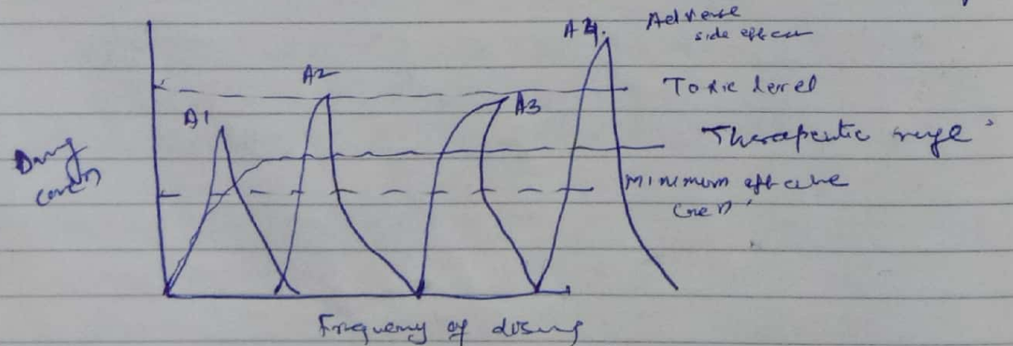
Controlled Release formulations

provide continuous release of active ingredients at a predetermined rate for a predetermined time.

These formulations are designed for oral administration but recently introduced for parenteral, ocular and TDS application.

Advantage:-

1) Decreased incidence and/or intensity of adv. effect and toxicity.
2) Better drug utilization
3) control rate and site of release
4) more uniform blood conc.
5) Improved patient compliance
6) Reduce dosing frequency
7) more consistent and prolonged therapeutic effect
8) A greater selectivity of pharmacological activity.



Imagination is useful only as long as it remains practical.

A1 = Immediate release

Disadvantage of controlled release prep:-

1) Increased variability among dosage unit.
2) Stability problems.
3) Toxicity due to dose dumping.
4) Increased cost
5) Rapid development of tolerance
6) Need for additional patient education and counselling

Guidelines for controlled release

First pass metabolism:-

First pass hepatic metabolism can significantly alter the change the rate at which the drug is presented to the enzyme system.

If enzyme system are saturable then a slower rate of presentation may result in greater fraction of drug metabolized.

Ex Steady state plasma level of propranolol observed with equal doses of the controlled release due to the increased metabolism.

Dose Dumping:-

It takes place more than the planned amount of the drug specified for the product is released.

A man without imagination is like a bird without wings.

10, 6, 22, 26, 25, 23, 5, 37, 32, 13

16 AUGUST SATURDAY 2.0.0.3

AUGUST

MO	TU	WE	TH	FR	SA	SU	WK
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4	5	6	7	8	9	10	32
11	12	13	14	15	16	17	33
18	19	20	21	22	23	24	34
25	26	27	28	29	30	31	35

released per unit time because controlled release may contain two or four times the usual dose of drug. It leads to toxicity.

Food effects:-

* Presence of food Effects on the pharmacokinetics of controlled release dosage form.
* Dose dumping problem may associate with presence of food.

For ex presence of high fat meal increase the rate and extent of bioavailability of controlled release prepn of theophylline.

Food delayed the rate and extent of absorption of theophylline

Every controlled release should be studied in a single dose, three way crossover study with treatment begins being

1) The controlled release dosage form administered under fasting conditions.
17 SUNDAY 2) a rapidly available dosage form administered under fasting conditions.
3) controlled release dosage form administered immediately following the ingestion of high fat

The purpose of this study is

A man without a smiling face must not open a shop.

SEPTEMBER

MO	TU	WE	TH	FR	SA	SU	WK
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8	9	10	11	12	13	14	37
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22	23	24	25	26	27	28	39
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2.0.0.3 MONDAY AUGUST 18

(1) Determine whether there is any need for labelling specifications of special conditions for administration with respect to meal.

2) To study pattern of absorption of controlled release dosage form as compared to conventional and rapidly available form.

Gastric emptying and Intestinal motility:-

It depends on degree of distension
- composition
- viscosity of stomach content
- PH
- temp.

For ex gastric emptying is inhibited by anticholinergics and narcotic analgesics.
Enhanced by metoclopramide.

Emptying of undisintegrated tablets from the stomach shows variations ranging from less than 0.5 to more than 7hr.
→ If release from the depot is PH dependent eg. low in and environment the release process will only start at Intestine.

Friendship increases in visiting friends, but in visiting them seldom.

Diurnal variation :-

Circadian rhythms may affect the bioavailability of controlled release products.

Occupancy time :-

Therapeutic occupancy time, the time during which the plasma conc stays within the therapeutic range. It is an important criteria for evaluation of controlled release formulation.

Fluctuations :-

Controlled release formulation must be evaluated under multiple dose steady state conditions.
ie comparision of C_{min} (trough values) on three or more consecutive dosing intervals.

