UNIT-I
PREFORMULATION STUDIES

Definition:

Preformulation is the first step in the rational development of dosages form of a drug substance/new chemical entity. It can be defined as an investigation of physical and chemical properties of the drug substances alone and when combined with excipients, in order to develop a stable, safe, effective and affordable dosage form.

Objectives:

- To develop the elegant dosage forms (stable, safe, effective and affordable).
- It is important to have an understanding of the physical description of a drug substance before dosage form development.
- It is first step in rational development of a dosage form of a drug substance before dosage form development.
- It generates useful information to the formulator to design an optimum drug delivery system.

Goals:

- To establish the physico-chemical parameters of new drug substance.
- To establish the physical characteristics.
- To establish the kinetic rate profile.
- To establish the compatibility with the common excipient.

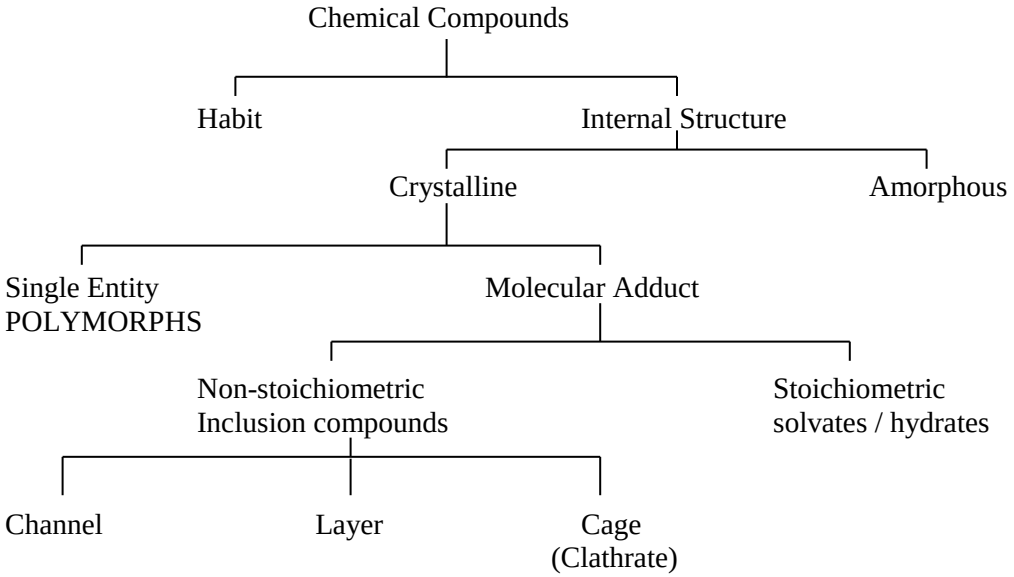
Principal areas of Preformulation

SL NO	PRINCIPAL AREAS	EXAMPLES
1	BULK CHARACTERIZATION	Crystallinity and polymorphism Hygroscopicity Fine particle characterization Powder flow
2	SOLUBILITY ANALYSIS	Ionization constant – pKa pH solubility profile Common ion effect – K_{SP}. Thermal effects Solubilization Partition coefficient Dissolution
3	STABILITY ANALYSIS	Stability in toxicology formulation Solution stability pH stability profile Solid state stability Bulk stability Compatibility

1. BULK CHARACTERIZATION

When a drug molecule is discovered all the solid-forms are hardly identified. So during bulk characterization the following characteristics are studied.

(i) Crystallinity and polymorphism



- Flow ability of powder and chemical stability depends on the habit and internal structure of a drug.

Habit is the description of the outer appearance of a crystal. A single internal-structure for a compound can have several different habits, depending on the environment for growing crystals. Different habits of crystals are given below.

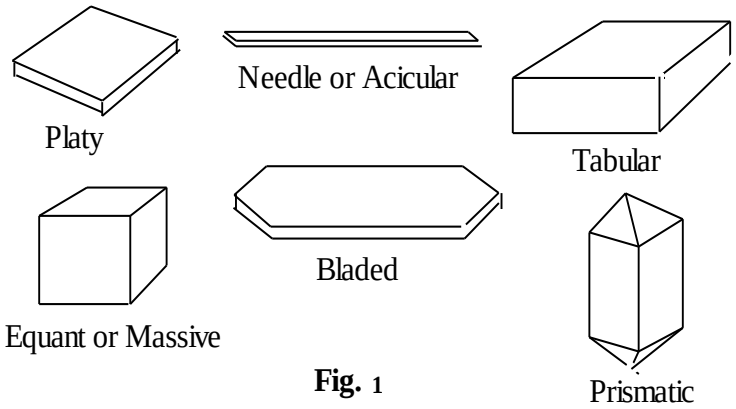


Fig. 1

Internal Structure

Crystalline state

In this state of matter atoms or molecules are arranged in highly ordered form and is associated with three-dimensional periodicity.

Amorphous forms

In this forms the solids do not have any fixed internal structure. They have atoms or molecules randomly placed as in a liquid.

e.g. Amorphous Novobiocin

Difference between crystalline and amorphous form

Crystalline forms	Amorphous forms
(i) Fixed internal structure (ii) More stable than its amorphous forms. (iii) More stable than its amorphous forms. (iv) Lesser solubility than its amorphous form. (v) Lesser tendency to change its form during storage.	(i) Do not have any fixed internal structure (ii) Higher thermodynamic energy than its crystalline form. (iii) Less stable than its crystalline forms. (iv) Greater solubility than its crystalline forms. (v) Tend to revert to more stable forms during storage.

Polymorphs

When a substance exists in more than one crystalline form, the various forms are called Polymorphs and the phenomenon as polymorphism.

e.g. Chloramphenicol palmitate has three polymorphs A, B and C .

Depending on their relative stability, one of the several polymorphic forms will be physically more stable than the others. Such a stable polymorph represents the lowest energy state, has highest melting point and least solubility. The representing polymorphs are called metastable forms which represent higher energy state; the metastable forms have a thermodynamic tendency to convert to the stable form. A metastable form cannot be called unstable because if it is kept dry, it will remain stable for years.

Molecular Adducts

During the process of crystallization, some compounds have a tendency to trap the solvent molecules.

1. Non-Stoichiometric inclusion compounds (or adducts)

In these crystals solvent molecules are entrapped within the crystal lattice and the number of solvent molecules are not included in stoichiometric number. Depending on the shape they are of three types :-

(1) ***Channel***

When the crystal contains continuous channels in which the solvent molecule can be included. e.g . Urea forms channel.

(2) ***Layers***:- Here solvent molecules are entrapped in between layers of crystals.

(3) ***Clathrates***(**Cage**):- Solvent molecules are entrapped within the cavity of the crystal from all sides.

2. Stoichiometric inclusion compounds (or stoichiometric adducts)

This molecular complex has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice and has stoichiometric number of solvent molecules complexed.

When the incorporated solvent is water, the complex is called hydrates and when the solvent is other than water, the complex is called solvates. Depending on the ratio of water molecules within a complex the following nomenclature is followed.

(i) *Anhydrous* : 1 mole compound + 0 mole water
(ii) *Hemihydrate*: 1 mole compound + ½ mole water
(iii) *Monohydrate:* 1 mole compound + 1 mole water
(iv) *Dihydrate* : 1 mole compound + 2 moles water

Properties of solvates / hydrates

(i) Generally, the anhydrous form of a drug has greater aqueous solubility than its hydrates. This is because the hydrates are already in equilibrium with water and therefore have less demand for water. e.g. anhydrous forms of theophyline and ampicillin have higher aqueous solubility than the hydrates.
(ii) Non aqueous solvates have greater aqueous solubility than the non-solvates. E.g. chloroform solvates of griseofulvin are more water soluble than their nonsolvate forms.

ANALYTICAL METHODS FOR CHARACTERIZATION OF SOLID FORMS

Methods of studying solid forms are listed as below:

Method	Material required per sample
Microscopy	1 mg
Hot stage microscopy	1 mg
Differential Scanning Calorimetry (DSC)	2 – 5 mg
Differential Thermal Analysis (DTA)	2 – 5 mg
Thermogravimetric Analysis	10 mg
Infrared Spectroscopy	2 – 20 mg
X-ray Powder Diffraction	500 mg
Scanning Electron Microscopy	2 mg
Dissolution / Solubility Analysis	mg to gm

Microscopy

In this type of microscope light passes through cross-polarizing filters.

Amorphous substances (e.g. super-cooled glass and non-crystalline organic compounds or substances with cubic crystal lattices e.g. NaCl) have single refractive index. Through this type of microscope the amorphous substances do not transmit light, and they appear black. They are called isotropic substances.

Hot-stage microscopy

In this case, the polarizing microscope is fitted with a hot stage to investigate polymorphism, melting points, transition temperatures and rates of transition at controlled rates.

It facilitates in explaining the thermal behavior of a substance from the DSC and TGA curves.

[N.B. A problem often encountered during thermal microscopy is that organic molecules can degrade during the melting process, and recrystallization of the melt may not occur, because of the presence of contaminant degradation products.]

Thermal Analysis

Differential Thermal Analysis

In DTA instrument a record is produced where temperature difference (ΔT) (between the sample and reference material) is plotted against temperature (T) when two specimens are subjected to an identically controlled temperature regime.

The reference material is alumina, keiselguhr.

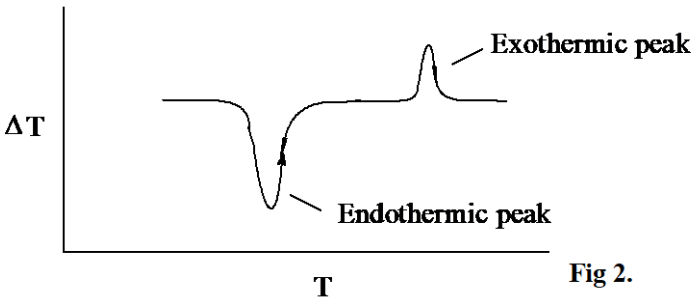


Fig 2.

Differential Scanning Calorimetry

In DSC method the difference in energy inputs (ΔH) into a sample and reference material is measured as a function of temperature as the specimens are subjected to a identically controlled temperature programme.

Samples that may be studied by DSC or DTA are:

Powders, fibres, single crystals, polymer films, semi-solids or liquids.

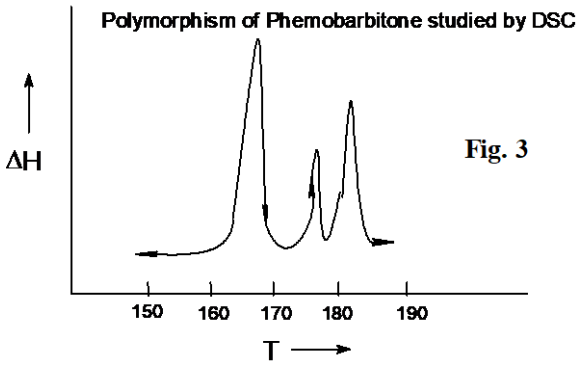


Fig. 3

Applications of DTA / DSC in preformulation studies

1. To determine the purity of a sample
2. To determine the number of polymorphs and to determine the ratio of each polymorph.
3. To determine the heat of solvation
4. To determine the thermal degradation of a drug or excipients.
5. To determine the glass-transition temperature (t_g) of a polymer.

Thermogravimetric Analysis (TGA)

TGA measures the changes in sample weight as a function of time (isothermal changes) or temperature.

Application of TGA in preformulation study

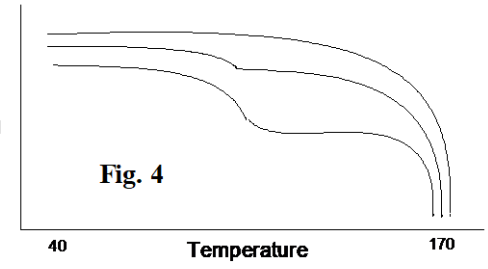


Fig. 4

1. Desolvation and decomposition processes are monitored.
2. Comparing TGA and DSC data recorded under identical conditions can greatly help in the explanation of the thermal process.

TGA and DSC analysis of an acetate salt of an organic amine that has two crystalline forms, anhydrous and dihydrate are shown above. Anhydrous / dihydrate (10:1) mixture was prepared by dry blending. Heating rate was 5^0C/min.

From DSC curve, it is evident that the dihydrate form loses two molecules of water via an endothermic transition between 70^0C and 90^0C. The second endotherm at 155^0C corresponds to melting process.

From TA curve, it is evident that at 70 – 90^0C weight-loss was due to the loss two molecules of water and the weight loss at 155^0C was due to vaporization of acetic acid and decomposition.

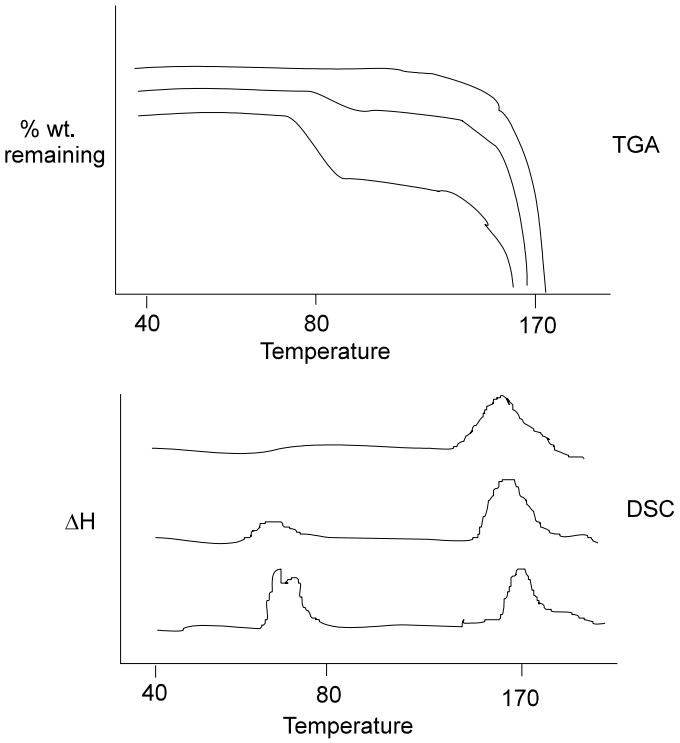


Fig. 5

X-RAY POWDER DIFFRACTION

When a X-ray beam falls on a powder the beam is diffracted. This diffraction in found only in case of crystalline powder. Amorphous forms do not show X-ray diffraction.

