket coated with Gold. Gold-coating is done to avoid corrosion (Thickness: 0.0001 μm)
- Apparatus (3) – Flat bottom (Rest all hemispherical)
- Dissolution apparatus
  Length – 168-176 mm
  Width – 98-106 mm
- Distance b/w paddle and inside bottom: 25 ± 2 mm / 25 ± 0.2 cm

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Stage 3 (S3) – If the tablet still fails the test, additional 12 tablets are tested (Tolerance for all 24 tablets Q – 15%)

I.P. 2010

Disintegration apparatus	18 tablets
Dissolution apparatus	Cylindrical vessel (1000 ml) 24 tablets
Uniformity of weight	20 tablets
Content uniformity	30 tablets

tablet edge.

Rough handling tests include:

- Vibration test
- Drop test

Uncoated → 300 rpm
Sugar. → 60 min
Film coated → 30 min
Enteric coated → 120 min only

- Incline plane impact test

Weight variation tolerances for uncoated tablets

Average weight of tablets (mg) USP	Average weight of tablets (mg) IP	Maximum percentage difference allowed (IP)
130 or less	80 or less	10
130-324	80-250	7.5
More than 324	More than 250	5

tablet edge.

Rough handling tests include:

- Vibration test
- Drop test

I → Rotating Basket

II → Paddle

III → Reciprocating cylinder

- Incline plane impact test

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Tablet Compression Machines

Machine parts	Function
Hopper(s)	Holding and feeding granulation to be compressed
Dies	Size and shape of tablet
Punches	Compressing the granulation within dies
Cam tracks	Guiding the movement of punches
Turrets	Holding the upper and lower punches
Feeding mechanism	Moving granulation from hopper into dies

Fette machines

- Device that chills the compression components.
- Compression of low-melting point substances such as waxes, to compress products such as suppositories.

Tooling

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Tooling

Type of tooling	Length	Barrel diameter	Head diameter
BB	5.25 inches	0.75 inches	1-inch
B	3.	0.75 inches	1 inch
D (large tablets)	5.25 inches	1 inch	1.25 inch

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Processing Problems

Problems	Meaning of term
Capping	Partial or complete separation of the top or bottom crowns of tablet, due to concave punches. Avoided by flat punches.
Lamination	Separation of tablet into two or more distinct layers
Picking and Sticking	Picking - 'Punch tips' Sticking – 'Die walls' Avoided by plating punches with chromium & colloidal silica.
Mottling	Unequal distribution of color on tablet
Poor flow	Causes –'arching' or 'bridging' and 'rat holing'

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Shape coefficient

Shapes	Shape coefficient
Sphere	6
Cube	6.8

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Method of Preparation:

Type of granulation	Method of preparation
Dry granulation	Slugging, Roller compaction
Wet granulation	Sigma blade mixers, Planetary mixers

Powder mixer / Granulators

1. Littleford Lodige mixer
2. Diosna mixer / granulator
3. Littleford MGT mixer

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Commonly used tablet excipients

Type of Excipients	Function	Examples
Diluents	To make the required bulk of tablet	Lactose, Starch, Dextrose (Cerelose), Mannitol, Sorbitol, Sucrose, Microcrystalline cellulose (MCC) etc.
Binders and Adhesives	To form granules or to promote cohesive compacts for directly compressed tablets	Acacia, Tragacanth, Gelatin, Starch paste, Liquid glucose, Alginates and Cellulose derivatives.
Disintegrants	To break up the tablet	Starch USP, Veegum HV, Bentonite (montmorillonite

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Lubricants	Reduce the friction b/w die walls	Calcium and magnesium stearates, Talc, PEG
Antiadherents	Reduce the sticking	Colloidal silicas
Glidants	To improve flow properties	Talc, Corn starch, Colloidal silicas (Cab-O-Sil, Syloid, or Aerosil)
Sweeteners	To mask the bitter taste of drug	Mannitol, Saccharin

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Diluents

Lactose

- Lactose X Amines – Maillard type of condensation reaction
- Hydrous form of lactose is employed for wet granulation.

Grades of lactose	Mesh
Coarse	60 to 80 mesh
Regular	80 to 100 mesh

Starch

Types of starches	Examples	Moisture content (%)
Starch USP	Corn, wheat or potatoes	11-14
Directly compressible	Sta-Rx 1500	10

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Starch USP	Corn, wheat or potatoes	11-14
Directly compressible	Sta-Rx 1500	10
Hydrolysed	Emdex / Celutab	8-10
Modified	Primogel / Explotab	4-8

Sta-Rx 1500 (free-flowing)

- Diluent
- Binder
- Disintegrating agent
- Self-lubricant

Mannitol

- Most expensive sugar used as diluent
- Negative heat of solution
- Widely used in chewable tablets
- Non-hygroscopic used in vitamin formulations

Sorbitol

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Sorbitol

- Optical isomer of mannitol
- Hygroscopic at humidities above 65%

Sucrose

Grades of sucrose	Excipients present
Sugartab	90-93 % sucrose + 7-10 % invert sugar
DiPac	97% sucrose + 3% modified dextrins
Nu Tab	95% sucrose + 4% invert sugar

Microcrystalline cellulose (Avicel)

- Commonly used excipient
- Also acts as an disintegrating agent

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Grades of Microcrystalline Cellulose (MCC)	Form
PH 101	Powder
PH 102	Granules
PH 301	Crystalline
PH 302	Amorphous

Note: Pearl coating (use of finely divided talc)

Sweeteners

- Mannitol is about 72% as sweet as sucrose.
- Saccharin is about 500 times sweeter than sucrose. But major disadvantages, are it has a bitter aftertaste and is carcinogenic.
- Saccharin is replaced by aspartame. Disadvantage is lack of stability in presence of moisture.
- Cyclamate is 30 times as sweeter as sucrose.

Type of tablets: Disintegration time

Type of tablet	Disintegration time
Dispersible tablet	Less than 3 min
Effervescent tablet	Less than 5 min
Uncoated tablet	Less than 15 min

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Film coated tablet	Less than 30 min
Sugar coated tablet	Less than 1 hr
Enteric coated tablet	Should not disintegrate within 2 hour in gastric fluid. Must disintegrate within 1 hr in intestinal fluid.
Buccal tablet	Should not disintegrate up to 4 hrs

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TABLET COATING

- **Booster process** used in tablet coating

Coating process	Performed for
Accela-Cota	Perforated Coating pan
Dria Coter	Film Coating
Manesty Dry-Cota	Compression Coating
Glatt Coater	Perforated coating pan
Pellegrini Pan	Drying efficiency
Wurster Process	Air suspension coating

- **Sugar Coating**

Step	Steps of sugar coating	Function	Examples
1	Seal Coating	To prevent moisture penetration	Zein (alcohol-soluble protein derivative from corn)

Accela-Cota	Perforated Coating pan
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Sugar Coating

Step	Steps of sugar coating	Function	Examples
1	Seal Coating	To prevent moisture penetration	Zein (alcohol-soluble protein derivative from corn)
2	Subcoating	To round the edges and build up the tablet size (50-100 %)	Sticky binder (Gelatin, Acacia); Dusting (Kaolin, Dextrin)
3	Syrup (Smoothing/Color) Coating	To cover and fill in the imperfections / To impart the desired color	First syrup coats contain suspended powders called grossing syrups
4	Polishing	To obtain desired luster	Bees wax or carnauba
Marbeling is a problem that occurs during sugar coating			

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Materials used in coating:

Type of Coating	Polymers
Sugar coating	Zein

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Sugar coating	Zein

Enteric coating (dissolves in intestine)	Shellac, Zein, Cellulose Acetate Phthalate (CAP), Acrylates (Eudragit L, S), Polyvinyl Acetate Phthalate

Note: Colloidal dispersion of Cellulose Acetate Phthalate (CAP) – Aquateric

Type of surfactants:

Type of surfactant	Polymers
BRIJ	Polyoxyethylene lauryl ether
MYRJ 52	Polyoxyethylene monostearate
SPAN	Sorbitan esters
TWEENS	Polyoxyethylene sorbitan

- **Colorants**
  - Use of fine-powdered colorants (< 10 μ)
  - Lakes – Derived from dyes by precipitating with carriers (e.g. alumina or talc)
  - Lakes – Colorants of choice for sugar or film coating systems.
  - Lakes contain 10-30 % of dye content.

Shades	Concentration

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Shades	Concentration
Light shade	Less than 0.01%
Dark shade	More than 2.0%

Coloring materials:

Type of coloring materials	Examples
Natural	Anthocyanins, caramel, carotenoids, chlorophyll, indigo, flavones, turmeric & carminic acid

Coloring materials:

Type of coloring materials	Examples
Natural	Anthocyanins, caramel, carotenoids, chlorophyll, indigo, flavones, turmeric & carminic acid
Inorganic	Iron oxides

Coating solutions:

Coating solution	Function
Opadry	Complete colour concentrate for film coating
Opalux	Opaquant colour concentrate for sugar coating
Opaspray	Opaquant colour concentrate for film coating

Film Defects

Film defects	Causes
Sticking	Overwetting or excessive film tackiness
Picking	Piece of film adhered to the pan

Opaspray	Opaquant colour concentrate for film coating

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Specialized Coatings

Type of coating	Features
Compression coating	Tablet within a tablet
Dip coating	Repeating coating and drying
Electrostatic coating	Application of coating to conductive substrates
Vacuum film coating	Air in coating pan replaced with nitrogen

POLYMERS

Polymers	Co-polymer
Carbopols	Polyacrylic acid crosslinked with polyalkenyl ethers or divinyl glycol
Polyethylene	Ethylene
Polycarbonate	Bis-phenol + Phosgene

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Complete

Effervescent Delivery

CAPSULES

- Decalcification of bone is done to get Ossein.
- Type A gelatin (Acid-treated): pH 9
- Type B gelatin (Alkali-treated): pH 4.7
- Isoelectric point (pH 5.5-6.0)
- Green (fresh) bones are used as a source of Type B gelatin.
- Bone skin- Hard capsule production
- Pork skin- Plasticity
- 150 pairs (300) of the pins are used for capsule production.
- Entire cycle- 45 mins.

Type of machine	Function	Capacity
ROTOFILL	Used to fill pellets	1200 cap./min.
ROTOWEIGH	Used to weigh the capsules	73,000 cap./hr.
ROTOSORT	Used to sort the filled capsules	150,000 cap./hr.
VERICAP 1200	Used for measured change in	73,000 cap./hr.

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PM60	Used for cleaning and polishing	-

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ROTOWEIGH	Used to weigh the capsules	73,000 cap./hr.
ROTOSORT	Used to sort the filled capsules	150,000 cap./hr.
VERICAP 1200	Used for measured change in dielectric constant	73,000 cap./hr.
ERWEKA KEA	Used for dedusting and polishing machine	-
PM60	Used for cleaning and polishing machine	-
ACCOFIL	Used for filling the powders in hard gelatin capsules	-
ACCOGEL	Used for filling the powders in soft gelatin capsules	-
DOSATORS	Used for unit dose filling	40,000-160,000 cap./hr.
HOFLIGER AND KARG	Used for filling thixotropic liquids into hard gelatine	-
ZANASI/MACOFAR /	Used for filling cohesive powders	-

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ACCELA COTA	Used to dust and polish capsules (polyurethane or cheese cloth is used)	-

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Quick seal →

Moisture Content in Capsules:

Type of capsules	Moisture Content (%)
Empty Capsules	12-15
Hard Gelatin	30-45
Soft Gelatin	10-15

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Soft Gelatin	10-15

Filling Capacity of Empty Capsules:

Capsule Size	Approx. Volume (ml)
000	1.36
00	0.95
0	0.75
1	0.55
2	0.4
3	0.3
4	0.25
5	0.15

Note: Capsule size 000 is the largest while 5 is the smallest.

Gelatin:

Bloom strength is a measure of the cohesive strength of the cross-linking that occurs between gelatin molecules and is proportional to the molecular weight of the gelatin.