Characterization of Drug entity

(1) Physicochemical characteristics :-

(2) Diffusion :-

Most of the drugs are transported across membrane by passive diffusion.
More than 75% of all drugs follow this path

Lower the molecular wt, the faster and more complete is the transport

2) PKa :-

Non-ionized moiety is usually lipid soluble hence may dissolve in the lipid material of membrane and may be transported by passive diffusion.

Ionized moiety is not lipid soluble so less permit to permeation.

To cross or to reach membranes by passive diffusion, the presence of drug non-ionized at that site should be between at least 0.1 and 5%

(3) Solubility :-

* Drug should be in the form of solution at the site of absorption
* The aq. and PH dependent solubility is of important to drug release
* so for controlled release we have to select limit of solubility in order to utilize the conc gradient as the driving force for drug release.

Pharmacokinetic consideration :-

1) Elimination or terminal half life ($t_{1/2}$)

The $t_{1/2}$ is the time required to reduce the conc in blood, plasma or serum to one half after

equilabrium is reached.

The $t_{1/2}$ can be determined from the slope of the terminal line of semilogarathmic plot of Serum conc V/s time plote by regression analysis.

The shorter is the $t_{1/2}$ the greater will be the amount of drug to be incorporated into controlled delivery system.

2) AUC :-

AUC is a measure of the quantity of drug in body. The AUC can be determined by using trapezoidal rule.

It is used for the estimation of total clearance and apparent vol. of distribution

The ratio of AUC's between extravascular and intravascular administration is the absolute bioavailability.

AUC's between a test and Standard product ~~the~~ given by the same route of administration is the relative bioavailability.

3) Total clearance (C_L)

The C_L is the hypothetical vol. of distribution of unmetabolized drug that is cleared per unit of time by any pathway of drug removal.

The value of C_L can be determined from the dose administered D and absolute bioavailability and AUC

Happiness is a wondrous commodity; the more you give, the more you have.

$$CL = \frac{D \cdot F}{AUC}$$

$$C_L = \frac{0.693 \, V_d}{t_{1/2}}$$

multiple dosing

$$C_L = \frac{D}{AUC_{(n+1)}}$$

$AUC_{(n+1)}$ is the AUC during any dosing Interval.

4) Mean steady state conc (C_{ss})

C_{ss} is not the numeric mean between peak ($C_{ss\,max}$) and trough ($C_{ss\,min}$) at steady state but an Integrated concentration.

For Ideal controlled rate $C_{ss} = C_{ss\,max} = C_{ss\,min}$

The value of C_{ss} can be estimated from the dose rate R^0 and C_L

$$C_{ss} = \frac{R^0}{C_L}$$

or from AUC of any dosing Interval at steady state

$$C_{ss} = \frac{AUC_{(\tau - \tau_{n+1})}}{\tau}$$

Do not bite the hands that feeds you.

6) Mean residence time (MRT):

The MRT is the mean time a drug molecules resides in the body.

$$MRT = \frac{AVMC}{AVC}$$

AVMC :- Area under the first moment curve

7) Dosage form Index (DI)

DI is the ratio between peak ($C_{ss\,max}$) and trough ($C_{ss\,min}$) values within dosing interval.

$$DI = \frac{C_{ss\,max}}{C_{ss\,min}}$$

DI = 1 thus $C_{ss} = C_{ss\,max} = C_{ss\,min}$

24 SUNDAY

Pharmaceutically controlled Release methods and Devices :-

Drug delivery :-

In recent years, there have been numerous development in polymeric carriers and controlled release system. Few examples are

1) Films with the drug in a polymer matrix. (monolithic devices).
2) Drug contained by the polymer (reservior devices).
3) Polymeric colloidal particles or microencapsulates in the form of reservior and matrix devices.
4) Drug contained by a polymer containing hydrophilic and or leachable additives eg. a second polymer, surfactant or plasticizer to give a porous device or a device in which the drug release may be osmotically controlled.
5) enteric coating (Ionise and dissolve at suitable pH)
6) soluble polymers with (covalently) attached pendant drug molecule.
7) devices where release rate is controlled dynamically eg. osmotic pump.

Reservior Devices :-

A typical approach to controlled release is to encapsulate or contain the drug entirely within a polymer film or coat (Microcapsules for spray/pan coated pores)

There can be no true friendship without sincerety.

The various factors that can affect the diffusion process may readily be applied to reservior devices. (Ex effect of additives, polymer functionality, porosity, film casting conditions) etc.

* Hence choice of polymer must be important consideration in the development of reservior devices.

Modelling

The Release characteristics of reservior devices (and monolithic devices) in which the transport of the drug is by a solution diffusion mechanism therefor involves a Ficks second law (unsteady state conditions, conc dependent flux) for the relevant boundary conditions.

When the device contains dissolved active agents the rate of release decreases exponentially with time as the conc (activity) of the agent (ie driving force for release) within the devices decreases (ie first order release).

(2) monolithic Devices (Matrix devices):—

It is the most common devices for controlling the release of drugs.

* Easy to fabricate compare to reservior type.
* Danger of burst is less

In this Active agent is present as a dispersion within the polymer matrix, they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting.