Uses:

(i) Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound. So in a mixture different crystalline forms can be analyzed using normalized intensities at specific angles.

(ii) Identification of crystalline materials by using their diffraction pattern as a 'finger print'. First, the powder diffraction photograph or diffractometer trace are taken and matched with a standard photograph. All the lines and peaks must match in position and relative intensity.

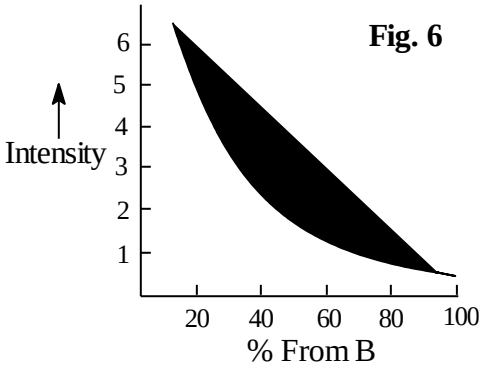


Fig. 6

HYGROSCOPICITY

Definition: Many pharmaceutical materials have a tendency to adsorb atmospheric moisture (especially water-soluble salt forms). They are called hygroscopic materials and this phenomenon is known as hygroscopicity.

Equilibrium moisture content depends upon:

(i) the atmospheric humidity
(ii) temperature
(iii) surface area
(iv) exposure time
(v) mechanism of moisture uptake.

Deliquescent materials:

They absorb sufficient amount of moisture and dissolve completely in it. (e.g. anhydrous calcium chloride).

Tests of hygroscopicity

Procedure
Bulk drug samples are placed in open containers with thin powder bed to assure maximum atmospheric exposure. These samples are then exposed to a range of controlled relative humidity (RH) environments prepared with saturated aqueous salt solutions.

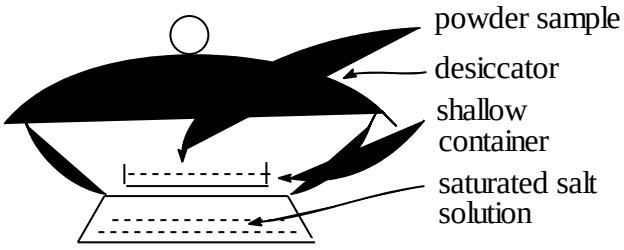


Fig. 7

The amount of moisture adsorbed can be determined by the following methods:

(i) Gravimetry
(ii) Thermogravimetric analysis (TGA)
(iii) Karl-Fischer titration (KF-titration)
(iv) Gas chromatography (GC)

Time of monitoring depends on the purpose:

(i) For the purpose of '*handling'* data points from 0 to 24 hours are taken
(ii) For the purpose of '*storage*' data points from 0 to 12 weeks are taken.

Significance of hygroscopicity test

(a)

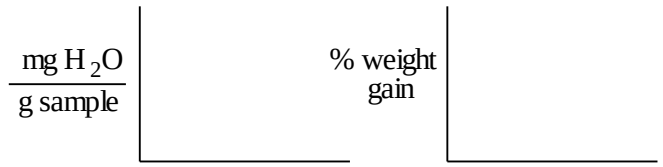


Fig. 8

To decide special handling procedure (with respect to time).

(b)

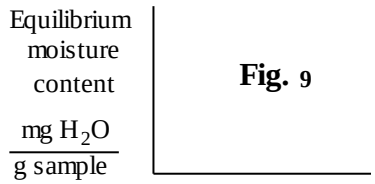


Fig. 9

To decide
(i) the storage condition i.e. at low humidity environment.
(ii) special packaging – e.g. with desiccant.

(c) Moisture level in a powder sample may affect the flowability and compactibility which, are important factors during tableting and capsule filling.

(d) After adsorption of moisture, if hydrates are formed then solubility of that powder may change affecting the dissolution characteristics of the material.
(e) Moisture may degrade some materials. So humidity of a material must be controlled.

FINE PARTICLE CHARACTERIZATION

Parameters those are measured:

(i) particle size and size-distribution
(ii) shape of the particle
(iii) surface morphology of the particles

Instrumental methods of particle size characterization

(i) Light microscope

First a standard graticule (BS 3625) is standardized with a stage micrometer. Then snall number of particles are spread over a glass slide and placed on the stage of the microscope. Particles

are focussed and the particle diameters are measured. Several hundred particles are measured and reported as a histogram.
Disadvantage: The procedure is time consuming.

(ii) Stream counting devices

Examples: (a) Coulter counter – electrical sensing zone method
(b) HIAC – counter – optical sensing zone
(c) Malvern particle & droplet sizer – Laser diffraction method.

Procedure:

Samples prepared for analysis are dispersed in a conducting medium (e.g. saline) with the help of ultrasound and a few drops of surfactant (to disperse the particles uniformly). A known volume (0.5 to 2 ml) of this suspension is then drawn into a tube through a small aperture (0.4 to 800 μm diameter) across which a voltage is applied.
As each particle passes through the hole, it is counted and sized according to the resistance generated by displacing that particle's volume of conducting medium.
Size distribution is reported as histogram.

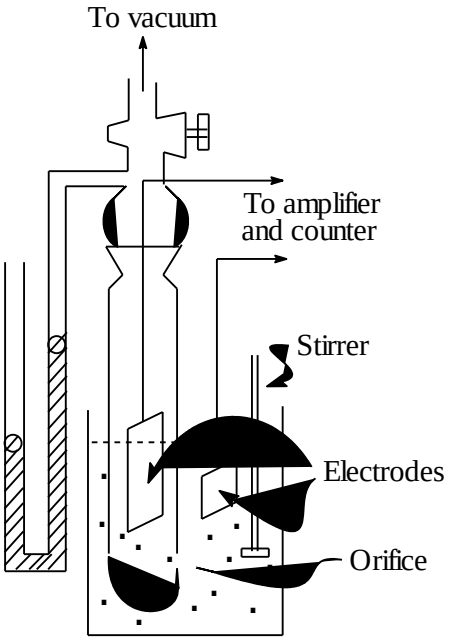


Fig. 10 Coulter counter

(iii) Sieve analysis

A powder sample is passed through a standard sieve set. The particle size is plotted against % weight retained on each sieve.
Use: This method is used generally for large samples.

Instrumental method for determination of specific surface area

Brunauer, Emmett and Teller (BET) nitrogen adsorption method:

A layer of nitrogen molecules is adsorbed to the sample surface at -196^0C. Once the surface is saturated, the sample is heated to room temperature, the nitrogen gas is desorbed, and its volume is measured and converted to the number of adsorbed molecules via the gas law. Since each N_2 molecule occupies an ara of 16 A^2, one may readily compute the surface area per gram of each pre-weighed sample.

Instrumental method for characterization of surface morphology

The scanning electron microscope creates the magnified images by using electrons instead of light waves. The images are black and white.

Procedure

- Biological materials are dried in a special way that prevents them from shrinking.
- Since SEM illuminates them with electrons, they are made conductive by coating with a very thin layer of gold by a machine called *sputter-coater*.
- The sample is placed inside the microscope's vacuum column through an airtight door.
- After the air is pumped out of the column, an electron gun emits a beam of high-energy electrons. This beam travels downward through a series of magnetic lenses designed to focus the electrons to a very fine spot.

- Near the bottom, a set of scanning coils moves the focussed beam back and forth across the specimen, row by row.
- As the electron beam hits each spot on the sample, secondary electrons are knocked loose from its surface. A detector counts these electrons and sends the signals to an amplifier.
- The final image is built up from the number of electrons emitted from each spot on the sample.

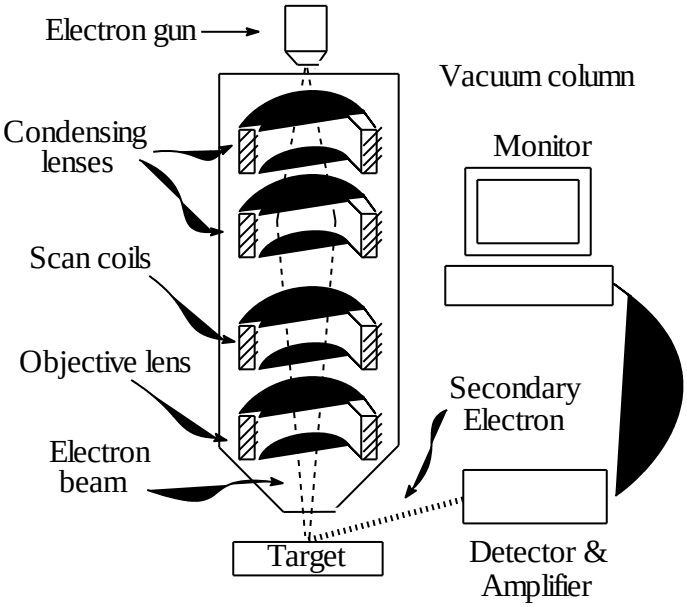


Fig. 11 Scanning Electron Microscope

BULK DENSITY

Apparent Bulk Density (g/cm^3)

Bulk drug powder is sieved through 40 mesh screen. Weight is taken and poured into a graduated cylinder via a large funnel. The volume is called *bulk volume*.

$$Apparent\ Bulk\ \ Density = \frac{Weight\ of\ the\ powder}{Bulk\ Volume}$$

Tapped density (g/cm^3)

Bulk powder is sieved through 40 mesh screen. Weight is taken and poured into a graduated cylinder. The cylinder is tapped 1000 times on a mechanical tapper apparatus. The volume reached a minimum – called *tapped volume*.

$$Tapped\ density = \frac{Weight\ \ of\ \ the\ \ powder}{Tapped\ \ volume}$$

True density (g/cm^3)

Solvents of varying densities are selected in which the powder sample is insoluble. Small quantity of surfactant may be mixed with the solvent mixture to enhance wetting and pore penetration. After vigorous agitation, the samples are centrifuged briefly and then left to stand undisturbed until floatation or settling has reached equilibrium.

The samples that remains suspended (i.e. neither suspended not floated) is taken. So the true density of the powder are equal. So the true density of the powder is the density of that solvent. The density of that solvent is determined accurately with a pycnometer.

Source of variation of bulk density

Method of crystallization, milling, formulation.

Methods of correction

By milling, slugging or formulation.

Significance

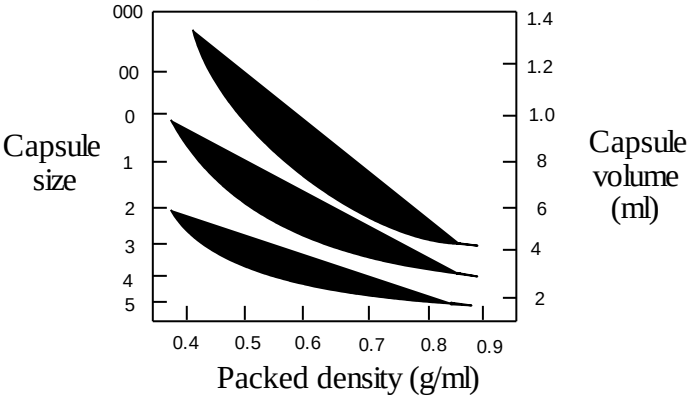
(i) Bulk density

Bulk density is required during the selection of capsule size for a high dose drug.

In case of low dose drug mixing with excipients is a problem if the bulk densities of the drug and excipients have large difference.

(ii) Tapped density

Fig. 12



Knowing the dose and tapped density of the formulation, the capsule size can be determined.

(iii) True density

From bulk density and true density of powder, the void volume or porosity can be measured.

$$Void\ volume = \left(\frac{m}{\rho_{bulk}} - \frac{m}{\rho_{ture}}\right) = m\left(\frac{1}{\rho_{bulk}} - \frac{1}{\rho_{true}}\right)$$

$$Porosity = \frac{Void\ volume}{Bulk\ volume} = \frac{m\left(\frac{1}{\rho_{bulk}} - \frac{1}{\rho_{true}}\right)}{\frac{m}{\rho_{bulk}}} = 1 - \frac{\rho_{bulk}}{\rho_{true}}$$

Powder flow properties

Powder flow properties depends on

(i) particle size
(ii) density
(iii) shape
(iv) electrostatic charge and adsorbed moisture

that may arise from processing or formulation.

A free-flowing powder may become cohesive during development. This problem may be solved by any of the following ways.

(i) by granulation
(ii) by densification via slugging
(iii) by filling special auger feed equipment (in case of powder)
(iv) by changing the formulation.

Procedure

For free flowing powder

A simple flow rate apparatus consisting of a grounded metal tube from which drug flows through an orifice onto an electronic balance, which is connected to a strip chart recorder. Several flow rate (g/sec) determinations at various orifice sizes (1/8 to ½ inch) should be carried out.

The grater the standard deviation between multiple flow rate measurements, the greater will be the weight variation of the product (tablets or capsules).

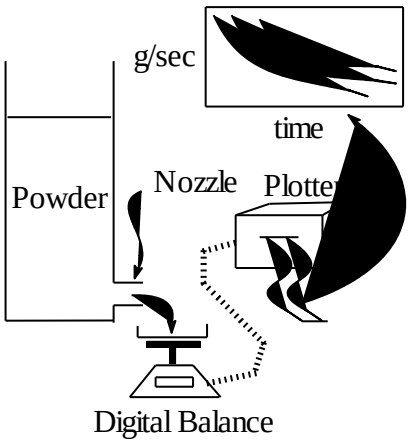
Compressibility :-

$$\%\,compressibility = \frac{\rho_t - \rho_0}{\rho_t} x100$$

ρ_t = tapped bulk density

ρ_0 = Initial bulk density

Fig. 13



Solubility Analysis

Determination of equilibrium solubility of a drug

The drug is dispersed in a solvent. The suspension is agitated at a constant temperature.

