2.0.0.3 WEDNESDAY OCTOBER 1

OSMOTIC PUMP:

Introduction :-

In Recent years considerable attention has been focused on the development of NDD due to ease of administration and better patient compliance systems.

The reason for this

1) Relatively low development cost and time required for introducing a NDDS ($ 20-50 million and 3-4 years) as compared to New chemical entity (approx $ 500 million and 10-12 yrs).

2) In the form of NDDS an existing drug can get a new life thereby increasing its market value, competitiveness and patent life

3) Among the various NDDS available in market controlled Release (CR) systems which hold the major market share due to ease of administration and better patient compliance

4) Majority of oral CR dosage forms fall in the category of matrix, reservoir or osmotic systems.

Glory is a poison that can only be taken in small doses.

Osmotically controlled oral drug delivery.

(i) Osmotic system utilize the principles of osmotic pressure for the delivery of drugs.

2) Drug release from the system is independent of PH and other physiological parameters to a large extent and we can optimize modulate the release characteristics by optimizing the properties of drug and system.

4) Alza corporation of USA (Now merged with Johnson & Johnson USA) was first develop an oral osmotic pump

5) They are also known as OROS (Oral Osmotic System) and today different types of oral osmotic pumps are available

6) It can be used as experimental tool to determine important pharmakokinetic parameters of new or existing drug.

7) They can also be utilized to deliver drugs at controlled and predetermined rate.

OSMOSIS:-

Diffusion of fluid through a semipermeable membrane from a soln with a low solute concn to a soln with higher concn until there is an equal conc

Do good to your friend, to keep him, and to your enemy, to make him your friend.

of fluid on both sides of the membrane.

Theory of osmotic pump:-

The general expression for the solute delivery rate (dm/dt) from a osmotic pump can be described

$$\frac{dm}{dt} = (A/h)\, L_p(\sigma\Delta\pi - \Delta p)\cdot C$$

A = membrane Area.

h = membrane thickness

L_p = mechanical permeability

σ = the reflection efficient.

π = the osmotic pressure

p = hydrostatic pressure.

C = conc of compound in the dispersed fluid

1) As the size of delivery orifice ↑ hydrostatic pressure inside the system is minimized ($\Delta\pi > \Delta P$)

2) Also when the osmotic pressure of the formulation is large compared to the osmotic pressure of environment, π can be substituted for $\Delta\pi$.

3) L_p can be replaced with constant

A man without patience is a lamp without oil.

$$\frac{dm}{dt} = (A/h) K \pi \cdot C$$

Factors affecting the release rate

1- solubility

* Delivery rate of a drug from an osmotic pump depends ~~on~~ to a large extent on the solubility of drug at saturation.

Water solubility of drug in the range of 50 - 300 mg/ml.

* By modulating the solubility of drug within the core effective release pattern may be obtained for the drug

Some of approaches that have been used to deliver drugs having extremes of solubility are

5 SUNDAY 1) Co- compression of drug with excipients

Drugs have high water solubility, their solubility was reduced by incorporation of Niacl into the core tablet formulation (ex diathozem).

2) Addition of solubility modulating agents are either

surfactant (SLS)

Complexing agent (sod. salicylate)

organic acid (succinic, adipic acid) ex doxazosin.

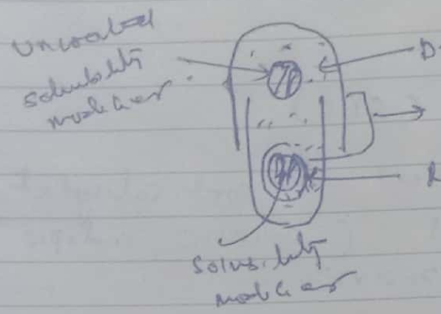
3) Use of polymer coated buffer components to modulate the drug solubility within the core

4) Use of buffers which react with the drug to produce a new compound having thermodynamic properties different from parent drugs (ex theophylline)

2) Use of encapsulated excipients:—

* solubility of poorly water soluble drugs was improved by incorporation of encapsulated excipients (pH- controlling excipients) within the capsule device.

* Formulating as mini tablets which coated with a rate controlling membrane to prolong its availability within the core



Delivery system having encapsulated excipients

3) Use of Swellable polymers :—

Swellable polymers can be utilized for osmotic delivery of drugs having poor aqueous solubility

* The formulation mainly consist of a compartment containing the drug swelling agent and osmagents coated with a rate controlling membrane.
* Vinyl pyrrolidone / vinyl acetate copolymer and polyethylene oxides were used as swelling agent
* Uniform rate of swelling of these polymers ensure that the drug is released at a relatively constant rate
* Also, the pressure produced during swelling doesn't lead to rupture of the system

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

Use of Effervescent mixtures :—

to delivery poor water soluble drugs.