The dosage release property of monolithic devices depends on the solubility of the drug in polymer matrix or in the core of porous matrixes the solubility in the smk solution within the particles pore net work and also the tortuosity of the network.

For Low loading of drugs (0 to 5% w/w) the drug will be released by a solution-diffusion mechanism.

At higher Loading (5 to 10-1 w/w), the release mechanism will be complicated by the presence of cavities formed near the surface of device as the drug is lost.

It is common to add a plasticizer (PEG or surfactant or adjuvant) to matrix devices as a means to enhance the permeability

Other methods of drug carriage and controlled release:—

a) Variation on the theme of microsphere:-

Hollow microsphere (microballons) with the drug dispersed in the spheres shell

Highly porous matrix type microsphere (microsponges)

The microsphores were prepared by dissolving the drug and polymer in ethanol. On addition to water the ethanol diffuse from the emulsion droplets to leave a highly porous particle.

Hollow microspheres were formed by preparing a solution of ethanol/dichloromethane containing the drug and polymer. On pouring into water, thus formed an emulsion containing the dispersed polymer / drug / solvent particle by a coacervation type process, from which the ethanol (good solvent for polymer) rapidly diffused precipitating the polymer at the surface of the droplets to give a hard shelled particle enclosing the drug dissolved in the dichloromethane.

b) Pendent devices:-

Attaching a range of drugs such as analgesics and antidepressants by means of an ester linkage to poly (acrylate) ester latex particles prepared by aqueous emulsion polymerization. These latices when passed through an ion exchange resins such that the polymer ered gps were converted to their strong acid forms could 'self catalyse' the release of the drug by hydrolysis of the ester link.

If you wish to reach the highest, begin at the lowest.

c) Enteric Gems:-

It consist of PH sensitive polymers.

At high PH polymers ionising cause swelling or dissolving the polymer.

d) Osmotically controlled devices:-

The osmotic pumps is similar to reservoir devices but contain an osmotic agent (Active agent in salt form) which acts to imbibe water from the surrounding medium via a semi-permeable membrane.

Electrically stimulated release devices:-

Monolithic devices using polyelectrolyte gel which swelled when for example external electrical stimulus was applied causing a change in PH. It gives a pulsable release profile.

Hydrogels

used in soft contact lenses
soft Implants.

If you lend, you either lose the money or gain an enemy.

30 AUGUST SATURDAY 2.0.0.3

AUGUST

WK	MO	TU	WE	TH	FR	SA	SU
					1	2	3
	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
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Oral Controlled release systems: —

1) Diffusion controlled systems.
   a) Reservior system. ✓
   b) Monolithic (matrix) system. ✓

2) Dissolution controlled systems
   a) Encapsulation ✓
   b) matrix. ✓

3. diffusion and dissolution controlled systems.

4. Water penetration controlled systems
   a) Swelling Controlled
   b) Osmotically controlled.

5) Ion-exchange resins: — ✓

6) PH-dependent formulations ✓

7. Altered density formulations ✓
   a) High density
   b) Low density
   c) Floating / buoyant tablets ✓
   d) Floatation chamber.

31 SUNDAY

1) Diffusion Controlled systems: —

a) Reservior System: —

Thre system consist of a reservior of drug

SEPTEMBER

WK	MO	TU	WE	TH	FR	SA	SU
36	1	2	3	4	5	6	7
37	8	9	10	11	12	13	14
38	15	16	17	18	19	20	21
39	22	23	24	25	26	27	28
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2.0.0.3 MONDAY SEPTEMBER 1

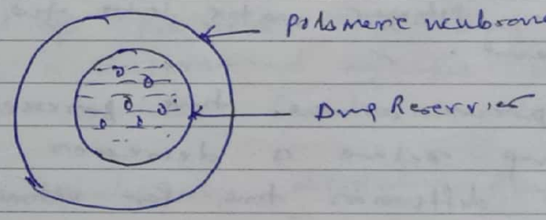
in the form of a dilute solution or highly Concentrated solution within a polymer matrix.

This polymer matrix is surrounded by a form or membrane of a release rate controlling material.

The polymer layer surrounding the reservior is the rate limiting structure.

For these systems the drug delivery rate remains fairly constant ✓

Release rate mechanism of this system is the diffusion of drug from the central core to the surrounding medium through the polymeric membrane. ✓



Advantages: —

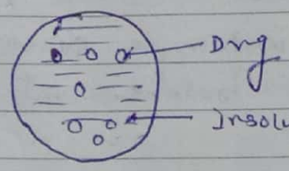
1) Achievement of zero order release is easy ✓
2) Very easy to fabricate in a wide ranges of size and shapes. ✓
3) Drug inactivation by contact with the polymeric matrix can be avoided. ✓

Disadv: —

1) Rupture of system can results in dose dumping ✓

2) Degradable reservior system are difficult to design ✓

B) Monolithic (matrix) systems:-



In these systems, the drug is dispersed in a polymer matrix.

The release of a drug is controlled by its diffusions from the matrix into the surrounding environment.

Formulation of such systems involves homogeneous mixing of drug and polymer.