Properties of Gelatin	Content
Bloom Strength	150-250 gm

Capsule Size	Approx. Volume (ml)
000	1.36
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Viscosity	25-32 millipoise
Iron content	15 ppm

Typical Shell "Hardness" Ratios and their Uses:

Hardness	Dry Glycerine/Dry Gelatin Ratio	Usage
Hard	0.4/1	Shell-softening, oil-based products/Hot, humid areas

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Hardness	Dry Glycerine/Dry Gelatin Ratio	Usage
Hard	0.4/1	Shell-softening, oil-based products/Hot, humid areas
Medium	0.6/1	Temperate areas
Soft	0.8/1	Cold dry area

Excipients used in capsules:

Type of Excipients	Examples
Binders	Mineral oil
Diluents	Lactose, Bentonite, Mannitol, Starch etc.
Glidants	Glycol esters, Silicones, Talc etc.
Lubricants	Magnesium stearate
Plasticisers	Sorbitol, Glycerol, Glycerine

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Plasticisers	Sorbitol, Glycerol, Glycerine
Preservatives	Chlorocresol
Surfectants	Polysorbate 80 (Tween 80)
Viscosity modifier	Polyethylene glycols (400/600)

Effect on Solubility:

- Fumaric acid increases solubility of gelatin
- Formalin reduces solubility of gelatin

Sealing temperature: 37-40 °C

pH: 2.5-7.5

If acidic- Hydrolysis of gelatin (leakage) occurs

If basic- crosslinking (tanning) occurs

Base adsorption:

Number of grams of liquid base required to produce a capsule-forming mixture, when mixed with one gram of solid(s).

- Moisture content of shell: Toluene distillation method.
- Hard gelatin capsules most preferred for Clinical Trials.

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B.A =

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30 ⇒ 10 → 85-115%

75-125%

11

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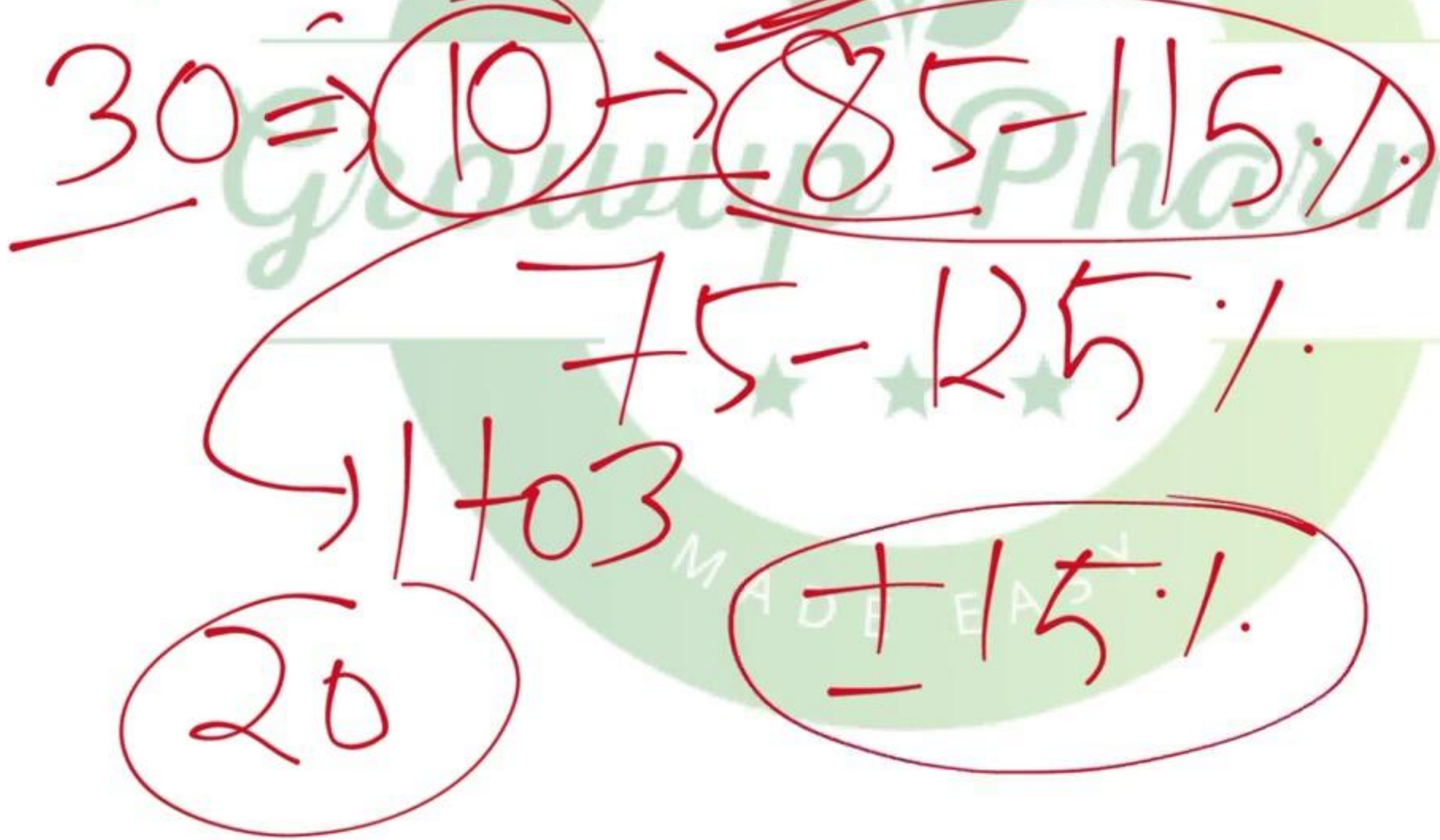

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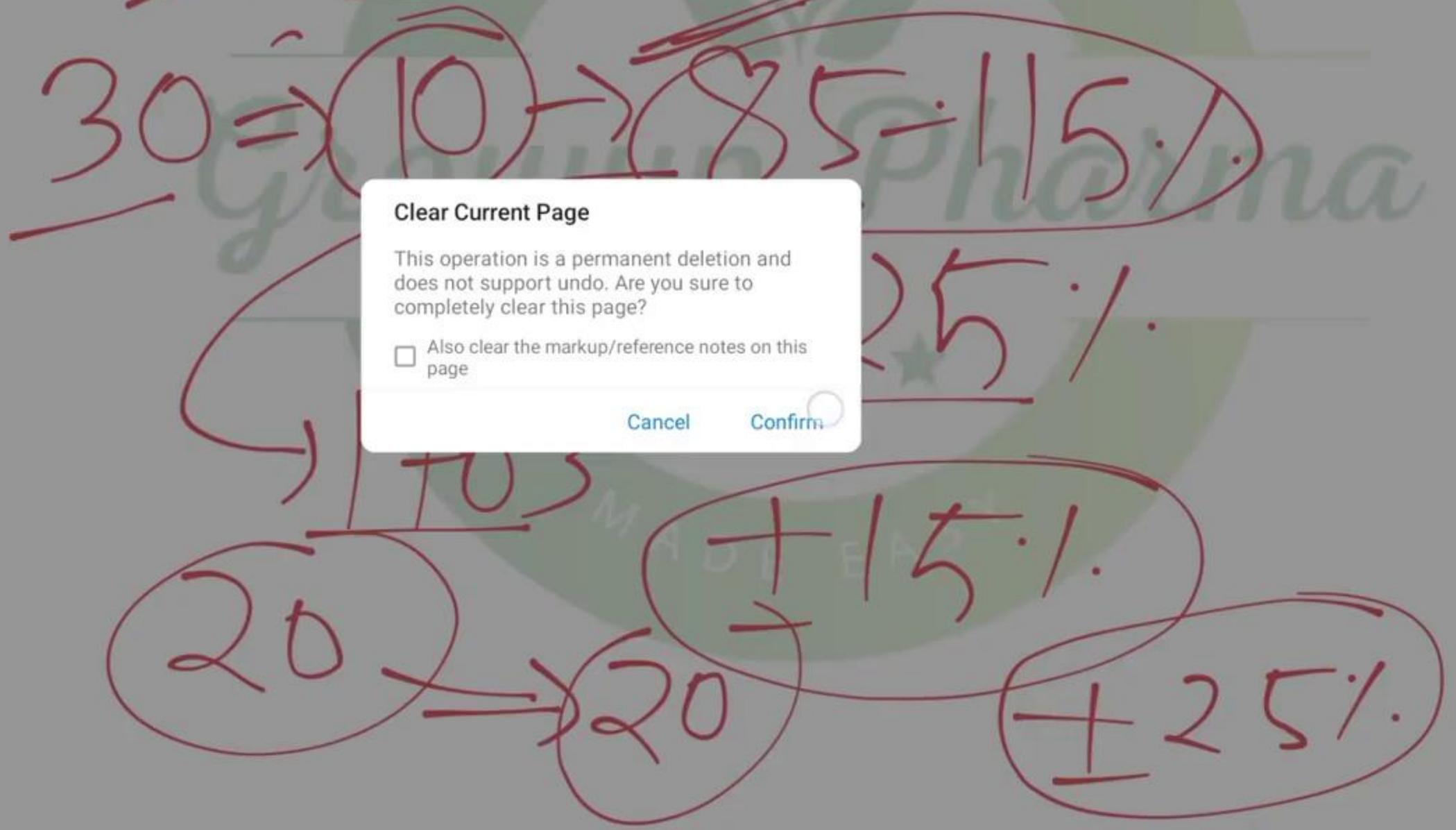

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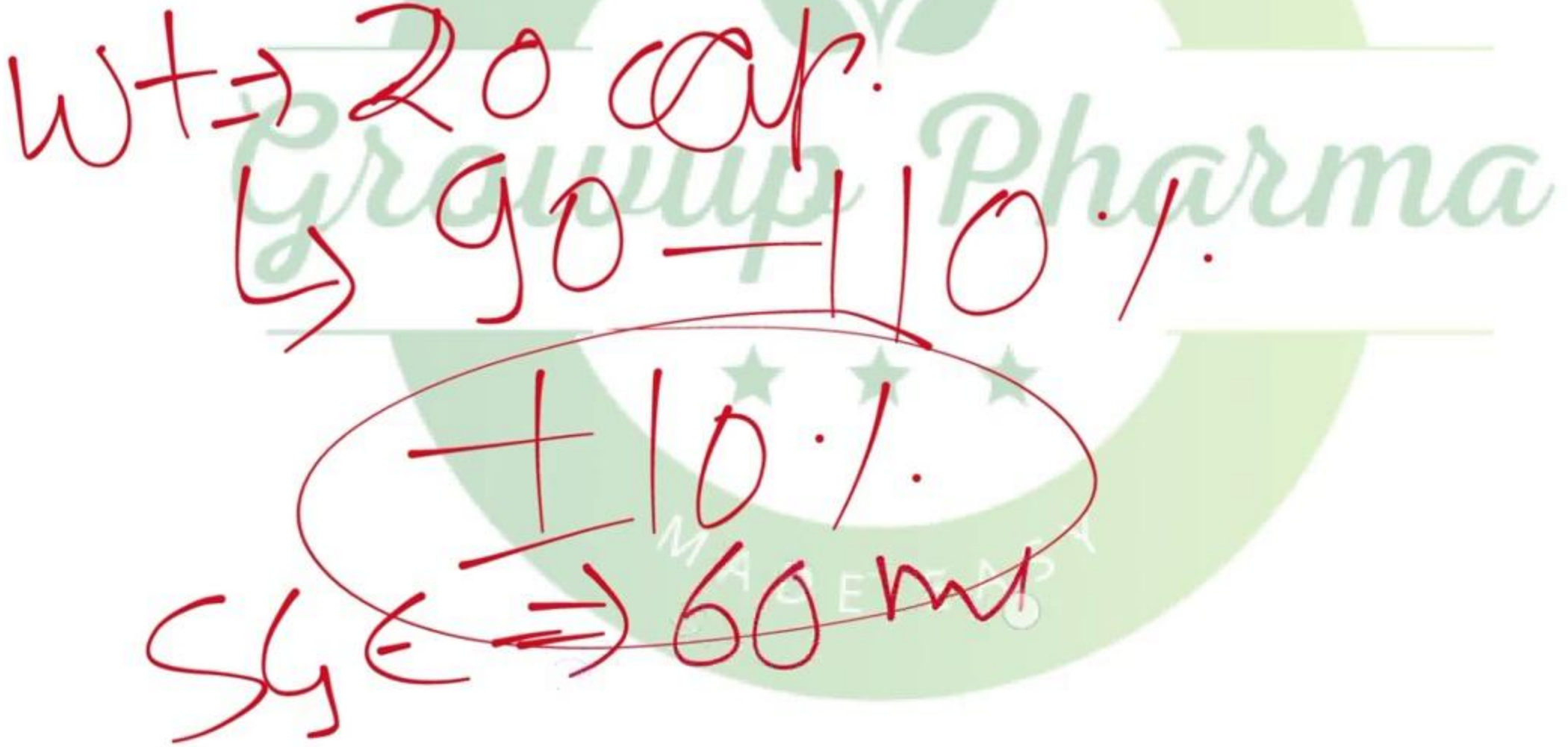

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AEROSOLS

An aerosol or pressurised package is defined as "a system that depends on the power of a compressed or liquefied gas to expel the contents of the container".