Citric acid and sod. bicarbonate

Use of Cyclodextrin derivatives :—

Incorporation of cyclodextrin-drug complex has also been used for delivery of poorly water soluble drugs from the osmotic system

ex Sulfobutyl ether - β cyclodextrin sod. salt; β cyclodextrin ethers as solubilizer and osmotic agents

Resin modulation approach.

Release of higher water soluble drugs was modulated using positively charged anion exchange resins ex poly (4 vinyl pyridine).

use of Alternative salt form :—

These salt forms were found to have optimum solubility and provided extended release for some drugs

use of Crystal habit modifier :—

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

If the drug exist in more than one crystal form, each having different eg. solubility, it is beneficial to include a crystal modifying agent such as combination of hydroxy methyl cellulose + HEC

Use of lyotropic crystals:-

There are non polymeric compounds generally in the ~~range~~ MW range of 200-1500. (Amphiphatic compounds). for poorly water soluble drugs.

ex Phosphatidyl controlled choline (lecithin) phosphatidyl ethanolamine, Senne, phosphatidyl glycerol,

Use of Wicking Agents:-

Wicking agent is dispersed throughout the composition that enhances the contact surface area of drug with the incoming Aq. fluids.

ex Colloidal silicon dioxide, PVP, SLS

(2) Osmotic pressure:-

The release rate of drug from an osmotic system is directly ∝ to the osmotic pressure of the core formulations.

* The osmotic pressure gradient between inside the compartment and the external environment should be optimized to control rate of drug release.

* It is possible to achieve and maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in the compartment.

Category	Examples
water soluble salts of inorganic acids.	$MgCl_2$ or sulfate, lithium, sod or potassium chloride lithium sodium or Potassium sulfate, sodium or potassium hydrogen Phosphate
water soluble salts :- of organic acids.	sodium and potassium acetate, magnesium succinate, sod. benzoate, sodium citrate, sodium ascorbate etc.
carbohydrates :-	Arabinose, ribose, Xylose, glucose, raffinose

Water soluble auxiroads – Glycine, leucine alanine, methanol

organic polymeric osmogents – Sod. CMC, HPMC HEMC cross linked polyethylene oxide carbopols, polyacrylamide

Osmotic pressure of saturated soln of common pharmaceutical solutes: –

Compound or mixture	Osmotic pressure (atm)
Lactose - fructose	500
Dextrose - fructose	450
Sucrose - fructose	430
mannitol - fructose	415
NaCl	356
Fructose	335
Lactose - sucrose	290
KCl	245
Lactose - dextrose	225
Sucrose	150
12 SUNDAY Mannitol - lactose	130
Dextrose	82
Mannitol	38

3.) Size of delivery orifice: –

* Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release
+ The size of delivery orifice must be optimized in order to control the drug release from osmotic systems.
* If the size of delivery orifice is too small zero order delivery will be affected because of

development of hydrostatic pressure within the core which may lead to deformation of delivery system and unpredictable drug delivery

* If the size of delivery orifice is too large lead to increase diffusion of drug through the orifice
* Delivery orifice in the osmotic system can be created by the following means

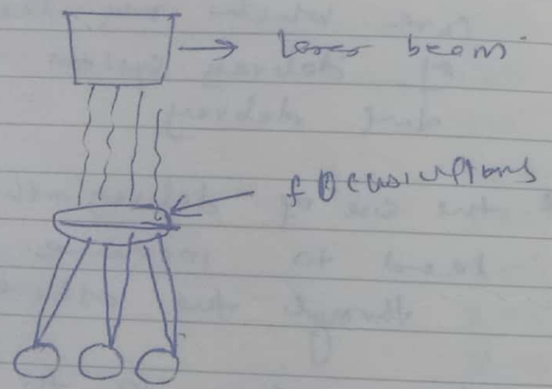
- Laser drilling
- Use of modified punches
- Systems with passageway formed in situ
- Use of pore formers