Diffusion takes place when the drug passes from the polymer matrix into the external environment.

So this process as the time progresses the rate of drug release is decreases and here a longer diffusion time for ultimate delivery of drugs.

Adv:- (1) It is very easy to fabricate in a wide range of sizes and shapes
2) suitable for both degradable and non degradable systems
3) There is no dose dumping.

Disadv:-

(1) Zero order is difficult.
2) It is not possible to blend all types of drugs with a given polymer matrix.

(2) Dissolution controlled release systems:-

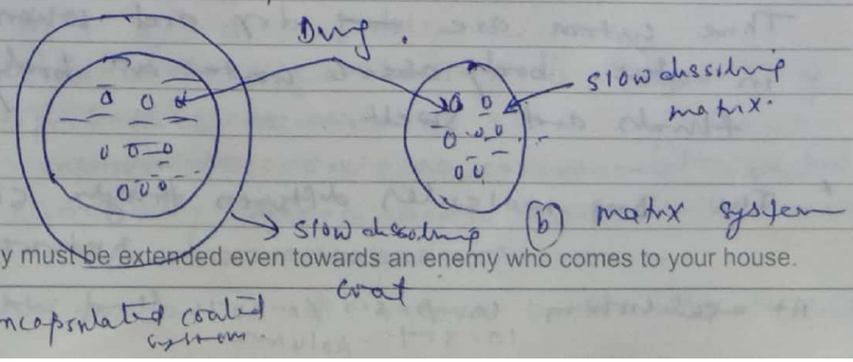
a) Encapsulation / coating:- These systems can be prepared by coating the individual particles of drug with a slow dissolving material.

The coated particles can be placed in capsules or compressed directly into tablets.

b) matrix (monolith):-

Drug is dispersed in a slow dissolving matrix consisted of polymers. The drug dissolution and release is determined by the rate of penetration of the dissolution fluid into the matrix.

The penetration of dissolution fluid depends on the matrix porosity, presence of hydrophobic additives and the wettability of systems and surface particle.

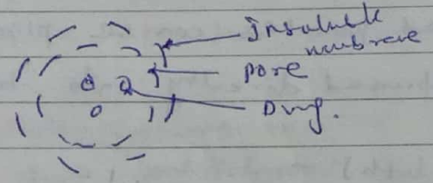


(3) Diffussion and Dissolution controlled systems :—

These systems consist of drug core enclosed in a membrane, which is practically soluble.

Dissolution of part of outer membrane results in facilitated diffusion of the contained drug through pores in the outer membrane.

The fraction of soluble material in the coating is a release rate controlling factor



4) Water penetration controlled systems :—

Rate controlled is obtained by the penetration of water into system. Two types

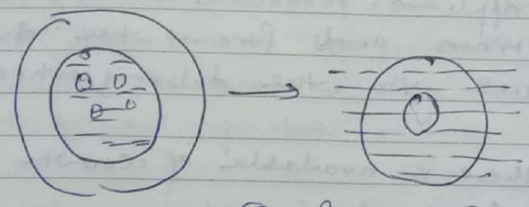
a) Swelling controlled release
b) Osmotically controlled delivery system

a) Swelling controlled release :—

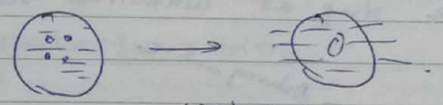
These system are ~~drug~~ dry and when kept in the body absorb water or body fluids and swell.

* The Drug molecules diffuses through swollen matrix.

At equilibrium comprises 60-90% fluid and only 10-30% polymer.

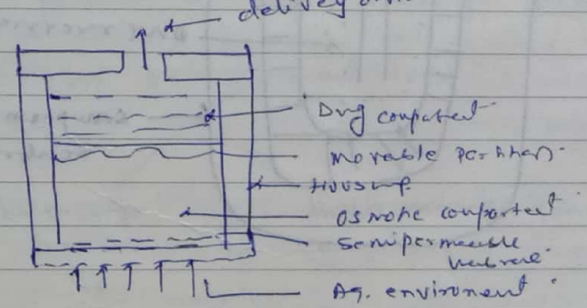


(A) Reservior.



Matrix.

b) Osmotically controlled system :—



Osmotic pump consists of ~~rigid~~ rigid housing containing ~~osm~~ osmotic agent and is seperated from the drug by a movable fraction.

One wall of rigid housing is composed of semipermeable membrane

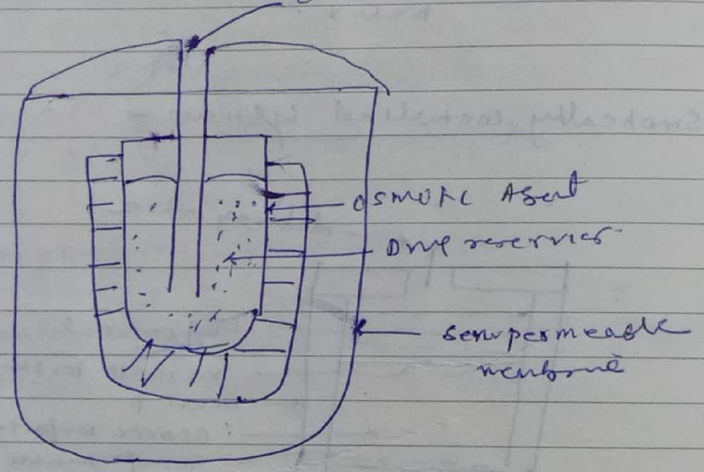
On exposure to an aq. environment water is osmotically driven across the semipermeable membrane,

which results in ↑ volume within osmotic compartment

This in turn applied pressure on the movable ~~Portion~~ portion and forces the drug out of device via the delivery orifice.