Components of Aerosol Package

An aerosol product consists of the following component parts:

1. Propellant
2. Container
3. Valve and actuator
4. Product concentrate

Propellants

- The propellant is responsible for developing the proper pressure within the container.
- It expels the product when the valve is opened and aids in the atomization or foam production.

Types of propellants

Sr. No	Type of propellants	Examples

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Types of propellants

Sr. No.	Type of propellants	Examples
1.	Fluorinated hydrocarbons	Trichloromonofluoromethane, Dichlorodifluoromethane, Dichlorotetrafluoromethane
2.	Topical hydrocarbons	Propane, Butane, Isobutane
3.	Compressed gases	Nitrogen, carbon dioxide, nitrous oxide

Numerical designation

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3.	Compressed gases	Nitrogen, carbon dioxide, nitrous oxide

Numerical designation

Chemical Name	Numerical Designation
Trichloromonofluoromethane	11
Dichlorodifluoromethane	12
Dichlorotetrafluoromethane	114
Difluoroethane	152a
Butane	A-17
Isobutane	A-31
Propane	A-108

Note: - A-70 produces a drier particle, while A-17 and A-31 produce a wetter spray.

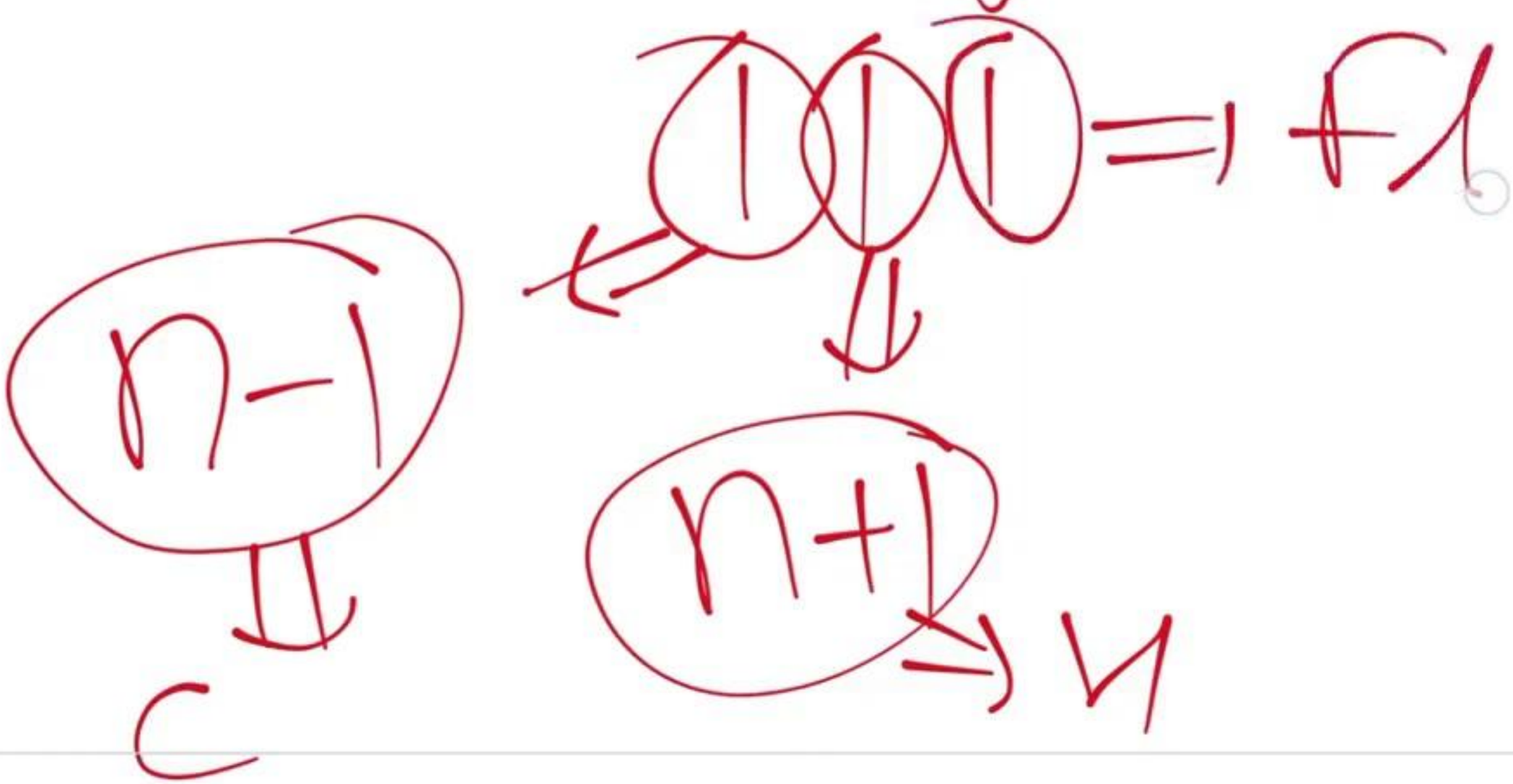
- The amount of propellant used varies from 5% (foams) to 95% (inhalation products).

Vapor pressure of propellant:

- **Propellant 12** – High vapour pressure

Trichloro monofluoro methane

Trichloro monofluoro methane



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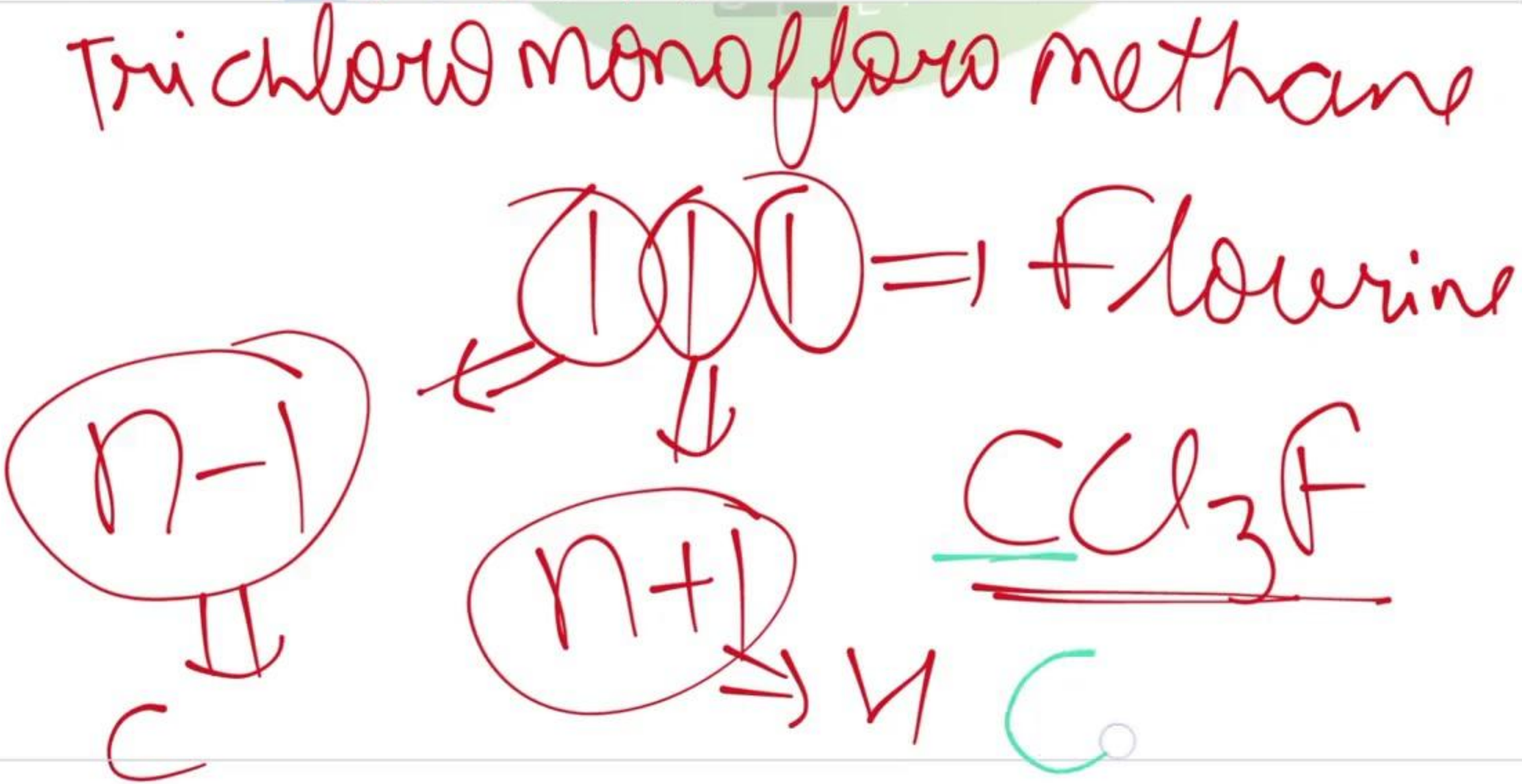

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Laws:

- **Dalton's law:** Total vapour pressure
- **Raoult's law:** Partial vapour pressure

Containers

Aerosol containers must withstand pressures as high as 140-180 psig at 130°F.

psig = pounds per sq. inch gauge; psia = pounds/sq. inch absolute

psig = psia – 14.7

1. **Tinplate containers**

- The tinplated steel container consists of a sheet of steel plate that has been electroplated on both sides with tin.
- A recent development in metal tinplate containers is the welded side-seam.
- Two processes: (i) Soudronic system (ii) Conoweld system
- Soudronic system uses copper wire as an electrode.
- Conoweld system passes the folded body through two rotating electrode rings.

2. **Aluminium containers**

- Used to manufacture extruded (seamless) containers.
- Lessened danger of incompatibility due to its seamless nature and greater resistance to

- Used for inhalation aerosols.

4. Glass containers

- Corrosion problems are eliminated.
- Allows for a greater degree of freedom in design of container.

Valves

- Aerosol valve is multifunctional, capable of being easily opened and closed.
- It is capable of delivering the content in the desired form.

Valve parts	Made from
Ferrule or Mounting Cup	Aluminium or brass

Valve body or Housing	Nylon or Delrin

Valve body or Housing	Nylon or Delrin
Stem	Nylon or Delrin
Gasket	Buna-N and Neoprene rubber
Spring	Stainless steel
Dip tube	Polyethylene or Polypropylene

Ferrule or Mounting Cup

- It is used to attach the valve properly to the container.
- Single or double epoxy or vinyl coating can be added to increase resistance to corrosion.

Valve Body or Housing

- It contains an opening at the point of the attachment of the dip tube, ranges from 0.013-0.080 inch.
- The housing may or may not contain opening referred to as vapour tap.
- Vapor tap produces a fine particle and prevents valve clogging.