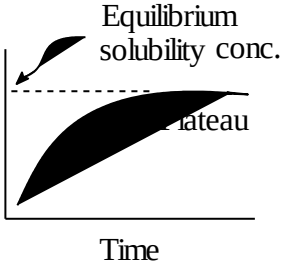


Fig. 14

Samples of the suspension are withdrawn as a function of time, clarified by centrifugation, and assayed to establish a plateau concentration.

Solvents taken

(i) 0.9% NaCl at room temperature
(ii) 0.01 M HCl at RT
(iii) 0.1 M HCl at RT
(iv) 0.1 M NaOH at RT
(v) At pH 7.4 buffer at 37^0C

Drug concentration is determined by the following analytical methods

(i) HPLC
(ii) UV –Spectroscopy
(iii) Fluorescence Spectroscopy
(iv) Gas Chromatography

Solubility depends on

(i) pH
(ii) Temperature
(iii) Ionic strength
(iv) Buffer concentration

Significance

(i) A drug for oral administrative should be examined for solubility in an isotonic saline solution and acidic pH. This solubility data may provide the dissolution profile invivo.
(ii) Solubility in various mediums is useful in developing suspension or solution toxicologic and pharmacologic studies.
(iii) Solubility studies identify those drugs with a potential for bioavailability problems. E.g. Drug having limited solubility (7 %) in the fluids of GIT often exhibit poor or erratic absorption unless dosage forms are tailored for the drug.

pK_a Determination

When a weakly acidic or basic drug partially ionizes in GI fluid, generally, the unionized molecules are absorbed quickly.
Handerson-Hasselbach equation provides an estimate of the ionized and unionized drug concentration at a particular pH.
For acidic drug : e.g.

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

Weak acid — Strong base

$$pH = pKa + \log \frac{[ionized]}{[unionized]} = pKa + \log \frac{[A^-]}{[HA]} = pKa + \log \frac{[base]}{[acid]}$$

For basic compounds e.g.

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O$$

Weak base — Strong acid

$$pH = pKb + \log \frac{[unionized]}{[ionized]} = pKa + \log \frac{[B]}{[BH^+]} = pKa + \log \frac{[base]}{[acid]}$$

Drug	Stomach PH 1.5	Plasma PH = 7.4	Duodenum PH = 5.0
Weak acid e.g. Ibuprofen pKa = 4.4	[HA] = 100 ⇌ ⇅ $[A^-] = 0.13$ [Total] = 100.13	[HA] = 100 ⇌ ⇅ $[A^-] = 100{,}000$ [Total] = 100,100	[HA] = 100 ⇅ $[A^-] = 398.1$ [Total] = 498.1
Weak base e.g. Nitrazepam pKa = 3.2	[B] = 100 ⇌ ⇅ $[BH^+] = 5012$ [Total] = 5112	[B] = 100 ⇌ ⇅ $[BH^+] = 0.006$ [Total] = 100.006	[B] = 100 ⇅ $[BH^+] = 1.6$ [Total] = 101.6

Method of determination of pKa of a drug

(i) Detection of spectral shifts by UV or visible spectroscopy at various pH.
Advantage: Dilute aqueous solutions can be analyzed by this method.
(ii) Potentiometric titration
Advantage: Maximum sensitivity for compounds with pKa in the range of 3 to 10.
Disadvantage: This method is unsuccessful for candidates where precipitation of the unionized forms occurs during titration. To prevent precipitation a co-solvent e.g. methanol or dimethylsulfoxide (DMSO) can be incorporated.
(iii) Variation of solubility at various pH.

Effect of temperature on stability
Heat of solution, ΔH_S represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent.

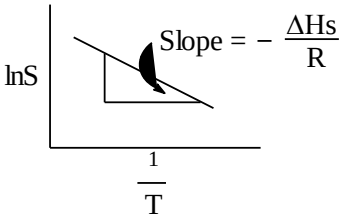
Significance
- Most commonly, the solubility process is endothermic, e.g. non-electrolytes, unionized forms of weak acids and bases ⇒ ΔH is positive ⇒ Solubility increases if temperature increases.
- Solutes that are ionized when dissolved releases heat

⇒ the process is exothermic ⇒ ΔH_S is negative ⇒ Solubility increases at lower temperature.

Determination of ΔH_S.

The working equation $\ln S = -\frac{\Delta H_S}{R}\left(\frac{1}{T}\right) + C$ where, S = molar solubility of the drug at T^0K and R = gas constant

S is detemined at 5^0C, 25^0C, 37^0C and 50^0C.
ΔH_S = – Slope x R



Solubilization
For drug candidates with poor water solubility, preformulation studies should include limited experiments to identify the possible mechanisms for solubilization.
Means of increasing the solubility are:
(i) Addition of a cosolvent to the aqueous system e.g. ethanol, propylene glycol and glycerin.
MOA: These co-solvents disrupt the hydrophobic interactions of water at the non-polar solute / water interfaces.
(ii) Solubilization in micellar solutions such as 0.01 M Tween 20 solution.

(iii) Solubilization by forming molecular complexes e.g. benzoic acid forms complex with caffeine.

Partition coefficient

Partition coefficient is defined, as the ratio of un-ionized drug concentrations between the organic and aqueous phases, at equilibrium.

$$K_{O/W} = \left[\frac{C_{oil}}{C_{water}} \right] \ at\ equilibrium$$ Generally, octanol and chloroform are taken as the oil phase.

Significance

Drug molecules having higher $K_{O/W}$ will cross the lipid cell membrane.

Dissolution

The dissolution rate of a drug substance in which surface area is constant during disintegration is described by the modified Noyes-Whitney equation.

$$\frac{dc}{dt} = \frac{DA}{hV}(C_S - C)$$

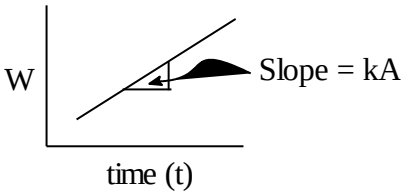
where, D = diffusion coefficient of the drug in the dissolution medium
h = thickness of the diffusion layer at the solid/liquid interface
A = surface area of drug exposed to dissolution medium.
V = volume of the medium
C_S = Concentration of saturated solution of the solute in the dissolution medium at the experimental temperature.
C = Concentration of drug in solution at time t.

When A = constant and $C_S >> C$ the equation can be rearranged to

$$\frac{dC}{dt} = \frac{DA}{hV} C_S \quad or, \frac{V\,dC}{dt} = \frac{DA}{h} C_S \quad or, W = k\,A\,t$$ where, $k = \frac{D}{h}$

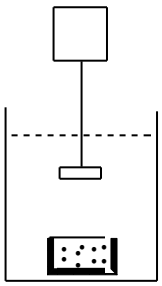
where, W = weight (mg) of drug dissolved at time t

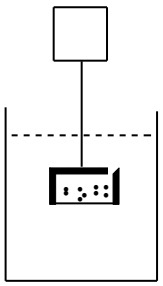
k = intrinsic dissolution rate constant $\left(\frac{mg}{\min\ cm^2} \right)$



Determination of k

- Pure drug powder is punched in a die and punch apparatus to give a uniform cylindrical shape. The tablet is covered with wax in all sides. One circular face is exposed to the dissolution medium. Thus, as dissolution proceeds, the area, A, remains constant.
- Time to time dissolution medium is taken out and fresh medium added to the chamber.
- With two types of assembly, the experiments can be carried out.


Static disc dissolution apparatus


Rotating disc dissolution apparatus

Stability analysis

Preformulation stability studies are the first quantitative assessment of chemical stability of a new drug. This may involve

1. Stability study in toxicology formulation
2. Stability study in solution state
3. Stability study in solid state.

Stability study in toxicology formulation

A new drug is administered to animals through oral route either by

(i) mixing the drug in the feed
(ii) in the form of solution
(iii) in the form of suspension in aqueous vehicle

- Feed may contain water, vitamin, minerals (metal ions), enzymes and different functional groups that may severely reduce the stability of the new drug. So stability study is should be carried out in the feed and at laboratory temperature.
- For solution and suspension, the chemical stability at different temperature and pH should be checked.
- For suspension-state the drug suspension is occasionally shaken to check dispersibility.

Solution stability

Objective: Identification of conditions necessary to form a stable solution.

Stability of a new drug may depend on:

(i) pH	(ii) ionic strength	(iii) co-solvent
(iv) light	(v) temperature	(vi) oxygen.

pH stability study

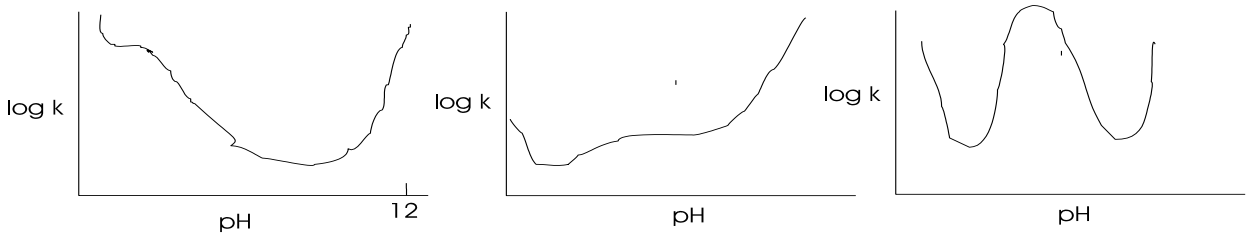
(i) Experiiments to confirm decay at the extremes of pH and temperature. Three stability studies are carried out at the following conditions

(a) 0.1N HCl solution at 90^0C
(b) Solution in water at 90^0C
(c) 0.1 N NaOH solution at 90^0C

These experiments are intentionally done to confirm the assay specificity and for maximum rates of degradation.

(ii) Now aqueous buffers are used to produce solutions with wide range of pH values but with constant levels of drug concentration, co-solvent and ionic strength.

All the rate constants (k) at a single temperature are then plotted as a function of pH.



Ampicillin degradation | Hydrolysis of Aspirin | Hydrolysis of Hydrochlorthiazide

(ii) *Ionic strength*

Since most pharmaceutical solutions are intended for parenteral routes of administration, the pH-stability studies should be carried out at a constant ionic strength that is compatible with body fluids. The ionic strength (μ) of an isotonic 0.9%w/v sodium chloride solution is 0.15.

Ionic strength for any buffer solution can be calculated by

$$\mu = \frac{1}{2}\sum m_i Z_i^2$$

where, m_i = molar concentration of the ion
Z_i = valency of that ion

For computing, μ all the ionic species of the buffer solution and drugs are also taken into calculation.

(iii) *Co-solvents*

Some drugs are not sufficiently soluble to give concentrations of analytical sensitivity. In those cases co-solvents may be used. However, presence of co-solvents will influence the rate constant. Hence, k values at different co-solvent concentrations are determined and plotted against % of co-solvent. Finally, the line is extrapolated to 0% co-solvent to produce the actual k value (i.e. in pure solvent).

(iv) *Light*

Drug solutions are kept in

(a) clear glass ampoules

(b) amber color glass container
(c) yellow-green color glass container
(d) container stored in card-board package or wrapped in aluminium foil – this one acts as the control.

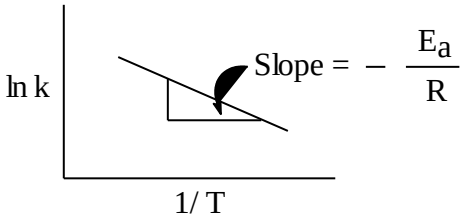
Now the stability studies are carried out in the above containers.

(v) *Temperature*

The rate constant (k) of degradation reaction of a drug varies with temperature according to Arrhenius equation.

$$k = Ae^{-\frac{E_a}{RT}} \qquad \text{or, } \ln = \ln A - \frac{E_a}{R}\left(\frac{1}{T}\right)$$

where, k = rate constant
A = frequency factor
E_a = energy of activation
R = gas constant
T = absolute temperature



Procedure

Buffer solutions were prepared and kept at different temperatures. Rate constants are determined at each temperature and the ln k value is plotted against (1/T)).

Inference

- The relationship is linear ⇒ a constant decay mechanism over the temperature range has occurred.
- A broken or non-linear relationship ⇒ a change in the rate-limiting step of the reaction or change in decay mechanism.

Uses

Shelf life of the drug may be calculated.

e.g.

Time	Concentration of drug remaining
0	100 %
$t_{10\%}$	90%

Therefore, $\ln C = \ln C_0 - k_1 t$

$\text{Ln } C/C_0 = -k_1 t$

or, $\ln \frac{90}{100} = -k_1 t_{10\%}$ or, $t_{10\%} = \frac{\ln 0.90}{-k_1} = \frac{0.105}{k_1}$

where, $t_{10\%}$ = time for 10% decay to occur if the reaction follows 1st order kinetics

Conclusion

If the drug is sufficiently stable, liquid formulation development may be started at once.
If the drug is unstable, further investigations may be necessary.

Solid state stability

Objectives

Identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation.

Characteristics

Solid state reactions are much slower, so the rate of appearance of decay product is measured (not the amount of drug remaining unchanged).

- To determine the mechanism of degradation thin layer chromatography (TLC), fluorescence or UV / Visible spectroscopy may be required.
- To study polymorphic changes DSC or IR-spectroscopy is required.
- In case of surface discoloration due to oxidation or reaction with excipients, surface reflectance equipment may be used.