In market there is available of osmotic pump ie Alzet.

It is implanted in the tissue of animals to deliver the drug at controlled rate.



The drug is placed in an Impermeable flexible wall reservior which is surrounded by an osmotic agent.

7 SUNDAY

The osmotic Agent is surrounded and sealed within a rigid cellulose acetate membrane, which is Semipermeable membrane.

In an aqueous environment water is osmotically driven across the semipermeable membrane and the resultant pressure on the reservior wall forces the drug out of the orifice.

Ex It can be implants to opthalmic region, SubCutaneous region etc.

5) Ion Exchange resins:—

Zero-order release kinetics can be obtained by using Ion-exchange resin based drug delivery system.

The rate of release is proportional to the conc of Ions present in the vicinity of administration site.

It can be divided into.

Cation exchange resin. Anion exchange Resin.

The negatively or positively charged molecules combines with appropriate ions producing Insoluble Polysalt resinates.

The drugs which possesses following properties are Suitable candidates to prepare controlled release resinates

1) Acidic or basic drugs ✓
2) Absorption window through the whole length of GI tract
3) Biological half life in between 2-6 hr.

4) Sufficiently stable in gastric juice.

The drug-resinate complex can be prepared either by

1) Incubating the drug-resin solution
2) Passage of drug solution through a column containing Ion-exchange resin.

5) PH-Independent formulations:- ✓

Two systems have been developed to nullify the influence of GI PH on dissolution and absorption of drugs.

Buffering agent (such as physiologically acceptable salts of amino acids, citric acid, tartaric acid) are added to the formulation to maintain a constant PH thereby rendering PH independent drug release.

In this PH Independent granules are designed for the oral delivery of acidic or basic drugs at the rate ie Independent of the PH in the GI tract. ✓

7) Altered density formulations:-

The GI transit time is normally less than 24 hr. This is a major limiting factor for oral controlled release dosage form.

ways by which this can be achieved are

1) Altering the density of formulations. ✓
2) Bioadhesion or mucoadhesion approach. ✓

Altering the formulation Density

a) High density approach.

The density of the pellets must be higher than that of normal stomach content ie 1.4 gm/cc. ✓

Such types of formulations can be prepared by coating the drug on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder and ZnO and covered by diffusion controlled membrane. ✓

b) Low Density Approach:-

Shells which have an apparent density lower than that of gastric fluid ie 1.4 gm/cc can be used as a carrier of drug for Low density sustained release formulations. ✓

Polystyrol, PVP. etc. and the empty shell is undercoated with sugar or polymeric material such as cellulose Acetate Phthalate and methacrylic polymer.

c) Buoyant / Floating Tablets :-

The formulation is prepared by granulating a mixture of drug, excipients and 20-75% w/w of hydrocolloids, such as hydroxyethyl cellulose, hydroxypropyl cellulose HPMC. These granules are then compressed. ✓

When tablet contacts with gastric fluid, it forms a water impermeable colloid gel barrier around its surface and remains float in the gastric fluid. ✓

This can be applied for sustained release bilayer tablet containing immediate and maintaince dose. ✓

d) Floatation chamber :-

This principle is applied to introduce a gas filled floatation chamber into a microporous compartment, which contains a drug reservior.

The compartment has apertures at the top and bottom walls for the passage of gastric fluid that can dissolve the drug. The peripheral walls are sealed to prevent the contact of undissolved drug with stomach

A man without a smiling face must not open a shop.

parenteral controlled release system :-

Sustained / controlled release parenterals are

1) Aq. soln ✓
2) aq. suspension ✓
3) oil soln ✓
4) oil suspension ✓
5) Emulsions ✓
6) Biocompatible carriers. ✓
   a) erythrocytes
   b) Biological and synthetic macromolecules.
7) liposomes ✓
8) Nanoparticles ✓
9) Implants. ✓

(1) Aq. solutions :-

a) High viscosity products :-

As viscosity ↑, the diffusion coff of the drug ↓ and delay the drug transfer.

Ex. methyl cellulose, sod. CMC, PVP etc.

Water soluble drug form a complex with these macromolecules & delay drug release.

Friendship increases in visiting friends, but in visiting them seldom.

b) Complex formation :-

Dissociable complex with MC, sod. CMC and PVP for IM administration can prolong the drug action.

It is similar to that of plasma protein binding.