Stem

One or more orifices are set into the stem; they range from one orifice of about 0.013-0.030

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Dip tube

Diameter

Types of dip tube	Diameter (inch)
Commonly used dip tube	0.120-0.125

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Dip tube

Diameter

Types of dip tube	Diameter (inch)
Commonly used dip tube	0.120-0.125
Capillary dip tubes	0.050
Dip tube for highly viscous products	0.195

Metering Valves

- Metering valves are applicable to the dispensing of potent medication.
- Approximately 50-150 mg ± 10% of liquid material can be dispensed at one time.

Actuators

The actuator allows for easy opening and closing of the valve and is an integral part of every aerosol package.

Types of actuators:

1. Spray

2. Foam
3. Solid stream
4. Special applications

Type of actuators	Diameter (inch)
Spray	0.016 - 0.040
Foam	0.070 - 0.125

Metered-Dose Inhalers

- To minimise the number of administration errors
- Records of rejection on-line check weighing

Manufacture of Pharmaceutical Aerosols

- Pressure filling (Room temp.)
- Cold filling (–30 - – 40 ^{o}F)
- Compressed gas filling

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Types of actuators:

Actuator → Stem → Gasket → Spring → Ferrule/cap → Mounting → Housing

1. Spray
2. Foam
3. Solid stream
4. Special applications

Type of actuators	Diameter (inch)

- To minimise the number of administration errors
- Records of rejection on-line check weighing

Manufacture of Pharmaceutical Aerosols

- Pressure filling (Room temp.)
- Cold filling (–30 - – 40 °F)
- Compressed gas filling

Quality Control of Pharmaceutical Aerosols

Valve Acceptance:

- 54 µL or less, the limits are ±15%
- 55 to 200 µL, the limits are ±10%

Leak testing:

- Checking the crimping of the valve
- Temperature: 130°F

Testing of Pharmaceutical Aerosols

All aerosol products that are shipped in interstate commerce are subject to the regulations of

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- Checking the crimping of the valve
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Testing of Pharmaceutical Aerosols

All aerosol products that are shipped in interstate commerce are subject to the regulations of the DOT (Department of Transportation).

Test	Determined by
Flame Projection	Ruler (Product is sprayed for 4 sec into flame)
Flash Point	Tag Open Cup Apparatus (Product is chilled to a temp. of –25°F)
Vapor Pressure	Can puncturing apparatus, pressure gauge, water bath
Density	Hydrometer or Pycnometer
Moisture	Karl Fischer method, Gas chromatography
Identification of Propellants	Gas chromatography & Infrared spectrophotometry
Foam stability	Rotational viscometers
Particle size (0.1-30 μ)	Cascade impactor and Light scatter decay method

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IMPORTANT POINTS TO REMEMBER:

- Moisture content in aerosols: Below 300 ppm (200-300 ppm)
- Dry Spray Product: Propellant ratio - 6:1
- Concentration of surfactant: 0.01-1 %
- Non-ionic surfactant – Sorbital trioleate / tweens
- Coating: (i) Under coat (vinyl resin) (ii) Top coat (epoxy resin)

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MICROENCAPSULATION

Definition: It is a process of applying relatively thin coating to small particles of solids or droplets of liquids and dispersions of size up to 5000 µ.

Application:

1. Taste masking
2. Stabilisation to oxidation
3. Reduction of volatility
4. Conversion of liquid to solid
5. Reduce gastric irritation
6. Sustained release medication

Microencapsulation Processes and their Applications

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Microencapsulation Processes and their Applications

Microencapsulation Process	Applicable core material	Particle size (µm)
Air suspension	Solids	35
Coacervation-phase separation	Solids and liquids	2
Multiorifice centrifugal	Solids and liquids	1
Pan coating	Solids	600
Solvent evaporation	Solids and liquids	5
Spray drying and congealing	Solids and liquids	600
Interfacial polymerisation	Solids and liquids	600

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Spray drying and congealing	Solids and liquids	600
Interfacial polymerisation	Solids and liquids	600

Coating Materials used for Microencapsulation:

Water-soluble material	Water-insoluble material
Gelatin	Ethyl cellulose
Gum Arabic	Polyethylene
Starch	Polymethacrylate
PVP	Polyamide (Nylon)
Carboxy methylcellulose	Cellulose nitrate
Hydroxyethyl cellulose	Poly(ethylene-vinyl acetate)

Interfacial polymerisation	Solids and liquids	600

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PVP	Polyamide (Nylon)
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Hydroxyethyl cellulose	Poly(ethylene-vinyl acetate)
Arabinogalactan	Poly(lactic-co-glycolic acid)
Polyvinyl alcohol	
Polyacrylic acid	

Note: All gums are anionic and acidic

Coacervation phase separation:

The process consists of three steps-

(A) Formation of three immiscible chemical phases, i.e.,
   (a) Liquid manufacturing vehicle phase, i.e., solvent for polymer
   (b) A core material phase
   (c) A coating material phase or polymer

The formation of three chemical phases can be achieved by-

1. Temperature change
2. Addition of salt
3. Addition of non-solvents
4. Incompatible polymer addition
5. Polymer-polymer interaction (gelatine-acacia)

(B) Deposition of coating on core material
(C) Rigdization of coating

Pellets:

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3. Addition of non-solvents
4. Incompatible polymer addition
5. Polymer-polymer interaction (gelatine-acacia)

(B) Deposition of coating on core material

(C) Rigdization of coating

Pellets:

The formation of three chemical phases can be achieved by-

1. Temperature change
2. Addition of salt
3. Addition of non-solvents
4. Incompatible polymer addition
5. Polymer-polymer interaction (gelatine-acacia)

(B) Deposition of coating on core material

(C) Rigdization of coating

Pellets:

Pellet size:	0.5-1.5 mm
Method of preparation:	Extrusion, Spheronisation

1. Taste masking
2. Stabilisation to oxidation
3. Reduction of volatility
4. Conversion of liquid to solid
5. Reduce gastric irritation
6. Sustained release medication

Wurster Process

Microencapsulation Processes and their Applications

Microencapsulation Process	Applicable core material	Particle size (µm)
Air suspension	Solids	35
Coacervation-phase separation	Solids and liquids	2
Multiorifice centrifugal	Solids and liquids	1
Pan coating	Solids	600
Solvent evaporation	Solids and liquids	5
Spray drying and congealing	Solids and liquids	600
Interfacial polymerisation	Solids and liquids	600

Coating Materials used for Microencapsulation:

Water-soluble material	Water-insoluble material

COSMETICS

Antioxidants used in cosmetics:

Type	Antioxidant used
Aqueous	Sodium formaldehyde sulfoxylate
Oily	α-tocopherol

LIPSTICK

Lipstick is a moulded stick, composed of coloring material dispersed in a blend of fatty bases, i.e., oils and waxes.

Formulation:

Formulation parameter	Function	Examples
Base (Waxes)	To achieve desired melting point viscosity & physical properties of stick	Hard paraffin, ozokerite wax, white beeswax, lanolin, ceresin wax, candelilla wax, carnauba wax, cetyl alcohol
Base (Oils)	For dispersing insoluble	Castor oil, liquid paraffin,

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Base (Oils)	For dispersing insoluble pigments, dissolving of eosin dyes, thin film to lips	Castor oil, liquid paraffin, isopropyl myristate
Bromo Mixture	Staining property	Tetrabromo fluoroscein
Color mixture (Insoluble dyes and lakes)	Modify shades of basic pigments	Titanium dioxide
Antioxidants	Prevent rancidity	Propyl gallate, Butylated hydroxy anisole (BHA), Butylated hydroxy toluene (BHT)
Flavors	Good taste; masks the fatty odour of the base	-

Liquid Lipsticks:

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Liquid Lipsticks:

- Also known as lip rouges / lip gloss / lip paint.
- No Wax
- Lake colors are used, along with small proportions of bromo acid.

Formulation of liquid lipsticks:

Formulation	Examples
Film former	Ethyl cellulose
Plasticiser	Glycerol

Preservative	
Antioxidant	

Lip Salves:

- Used as "Protective"
- No colors used, form adherent films
- Used in winter

Evaluation of Lipsticks:

1. Droop Point test – Temperature at which lipstick comes out.
2. Force of application – Weigh on paper after application.
3. Breaking Point test
4. Test for penetrability – Rheologic property
5. Stability testing – 45°C

SHAMPOOS

Shampoo is a preparation meant for cleansing hairs of dust, grime, crust and to impart gloss to hairs.

Formulation of shampoos

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Formulation of shampoos

Formulation parameters	Function	Examples
Surfactants	Anionic surfactants are commonly used. Cationic surfactants are used in conditioners. Non-ionic surfactants have poor foaming properties	Sodium lauryl sulphate, triethanolamine lauryl sulphate, monoethanol lauryl sulphate etc.
Conditioning agents	Improve manageability, feel and lustre of hairs	Lanolin, mineral oil, egg albumin, amino acids, lecithin & herbal extracts like shikakai and henna
Thickeners	Improve viscosity (easy to pour and handle)	Gum karaya, gum tragacanth, CMC, HPMC, polyvinyl alcohol, carbopol 934P etc.
Chelating agents	Prevent deposition of Ca and Mg salts of soaps on hairs	EDTA, polyphosphate, citric acid
Anti-dandruff agents	-	Zinc pyridinium thiol N-oxide (ZPTO), selenium sulphide, zinc undecylnate, bithinol, resorcinol etc

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NAIL PREPARATIONS

Nail preparations are also called as manicure preparations.

Types of Nail preparations:

1. Nail bleaches
2. Nail lacquer or Nail enamel
3. Enamel removers
4. Nail elongators

Nail preparations	Function
Nail bleaches	To whiten the nails and remove stains from nails Oxidising agent – Hydrogen peroxide Reducing agent – Sulphites
Nail enamels / Lacquers	To impart lustre / color to the nails
Enamel remover	To remove enamel from the nails

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Formulation of Nail Enamel

Formulation parameters	Function / Comment	Examples
Film formers	Cellulose nitrate most widely used	Cellulose nitrate (Nitrocellulose), cellulose acetate, cellulose acetobutyrate, ethyl cellulose, methacrylate & vinyl polymers
Solvents	Mixture of solvents used to avoid precipitation of cellulose nitrate	-
High boiling	-	Butyl lactate, ethyl oxalate, isoamyl acetate etc.
Low boiling	-	Ether, carbon disulphide,

	used	(Nitrocellulose), cellulose acetate, cellulose acetobutyrate, ethyl cellulose, methacrylate & vinyl polymers
Solvents	Mixture of solvents used to avoid precipitation of cellulose nitrate	-
High boiling	-	Butyl lactate, ethyl oxalate, isoamyl acetate etc.
Low boiling	-	Ether, carbon disulphide, acetone, methyl acetate, ethyl acetate etc.
Medium boiling	-	Isopropyl acetate, toluene, isopropyl alcohol, amyl formate etc.
Plasticizers	Impart flexibility and gloss to the film, help in adhesion of film to nails	Dibutyl phthalate, resorcinol diacetate, castor oil, butyl acetyl ricinoleate etc.
Colors	Insoluble pigments and lake colors are used	-
Pearlescent	Impart pearly appearance to the film	2-amino, 6-oxypurine (crystalline guanine), bismuth oxychloride-coated pigments

Amorolfine: Oncomysis (Nail infection / used in nail lacquer)

DENTRIFICES

Dentrifices are the preparations intended to cleanse the teeth of food debris, prevent calculus and plaque formation, polish to impart lustre to the teeth and to leave a refreshing feeling in mouth.