A sample scheme for determining the bulk stability profile of a new drug:

Storage condition	*4 weeks*	*8 weeks*	*12 weeks*
5^0C – Refrigerator			
22^0C – Room Temperature			
37^0C – Ambient humidity			
37^0C / 75% RH (Relative Humidity)			
Light box			
Clear box			
Amber glass			
Yellow-Green glass			
No exposure (Control :- Card-board box or wrapped with aluminium foil)			
50^0C – Ambient Humidity			
– O_2 Head Space			
– N_2 Head Space			
70^0C – Ambient Humidity			
90^0C – Ambient Humidity			

Procedure

1. Weighed samples are placed in open screw-capped vials are exposed to a variety of temperatures, humidities an dlight intnesities. After the desired time samples are taken out and measured by HPLC (5 – 10 mg), DSC (10 to 50mg), IR (2 to 20mg).
2. To test for surface oxidation samples are stored in large (25ml) vials for injection capped with Teflon-lined rubber stopper. The stoppers are penetrated with needles and the headspace is flooded with the desired gas. The resulting needle holes are sealed with wax to prevent degassing.
3. After fixed time those samples are removed and analyzed.

Drug-excipient stability profile

Hypothetical dosage forms are prepared with various excipients and are exposed to various conditions to study the interactions of drug and excipients.

UNIT-II

Design of Controlled Drug Delivery System

An ***ideal drug delivery system*** should deliver the drug at a rate dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery –

Spatial delivery *of drug* which relates to targeting a drug to a specific organ or tissue, *and*

Temporal delivery *of drug* which refers to controlling the rate or specific time of drug delivery to the target tissue.

An appropriately designed controlled-release drug-delivery system (***CRDDS***) can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required.

The several advantages of a controlled drug delivery system over a conventional dosage form are—

1. Improved patient convenience and compliance due to less frequent drug administration.
2. Reduction in fluctuation in steady-state levels and therefore –
   - Better control of disease condition, and
   - Reduced intensity of local or systemic side-effects.
3. Increased safety margin of high potency drugs due to better control of plasma levels.
4. Maximum utilization of drug enabling reduction in total amount of dose administered.
5. Reduction in health care costs through –
   - Improved therapy
   - Shorter treatment period
   - Lower frequency of dosing, and
   - Reduction in personnel time to dispense, administer and monitor patients.

Disadvantages of controlled-release dosage forms include —

1. Decreased systemic availability in comparison to immediate-release conventional dosage forms. This may be due to –
   - Incomplete release
   - Increased first-pass metabolism

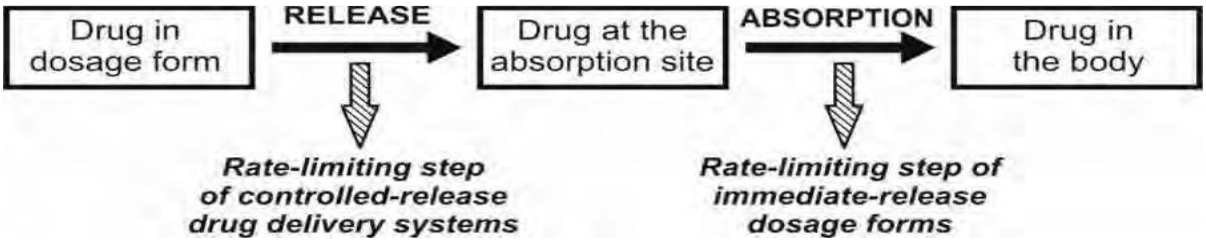
Increased instability

- Insufficient residence time for complete release
- Site-specific absorption
- pH-dependent solubility.

2. Poor *in vitro–in vivo* correlation.
3. Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
4. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

5. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
6. Higher cost of formulation.

FACTORS IN THE DESIGN OF CONTROLLED-RELEASE DRUG DELIVERY SYSTEMS



Scheme representing the rate-limiting step in the design of controlled-release drug delivery system

A. Biopharmaceutic Characteristics of a Drug in the Design of CRDDS

The performance of a drug presented as a controlled-release system depends upon its:
1. Release from the formulation.
2. Movement within the body during its passage to the site of action.

The former depends upon the fabrication of the formulation and the physicochemical properties of the drug while the latter element is dependent upon pharmacokinetics of drug. In comparison to conventional dosage form where the rate-limiting step in drug availability is usually absorption through the biomembrane, the rate-determining step in the availability of a drug from controlled delivery system is the rate of release of drug from the dosage form which is much smaller than the intrinsic absorption rate for the drug.

The desired Biopharmaceutic properties of a drug to be used in a controlled-release drug delivery system are discussed below
.
1. Molecular Weight of the Drug: Lower the molecular weight, faster and more complete the absorption. For drugs absorbed by pore transport mechanism, the molecular size threshold is 150 Daltons for spherical compounds and 400 Daltons for linear compounds. However, more than 95% of drugs are absorbed by passive diffusion.
Diffusivity, *defined as the ability of a drug to diffuse through the membranes*, is inversely related to molecular size. The upper limit of drug molecular size for passive diffusion is 600

Daltons. Drugs with large molecular size are poor candidates for oral controlled-release systems e.g. peptides and proteins.

2. Aqueous Solubility of the Drug: A drug with good aqueous solubility, especially if pH-independent, serves as a good candidate for controlled-release dosage forms e.g. pentoxifylline. The lower limit of solubility of a drug to be formulated as CRDDS is 0.1mg/ml. Drugs with pH-dependent aqueous solubility e.g. phenytoin, or drugs with solubility in non-aqueous solvents e.g. steroids, are suitable for parenteral (e.g. i.m depots) controlled-release dosage forms; the drug precipitates at the injection site and thus, its release is slowed down due to change in pH or contact with aqueous body fluids. Solubility of drug can limit the choice of mechanism to be employed in CRDDS, for example, diffusional systems are not suitable for poorly soluble drugs. Absorption of poorly soluble drugs is dissolution rate-limited which means that the controlled-release device does not control the absorption process; hence, they are poor candidates for such systems.

3. Apparent Partition Coefficient/Lipophilicity of the Drug: Greater the apparent partition coefficient of a drug, greater its lipophilicity and thus, greater is its rate and extent of absorption. Such drugs have increased tendency to cross even the more selective barriers like BBB. The apparent volume of distribution of such drugs also increases due to increased partitioning into the fatty tissues and since the blood flow rate to such tissues is always lower than that to an aqueous tissue like liver, they may exhibit characteristics of models having two or more compartments. The parameter is also important in determining the release rate of a drug from lipophilic matrix or device.

4. Drug pKa and Ionisation at Physiological pH: The pKa range for acidic drugs whose ionisation is pH-sensitive is 3.0 to 7.5 and that for basic drugs is 7.0 to 11.0. For optimum passive absorption, the drugs should be non-ionised at that site at least to an extent 0.1 to 5%. Drugs existing largely in ionised forms are poor candidates for controlled delivery e.g. hexamethonium.

5. Drug Permeability: The *three major drug characteristics* that determine the permeability of drugs for passive transport across intestinal epithelium are –

Lipophilicity, expressed as log P.

Polarity of drug which is measured by the number of H-bond acceptors and number of H-bond donors on the drug molecule.

Molecular size.

6. Drug Stability: Drugs unstable in GI environment cannot be administered as oral controlled-release formulation because of bioavailability problems e.g. nitroglycerine. A different route of administration should then be selected such as the transdermal route. Drugs unstable in gastric pH, e.g. propantheline can be designed for sustained delivery in intestine

with limited or no delivery in stomach. On the other hand, a drug unstable in intestine, e.g. probanthine, can be formulated as gastroretentive dosage form.

7. Mechanism and Site of Absorption: Drugs absorbed by carrier-mediated transport processes and those absorbed through a *window* are poor candidates for controlled-release systems e.g. several B vitamins.

8. Biopharmaceutic Aspects of Route of Administration: Oral and parenterals (i.m.) routes are the most popular followed by transdermal application. Routes of minor importance in controlled drug delivery are buccal/sublingual, rectal, nasal, ocular, pulmonary, vaginal and intrauterinal. The features desirable for a drug to be given by a particular route are discussed below.

(a) Oral Route: For a drug to be successful as oral controlled-release formulation, it must get absorbed through the entire length of GIT. Since the main limitation of this route is the transit time (a mean of 14 hours), the duration of action can be extended for 12 to 24 hours. The route is suitable for drugs given in dose as high as 1000 mg. A drug, whose absorption is pH-dependent, destabilized by GI fluids/enzymes, undergoes extensive presystemic metabolism (e.g. nitroglycerine), influenced by gut motility, has an absorption window and/or absorbed actively (e.g. riboflavin), is a poor candidate for oral controlled-release formulations.

(b) Intramuscular/Subcutaneous Routes: These routes are suitable when the duration of action is to be prolonged from 24 hours to 12 months. Only a small amount of drug, about 2 ml or 2 grams, can be administered by these routes. Factors important in drug release by such routes are solubility of drug in the surrounding tissues, molecular weight, partition coefficient and pKa of the drug and contact surface between the drug and the surrounding tissues.

(c) Transdermal Route: Low dose drugs like nitro glycerine can be administered by this route. The route is best suited for drugs showing extensive first-pass metabolism upon oral administration. Important factors to be considered for percutaneous drug absorption are partition coefficient of drug, contact area, skin condition, skin permeability of drug, skin perfusion rate, etc.

In short, the main determinants in deciding a route for administration of a controlled release system are physicochemical properties of the drug, dose size, absorption efficiency and desired duration of action.

B. Pharmacokinetic Characteristics of a Drug in the Design of CRDDS

A detailed knowledge of the ADME characteristics of a drug is essential in the design of a controlled-release product. An optimum range of a given pharmacokinetic parameter of a drug is necessary beyond which controlled delivery is difficult or impossible.

1. Absorption Rate: For a drug to be administered as controlled-release formulation, its absorption must be efficient since the desired rate-limiting step is rate of drug release Kr i.e. Kr << Ka. A drug with slow absorption is a poor candidate for such dosage forms since continuous release will result in a pool of unabsorbed drug e.g. iron. Aqueous soluble but poorly absorbed potent drugs like decamethonium are also unsuitable candidates since a slight variation in the absorption may precipitate potential toxicity.

2. Elimination Half-Life: *An ideal CRDDS is the one from which rate of drug of absorption (for extended period of time) is equal to the rate of elimination.* Smaller the t½, larger the amount of drug to be incorporated in the controlled-release dosage form. For drugs with t½ less than 2 hours, a very large dose may be required to maintain the high release rate. Drugs with half-life in the range 2 to 4 hours make good candidates for such a system e.g. propranolol. Drugs with long half-life need not be presented in such a formulation e.g. amlodipine. For some drugs e.g. MAO inhibitors, the duration of action is longer than that predicted by their half-lives. A candidate drug must have t½ that can be correlated with its pharmacological response. In terms of MRT, a drug administered as controlled-release dosage form should have MRT significantly longer than that from conventional dosage forms.

3. Rate of Metabolism: A drug which is extensively metabolized is suitable for controlled-release system as long as the rate of metabolism is not too rapid. The extent of metabolism should be identical and predictable when the drug is administered by different routes. A drug capable of inducing or inhibiting metabolism is a poor candidate for such a product since steady-state blood levels would be difficult to maintain.

4. Dosage Form Index (**DI**)**:** *It is defined as the ratio of Css,max to Css,min*. Since the goal of controlled-release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to *one* as possible.

C. Pharmacodynamics Characteristics of a Drug in the Design of CRDDS

1. Drug Dose: In general, dose strength of 1.0 g is considered maximum for a CRDDS.

2. Therapeutic Range: A candidate drug for controlled-release drug delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in a concentration beyond this level.

3. Therapeutic Index (**TI**)**:** The release rate of a drug with narrow therapeutic index should be such that the plasma concentration attained is within the therapeutically safe and effective range. This is necessary because such drugs have toxic concentration nearer to their therapeutic range. Precise control of release rate of a potent drug with narrow margin of safety is difficult. A drug with short half-life and narrow therapeutic index should be

administered more frequently than twice a day. One must also consider the activity of drug metabolites since controlled delivery system controls only the release of parent drug but not its metabolism.

4. Plasma Concentration-Response (PK/PD) Relationship: Drugs such as reserpine whose pharmacological activity is independent of its concentration are poor candidates for controlled-release systems.

A summary of desired Biopharmaceutic, pharmacokinetic and pharmacodynamics properties of a drug is given in below.