2) Ag. suspension :-

It gives longer duration of action than aq. soln when given IM or SC.

a) Use of viscosity builders :-

↑ the viscosity of the vehicle and ↓ diffusion coefficient of drug.

b) Microspheres :-

solid spherical particle that contain dispersed drug molecules in soln.

14 SUNDAY

suspending the drug in biodegradable/ bioerodable polymer followed by decreasing the mixture of particle at <600 μm, then injected as a suspension in CMC soln.

Ex of Polymers :- Poly (Isobutyl cyanoacrylate).

c) Micro capsules :-

coating material can be natural or synthetic polymer such as Nylon, albumin.

film thickness varies from 1-200 μm.

Release may be dissolution diffusion or dissolution and diffusion control.

Ex Antineoplastic drug, narcotic, steroids, harmones etc.

d) Magnetic microsphere :-

prepared to minimize RES clearance ↑ target specificity.

Used for localized tumor treatment.

= prepared from Albumin and magnetite (Fe_3O_4)
= About 1 μm in size and can be injected IV.

Ex Doxorubicin.

3) Oil solutions :-

Drug release mechanism is the partitioning of drug out of the oil into the surrounding aq. medium.

Approach is applicable for oil soluble drug and possesses optimum partition coefficient.

Ex In Injection sesame oil, olive oil, arachis oil, almond oil, maize oil, cotton seed oil, castor oil.

4) Oil suspension:-

Suspended particles ~~acts~~ acts as drug reservior.

Drugs are available by the process of dissolution of drug particles followed by partitioning from the oil solution to the aq. medium.

5) Emulsion:-

Multiple emulsion as W/O/W and O/W/O.

The rate of release is effected by
1) Internal phase vol.
2) Size of emulsion
3) osmolarity of the dispersed phase.

6) Biocompatible carriers:-

a) Liposomes
(Already discussed)

Happiness is a wondrous commodity; the more you give, the more you have.

7) Liposomes:-

— Under Discussion.

8) Nanoparticles.

— Discussed —

9. Implants:-

They are placed sc to obtain sustained drug delivery. A micro surgery is required for implantation of device.

Mechanism:- Drug diffusion, polymer dissolution or combination of both.

Ex Implants of non-biodegradable Polymers polydimethyl siloxane,
Biodegradable :- poly (caprolactone), poly (lactic acid), poly (glycolic acid) and poly (orthoesters) deliver drug by diffusion and/or erosion.

10) Infusions:-

These system consists of
a) a drug reservior
b) a rate controlling unit (Pump)
c) an energy source
d) Safety device for possible failure of system
Safety

Do not bite the hands that feeds you

→ The variety of pumps differing mainly energy source are

1) simple gravity feed pump uses gravity as energy source ✓
2) Syringe pump used as synchronous motor to drive a plunger to meter drug into the body. ✓
3) The non-volumetric peristaltic pump which forces drug solution by external pressure through tubing to obtain continuous drug delivery ✓

All these pumps are inconvinent for patient to use. so small implantable pumps such as osmotic pumps and electrostatic pumps are developed.

The desirable features should be

1) Should be biocompatible ✓
2) It should allow easy adjustment post implantation ✓
3) maintain zero order ✓
4) Drug reservior should be small enough for easy implantation large enough to minimize frequency of refill.

Trans dermal Delivery system

→ Discussed

When money speaks truth remains silent.

Ophthalmic Drug delivery system :—

Necessities of controlled ocular delivery system is

1) To overcome side effects of frequent dosing and high cover of drugs by conventional ocular dosage form
2) provide sustained or controlled release
3) to ↑ ocular bioavailability of drugs by increasing corneal contact time.
4) To improve patient compliance.

a) Polymeric solution :—

The addition of polymers like cellulose, PVP, hydroxypropyl cellulose and PVA to the eye drop solution, increases tear viscosity which in turn prolong the contact time of drug with corneal surface

b) Mucoadhesive or Bioadhesive dosage form :—

They adhere to mucin or epithelium in the cul-de-sac and ↑ the corneal contact time.

c) collagen shields :—

collagen is the structural protein of bones tendons ligaments and skin comprises more than 25% of the total body protein in mammels.

There can be no true friendship without sincerety.

For drug delivery, the shields are soaked in an eg. soln of drug whereby the drug is absorbed by the protein matrix and is released once the shield dissolves in the eye.

Ocular drug delivery devices:-

1) Matrix type drug delivery system
   a) hydrophilic soft contact lenses
   b) Soluble ocular drug inserts (SODI)
2) Capsule type drug delivery systems (Ocuserts and related devices)
3) Implantable drug delivery pumps. osmotic minipumps, Alzet, Infusaid-

1) Matrix type Drug delivery system:-

a) Hydrophilic soft contact lenses:-

These are made up of hydrogels. They have ability to absorb certain quantity of drug solution and release them.

21 SUNDAY

Ex ocular delivery of pilocarpine, Idoxuridine, ciprofloxacin HCl

b) Soluble Ophthalmic Drug Inserts:-

They are thin, elastic, oval shaped plates prepared from polymer and co-polymers of polyacrylamides, ethacrylates and vinyl pyrrolidone.