Types of Dentrifices:

- Tooth Powder
- Tooth Pastes

Formulation of Tooth Powder:

Formulation parameters	Examples
Abrasives and polishing agents	Calcium carbonate, dicalcium phosphate, tricalcium phosphate, sodium metaphosphate
Detergents and foaming agents	Sodium lauryl sulphate, sodium lauryl sarcosinate, diethyl sodium lauryl sulphosuccinate, magnesium lauryl sulphate

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Soaps	Sodium palmitate
Sweetening agents	Saccharin sodium
Flavoring agents	Anise oil, peppermint oil, clove oil, cinnamon oil, spearmint oil

Formulation of Tooth Pastes

Formulation of tooth pastes is similar to tooth powders, except that pastes contain humectants, binding agents and preservatives, which are not added to tooth powders.

Formulation parameters	Examples

	tricalcium phosphate, sodium metaphosphate
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Formulation parameters	Examples
Humectants	Glycerine, propylene glycol, sorbitol (10-30 %)
Binding agents	Gum tragacanth, gum arabic, karaya gum, sodium alginate, agar veegum, bentonite etc.
Preservatives	Methyl and propyl paraben
Anti-caries agent	Sodium fluoride, sodium lauryl sarcosinate
Antibacterials	Triclosan
Desensitizers	Potassium nitrate, strontium chloride

Evaluation of Dentrifices

	oil, spearmint oil

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- Abrasiveness
- Particle size
- Cleansing property

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Evaluation of Dentrifices

- Abrasiveness
- Particle size
- Cleansing property

- Foaming ability
- pH
- Consistency

CREAMS

Type of creams	Base
Cold cream	Absorption base (o/w)
Vanishing cream	Emulsion base (w/o)

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Cold cream	Absorption base (o/w)
Vanishing cream	Emulsion base (w/o)

→ Stearic Acid
Bleaching Cream

Bleaching Cream
↓↓
H_2O_2
↓↓
Anti Wrinkle Cream
↓↓
Retinol, Argireline
Coenzyme Q10

OPHTHALMIC PREPARATIONS

Formulation of Ophthalmic Products-

- Mean volume of tears: 7 µl
- Capacity of cul-de-sac: 30 µl
- Volume administered by dropper: 50 µl
- Viscosity: 15-25 centipoise
- pH of tears: 7.2
- Sterilization: Autoclaving (121°C for 15 mins) or by bacteria retentive filters

Formulation Parameters	Function	Examples
Viscosity increasing agents	Increase residence time of drug in eye hence its bioavailability	Methyl cellulose, polyvinyl alcohol, povidone, dextran, macrogol
Tonicity adjuster	To minimise irritation of eye, locally be isotonic with lachrymal secretion	Sodium chloride, Potassium chloride, Glucose, Glycerol
Wetting and spreading agents	To facilitate the dispersion of the finely divided powdered drug	Polysorbate-80 (Tween 80)
Stabilisers	To prevent the drug from oxidative decomposition	Sodium metabisulphite, sodium sulphite

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Chelating agent	-	Disodium edentate
Diagnostic agent	-	Fluorescein sodium
Preservatives	To ensure sterility during course of use	Benzalkonium chloride, Phenyl mercuric nitrate

- *Pseudomonas aeruginosa*, an organism that can invade an abraded cornea and cause ulceration and blindness.
- Preservative mixture of benzalkonium chloride (0.01%) and 1000 USP units of

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Ophthalmic Suspension

- Particle size – 10 µm

Ocusert

- The number '20' in 'Ocusert Pilo-20' refers to "Strength of preparation as a percentage".

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Classification of Semisolids:

Type of Semisolid	Flow behaviour
Creams	Non-newtonian, Pseudoplastic flow, low yield value
Gel	Pseudoplastic flow
Pastes	Dilatant flow

Bases Classification:

Type of Bases	Examples
Absorption bases	Anydrous lanolin (Wool fat)
Emulsion bases	Lanolin (Hydrous wool fat)
Water-soluble bases	Macrogol (Polyethylene glycol)

Bases used in Suppositories:

Bases	Examples
Water-soluble base	Macrogols, Soap glycerine
Oleaginous base	Theobroma oil, Cocoa butter, Palm kernel oil
Emulsifying base	Witepsol

SUSPENSIONS

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SUSPENSIONS

Suspensions follow Pseudo zero-order kinetics.

Freeze thaw cycling: (–25 - –5°C). Applying stress for checking stability of suspension.

Novel Drug Delivery Systems:

- Drug Delivery system using high voltage current is called Electroporation.
- Drug Delivery system using low voltage current is called Iontophoresis.
- Current used in Iontophoresis is upto 0.5 mA/cm^2
- **LIPOSOMES:** made up of phospholipids.
- **NIOSOMES:** made up of non-ionic surfactants.
- **DISCOSOMES:** used in ophthalmics.

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- In order to prepare a Novel Drug Delivery System (NDDS) from resealed erythrocytes, the erythrocytes for the purpose of loading the drug are placed in a Hypotonic solution.
- **ZYDIS SYSTEM:** Modified release tablets (Melt-in-mouth tablet)
- **OROS SYSTEM:** Osmotic Drug Delivery System (Noyes-Whitney equation)
- Diagnostic ultrasound (High frequency > 3 mHz)
- **Sonophoresis/Phonophoresis:** Power ultrasound (Low frequency, 20-100 kHz)
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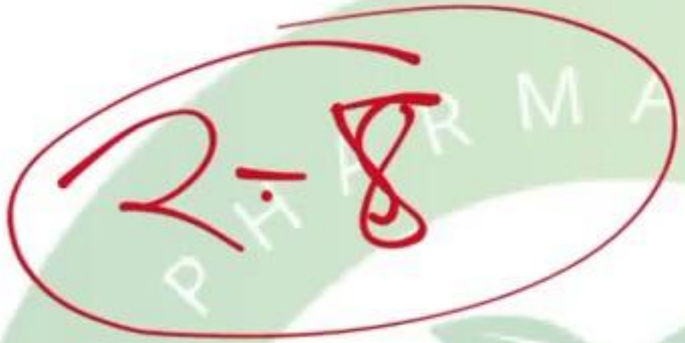

PARENTERALS

(Para – outside ; Enteron – intestinal)

Routes of administration:

I. Primary routes:

Routes of administration	Volume	Remarks	Examples
Intramuscular (IM / Depot injections)	Gluteal muscle (5 ml) Deltoid muscle (2 ml)	• Rapid absorption than SC injection • Prolonged drug release	Penicillins, Cephalosporins
Intravenous (IV)	Medial basilic vein at	• Rapid drug	Dextrose,

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Intravenous (IV)	Medial basilic vein at anterior surface of elbow (> 100 ml)	• Rapid drug action • Irritating drugs administered	Dextrose, NaCl, saline
Subcutaneous (hypodermic / SC)	Maximum 1 ml	• Drug action rapid than ID	Insulin
Intradermal (ID)	0.1-0.2 ml	• Diagnostic purposes	Tuberculin antigen, Schick test toxin

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II. Secondary routes:

Routes	Portion	Examples
Intra-arterial	Arteries	Anticancer agents for drug targeting to a particular organ
Intra-articular / Intra-bursal / Intra-synovial	Joint cavity	Steroids
Intra-cardiac	Ventricles of heart	Antiarrythmics

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Intra-spinal	Spinal cord	Anaesthetics
Intra-cerebral	Cerebral hemisphere	Adrenaline
Intra-pleural	Pleural cavity (lung)	Antibiotics
Intra-ocular	Eyes	Carbachol
Intra-abdominal / Intra-peritoneal	Peritoneal cavity (abdomen)	Dialysis solution
Intra-mammalian	Cattles	-

SMALL VOLUME PARENTERALS:

peritoneal		
Intra-mammalian	Cattles	-

SMALL VOLUME PARENTERALS:

Vehicles: Water is widely used.

Type	Method of preparation	pH	Total solids	Pyrogenicity	Sterility	Use
Purified water	Distillation, Reverse osmosis, Ion exchange	5-7	0.001% (10 ppm)	Pyrogenic	Non-sterile	For making nonsterile products
Water for injection	Distillation	5-7	0.001%	Pyrogen free (NMT 0.25 endotoxin units per ml)	Non-sterile	For making parenterals sterilised during manufacturing
Sterile water for injection	Reverse osmosis	5-7	<30 ml (0.004%), 30-100 ml (0.003%), >100 ml (0.002%)	Pyrogen free (NMT 0.25 eu/ml)	Sterile	For reconstitution of sterile solids
Bacteriostatic	Deionisation	5-7	-	Pyrogen free	Sterile	For

peritoneal		
Intra-mammalian	Cattles	-

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Water for Injection						reconstitution of sterile solids
Sterile Water for Irrigation	Distillation, Reverse osmosis	5-7	-	Pyrogen free	Sterile	For making irrigation products
Sterile water for inhalation	Distillation, Reverse osmosis	5-7	-	Pyrogen free	Sterile	For making inhalation products

Water for Injection (WFI):

Parameters	Conditions
pH	5-7
Conductivity	NMT 2 µ siemen/cm
Total organic carbon (TOC)	NMT 0.5 mg/l or 500 ppb
Storage	80°C or 5°C in SS-316 tanks

Co-solvents (water miscible):

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Total organic carbon (TOC)	NMT 0.5 mg/l or 500 ppb
Storage	80°C or 5°C in SS-316 tanks

Co-solvents (water miscible):

- Glycerine
- PEG 300, 400, 600
- Propylene glycol
- Ethanol
- Dimethyl acetamide

Oily vehicles (used only by IM route)

Vegetable oils like Peanut oil, Sesame oil (antioxidant), Olive oil, Cottonseed oil, Safflower oil

Synthetic vehicles

Ethyl oleate, Isopropyl myristate, Benzyl benzoate

Antimicrobial Preservatives:

Oily vehicles (used only by IM route)

Vegetable oils like Peanut oil, Sesame oil (antioxidant), Olive oil, Cottonseed oil, Safflower oil

Synthetic vehicles

Ethyl oleate, Isopropyl myristate, Benzyl benzoate

Antimicrobial Preservatives:

Sr. No.	Preservatives	Concentration (%)
1.	**Phenolics** • Phenol • Cresol • Chlorocresol	 0.5 0.3 0.1
2.	**Parabens** • Methyl paraben • Propyl paraben	 0.2 0.02-0.04
Usually used in the ratio of 10:1 or 5:1		
3.	**Alcohols**	

	• Methyl paraben • Propyl paraben	0.2 0.02-0.04
Usually used in the ratio of 10:1 or 5:1		
3.	**Alcohols**	
	• Benzyl alcohol • Chlorobutanol	1 0.5
4.	**Mercurials** • Thiomersal • Phenyl mercuric nitrate/acetate	 0.01 0.001
5.	**Quarternary ammonium compounds** • Benzalkonium chloride	0.01

Note:

- Preservatives are required for multiple-dose containers to maintain sterility of product

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Note:

- Preservatives are required for multiple-dose containers to maintain sterility of product.
- Maximum size of multiple-dose containers –30 ml (as per USP).
- Steaming at 100°C for 30 min. in presence of preservative is used for terminal sterilisation of products that are sensitive to temperature of 121°C. This method is called 'Heating with bactericide'.
- Preservatives are not added in:
  - IV infusions (toxicity due to large quantities)
  - Intraocular injections (toxicity to delicate eye tissues)
  - Intraspinal injections (damage nerve fibres / CNS side effects)
  - Intradermal injections (interfere with diagnostic tests)

	nitrate/acetate	
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Antioxidants:

Sr. No.	Antioxidants	Concentration (%)
Water-soluble antioxidants		
1.	**Sulfurous acid salt** • Sodium sulphite	0.1-0.2

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Antioxidants:

Sr. No.	Antioxidants	Concentration (%)
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1.	**Sulfurous acid salt** • Sodium sulphite • Sodium bisulphite • Sodium metabisulphite • Sodium thiosulfate • Sodium formaldehyde sulfoxylate	0.1-0.2
2.	**Ascorbic acid isomers** • L-ascorbic acid • Iso-ascorbic acid	0.1-0.2
3.	**Thiol derivatives** • Thioglycerol • Thioglycollic acid • Thiolactic acid • Thiourea	0.1

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3.	**Thiol derivatives** • Thioglycerol • Thioglycollic acid • Thiolactic acid • Thiourea • Butathiol • Acetylcysteine	0.1

Propyl gallate, Butylated hydroxyl anisole (BHA), Butylated hydroxyl toluene (BHT), α-Tocopherol (Vit. E), Ascorbyl palmitate, Nordihydroguaiaretic acid (NDGA)

Buffers:

- Buffers are not used for LVPs.
- Intraspinal injection should be adjusted to 7.4 as non-neural solution can cause aseptic meningitis.