Factors in the Design of CRDDS
Properties of Candidate Drug Desired Features

A. ***Biopharmaceutic Properties***
1. Molecular size Less than 600 Daltons
2. Aqueous solubility More than 0.1 mg/ml
3. Partition coefficient $K_{o/w}$ 1 – 2
4. Dissociation constant pK_a Acidic drugs, $pK_a > 2.5$
Basic drugs, $pK_a < 11.0$
5. Ionisation at physiological pH Not more than 95%
6. Stability in GI milieu Stable at both gastric and intestinal pH
7. Absorption mechanism Passive, but not through a window

B. ***Pharmacokinetic Properties***
1. Absorption rate constant K_a High
2. Elimination half-life $t_{½}$ 2 – 4 hours
3. Metabolism rate Not too high
4. Dosage form index One

C. ***Pharmacodynamic Properties***
1. Dose Maximum 1.0 g (in controlled release form)
2. Therapeutic range Wide
3. Therapeutic index Wide
4. PK/PD relationship Good

PHARMACOKINETIC PRINCIPLES IN THE DESIGN AND FABRICATION OF CONTROLLED-RELEASE DRUG DELIVERY SYSTEMS

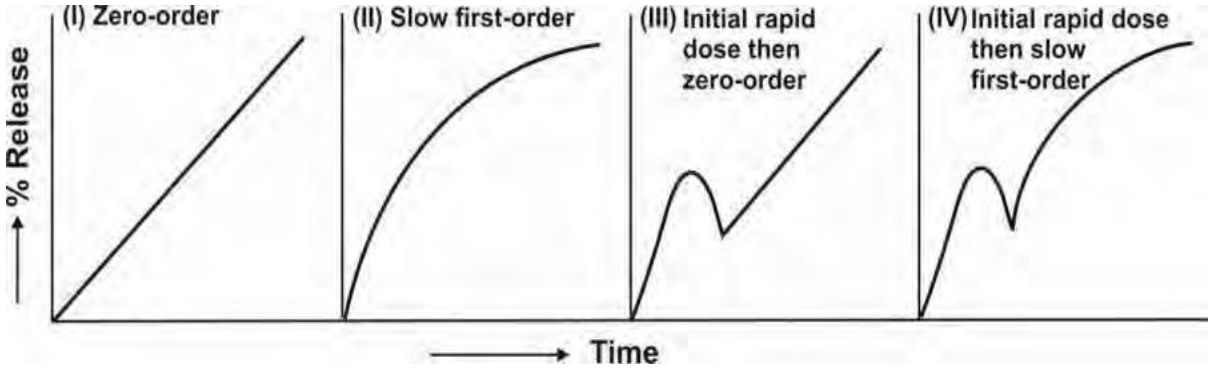
The controlled-release dosage forms are so designed that they release the medicament over a prolonged period of time usually longer than the typical dosing interval for a conventional formulation. The drug release rate should be so monitored that a steady plasma concentration

is attained by reducing the ratio Css,max/Css,min while maintaining the drug levels within the therapeutic window. The rate-controlling step in the drug input should be determined not by the absorption rate but by the rate of release from the formulation which ideally should be slower than the rate of absorption. In most cases, the release rate is so slow that if the drug exhibits two-compartment kinetics with delayed distribution under normal circumstances, it will be slower than the rate of distribution and one can, thus, *collapse* the plasma concentration-time profile in such instances into a one-compartment model i.e. *a one-compartment model is suitable and applicable for the design of controlled-release drug delivery systems*. Assuming that the KADME of a drug are first-order processes, to achieve a steady, non-fluctuating plasma concentration, the rate of release and hence rate of input of drug from the controlled release dosage form should be identical to that from constant rate intravenous infusion. In other words, the rate of drug release from such a system should ideally be zero-order or near zero-order. One can thus treat the desired release rate Ro of controlled drug delivery system according to constant rate i.v. infusion. In order to maintain the desired steady-state concentration Css, the rate of drug input, which is zero-order release rate (Ro), must be equal to the rate of output (assumed to be first-order elimination process).

DRUG RELEASE PATTERNS OF CONTROLLED DELIVERY DOSAGE FORMS

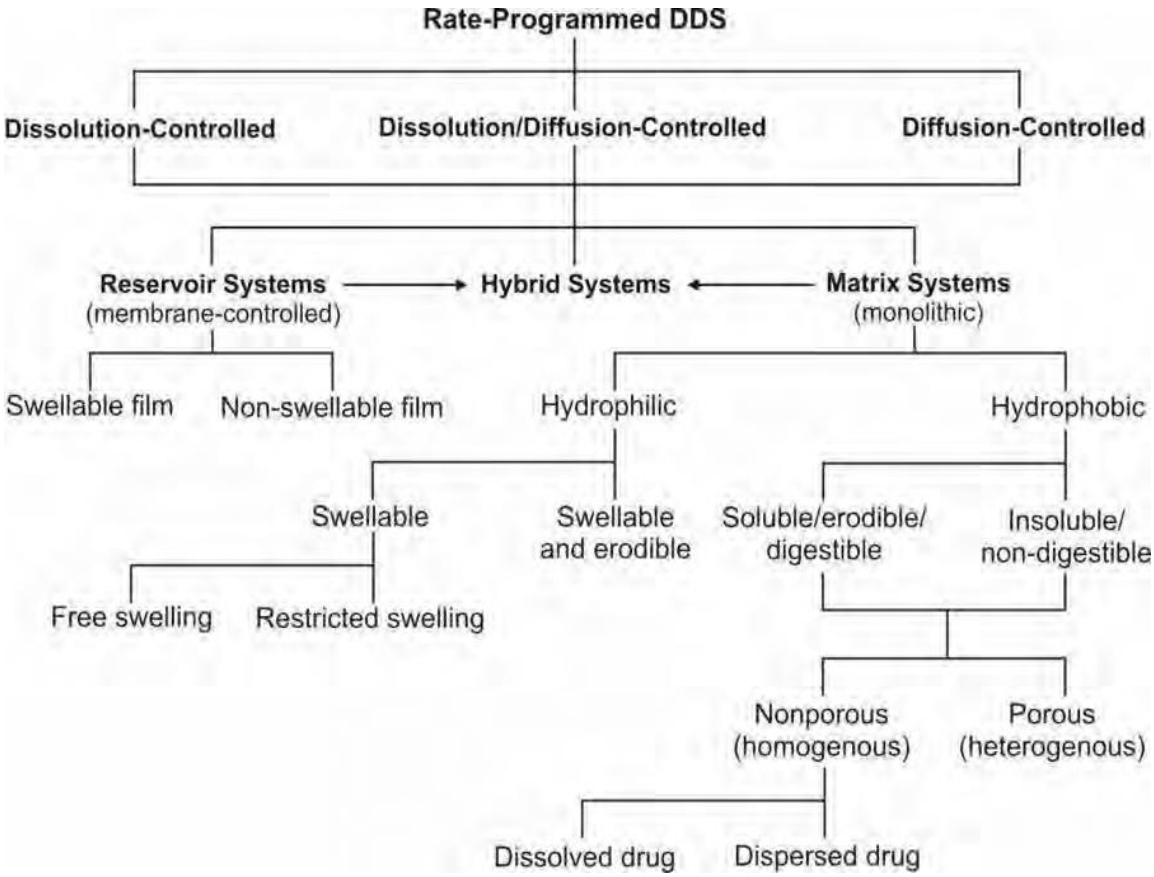
If one assumes that —
1. Drug disposition follows first-order kinetics
2. Rate-limiting step in the absorption is rate of drug release from the controlled release formulation (i.e. Kr < Ka), and
3. Released drug is rapidly and completely absorbed,

then, the four models for drug input based on the drug release pattern can be defined:
1. Slow zero-order release
2. Slow first-order release
3. Initial rapid release of loading dose followed by slow zero-order release
4. Initial rapid release of loading dose followed by slow first-order release.



Schematic representation of four major types of drug release characteristics from controlled-release formulations

CLASSIFICATION OF CRDDS



CRDDS can be classified in various ways –

1. On the basis of technical sophistication

2. On the basis of route of administration

On the basis of technical sophistication, CRDDS can be categorised into 4 major classes:
1. Rate-programmed DDS
2. Activation-controlled DDS
3. Feedback-controlled DDS
4. Site-targeted DDS

In the former three cases i.e. except site-targeted DDS, the formulation comprise of three basic components –
i. The drug
ii. The rate controlling element
iii. Energy source that activates the DDS.

Rate-Programmed DDS

These DDS are those from which the drug release has been programmed at specific rate profiles. They are further subdivided into following subclasses:

1. Dissolution-controlled DDS
2. Diffusion-controlled DDS
3. Dissolution and diffusion-controlled DDS.

All the above systems can be designed in one of the following ways –

i. Reservoir systems (membrane-controlled DDS)
ii. Matrix systems (soluble/erodible/swellable/degradable)
iii. Hybrid systems (i.e. membrane cum matrix systems)

1. Dissolution-Controlled DDS

These systems are those where the rate-limiting phenomenon responsible for imparting the controlled-release characteristics to the DDS is either of the two -

(a) ***Slow dissolution rate of the drug -*** the drug present in such a system may be one of the following two types:

i. ***Drug with inherently slow dissolution rate*** e.g. griseofulvin, digoxin and nifedipine. Such drugs act as natural prolonged-release products, or

ii. ***Drug that transforms into slow dissolving forms*** on contact with GI fluids e.g. ferrous sulphate.

(b) ***Slow dissolution rate of the reservoir membrane or matrix -*** the drug present in such a system may be the one having high aqueous solubility and dissolution rate e.g. pentoxifylline and metformin. The challenge in designing such systems lies in controlling the drug dissolution rate by employing either or combination of following techniques –

i. Embedment in slowly dissolving, degrading or erodible matrix. The matrix in addition may have low porosity or poor wettability.

ii. Encapsulation or coating with slow-dissolving, degrading or erodible substances. In this approach, the rate of dissolution fluid penetration and/or wettability of the reservoir system are controlled.

Slowly soluble and erodible materials commonly employed to achieve these objectives include hydrophobic substances such as ethyl cellulose (containing an added water-soluble release modifying agent such as PVP), polymethacrylates with pH independent solubility (e.g. Eudragit RS and RL 100) and waxes such as glyceryl monostearate, and hydrophilic materials like sodium CMC.

2. Diffusion-Controlled DDS

These systems are those where the rate-controlling step is not the dissolution rate of drug or release controlling element, but the diffusion of dissolved drug molecule through the rate-controlling element. The rate-controlling element in such a system is thus neither soluble, erodible nor degradable but is water-swellable or water-insoluble. Water swellable materials include hydrophilic polymers and gums such as xanthan gum, guar gum, high viscosity

grades of HPMC and HPC, alginates, etc. Water-insoluble polymers most commonly used in such systems are ethyl cellulose and polymethacrylates.

3. Dissolution and Diffusion-Controlled DDS

These systems are those where the rate of drug release is controlled by drug or polymer dissolution as well as drug diffusion i.e. the system is a combination of the two systems discussed above.

i. ***Reservoir systems (membrane-controlled DDS)*** –

These systems are those where the drug is present as a core in a compartment of specific shape encased or encapsulated with a rate controlling wall, film or membrane having a well-defined thickness. The drug in the core must dissociate themselves from the crystal lattice and dissolve in the surrounding medium, partition and diffuse through the membrane.

Depending upon the physical properties of the membrane, two types of reservoir systems are possible –

(a) *Non-swelling reservoir systems* – are those where the polymer membrane do not swell or hydrate in aqueous medium. Ethyl cellulose and polymethacrylates are commonly used polymers in such systems. Such materials control drug release owing to their thickness, insolubility or slow dissolution or porosity. Reservoir system of this type is most common and includes coated drug particles, crystals, granules, pellets, minitablets and tablets.

(b) *Swelling-controlled reservoir systems* – are those where the polymer membrane swell or hydrate on contact with aqueous medium. In such systems drug release is delayed for the time period required for hydration of barrier and after attainment of barrier hydration, drug release proceeds at a constant rate. HPMC polymers are commonly employed in such systems.

ii. ***Matrix systems (monolithic DDS)*** –

These systems are those where the drug is uniformly dissolved or dispersed in release-retarding material. Such devices can be formulated as conventional matrix, or bi-or tri-layered matrix systems.

Depending upon the physical properties of the membrane, two types of matrix devices are possible –

(a) *Hydrophilic matrix* – is the one where the release retarding material is a water swellable or swellable cum erodible hydrocolloid such as high molecular weight HPMCs, HPC, HEC, xanthan gum, sodium alginate, guar gum, locust bean gum, PEO (polyethylene oxide) and cross linked polymers of acrylic acid.

Hydrophilic matrices are porous systems.

Depending upon the swelling behaviour of hydrophilic polymer, two types of matrices are possible –

- *Free-swelling matrix* – is the one in which swelling is unhindered.
- *Restricted-swelling matrix* – is the one in which the surface of the device is partially coated with an impermeable polymer film that restricts the hydration of swellable matrix material.

(b) *Hydrophobic matrix* – is the one where the release retarding material is either –

 Slowly soluble, erodible or digestible, for e.g. waxes such as glyceryl monostearate, cetyl alcohol, hydrogenated vegetable oils, beeswax, carnauba wax, etc.
 Insoluble or non-digestible, for e.g. ethyl cellulose, polymethacrylates, etc.

Depending upon the manner of incorporation of drug in the matrix,
hydrophobic matrices can be further classified as –
 Porous (heterogeneous) matrix – is the one where the drug and release retarding matrix microparticles are simply mixed with each other and compressed into a tablet or the drug is dispersed in the polymer solution followed by evaporation of the solvent.
 Nonporous (homogeneous) matrix – is the one in which the release-retarding matrix material is first melted and the drug is then incorporated in it by thorough mixing followed by congealing the mass while stirring.
Two types of nonporous matrix systems are possible –
Dissolved drug nonporous system – is the one where the drug is dissolved in the molten release-retarding matrix material.
Dispersed drug nonporous system – is the one where the quantity
of drug is greater than its solubility in molten matrix polymer.
iii. ***Hybrid systems (membrane cum matrix DDS)*** –
These systems are those where the drug in matrix of release retarding material is further coated with a release-controlling polymer membrane. Such a device thus combines the constant release kinetics of reservoir system with the mechanical robustness of matrix system.

Activation-Controlled DDS

In this group of CRDDSs, the release of drug molecules from the delivery systems is activated by some physical, chemical, or biochemical processes and/or facilitated by an energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input. Based on the nature of the process applied or the type of energy used, these activation-controlled DDSs can be classified into following categories:

A. ***Activation by Physical Processes***
1. Osmotic pressure-activated DDS
2. Hydrodynamic pressure-activated DDS
3. Vapour pressure-activated DDS
4. Mechanical force-activated DDS
5. Magnetically-activated DDS
6. Sonophoresis-activated DDS
7. Iontophoresis-activated DDS

B. ***Activation by Chemical Processes***
1. pH-activated DDS
2. Ion-activated DDS
3. Hydrolysis-activated DDS

C. Activation by Biochemical Processes
1. Enzyme-activated DDS

A. Physical Process-Activated DDS

1. Osmotic Pressure-Activated DDS

Osmotic systems release drug at a predetermined, typically zero-order rate, based on the principle of osmosis. Osmosis is natural movement of a solvent through a semi permeable membrane into a solution of higher solute concentration, leading to equal concentration of the solute on either sides of the membrane. Osmotic systems imbibe water from the body through a semi permeable membrane into an osmotic material which dissolves in it and increase in volume and generate osmotic pressure that results in slow and even delivery of drug through an orifice.