They are well tolerated by eye tissues.

SODI's are impregnated with antibiotics, sulfonamides pilocarpine, atropine.

When SODI's is inserted into the conjuctival sac, it absorbs tears rapidly swell and dissolves in about 30 to 90 minutes, releases drug in controlled manner.

2) Capsular type:-

Contains drug encapsulated within a closed compartments surrounded by a polymeric membrane.

Ocuserts:-

Ocuserts provide the controlled and continuous delivery of pilocarpine at a zero order rate of 20 or 40 µg/hr for seven days.

It was marketed by Alza corporation of California.

It is a membrane reservior type flate, flexible elliptical device. It consists of two outerlayer of rate controlling ethylene vinyl

acetate (EVA) and an inner layer of pilocarpine

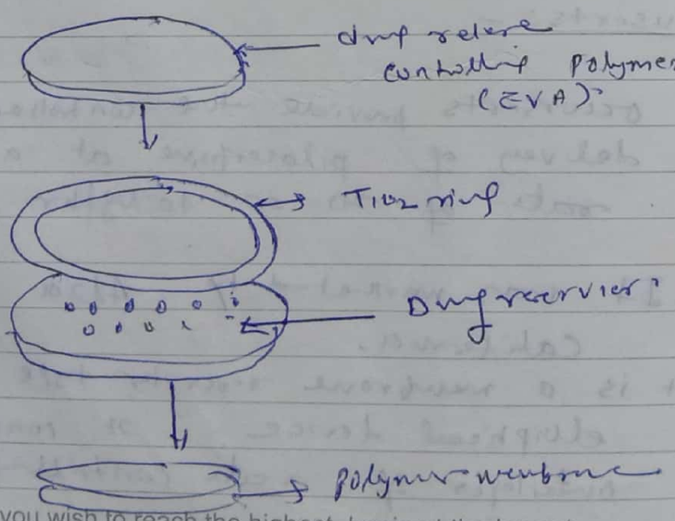
in an alginate gel.
A retaining ring of EVA impregnated with TiO_2 enclosed the drug reservoir circumferentially.

↑ rate of release of pilocarpine in a device is facilitated by addition of flux enhancer ie di-(ethylhexyl) phthalate.

The disadvantage of nonbiodegradable therapy are

1) High cost due to complicated fabrication procedure
2) It is non-biodegradable device and must be remove after seven days.

It improves non compliance problems low intraocular drug bioavailability and potential systemic side effects of pilocarpine.



3) Implantable Drug Delivery pumps.

Intravaginal and Intrauterine Drug Delivery system:-

controlled release Intravaginal systems are used for contraceptive steroids.

The advantages are

1) Self Insertion and removal of device is possible
2) Continious administration of an effective dose level and better patient compliance
3) Avoid hepatic first pass metabolism.
4) Improved bioavailability and lesser drug dose compaired to oral route.

medicated Vaginal rings:-

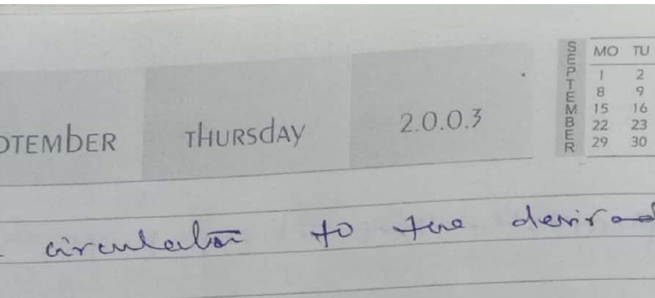
Release and subsequent absorption involves dissolution of the finely divided, well dispersed drug particles into the surrounding polymer, diffusion across the polymer matrix to the surface of device portion and subsequents diffusion of drug across the Vaginal fluid uptake by Vaginal epithelium and permeation across it followed by transport and distribution of drug molecules

by systemic circulation to the desired site.

Contraceptive vaginal ring:-

prepared by dispersing medroxy progesterone acetate (MPA) as micronised solid particles in a viscous mixture of silicone elastomer and a catalyst and then extruding the steroid - polymer dispersion into a mould to form a doughnut shaped vaginal ring.

It is matrix diffusion controlled device.



Other ex progestin + estrogen + Ag. soln of PEG-400 + silicone elastomer.

How poor are they, that have no patience.

Intrauterine Drug delivery system (IUD).

1) Encapsulated drug delivery devices
2) Drug dispersing matrix devices
3) Composite drug delivery devices

1) Encapsulated :-

contains polymeric membrane which encapsulates the drug and also controls the release rate of drug. zero order

2) Drug dispersing matrix devices:-

Homogeneously dispersed drug particles in a cross linked polymer matrix.

a) Retrievable matrix devices:-

Solid drug powder + semi solid silicone polymer + low density polyethylene particle → melt extrusion process.

Example:- Progestin release IUD.

b) Biodegradable matrix devices:-

Dissolving Drug + poly lactic acid particles

Children are like wet cement. Whatever falls on them makes an impression.