Buffer	pH range
Acetate	3-6
Citrate	3-6
Phosphate	6-8
Glutamate B	8-10

Tonicity adjusters:

Tonicity adjusters	Examples
Electrolytes	Sodium chloride
Non-electrolytes	Glucose, Mannitol, Glycerine, Sorbitol

Note:

- Isotonic solutions have same osmotic pressure as that of plasma.
- Solutions that are not isotonic are called paratonic (hyper or hypotonic).

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Non-electrolytes	Glucose, Mannitol, Glycerine, Sorbitol

Note:

- Isotonic solutions have same osmotic pressure as that of plasma.
- Solutions that are not isotonic are called paratonic (hyper or hypotonic).
- Hypotonic solutions cause lysis of RBCs, while hypertonic solutions cause shrinkage (crenation).
- Dextrose injection (5%), Sodium chloride (0.9%) and Boric acid (1.5%) are isotonic.
- Isotonicity is important in case of intradermal and intraspinal injections.
- Isotonicity is not important in case of IM and SC injections.
- Osmolarity of blood: 250-350 mosmol/litre.
- Osmolarity of sodium chloride: 300-308 mosmol/litre.

Other additives:

Additives	Examples
Surfactants (Non-ionic)	Polysorbate 80 (Tween 80), Polyoxyethylene-Polyoxypropylene co-polymers (Pluronics / Poloxamers / Lutrol / Intelligent polymer)
Suspending agents	Methyl cellulose, CMC, PVP
Emulsifier	Lecithin
Chelating agent	Disodium EDTA

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Complexing agent	Hydroxypropyl β-cyclodextrin
Antiseptic	Carbolic acid (Phenol)
Protein stabilizers	Amino acids (Glycine, lysine), PVP
Bulking agents	Mannitol, lactose, sucrose

Packaging Materials for Injections:

GLASS:

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Antiseptic	Carbolic acid (Phenol)
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Packaging Materials for Injections:

GLASS:

- Glass is supercooled liquid of viscosity greater than 10^{13} poise.
- It is composed of SiO_2 (65-75 %), Tetrahedron modified physicochemically by oxides of Na^+, K^+, Ca^{+2}, Mg^{+2}, Al^{+3}, B^{+3} etc.
- It is relatively brittle and has very high melting point (1700°C).
- Leaching and flake formation (alkaline solution) enhanced during autoclaving.

Type	Description	Test	Overflow capacity of container	Vol of 0.02 N H_2SO_4 (ml)	Use
I	Highly resistant borosilicate glass (Neutral)	Powdered glass	All	1.0	Aqueous solutions
II	Surface treated soda lime glass	Water attack	<100 ml >100 ml	0.7 0.2	Aqueous solution, dry powder, oily solution
III	Soda lime glass	Powdered	All	8.5	Dry powders

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III	Soda lime glass (Regular)	Powdered glass	All	8.5	Dry powders, oily solutions
IV	Non-parenteral glass	Powdered glass	All	15.0	Non-parenteral use

Surface treated soda lime glass:

- Ammonium sulphate or Ammonium chloride used for surface treatment.

Amber-coloured glass:

- It is produced by iron and manganese oxide (MnO_2).

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- It filters out UV radiation.
- Also called non-actinic glass.

Flint glass:

- It is colourless glass.

RUBBER:

- All rubbers are opaque, except silicone rubber, which is translucent.

Ingredients of rubber:

Ingredients	Examples
Polymer	Elastomer
Vulcanising agent	Sulphur
Accelerator	2-Mercapto Benzothiazole, Tetramethylthiourea
Activator	Zinc oxide, Zinc stearate, stearic acid
Filler	Cobalt black, limestone, talc, calcium carbonate
Antioxidant	-
Lubricant	Zinc stearate, talc
Softener	Mineral oil
Pigments / Colours	Coal-tar dyes
Coating agent	Epoxy or Teflon coating

Types of rubber:

Sr. No.	Types	Made up of
1.	Natural	Polyisoprene latex of tree *Hevea brasiliensis*
2.	Grey butyl (widely used)	Polyisobutylene (synthetic)

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3.	Nitrile rubber (Hycar)	Butadiene acrylonitrile
4.	Chloroprene	Neoprene (synthetic)
5.	Silicone rubber	Polymethylsiloxane

Note: If there is a formation of rubber particles after insertion of needle, it causes contamination of the product. This is called coring.

PLASTIC

- All plastics can be autoclaved except LDPE (Low-density polyethylene) and polystyrene.

Sr. No.	Plastic	Physical properties

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Sr. No.	Plastic	Physical properties
1.	LDPE (Low density polyethylene)	Translucent, Flexible
2.	HDPE (High density polyethylene)	Translucent, Semirigid
3.	Polypropylene (PP)	Translucent, Semirigid
4.	Polyvinyl chloride (PVC)	Transparent, flexible
5.	Polyvinyl chloride (PVC)	Transparent, rigid
6.	Polycarbonate (PC)	Transparent, rigid
7.	Polystyrene (PS)	Transparent, rigid
8.	Polyamide (PA)	Translucent, rigid
9.	Polytetrafluoroethylene (PTFE / Teflon)	Translucent, rigid

- Most widely used plastic is flexible PVC, which is used for packaging of IV infusion.
- Polyolefin semi-rigid containers (PE and PP) are used more now-a-days for IV infusions.
- HDPE, PP and Polystyrene (PS) are used for making disposable syringes.

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RECONSTITUTABLE SOLIDS

- Used within time period of usually 1-15 days.

Freeze Drying (Lyophilisation / Gelification / Drying by sublimation):

- Freeze drying is carried out at temperature and pressure less than the triple point of water.
- Freezing point of blood plasma and tears is –0.52°C.

Parameters	Triple point	Freeze drying
Temperature	0.0098°C	-40 to -10°C
Pressure	4.58 mm Hg	0.1 mm Hg

STERILISATION

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STERILISATION

Sterility: It is complete freedom from viable microorganisms within a probability limit of 10^{-6}.

D-value or Decimal reduction time – Time, in minutes, at any defined temperature, required to destroy 90% of viable organisms present in the product.

Z-value or Thermal destruction value – The number of degrees of temperature change required to produce a ten-fold change in D-value.

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Q-value or Temperature coefficient – $Q = \frac{\text{Time to kill at x°C}}{\text{Time to kill at x + 10° C}}$

STERILIZATION PROCESSES:

Sterilization	Mechanism	Application	Biological indicators	Chemical indicators
Dry Heat	Oxidation of Proteins	Glass syringes, Needles, Dry powders,	*Bacillus subtilis* var. niger	Browne's tubes/Bowie-Dick heat sensitive tapes

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Moist Heat	Denaturation and coagulation of proteins	Aqueous solution, Suspension, Emulsion, Surgical Dressings, Rubber	*Bacillus sterothermophilus/ Clostridium sporogenes*	Stripe papers
Gaseous	Alkylation of Proteins	Disposable syringes, Fragile rubber,	*Bacillus subtilis* var. niger	Royce sachet

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		Bottles, Dressing, Rooms (Formaldehyde)		
Radiation	Nucleoprotein damage by UV of λ 265	Plastic syringe, Rubber	*Bacillus pumilus*	Dosimeters

		Bottles, Dressing, Rooms (Formaldehyde)		
Radiation	Nucleoprotein damage by UV of λ 265 nm/Ionisation/ Free radical formation	Plastic syringe, Rubber gloves, Disposable instruments	*Bacillus pumilus*	Dosimeters
Filtration	Retention of bacteria	Thermolabile liquids and solutions	Bubble point test	*Pseudomonas diminuta/ Serratia marcescens*

Temperature-time combinations:

1) Moist Heat Sterilisation:

Temperature (°C)	Pressure (psig)	Time (min.)
115	10	30
121	15	15
126	20	10
134	30	3

- Most commonly used combination is 121°C for 15 mins.

	bacteria	liquids and solutions	test	*diminuta*/ *Serratia marcescens*

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- For fabrics, temperature of 134°C for 3 mins is used.

2) Dry Heat Sterilisation:

Temperature (°C)	Time (Hr)
140	3
150	2.5
160	2
170	1

- Most widely used combination is 160°C for 2 hr.

Sterilisation by Filtration:

Temperature (°C)	Pressure (psig)	Time (min.)
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Sterilisation by Filtration:

Following sterilisation filters are available:

1. Unglazed porcelain filter candles (Ceramic filter)
2. Diatomaceous earth filter candles (Ceramic filter)
3. Asbestos fibre pads (Sietz filter)
4. Sintered glass filters (Fritted glass filter)
5. Membrane filters (Millipore filters)

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5. Membrane filters (Millipore filters)

- Ceramic filters may adsorb active ingredients.
- Asbestos pads impart alkalinity to filtrate.

Membrane filters:

Bacteria	Pore size (µm)
Pseudomonas diminuta	0.22
Serratia marcescens	0.45

Membrane filtration

- The pressure required to force air through the wet filter is called bubble point pressure of the membrane.
- **Bubble point pressure** (40-50 psig), is inversely proportional to size of largest pore in the membrane.
- **Routine filtration** is done at pressure lower than the bubble point (15-20 psig).

Radiation Sterilisation:

γ-radiation	
Source	Cobalt 60, Cesium 137 (Cs-137)
Half-life	5.3 years (Co-60)
Emission energy	1.3 megaelectron volt
Dose	2.5 Mega rad
Radiation	25 KGy (kilogray)
UV radiation	

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UV radiation	
Source	Mercury vapour lamp
Radiation	265 nm

Gaseous sterilisation:

1) **Ethylene oxide sterilisation:**
   - Pure EtO is used in combination with CO_2 or Freon 12 (fluorinated hydrocarbons).
   - EtO and CO_2 mixtures are used in ratio of 10:90.

Parameters	**Conditions**
Temperature	50-60 °C

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Ionising

Non-Ionising

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Non Ionising

Gaseous sterilisation:

1) Ethylene oxide sterilisation:

- Pure EtO is used in combination with CO_2 or Freon 12 (fluorinated hydrocarbons).
- EtO and CO_2 mixtures are used in ratio of 10:90.

Parameters	Conditions
Temperature	50-60 °C
Relative humidity	60%
Time	4-16 hrs
Conc. of EtO	300-450 mg/l
Content of EtO	10 ppm

2) Formaldehyde sterilisation:

Formaldehyde gas is produced by heating formalin (37%) solution of formaldehyde.

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Parameters	Conditions
Temperature	50-60 °C
Relative humidity	60%
Time	4-8 hrs
Gas conc.	4 mg/l

Others methods of sterilisation by moist heat:

Sterilisation	Conditions
Vaccines	Stable up to 60°C Plague vaccine (55°C for 15 min.) Cholera / Typhoid (56°C for 1 hr.)
Pasteurization	Holder method (63°C for 30 min.) Flask method (72°C for 15 sec.)
Tyndallization	80°C for 1 hr on 3 successive days

Parameters	Conditions
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Tyndallization	80°C for 1 hr on 3 successive days
Heating with bactericide (chlorocresol, phenyl mercuric nitrate)	100°C for 30 min.

PARTICULATE MATTER

- Particles larger than 50 µm can be observed with naked eye.

USP Limits for particulate matter in injection:

Particle size	Light obstruction method	Microscopy method
For SVP		

(chlorocresol, phenyl mercuric nitrate)	

PARTICULATE MATTER

- Particles larger than 50 µm can be observed with naked eye.