A semipermeable membrane (e.g. cellulose acetate) is the one that is permeable to a solvent (e.g. water) but impermeable to ionic (e.g. sodium chloride) and high molecular weight compounds.

In comparison to DDS based on diffusion and erosion, osmotic systems are more complex in design but provide better zero-order drug delivery.

2. Hydration/Hydrodynamic Pressure-Activated DDS

These systems are identical to osmotic systems that release drug at a zero-order rate. It however differs from osmotic system in that hydrodynamic pressure generating agent which is typically a water swellable hydrocolloid such as HPMC is contained in one compartment and the drug solution/dispersion in another collapsible reservoir. Both these compartments are housed in a rigid, shape retaining but water permeable housing. The hydrocolloid imbibes water and swells to generate hydrodynamic pressure that pushes the drug reservoir compartment and thus force the drug through an orifice at a slow and uniform rate.

3. Vapour Pressure-Activated DDS

These systems are identical to hydrodynamic systems in that the pumping compartment and the drug solution/dispersion compartment are separated by a freely movable partition and the whole system is enclosed in a rigid housing. The pumping compartment contains a liquefied compressed gas that vaporises at body temperature and creates vapour pressure that moves the partition to force the drug out of the device through a series of flow regulator and delivery cannula into the blood circulation at a constant rate. A typical example is the development infusion pump of heparin in anticoagulant therapy, of insulin in the control of diabetes and of morphine for patients suffering from the intensive pain of a terminal cancer.

4. Mechanical Force-Activated DDS

In these systems the drug reservoir is a solution in a container equipped with a mechanically activated pumping system. A metered dose of drug formulation can be reproducibly delivered into a body cavity, such as the nose, through the spray head upon manual activation of the drug-delivery pumping system. The volume of solution delivered is fixed and is independent of the force and duration of activation. **A** typical example of this type of drug-delivery system is the development of a metered-dose nebuliser for the intranasal administration of a

precision dose of luteinizing hormone releasing hormone (LHRH) and its synthetic analogues, such as buserelin.

5. Magnetically-Activated DDS

In these systems a tiny doughnut-shaped magnet is positioned in the centre of a hemispherical shaped drug-dispersing biocompatible polymer matrix and then coating the external surface of the medicated polymer matrix, with the exception of one cavity at the centre of the flat surface of the hemisphere, with a pure polymer, for instance, ethylene– vinyl acetate copolymer or silicone elastomers. This uncoated cavity is designed for allowing a peptide drug to release. When the magnet is activated, to vibrate by an external electromagnetic field, it releases the drug at a zero-order rate by diffusion process.

6. Sonophoresis-Activated DDS

This type of activation-controlled drug delivery system utilizes ultrasonic energy to activate or trigger the delivery of drugs from a polymeric drug delivery device. The system can be fabricated from either a non-degradable polymer, such as ethylene–vinyl acetate copolymer, or a bioerodible polymer, such as poly(lactide–glycolide) copolymer.

7. Iontophoresis-Activated DDS

This type of CRDDS uses electrical current to activate and modulate the diffusion of a charged drug molecule across a biological membrane, such as the skin, in a manner similar to passive diffusion under a concentration gradient but at a much faster rate. It is a painless procedure. Since like charges repel each other, application of a positive current drives positively charged drug molecules away from the electrode and into the tissues; and vice versa.

A typical example of this type of activation-controlled system is percutaneous penetration of anti-inflammatory drugs such as dexamethasone to surface tissues.

B. Chemical Process-Activated DDS

1. pH-Activated DDS

These systems are designed for acid-labile drugs or drugs irritating to gastric mucosa and target their delivery to the intestinal tract. It is fabricated by coating a core tablet of such a drug with a combination of intestinal fluid-insoluble polymer, like ethyl cellulose, and intestinal fluid-soluble polymer, like HPMCP. In the stomach, the coating membrane resists dissolution in pH 1-3. After gastric emptying, the system travels to the small intestine, and the intestinal fluid-soluble component in the coating membrane is dissolved in at pH above 5 thereby producing a microporous membrane that controls the release of drug from the core tablet. An example of such a system is oral controlled delivery of potassium chloride, which is highly irritating to gastric epithelium.

2. Ion-Activated DDS

Based on the principle that the GIT has a relatively constant level of ions, this type of system has been developed for controlling the delivery of an ionic or an ionisable drug at a constant

rate. Such a CRDDS is prepared by first complexing an ionisable drug with an ion-exchange resin. A cationic drug is complexed with a resin containing SO_3^- group or an anionic drug with a resin containing $N(CH_3)_3^+$ group. The granules of the drug–resin complex are further treated with an impregnating agent, like polyethylene glycol 4000, for reducing the rate of swelling upon contact with an aqueous medium. They are then coated by an air-suspension coating technique with a water-insoluble but water permeable polymeric membrane, such as ethyl cellulose. This membrane serves as a rate controlling barrier to modulate the release of drug from the CRDDS. In the GI tract, hydronium and chloride ions diffuse into the CRDDS and interact with the drug–resin complex to trigger the dissociation and release of ionic drug.

3. Hydrolysis-Activated DDS

This type of CRDDS depends on the hydrolysis process to activate the release of drug molecules. In this system, the drug reservoir is either encapsulated in microcapsules or homogeneously dispersed in microspheres or nanoparticles prepared from bioerodible or biodegradable polymers such as polylactide, poly(lactide–glycolide) copolymer, poly(orthoester) or poly(anhydride). The release of a drug from the polymer matrix is activated by the hydrolysis-induced degradation of polymer chains, and the rate of drug delivery is controlled by polymer degradation rate.

Objectives of IVIVC

1. For *in vitro* dissolution studies to be used as an alternative (surrogate) to the expensive, time consuming and hazardous *in vivo* BA studies.
2. To ensure consistency in *in vivo* performance between the batches of drug products.
3. To develop a new dosage form which exhibits desired *in vivo* performance.
4. To help in setting up dissolution specifications for the drug products.

Quantitative Linear IVIVC

A quantitative linear correlation between the *in vitro* dissolution and bioavailability of a drug product can be developed based on following.

1. *Plasma Level Data*

   In this approach, a linear relationship can be established between the various dissolution parameters and plasma level data.

Table: Correlation of *In vitro* Dissolution Parameters with *In vivo* Plasma Data Parameters

In vitro dissolution parameters	*In vivo* plasma data parameters
1. *In vitro* mean dissolution time (MDT).	*In vivo* mean residence time (MRT), mean dissolution time (MDT) etc.
2. Time for dissolution of specific amount of drug ($t_{50\%}$).	C_{max}, AUC.
3. Amount of drug dissolved at a specific time point (t).	Bioavailable fraction (F), absorption rate constant.

2. *Pharmacological Response*

   In this, the *in vitro* dissolution parameters are correlated with parameters like LD_{50} in animals.

2. TRANSDERMAL DRUG DELIVERY SYSTEMS

2.1 Fundamentals of TDDS

Introduction

Transdermal drug delivery system (TDDS) is an important NDDS that involves predetermined delivery of drug(s) through the surface of the skin. This system which enabled in the rate controlled administration of drugs through intact skin became available in 1981. The method involves usage of a transdermal patch (an adhesive patch) that serves as a self contained discrete dosage form. The patch when applied onto the intact skin releases the drug molecules that travel through the layers of the skin into the circulatory system. Presently, TDDS is being used to treat a wide range of disease conditions.

Applications

1. Scopolamine patches are commonly used for treatment of motion sickness.
2. Nicotine patches are the most commonly used transdermal patches used for cessation of smoking.
3. Nitroglycerine patches are sometimes used for the treatment of angina pectoris.
4. Rotigotine patches are prescribed for Parkinson's disease.
5. Estrogen patches are used in certain patients for the treatment of post-menopausal osteoporosis as well as menopausal symptoms.
6. Fentanyl patches are used for the treatment of moderate to severe pain related to osteo and rheumatoid arthritis.
7. Testosterone patches are prescribed for hypogonadism in males.
8. Clonidine, an antihypertensive drug, is also available as transdermal patch.
9. Buprenorphine patches are prescribed for the treatment of nociceptive pain.

10. 1% diclofenac transdermal patches are used for local treatment of ankle sprain and pain in epicondylitis.
11. Fentanyl HCl iontophoretic transdermal patches, the only opioid iontophoretic patches, are used specifically in the management of moderate-to-severe post operative pain.
12. Lidocaine patches are sometimes prescribed for the symptomatic relief of neuropathic pain associated with post-herpetic neuralgia.
13. Estradiol patches are used for hormone replacement therapy.

Advantages

TDDS offers many advantages over conventional dosage forms.

1. They are associated with low risk to digestive tract or liver.
2. They enhance patient compliance due to their non-invasiveness.
3. They reduce the harmful side effects of drugs caused due to temporary overdose.
4. Self administration is easy.
5. They prolong the steady release of drug molecules thereby preventing the need for frequent dosing.
6. By avoiding problems like decomposition of the drug due to first pass effect, GI irritation, low absorption, frequent dosing due to shorter half-life etc., they offer better drug utilization i.e., they increase the therapeutic value of many drugs. Hence, due to these reasons, a very low dose of drug via transdermal route can elicit an equivalent therapeutic effect when compared to that elicited by other dosage forms which require higher doses.

Disadvantages

1. Toxicity may occur due to dose dumping (more than the desired quantity of drug release/unit time).
2. Expensive.
3. Development of tolerance is very rapid.
4. Increased stability problems.
5. Skin irritation or contact dermatitis are common.
6. The barrier functions of the skin vary from person to person with age, and even from site to site in the same person.

Structure of Skin

A brief overview of the structure of skin is helpful to understand the concept of TDDS. Skin, also termed as cutaneous membrane or integument, is the protective outer covering of the human body. It is the largest organ with a surface area of about 1.5 to 2 m^2. The major functions of the skin are to provide protection against physical, chemical and microbial agents, thermoregulation (maintenance of constant body temperature), provide cutaneous sensation i.e., provide information about the surrounding environment, absorption of fat soluble substances, toxins, heavy metals etc. Dermatology is the branch of medicine that deals with the diagnosis and treatment of disorders affecting the integumentary system. The three basic layers of the skin are as follows.

1. Epidermis

It is the most superficial layer which is keratinized and composed of stratified squamous epithelial cells. Thickness of the epidermis varies in different parts of the body. It is thinnest on the eyelids and thickest on the palms and soles. Epidermis contains five layers i.e., stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale.

In most of the body regions, epidermis consists of only four layers i.e., it does not contain stratum lucidum. This is known as thin skin. However, in body parts such as palms, soles and finger tips which experience greater friction, the epidermis is made up of all the five layers. This is known as thick skin.

(a) *Stratum Corneum (Corneal Layer)*

It is the thick, outermost layer of the epidermis. It is made up of 20-30 layers of dead, flat keratinocytes that are continuously removed and replaced by new cells from the deeper layers. The cells of the stratum corneum contain keratin and lipids produced by lamellar granules.

Functions

1. This layer provides strength and elasticity to the skin.
2. The lipids impart water-repellant property.
3. Since it is made up of dead cells, it protects the deeper layers from microbes and injury.
4. It acts as a barrier for the inward and outward movement of substances.

(b) ***Stratum Lucidum* (*Clear Layer*)**

It is made up of 3-5 layers of flat, clear, dead keratinocytes that are found only in areas such as finger tips, palms and soles. These keratinocytes exhibit abundant amounts of keratin and their plasma membranes are highly thickened.

Functions

1. It protects the skin from harmful effects of UV rays.
2. It also helps to reduce the friction between stratum corneum and stratum granulosum.

(c) ***Stratum Granulosum* (*Granular Layer*)**

It is a thin middle layer composed of 3-5 layers of flat keratinocytes that are undergoing apoptosis i.e., programmed cell death. This layer is characterized by the presence of dark staining, protein granules called keratohyalin that convert tonofilaments into keratin. Keratin proteins and water proofing lipids are synthesized and organized in this layer.

Functions

1. The lipids prevent the entry and exit of water from the skin.
2. This layer also prevents the entry of foreign materials.

(d) ***Stratum Spinosum* (*Spinous/Prickle Cell Layer*)**

It is 8-10 layers of polygonal keratinocytes tightly linked together by desmosomes. These desmosomes give a spiny appearance to the keratinocytes and these cells shrink during the staining process. Stratum spinosum also contains melanocyte projections of the Langerhans cells.

Function

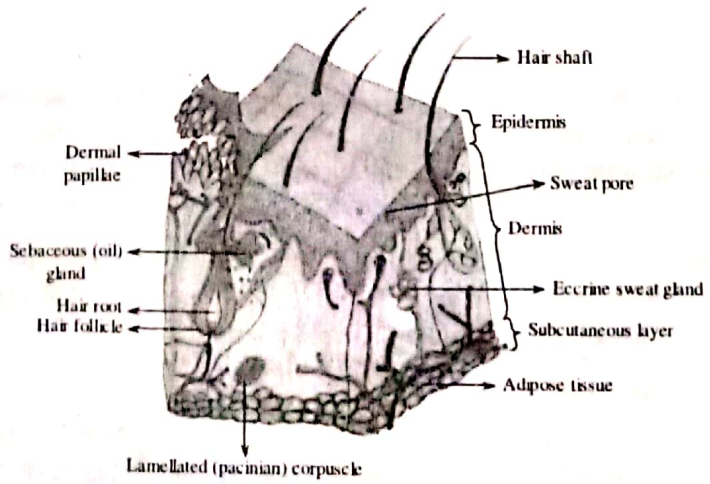
This layer provides strength and support to the skin and helps it to resist abrasion.