In an organic solvent and then melt pressing at an ↑ed temp to produce drug dispersed matrix devices.

3) Composite Drug Delivery devices:-

combination of encapsulated drug delivery with drug dispersing matrix devices.

a) Progestasert (Progesterone Release IUD):-

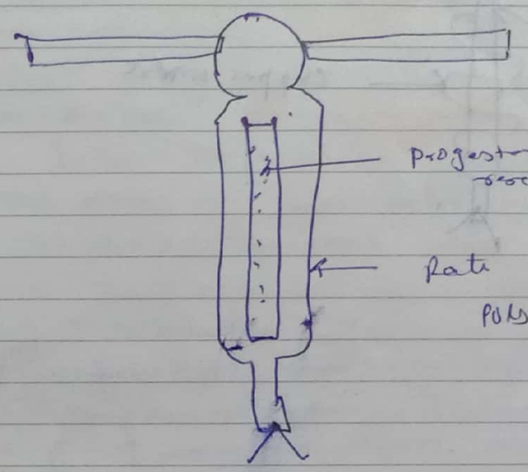
It contains drug reservior which is a suspension of progesterone crystal in liquid silicone polymer.

This reservior is encapsulated in a T shaped intrauterine devices. which is enclosed by a non-porous membrane of EVA copolymer.

It is designed to release 65 µg/day of progesterone locally to the uterine cavity to achieve contraception for 1 yr.

28 SUNDAY

Hold a true friend with both your hands.



b) Copper (T) (copper medicated IUD):-

A copper wire is wound around a plastic support of letter T.

The plastic support is of polypropylene or polyethylene.

The Cu wire of surface area 200 mm² exhibits maximum contraceptive activity.

The release of Cu ions in body fluids takes place by oxidation of copper.

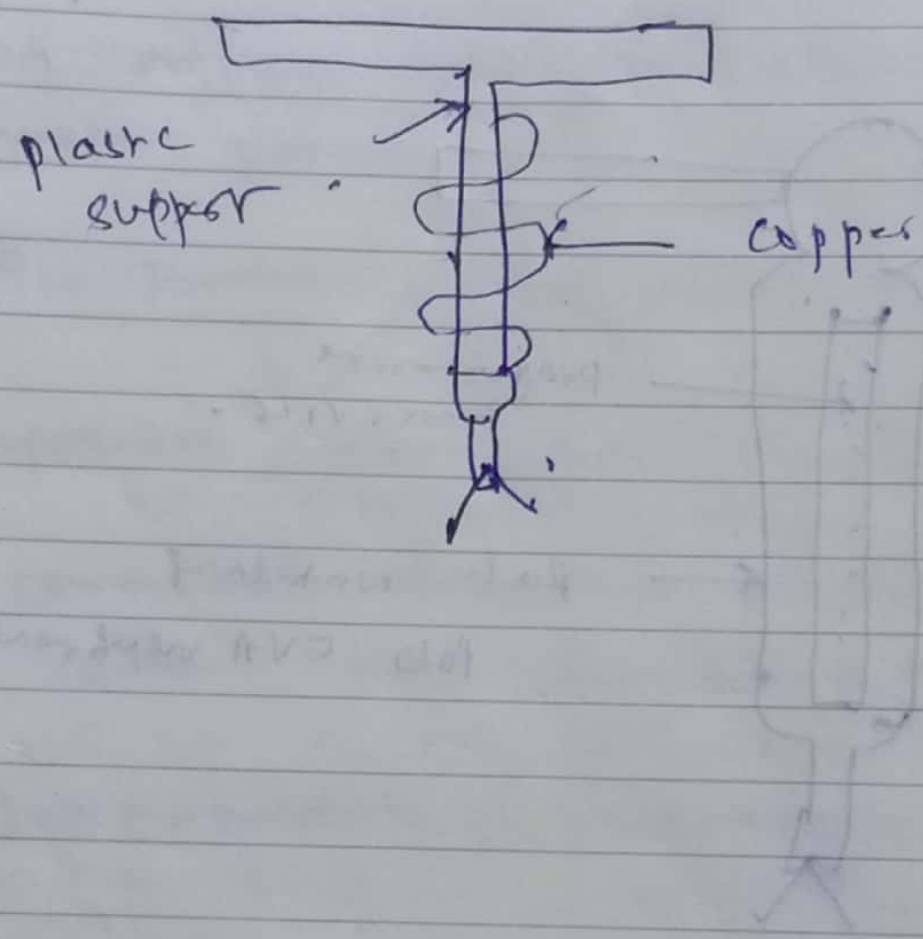
The device is for 3 yr.

Hospitality must be extended even towards an enemy who comes to your house.

30 SEPTEMBER TUESDAY 2.0.0.3

SEPTEMBER

MO	TU	WE	TH	FR	SA	SU	WK
1	2	3	4	5	6	7	36
8	9	10	11	12	13	14	37
15	16	17	18	19	20	21	38
22	23	24	25	26	27	28	39
29	30						40



Anger is a short-term madness.