USP Limits for particulate matter in injection:

Particle size	Light obstruction method	Microscopy method
For SVP		
>10 µm	6000 per container	3000 per container
>25 µm	600 per container	300 per container
For LVP		
>10 µm	25 per ml	12 per ml
>25 µm	3 per ml	2 per ml

CLEAN ROOM:

Class	Max^{m} no. of particles per ft^{3} of air		Max^{m} no. of live organism per ft^{3} of air
	Size > 0.5 µm	Size > 5 µm	
100	100	-	0.1
10,000	10,000	65	0.5
1,00,000	1,00,000	700	2.5

Layout of injection manufacturing area:

For SVP		
>10 µm	6000 per container	3000 per container
>25 µm	600 per container	300 per container
For LVP		
>10 µm	25 per ml	12 per ml
>25 µm	3 per ml	2 per ml

CLEAN ROOM:

Class	Max^{m} no. of particles per ft^{3} of air		Max^{m} no. of live organism per ft^{3} of air
	Size > 0.5 µm	Size > 5 µm	
100	100	-	0.1
10,000	10,000	65	0.5
1,00,000	1,00,000	700	2.5

Layout of injection manufacturing area:

- Total required area is not less than 60 m^2 excluding packaging.

HEPA (HIGH EFFICIENCY PARTICULATE AIR) FILTERS

Parameters	Conditions
HEPA (High efficiency particulate air filters)	
Efficiency	99.97 %
Particle size	0.3 µm
Efficiency testing	DOP (Dioctyl phthalate) test
Conc. of DOP	66.6 ppm
Alternative to DOP	Liquid paraffin
Reagent used to check efficiency	Hydrocarbon vapours
Flow rate	20 ± 5 ft/min.
ULPA (Ultra efficiency particulate air filters)	
Efficiency	99.997 %
Particle size	0.1 µm
VEPA (Very efficiency particulate air filters)	
Efficiency	99.999 %
Particle size	0.1 µm
Testing of HEPA filters:	
Efficiency testing	Hot DOP test
Integrity testing (once a year)	Cold DOP test
Airflow resistance	Pressure drop across filter (manometer)

LAMINAR AIR FLOW:

Parameters	Conditions
HEPA (High efficiency particulate air filters)	
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Integrity testing (once a year)	Cold DOP test
Airflow resistance	Pressure drop across filter (manometer)

LAMINAR AIR FLOW:

Particle size	0.1 μm
Testing of HEPA filters:	
Efficiency testing	est
Integrity testing (once a year)	Cold DOP test
Airflow resistance	Pressure drop across filter (manometer)

LAMINAR AIR FLOW:

Parameters	Conditions
Flow direction	Unidirectional
Velocity	80-120 ft / min
Laminarity (velocity) determination	Velometer / Anemometer
Cleanliness requirement	100 (Aseptic area)

AIR HANDLING UNIT (AHU): HEATING, VENTILATION AND AIR CONDITIONING (HVAC)

Parameters	Conditions
Temperature	15-25 °C
Air changes	20 per hour
Cleanliness requirement	Class 100 or 1,00,000
Relative humidity	45-55 %
Pressure differential	0.05-0.1 inch water gauge

- Pyrogens are fever producing substances.
- Pyrogens are high molecular weight lipopolysaccharides (10^6 mol. wt.).

Pyrogen test: Rabbit test

- When single dose of volume of injection is greater than or equal to 15 ml.
- Rabbit is used as test animal as it is highly sensitive to pyrogens.
- A preliminary test, called the Sham test, is carried out for selection of rabbits.
- Sample is injected into the marginal ear vein of the rabbits.
- Any animal showing temperature variation of 0.6°C should not be used in main test.

BACTERIAL ENDOTOXIN TEST: LIMULUS AMOEBOCYTE LYSATE (LAL) TEST

- Horseshoe crab (*Limulus polyphemus*)
- It only detects Gram-negative bacteria.

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- It is semi-quantitative test.
- It is based on gelling/coagulation/clotting of LAL in presence of endotoxins.

TESTING OF PARENTERALS

Leaker test	Methods	Vacuum applied (mmHg)
Ampoules	Dye bath method, Vacuum pull method	70
Vials	Water hammer test, Spark test	27

LARGE VOLUME PARENTERALS

Formulation of IV LVPs:

1. WFI (Water for Injection): is the vehicle used for all LVPs.
2. All LVPs are clear solutions, except IV fat emulsions.
3. Preservatives not added except intraperitoneal dialysis fluid (chlorocresol).
4. Antioxidants, such as sodium metabisulphite, may be added to some LVPs if required. N_2 flushing is done so that quantity of antioxidant is kept at minimum, e.g. multiple electrolyte solution.
5. Buffers are generally not added. Although acids and bases are used for simple adjustment of pH.
6. All LVPs are terminally sterilised by autoclaving.
7. Incompatibility may be avoided using double component containers. The solutions are mixed in the bag itself, prior to administration, e.g. Dextrose + Amino acid solution.

TOTAL PARENTERAL NUTRITION (TPN)

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LARGE VOLUME PARENTERALS

Formulation of IV LVPs:

electrolyte solution.

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TOTAL PARENTERAL NUTRITION (TPN)

Components of TPN:

Components	Examples
Proteins	Amino acids
Energy	Carbohydrates (dextrose) Fats (soyabean oil)
Electrolytes (millimole/litre)	Sodium, potassium, calcium, magnesium, chloride, phosphate
Trace elements (cofactor)	Copper, zinc, manganese, chromium

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Vitamins (coenzymes)	Fat soluble vitamins (A, D, E, K) Water-soluble vitamins (B, C)

ASEPTIC PACKAGING: BLOW FILL SEAL (BFS) / FORM FILL SEAL (FFS) TECHNOLOGY

This technology is useful for polyethylene / polypropylene plastic containers (PE / PP).

Four step continuous operation:

1. Heat of plastic granules to semisolid state (Parison extrusion).
2. Blow moulding to form containers (Parison moulding).
3. Filling of containers.
4. Sealing of containers.

PHYSICAL PHARMACY

Methods of Particle size distribution:

Sr. No.	Methods	Particle size (µm)
1.	Optical microscopy	0.2-100
2.	Sieving	50-1500
3.	Sedimentation	1-200
4.	Conductivity	0.5-500

- Sieving 30/45 – Passed/Retained

- Sedimentation (Stokes' diameter)

Anderson's pipette method
10 ml pipette capacity
550 ml cylindrical vessel
20 cm below the surface of suspension

- Coulter counter = Particle volume/Stream scanning (4000 particle/sec counted)

Methods of surface area determination:

1) BET adsorption: Specific surface/diameter

2) Air permeability

⇩

Kozeny-Carman equation ⟹ $V = A/ns_w^2 . \Delta pt/Kl . \varepsilon/(1 - \varepsilon)^2$

Where,

ε = porosity

s_w = surface area

Application – **Fischer sub-sieve sizer**

Derived properties of powders:

Sr. No.	Derived properties

s_w = surface area

Application – **Fischer sub-sieve sizer**

Derived properties of powders:

Sr. No.	Derived properties
1.	Particle size
2.	Density
3.	Volume
4.	Porosity

Density:

Types of density	Methods to determine
True density	Helium displacement method Liquid (N_2) displacement method
Granule density	Mercury displacement method

Porosity:

Porosity = Void volume / Bulk volume

Void volume = Bulk volume – True volume

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Volume:

Types of volume	Determination of
True volume	Volume of powder itself
Granule volume	Volume of powder + Intraparticle spaces
Bulk volume	Volume of powder + Interparticle spaces

Packing arrangements:

Packing arrangement	Porosity
Closely packed (closest)	26 %
Loosely packed (loosest)	48 %
Very closely	< 30 %
Flocculation	> 50 %

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SURFACE AND INTERFACIAL PHENOMENON:

Phenomenon	Force	MKS units	CGS units
Surface tension	Cohesive	Newton/m	Dynes/cm
Interfacial tension	Adhesive	Newton/m	Dynes/cm

- **Surface free energy – Wire frame apparatus**

Methods to determine surface tension:

1) Capillary rise method
2) Tensiometer [duNouy ring (platinum iridium silicone treated) method]
3) Bubble pressure
4) Drop weight/Drop count

HLB scale/Griffin scale:

Type	HLB value
Lipophilic	**1-10**
Antifoaming agent	1-3
W/O	3-8
Wetting/Spreading agent	7-9
Hydrophilic	**11-18**
O/W	8-16
Detergents	13-16

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Solubilising agent	16-18

HLB Values:

Compounds	HLB value
Tween 20	16.7
Tween 80	15
Sodium lauryl sulphate	40
Spans	1.8 - 8.6
Liquid paraffin	0 - 3

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Acacia	8
Tragacanth	13.3

Electrical Double Layer:

a) **Tightly bound layer**
In this, anions are termed as counter ions or gegen ions.

b) **Diffuse second layer**
In this, excess negative ions are present.

Tragacanth	13.3

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c) **Bulk liquid phase**

- **Nernst potential (Electrothermodynamic potential):**

Difference in potential between actual surface and electroneutral region of solution.

- **Zeta potential (Electrokinetic potential):**

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- **Nernst potential (Electrothermodynamic potential):**

Difference in potential between actual surface and electroneutral region of solution.

- **Zeta potential (Electrokinetic potential):**

Difference in potential between tightly bound layer and electroneutral region of solution. It can be positive, zero or negative.

VISCOSITY AND RHEOLOGY:

Newton's equation: $F = \rho G$

Where,

F = shearing stress

G = rate of shear

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Newton's equation: $F = \rho G$

Where,

F = shearing stress

G = rate of shear

Types of flow:

Sr. No.	Types of flow	Examples
1.	Newtonian flow	Human tears, castor oil
2.	Plastic flow (Bingham bodies)	Flocculated suspension
3.	Pseudoplastic flow (Shear thinning)	Polymers, Liquid paraffin
4.	Dilatant (Shear thickening)	Deflocculated suspension, suspension of starch in water

Thixotropy: Gel → Sol → Gel

Anti-thixotropy/Negative thixotropy: Sol → Gel → Sol

Determination of Viscosity:

Viscometers	
Single Point	**Multi point**
Single rate of shear	Several rate of shear
e.g. Ostwald (capillary) viscometer	e.g. Cup and Bob viscometer

1.	Newtonian flow	Human tears, castor oil
2.	Plastic flow (Bingham bodies)	Flocculated suspension
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Anti-thixotropy/Negative thixotropy: Sol → Gel → Sol

Determination of Viscosity:

Viscometers	
Single Point	**Multi point**
Single rate of shear	Several rate of shear
e.g. Ostwald (capillary) viscometer Falling sphere viscometer	e.g. Cup and Bob viscometer Cone and Plate viscometer
Newtonian fluid	Newtonian and Non-newtonian fluid

1) Capillary viscometer

- Ostwald viscometer → Poiseuille law

2) Falling sphere/Hoeppler falling sphere viscometer

Range: 0.5-2,00,000 drops/min.

3) Rotational viscometer

- **Cup and Bob viscometer**

a) Revolving cup: Couette type - e.g. MacMichael viscometer

b) Revolving bob: Searle type - e.g. Stormer viscometer

Disadvantage – Plug flow

- **Cone and Plate viscometer**

Small sample (0.1-0.2 ml) required

- **Brookfield viscometer**

Helipath arrangement (T-spindle)

DISPERSION SYSTEM:

Classification of colloids:

a) Lyophilic (Solvent loving) – Thermodynamically stable
b) Lyophobic (Solvent hating) – Thermodynamically unstable

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DISPERSION SYSTEM:

Classification of colloids:

a) Lyophilic (Solvent loving) – Thermodynamically stable
b) Lyophobic (Solvent hating) – Thermodynamically unstable
c) Association/Amphiphiles - Both for polar and non-polar

- Each micelle contains 50 monomers and size 50Å

Association colloids:

Types	Examples
Anionic	Sodium lauryl sulphate
Cationic	Cetyl trimethyl ammonium bromide
Non-ionic	Polyoxyethylene lauryl ether

Properties of colloids:

Properties	Determined by
Optical	- Microscopy - Light scattering
Kinetic	- Brownian motion (prevent sedimentation)
Electrical	- Electrophoresis
	- Donnan membrane equilibrium

- **Critical Micelle Concentration (CMC)** – Concentration of surfactant at which micelle starts forming.