(e) ***Stratum Basale* (*Germinatum*)**

It is the deepest layer of the epidermis containing a single layer of columnar or cuboidal keratinocytes. In this layer, few stem cells are present which divide continuously to form new cells which replace the older ones.

Keratinocytes have large nucleus and other regular cytoplasmic organelles. Moreover, they also contain intermediate filaments which are termed as tonofilaments. These filaments contain a protein that helps to synthesize keratin in the upper layers. These tonofilaments are attached to the following,

- Desmosomes - Such attachment helps to bind the cells of stratum basale with each other and also with the above epidermal layer.
- Hemidesmosomes - Such attachment helps the keratinocytes to bind with the dermis.



Replacement of the entire epidermis takes about a month. Maintenance of healthy epidermis depends upon the following processes,

(i) Continuous division of cells in the deeper strata to form new cells which push the older cells towards the surface

(ii) Effective keratinization of older cells reaching the surface

(iii) Shedding (desquamation) of old keratinized cells from the surface

2. Dermis (True Ski

It is the deeper thicker layer of the skin containing collagen fibres (provide strength), elastic fibres (provide flexibility) and reticular fibres (provide support).

Structurally it has two layers, upper papillary layer and lower reticular layer.

(a) *Upper Papillary Layer*

It is composed of loose areolar connective tissue with thin collagen and fine elastic fibres. It lies beneath the epidermis and is connected to it through finger-like projections called dermal papillae. These dermal papillae increase the surface area of contact between epidermis and dermis. Some of the dermal papillae contain capillary loops (blood vessels) that nourish the epidermis, while some contain sensory touch receptors (called Meissner corpuscles) and free nerve endings. A double row of papillae in finger pads, palms and soles produce ridged fingerprints and footprints respectively. These fingerprints and footprints are unique to every individual and even to identical twins. These ridges help to grip the objects.

(b) *Lower Reticular Layer*

It is composed of dense connective tissue with fibroblasts, bundles of collagen fibres and coarse elastic fibres. This layer contains the following structures.

(i) *Nerve Endings*

They sense pain, pressure, touch and temperature. Their sensitivity varies with different areas of the skin.

Example: Nerve endings of the finger tips and toes are highly sensitive to touch.

(ii) *Blood Vessels*

They supply nutrients to the skin and help in regulating the body temperature.

(iii) *Hair Follicles*

They produce hair throughout the body. They contain stem cells that are capable of regrowing the damaged epithelium.

(iv) *Glands*

The sweat (sudoriferous) and oil (sebaceous) glands are associated with the hair follicles.

Beneath the dermis, there is a layer of subcutaneous tissue, containing a network of fat cells (adipocytes) and collagen fibres, called as *hypodermis*. It is not a part of the skin. It insulates the body from heat and cold and also protects the organs from injuries by acting as a shock absorber. It acts as a storage site for fats and since it contains large blood vessels, it nourishes the skin.

Mechanism of TDDS

The mechanism of drug delivery in TDDS involves,

1. Transepidermal Absorption

The principle mechanism of TDDS is diffusion of drug molecules from the drug reservoir in the transdermal patch through the epidermal layers of the skin. The skin acts as a barrier and the major obstruction is posed by stratum corneum, the outermost layer of epidermis. This is considered as the rate limiting membrane in TDDS. This layer of skin is actually a tough and flexible membrane with intercellular spaces rich in lipids. Although, it is hygroscopic in nature, it is impermeable to water. Thickness of this layer varies from one part to another. Stratum corneum permits only few low molecular weight chemicals possessing lipophilicity to diffuse through it. Hence, permeation through the epidermis requires frequent crossings of cell membranes, with each crossing being a thermodynamically prohibitive event for water soluble drugs. However, extremely lipophilic drug molecules are thermodynamically constrained from dissolving in the cytoplasm. Therefore in case of non-polar compounds, epidermis is considered as the rate determining membrane.

After passing through the epidermis, the drug molecules should pass through the dermis to reach the systemic circulation. Passage of drug molecules through dermis is very easy and non-selective due to the presence of large gaps between the collagen fibres.

2. Transfollicular Absorption

The follicular pores (openings on the skin where the hair shaft exits) of follicular glands are comparatively larger than the sebaceous and eccrine sweat glands. These pores serve as the best route for percutaneous absorption. Partitioning of the drug molecules into the sebum followed by diffusion of drug molecules through the follicular pores upto the depth of the epidermis, serves as the mechanism of permeation by transfollicular route.

Kinetics of Rate-Controlled Transdermal Permeation

For a drug to reach systemic circulation, it should possess certain physicochemical properties which would help in its absorption by the stratum corneum, then its penetration through the viable epidermis and finally its uptake by the microvasculature of the dermal layer.

The mathematical expression which denotes the rate of skin permeation $\left(\frac{dQ}{dt}\right)$ across the several layers of the skin is given as,

$$\frac{dQ}{dt} = P_s (C_d - C_r) \quad \text{... (1)}$$

Where,

P_s = Overall permeability coefficient of the cutaneous tissues to the penetrating agent

C_d = Concentration of the penetrating agent in donor compartment i.e., on the surface of stratum corneum

C_r = Concentration of the penetrating agent in the receptor compartment i.e., in systemic circulation.

The permeability coefficient is mathematically given as,

$$P_s = \frac{K_{s/d} \times D_{ss}}{h_s} \quad \text{... (2)}$$

Where,

$K_{s/d}$ = Partition coefficient for the interfacial partitioning of the penetrating agent from a transdermal delivery system to the surface of stratum corneum

D_{ss} = Apparent diffusing ability of the penetrating agent through the cutaneous tissues

h_s = Total thickness of the skin tissues available for penetration.

The permeability coefficient (P_s) for a skin penetrant can be considered constant provided $K_{s/d}$, D_{ss} and h_s are constant under given conditions.

Consider equation (1),

$$\frac{dQ}{dt} = P_s (C_d - C_r)$$

From the above equation, it can be inferred that for obtaining constant rate of skin permeation, the concentration of drug on the stratum corneum should be greater than the concentration in the circulation i.e., $c_d >> c_r$. Therefore, c_r in equation (1) can be omitted and the equation reduces to,

$$\frac{dQ}{dt} = P_s . C_d \quad \text{... (3)}$$

Now, constant rate of skin permeation can be obtained provided that C_d remains constant throughout the process of skin permeation. Constant C_d value can be obtained when the rate of drug release from the transdermal device (R_r) is at least equal to or greater than its rate of uptake by the skin (R_a).

$\Rightarrow R_r >> R_a$.

When the above condition is satisfied i.e., $R_r >> R_a$, then the value of C_d can be equal to or greater than the saturation solubility of drug in stratum corneum. This in turn helps in obtaining the maximum rate of skin permeation and is mathematically expressed as,

$$\left(\frac{dQ}{dt}\right)_{max} = P_s \times C_s \quad \ldots (4)$$

According to the above equation, maximum rate of skin permeation is dependent on the permeability coefficient of the skin penetrant (P_s) and drug's saturation solubility in stratum corneum (C_s). Therefore, the rate limiting step in the transdermal delivery of drugs is passage through the stratum corneum.

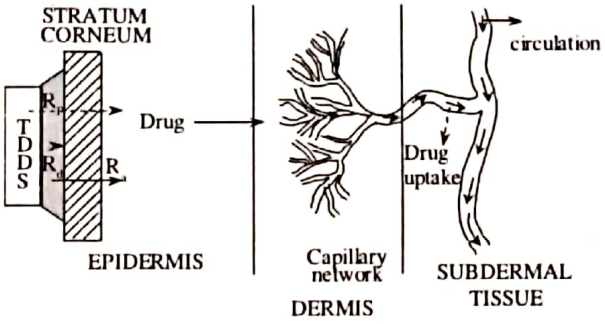


Figure: Kinetics of Transdermal Delivery of Drugs

2.2 Types of TDDS

Almost all the transdermal dosage forms comprise of certain number of layers wherein each layer has its own function.

1. *Backing Laminate/Backing Layer*

   It is the topmost layer, which is farthest from the skin. The function of this layer is to prevent the TDDS from water, dust, microorganisms etc., during usage.

2. *Drug Reservoir*

   This layer is present immediately below the backing layer. It is sandwiched between the rate controlling membrane and the backing layer. It is made up of homogenous dispersion of drug molecules which are continuously supplied for the predetermined functional lifetime of the TDDS. The rate of drug release from the drug reservoir is usually much greater than the amount of drug the skin can probably absorb so as to ensure constant drug supply to the circulatory system.

3. *Rate Controlling Polymer Membrane*

   This layer follows the drug reservoir. The membrane may be porous or non-porous. It controls the release of drug from the reservoir. The composition and thickness of this membrane varies greatly.

Depending upon the anatomy and release kinetics of the commercially available TDDS, their designs may be categorized into the following types.

1. Membrane Permeation-Controlled Systems

The drug reservoir in this type of system is a homogenous dispersion of drug molecules suspended in a viscous liquid to either form a gel, a paste-like suspension or a clear drug solution in a suitable solvent. The drug reservoir formed is completely encapsulated in a shallow compartment moulded from backing laminate and a rate controlling polymeric membrane with a defined permeability. The backing laminate is made up of a drug impermeable metallic plastic while the rate controlling membrane may be microporous or non-porous mostly prepared from ethylene vinyl acetate (EVA) copolymer, silicone rubber or polyurethanes. A thin layer of an adhesive polymer like silicone or polyacrylate is placed below this membrane to help secure the TDDS over the skin. This polymer is designed to be compatible with the drug and is hypoallergenic. The dosage per unit area of the device can be controlled by varying the composition, thickness as well as permeability coefficient of rate controlling membrane and adhesive.

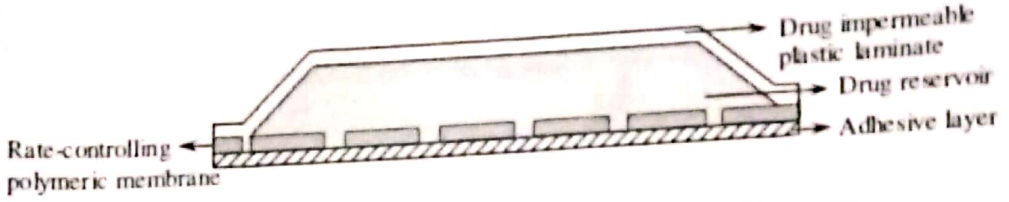


Figure: Membrane Permeation-Controlled Systems

The rate of drug release from this device may be maintained constant as long as the concentration of the inert polymeric membrane is kept constant. This is given by the equation,

$$\frac{dQ}{dt} = kt$$

Where,

k = Rate release constant

This expression may be applied to all the geometrics of the device and the type of drug release is of zero order. The intrinsic rate of drug release from membrane permeation-controlled systems is given by,

$$\frac{dQ}{dt} = \frac{C_R}{\frac{1}{P_m} + \frac{1}{P_a}}$$

Where,

C_R = Concentration of drug in the drug reservoir

P_a = Permeation coefficient of adhesive layer

P_m = Permeation coefficient of rate controlling membrane.

For any microporous rate-controlling membrane, P_m approximately represents the sum of the permeability coefficients across the pores and the polymeric material. P_a and P_m may be separately defined as,

$$P_a = \frac{K_{a/m}.D_a}{h_a} ; P_m = \frac{K_{m/r}.D_m}{h_m}$$

Where,

D_a = Diffusion coefficient of an adhesive layer

D_m = Diffusion coefficient of rate-controlling membrane

$K_{m/r}$ = Partition coefficient for interfacial partitioning of drug from reservoir to rate controlling membrane

$K_{a/m}$ = Partition coefficient for interfacial partitioning of drug from rate controlling membrane to adhesive layer

h_m = Thickness of rate-controlling membrane

h_a = Thickness of adhesive layer.

Table: Examples of Membrane-Permeation Controlled Systems

TDDS	Dosing interval	Indication
Clonidine-releasing transdermal system	7 days	Hypertension
Estradiol-releasing transdermal system	3-4 days	Menopausal syndrome
Nitroglycerin-releasing transdermal system	Every 24 hrs	Angina pectoris
Scopolamine-releasing transdermal system	Every 72 hrs	Motion sickness

Advantage

This type of TDDS provides a constant release pattern of the drug.

Disadvantage

Accidental breakage of the device may cause dose dumping or a sudden release of entire drug from the drug reservoir.

2. Adhesive Dispersion-Type Systems

This is a simplified form of membrane permeation-controlled systems. In this system, the drug and other selected excipients are directly incorporated into the adhesive solution. They are then mixed and casted as thin films and finally the solvent is evaporated by drying the film. The film (drug reservoir) is then sandwiched between the backing laminate and rate controlling adhesive polymer membrane.

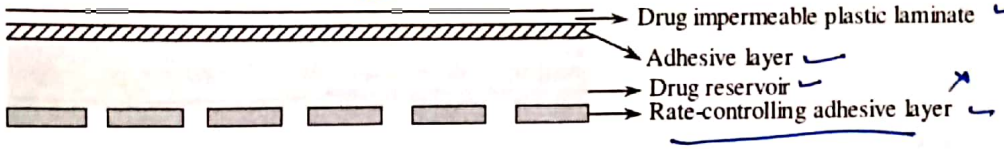


Figure: Adhesive Dispersion-Type Systems

The rate of drug release from this system is given by,

$$\frac{dQ}{dt} = C_R \frac{K_{a/r}.D_a}{h_a}$$

Where,

$K_{a/r}$ = Partition coefficient for interfacial partitioning of drug from reservoir layer to adhesive layer.

Table: Examples of Adhesive Dispersion-Type Systems

TDDS	Dosing interval	Indication
Isosorbide dinitrate-releasing TDDS	24 hrs	Angina pectoris
Verapamil-releasing TDDS	24 hrs	Hypertension

3. Matrix Diffusion-Controlled Systems

In this type of TDDS, the drug reservoir is prepared by homogenously dissolving or dispersing the finely ground drug particles in hydrophilic/lipophilic liquid polymer or a highly viscous base polymer. Required quantity of plasticizer like propylene glycol or polyethylene glycol and permeation enhancer are then added to the drug mixture with thorough mixing. The resulting polymer matrix is then moulded into discs with defined surface area and controlled thickness. The medicated disc is then mounted onto an occlusive base plate in a compartment made up of a drug impermeable backing. Finally, the adhesive polymer is spread along the circumference of the film rather than attaching it directly to the surface of the medicated disk.

The drug reservoir can also be prepared by dissolving the drug and the polymer in a common solvent. The medicated mixture is then moulded into discs followed by solvent evaporation at higher temperature and/or under vacuum. The film formed is then mounted with a drug impermeable backing and an adhesive polymer.

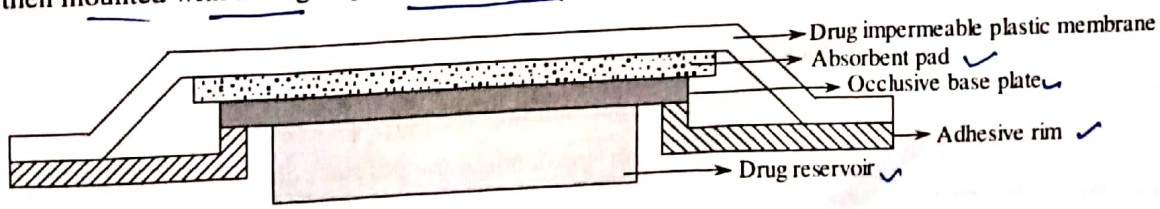


Figure: Matrix Diffusion-Controlled Systems

Rate of drug release in this system is given by the equation,

$$\frac{dQ}{dt} = \sqrt{\frac{AC_pD_p}{2t}}$$

Where,

A = Initial drug loading dose dispersed in polymer matrix

C_p = Solubility of drug in polymer

D_p = Diffusivity of drug in polymer.

Since only those drug molecules that are dissolved in the polymer are released from the device, solubility of drug in polymer (C_p) is essentially equal to the drug concentration in the reservoir compartment (C_R).

Example: Nitroglycerin releasing transdermal therapeutic system at a daily dose of 0.5 g/cm^2 for angina pectoris.

Advantage

Due to the presence of polymer within the drug reservoir, dose dumping may be avoided.

4. Microreservoir Type/Microreservoir Dissolution Controlled Systems

This type of TDDS may be considered as a combination of both reservoir and matrix type systems. In this system, the drug reservoir is initially formed by suspending the solid drug particles in an aqueous solution of water soluble liquid polymer like polyethylene glycol. The drug suspension is then homogenously dispersed by high mechanical force in the lipophilic polymer like silicone elastomers resulting in the formation of thousands of unleachable microscopic spheres of drug reservoirs known as microreservoirs.

The unstable dispersion is then rapidly stabilized by cross-linking the polymer chains *in situ* to produce medicated polymer discs. These discs have uniform surface area and constant thickness. The medicated discs can be further processed by mounting an occlusive base plate over it and coating the disc with a biocompatible polymer layer in order to modify the mechanism and rate of drug release. A microreservoir TDDS is thus formed with a medicated disc placed at the centre and surrounded by an adhesive rim.

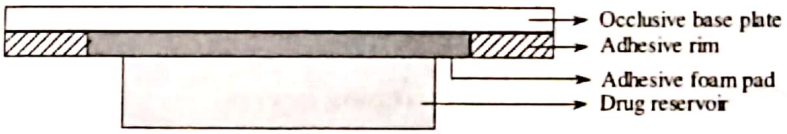


Figure: Microreservoir Dissolution Controlled Systems

This system of TDDS follows zero order release of drugs which is given by the equation,

$$\frac{dQ}{dt} = \frac{D_p D_d m K_p}{D_p h_d + D_d h_p m K_p} \left[n S_p \frac{D_l S_l (1-n)}{h_l} \left(\frac{1}{K_l} + \frac{1}{K_m} \right) \right]$$

Where,

$m = a/b$

a = Ratio of drug concentration in the bulk of elution medium to the drug solubility in the same medium

b = Ratio of drug concentration at the outer edge of the polymer coating to the drug solubility in the same polymer composition

n = Ratio of drug concentration at the inner edge of the interfacial barrier to the drug solubility in the polymer matrix

D_l = Drug diffusivity in liquid layer surrounding the drug particles of thickness h_l

D_p = Drug diffusivity in polymer coating membrane surrounding the polymer matrix of thickness h_p

D_d = Drug diffusivity in hydrodynamic diffusion layer surrounding the polymer coating of thickness h_d

K_l = Partition coefficient for interfacial partitioning of drug from liquid compartment to the polymer matrix

K_m = Partition coefficient for interfacial partitioning of drug from polymer matrix to polymer coating membrane

K_p = Partition coefficient for interfacial partitioning of drug from polymer coating membrane to elution solution

S_l = Solubility of drug in liquid compartment

S_p = Solubility of drug in polymer matrix.

2.3 Basic Components of TDDS

FDA regulations for TDDS are very strict. The basic factors that require consideration prior to the formulation and development of TDDS are to ensure that the drug from the drug reservoir or from the adhesive layer is delivered in a controlled manner and that the components used for the manufacturing of transdermal patches do not produce any unwanted effects. The materials employed in TDDS are as follows,

1. Polymer Matrix/Matrices

Polymers that control the rate of drug release from the patches serve as the backbone of TDDS. They are manufactured either as polymer matrices/reservoirs to hold the drug or as rate-controlling membranes. Polymer matrices are prepared by the dispersion of drug in solid or liquid polymer base.

Ideal Characteristics of Polymers

The polymers used in TDDS should meet the following criteria,

1. The polymer should provide a consistent and an effective delivery of drugs throughout the intended shelf-life of the product.
2. They should be chemically as well as biologically compatible with the drug and its excipients.
3. They should be safe to use, stable at conditions of handling and inexpensive.
4. The component or its degradation products must be non-toxic.
5. They should be non-sensitizing and non-irritating to the skin.
6. Glass transition temperature, chemical nature and molecular weight of the polymer must be suitable for easy diffusion and release of the drug from the patch.
7. Polymers must be easy to manufacture and fabricate into the required product.
8. Polymer must be consistent enough to allow the incorporation of huge quantities of therapeutic agents along with maintaining its mechanical strength.

Examples of Polymers

1. Natural Polymers : Cellulose derivatives, natural rubber, proteins, shellac, starch, waxes, zein etc.
2. Synthetic Elastomers : Acrylonitrile, butyl rubber, hydrin rubber, neoprene, nitrile, polysiloxanes, silicone rubber and styrenebutadiene rubber.
3. Synthetic Polymers : Polyamide, polyacrylene, polyethylene, polypropylene, polyurea, polyvinyl alcohol, polyvinyl chloride etc.

2. Drug

Transdermal drug delivery is a very attractive option for drugs with narrow therapeutic index, for drugs that undergo extensive first-pass metabolism, those drugs with short half-life and which require frequent dosing.

In order to formulate an effective transdermal patch, the drug should possess the following properties,

Physico-Chemical Properties

(a) Molecular Size/Weight: It serves as an important parameter to determine the cutaneous permeability of the drug. Drugs with molecular weight less than 1000 daltons are easily absorbed through the skin while those with higher molecular weight are poorly absorbed.

(b) Solubility: Solubility of drug molecules in the formulation influences its partition coefficient between the formulation and skin as well as its concentration gradient. Drug molecules should possess an adequate solubility in oil and water with log P in the range of 1-3.

(c) Melting Point: Drugs with low melting points show better penetration.

(d) Lipophilic/Hydrophilic Character: Drugs should possess a balanced lipophilic/hydrophilic nature. Drugs with extreme partitioning characters are not suitable.

Biological Properties

(a) Potency of the drug to be administered by transdermal route should be in the range of few mg/day.

(b) Drugs with relatively shorter $t_{1/2}$ i.e., about 2-6 hrs are preferred for this system. This is because drugs with longer $t_{1/2}$ (i.e., up to 24 hrs) may increase the plasma drug levels proving to be toxic.

(c) An ideal drug in TDDS must not induce any allergic response or cutaneous irritation. Moreover, the patient should not develop tolerance towards it.

(d) Drugs that decompose in the GIT or those drugs which undergo hepatic first pass metabolism are suitable for transdermal delivery.

3. Permeation Enhancers

Permeation enhancers, also known as *accelerants* or *sorption promoters*, are the chemical agents that promote the permeability of the stratum corneum to the flux (J) of the drug molecules in order to attain higher therapeutic levels. They do so by interacting with and altering the structural components (proteins or lipids) of the stratum corneum thereby temporarily diminishing the barrier property of skin.

Flux of the drug molecules across the skin is given by the equation,

$$J = D \frac{dc}{dx}$$

Where,

D = Diffusion coefficient

c = Concentration of diffusing species

x = Spatial coordinate.

In the above equation, diffusion coefficient is a function of size, shape and flexibility of the diffusing species while concentration of diffusing species is thermodynamic in origin. The commonly employed permeation enhancers are listed below,

(a) ***Solvents***

These act by swelling the polar pathway and/or by fluidizing lipids in the stratum corneum.

E.gs: Alcohols (methanol, ethanol), polyols (polyethylene glycol, propylene glycol), sulphoxides (dimethyl sulphoxide, alkyl methyl sulphoxide), pyrrolidones (N-methyl, 2-pyrrolidone), miscellaneous solvents (isopropyl palmitate, glycerol) etc.

(b) ***Surfactants***

These are actually skin irritants. They perform their function by enhancing the polar pathway transport (especially of hydrophilic drugs). The three major types of surfactants are,

(i) Anionic Surfactants: These surfactants penetrate into the skin, bind to the intracellular corneocytes and remove some of the intercellular lipids. However, they also induce skin irritation.

E.gs: Sodium lauryl sulphate, dioctyl sulphosuccinate, decodecylmethyl sulphoxide etc.

(ii) Cationic Surfactants: These surfactants penetrate into the skin and extract lipids from the stratum corneum. They cause greater skin irritation than the anionic surfactants, hence they are not employed as permeation enhancers.

E.g: Dodecyltrimethyl ammonium bromide.

(iii) Non-ionic Surfactants: These surfactants have minimum potential for irritation than the above mentioned types. Hence, they are widely used as permeation enhancers in TDDS.

E.gs: Pluronic F127, Pluronic F68 etc.

(c) ***Miscellaneous Agents***

(i) Urea: It is a keratolytic agent that functions by increasing the fluidity of intercellular bilayers, hence hydrating the stratum corneum.

(ii) Phosphatidyl Choline: It diffuses into the stratum corneum, extracts the intercellular lipids and hence promotes the penetration of drug into the skin.

(iii) Calcium thioglycolate

(iv) N,N-dimethyl-*m*-toluamide

4. Other Excipients

(a) *Adhesives*

Pressure sensitive adhesive is a material that helps to adhere transdermal devices to the skin over long periods of time. These adhesives can be placed on the face of the device (known as face adhesive system) or peripherally at the back of the device (known as peripheral adhesive system). The criteria for a good adhesive are as follows,

(i) It should adhere to the skin with only normally applied finger pressure.

(ii) It should be permanently tachy and should exert a strong holding force. Activities like washing, exercise, sweating etc., should not disturb the TDDS.

(iii) It should get removed from the skin surface without leaving an unwashable residue.

(iv) It should be physicochemically and biologically compatible with the drug, excipients and permeation enhancers.

(v) It should not irritate or sensitize the skin, also it should not alter the release pattern of the drug and other constituents of the device.

The major classes of widely used pressure sensitive adhesive polymers include polyisobutylene, acrylics and silicones. Among these polymers, acrylics have desirable features like moderate cost, resistance to oxidation and thermal degradation, permeability to oxygen and water vapour and high tackiness. However, the properties of all the polymers depend upon the components of TDDS, nature of the drug, excipients and chemical components of the adhesives.

(b) *Backing Membranes/Backing Laminate*

A comfortable backing membrane/laminate should exhibit high flexibility, good oxygen transmission and a high moisture vapour transmission rate. It should provide good bond with the drug reservoir, should not allow the additives to leach out or lead to diffusion of excipients, drugs or penetration enhancers. Backing membrane should also accept printing.

Examples of backing membranes include metallic plastic laminate, adhesive foam pad with occlusive base plate, plastic backing with absorbent pad and occlusive base plate.

2.4 Evaluation

Development of TDDS is a very complex process that requires systematic evaluation at different stages of its development. These evaluation studies have been classified into the following types,

1. Evaluation of Adhesives

In TDDS, contact between the patch and the skin is attained by the use of pressure sensitive adhesives. Adhesion properties of these adhesives are characterized by considering the following factors,

(a) *Peel Adhesive Properties*

Peel adhesion may be defined as the force required to remove an adhesive coating from the test substrate. Molecular weight of an adhesive polymer, nature and amount of additives and constituents of the polymer affect the adhesion properties of the polymer. The test is carried out by placing the patch over the substrate and measuring the force required to pull it out at an angle of 180°. The test is passed, if there is no residue left on the substrate.

(b) *Tack Properties*

Tack may be defined as the strength of the adhesive polymer to stick to the substrate upon application of little pressure. Molecular weight, constituents of the polymer and the use of tackifying resins used in the polymer influence the tack. Tack property can be tested from the following tests,

(i) *Thumb Tack Test*: The adhesive is applied over the thumb and the force required to remove it from the thumb is measured.

(ii) *Rolling Ball Test*: The adhesive is placed in an upward facing direction and a stainless steel ball is allowed to travel over it along its length. More tachy the adhesive, lesser is the distance travelled by the ball and vice versa.

(iii) *Quick Stick/Peel Tack Test*: The adhesive is placed over the substrate and the force required to break the bond between the adhesive and the substrate is measured while removing the adhesive from the substrate at a speed of 90 inch/min at an angle of 90°.