Unit: w/w, w/v %, moles/lit, moles/1000 gm

- **Protective colloid** – A colloid that helps to stabilise other colloid.

- **Gold number** – Minimum weight in mg of protective colloid.

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- **Gold number** – Minimum weight in mg of protective colloid.

Protective colloid	Gold number (mg)
Gelatin	0.005-0.01
Albumin	0.1
Acacia	0.1-0.2
Sodium oleate	1-5
Tragacanth	2

Sodium oleate	1-5
Tragacanth	2

Multiple emulsion:

a) W/O/W – W/O in aqueous phase
b) O/W/O – O/W in oil phase

Identification test:

a) **Dye solubility test**
   Water-soluble dyes: e.g. Amaranth, Methylene
   Oil-soluble dyes: e.g. Sudan III, Scarlet red
b) **Dilution test (miscibility)**
c) **Conductivity test:** Purity of water
d) **Creaming test**
   Cream downward – W/O
   Cream upward – O/W

TYPE : THEORY

Type	Theory
Crystal growth	Ostwald ripening
pH scale	Sorenson scale
HLB scale	Griffin scale
Interparticulate force	DLVO theory

ANGLE OF REPOSE:

HLB scale	Griffin scale
Interparticulate force	DLVO theory

ANGLE OF REPOSE:

Angle of Repose	Flowability
5 - 15	Excellent
12 - 16	Good
18 - 21	Fair-passable
23 - 35	Poor
33 - 38	Very poor
< 40	Very, very poor

CHEMICAL KINETICS:

Order	Integrated rate equation	Half-life equation
0	$x = kt$	$t_{1/2} = a/2k$
1	$\log a = k t$	$t_{1/2} = 0.693$

12 - 16	Good
18 - 21	Fair-passable
23 - 35	Poor
33 - 38	Very poor
< 40	Very, very poor

CHEMICAL KINETICS:

Order	Integrated rate equation	Half-life equation
0	$x = kt$	$t_{1/2} = a/2k$
1	$\log \frac{a}{a-x} = \frac{k}{2.303} . t$	$t_{1/2} = \frac{0.693}{k}$
2	$\frac{x}{a(a-x)} = kt$	$t_{1/2} = 1/ak$
3	$\frac{2ax-x^2}{a^2(a-x)^2} = 2kt$	$t_{1/2} = \frac{3}{2} . \frac{1}{a^2x}$

a = initial concentration, x = conc^n of reactant decomposed, k = rate constant, t = time

IMPORTANT TERMS TO REMEMBER:

1) **Kraft point:** Temperature at which solubility of surfactant equal to CMC.
2) **Cloud point:** Temperature above which cloudiness occurs.
3) **Upper consulate temperature:** Temperature above which two liquids get completely miscible, e.g. Phenol-water.
4) **Lower consulate temperature:** Temperature below which two liquids get completely

2	$\frac{x}{a(a-x)} = kt$	$t_{1/2} = 1/ak$
3	$\frac{2ax-x^2}{a^2(a-x)^2} = 2kt$	$t_{1/2} = \frac{3}{2} \cdot \frac{1}{a^2x}$

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4) **Lower consulate temperature:** Temperature below which two liquids get completely immiscible, e.g. Triethyl amine water.
5) **Syneresis:** Shrinkage of gel by extrusion of liquid.
6) **Draves test:** Efficiency of wetting agent.
7) **Pumice:** Gas in solid.
8) **Foam:** Gas in liquid.
9) **Bulges:** Bentonite magma.
10) **Spur:** Procaine penicillin gel.
11) **Schulze-Hardy rule:** Precipitating power of oppositely charged ion.
12) **Hofmeister Rank series:** Precipitating power directly related to ability to separate water molecule.
13) **Mark-Hou wink equation:** Intrinsic viscosity.
14) **Fanning equation:** Energy loss due to friction.
15) **Van der Waal's equation:** Real gases.

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15) **Van der Waal's equation:** Real gases.
16) **Clausius-Clapeyron equation:** Heat of vaporisation.
17) **Darcy equation:** Filtration rate.
18) **Instron tester:** Tackiness and stickiness.
19) **Cryoscopic constant:** Freezing point depression (Beckmann apparatus).
20) **Ebullioscopic constant:** Elevation of boiling point.
21) **Graham's law:** Diffusion of Gases.
22) **Dalton's law:** Total vapour pressure.
23) **Raoult's law:** Partial vapour pressure

PHARMACEUTICAL ENGINEERING

I. FLUID FLOW

$$\text{Reynolds number} = \frac{\text{Inertial Force}}{\text{Viscous force}}$$

- Up to 2100 = Laminar flow
- Above 4000 = Turbulent flow

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Note: Stokes' law can't be used if Reynolds Number > 2000

Bernoulli's Theorem:

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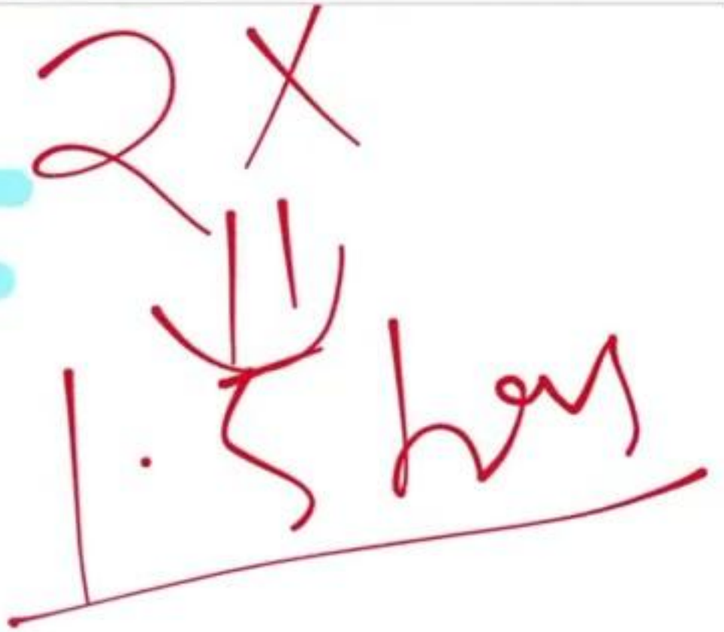

- Application of law of conservation of energy to flow of fluids.

II. HEAT TRANSFER

Mechanism:

Mechanism of heat transfer	Applicable to
Conduction	Solids
Convection	Liquids

Fourier's law: States that the time rate of heat transfer through a material is proportional to the negative gradient in the temperature and to the area, at right angles to that gradient, through which the heat is flowing.

Heat transfer by radiation:

(i) **Kirchoff's law:** Emissive power of a body E is radiant energy emitted per unit area in unit time.

(ii) **Stefan-Boltzmann law:** Emissive power of black body is proportional to the fourth power of absolute temperature.

Heat transfer by convection:

(i) **Natural convection:** Buoyancy force
(ii) **Forced convection:** Rate of heat transfer higher than natural convection.

III. EVAPORATION

- **Duhring Rule -** Elevation in boiling point

IV. DISTILLATION

Type of distillation	Features
Flash distillation	Equilibrium
Fractional distillation	Rectification
Molecular distillation	Clausius equation
Azeotropic distillation	A substance added to alter relative volatility is called Entrainer

Molecular distillation	Clausius equation
Azeotropic distillation	A substance added to alter relative volatility is called Entrainer, e.g. Benzene in ethanol and water Butyl acetate in acetic acid and water
Extractive distillation	A substance added to alter relative volatility for extractive distillation is called Solvent, e.g. P.G. in water-ethanol mixture

V. DRYING

- It involves heat transfer and mass transfer both.

VI. FILTRATION

Membrane filters

Pore size	0.22 µ to 0.45 µ

- It involves heat transfer and mass transfer both.

VI. FILTRATION

Membrane filters

Pore size	0.22 μ to 0.45 μ
Integrity testing	Bubble point test
Ultrafiltration size	20-1000 A^0

Pore size (μm)	Test organism
0.2	*Pseudomonas diminuta*
0.3	*Pseudomonas aeruginosa*
0.45	*Serratia marcescens*
0.65	*Saccharomyces cerevisiae*

VII. CRYSTALLISATION

Theory	Applicable to
Mier's	Supersaturation

Gibbs & Volmer	Nucleation

ZONES:

Type of zones	Features
Stable zone	Unsaturation + No crystallisation
Metastable zone	Nucleation + Crystallisation
Unstable / Labile zone	Supersaturation + Nucleation

Storage of corrosive material:

Corrosive material	Suitable material
Nitric acid	Stainless steel
Distilled water	Tin
Dilute Sulphuric acid	Lead

- **Surface coating** – to prevent corrosion, i.e. Electroplating, cladding, vapour deposition, organic coating
- **Cladding** – involves mechanical bonding of corrosion resistant material with material to be protected.

VIII. FIRE

DISPENSING OF MEDICATION

DOSAGE FORMS

1. **Elixirs:** Hydroalcoholic (alcohol NMT 40%) sweet solution for oral use.
2. **Linctuses:** Monophasic liquid with high concentration of syrup for treatment of cough.
3. **Draughts:** Monophasic liquid taken as a single dose orally.
4. **Paints:** Viscous preparation for local action in pharynx.
5. **Glycerites:** Viscous, hygroscopic solution of medicament applied externally.
6. **Sprays:** Aqueous or non-aqueous monophasic liquids spraying in throat/nose.
7. **Ear drops:** Solution, suspension, emulsion remove excessive cerumen (ear wax).
8. **Liniment:** Solution or emulsion in aqueous/oily vehicle massage to unbroken skin. "FOR EXTERNAL USE ONLY".

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DOSAGE FORMS

1. **Elixirs:** Hydroalcoholic (alcohol NMT 40%) sweet solution for oral use.
2. **Linctuses:** Monophasic liquid with high concentration of syrup for treatment of cough.
3. **Draughts:** Monophasic liquid taken as a single dose orally.
4. **Paints:** Viscous preparation for local action in pharynx.
5. **Glycerites:** Viscous, hygroscopic solution of medicament applied externally.
6. **Sprays:** Aqueous or non-aqueous monophasic liquids spraying in throat/nose.
7. **Ear drops:** Solution, suspension, emulsion remove excessive cerumen (ear wax).
8. **Liniment:** Solution or emulsion in aqueous/oily vehicle massage to unbroken skin. "FOR EXTERNAL USE ONLY".

"USED FOR SUBLINGUAL / ORAL USE".

11. **Lozenges:** Hard and intend
12. **Pills:** Small spherical for internal use.
    Veterinary use pills are called as "BOLUS".
13. **Poultices:** Pasty preparation applied hot onto the skin, to reduce inflammation.
14. **Gargles:** "NOT TO BE SWALLOWED IN LARGE AMOUNT".

INCOMPATIBILITIES

Type of incompatibility	Examples
Physical	Insolubility, Liquefaction, Immiscibility
Chemical	Precipitation by change in pH, chemical reaction, redox reaction, hydrolysis, effervescence
Incompatibility with container	Leaching, Sorption, Softening of container
Therapeutic	Error in prescription writing, pharmacokinetic and pharmacodynamic interaction, contraindications

PRESCRIPTION

Parts of prescription	Description
Superscription	Symbol Rx
Inscription	Formula / Dosage form
Subscription	Direction to Pharmacist
Signatura	Direction to patient

Primary Emulsion Oil:Water:Gum Ratio	
Fixed oil	4:2:1
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Suppositories:

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Oleaginous base	Theobroma oil/ Cocoa butter, Palm kernel oil
Emulsifying base	Witepsol

Macrogols = PEG = POE

Macrogol 200 = PEG 4

Creep test - used to test the viscosity (rheological properties) of Creams and Ointments.

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