Laser drilling :-

Tablets in which holes are to be formed are charged in the hopper

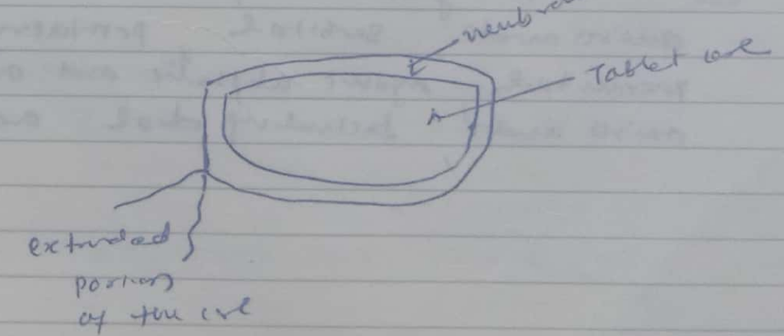
The tablet ~~drop~~ drop by gravity into the slots of rotating head wheel and are carried at a predetermined velocity to the passageway forming station.

* At the passageway forming station each tablet is tracked by an optical tracking system



Systems with passageway formed in site :-

* The system consists of a tablet core of the drug along with water swellable polymer and osmotic agents, which is surrounded by a rate controlling membrane.
* On contact with the env. environment water is imbibed osmotically at a controlled rate and water swellable polymer expands as the osmotic agents dissolves and increases the osmotic pressure inside the tablet.
* This results in a rate controlled slight expansion of the partially hydrated core.
* The expansion of core causes a small opening to form at the edge of the tablet (weakest point in the membrane) from where the formulation are released.



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OCTOBER

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MO	TU	WE	TH	FR	SA	SU
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Use of Mechanical Pruches :-

The dosage form is pierced using a piercing device that is biased in a sheathed position and unsheathed upon application of compression force.

* Both compression and piercing are done simultaneously

Use of pore formers :-

* Incorporation of water soluble additives in the membrane wall is the most widely reported method
* These water soluble additives dissolve on coming in contact with water leaving behind pores in the membrane through which drug release takes place

Ex dimethylsulfone, nicotinamide, saccharide, amino acids, sorbitol, pentaerythritol, mannitol, organic aliphatic and aromatic, amino acids, including diol and polyols,

Eat to live, not live to eat.

18 OCTOBER SATURDAY

4) membrane types and characterstics :-

The membrane must possess certain performance criteria.

* Sufficient wet strength and water permeability
* It should be selectively permeable to water
* Should be biocompatible
* Effectively isolating the dissolution process from the GIT environment.
* The membrane should be 200-300 nm thick to withstand the pressure within the device

Some of the membrane variables that are important in the design of oral drug system are

1) Type and nature of polymer

- Cellulose esters :-

cellulose acetate, cellulose diacetate, cellulose acetate butyrate

Cellulose ethers :-

ethyl cellulose and hydroxypropyl

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

2003 MONDAY OCTOBER 20

Cellulose Acetate :-

1) widely used to form rate controlling membrane

* CA films are insoluble and semipermeable to allow water to pass through the tablet coating
* Water permeability of CA is relatively high and can be adjusted by varying the degree of acetylation (As acetylation ↑ solvent resistance ↑).
* The permeability of these films can be further increased by the addition of hydrophilic flux enhancers.
* Incorporation of plasticizer in CA coating formulation generally

Lower the glass transition temp.
↑ the polymer chain mobility
Enhance the flexibility
Affect the permeability of the film

Ethyl cellulose :-

water permeability of pure EC is very low that may in slow release formulations.
* Drug release can be modified with addition of water soluble additives HPMC

Endrgit :-

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

21 OCTOBER TUESDAY 2.0.03

OCTOBER
MO	TU	WE	TH	FR	SA
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2 - Membrane thickness

Thickness of the membrane has a marked effect on the drug release from osmotic systems, which are inversely proportional to each other.

3) Type and amount of plasticizer :-

* They are Low M.W. diluents to modifying the physical properties and improve flow forming characteristics of polymers
* Plasticizer can change viscoelastic behavior of polymers significantly
* plasticizer can turn a hard and brittle polymer into a softer, more pliable material
* Also effects on mechanical permeability
Ex polyethylene glycols

How poor are they, that have no patience.

NOVEMBER
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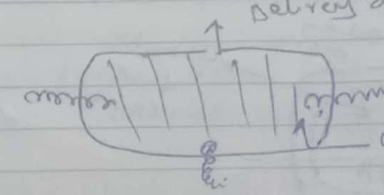
10	11	12	13	14	15	16	46
17	18	19	20	21	22	23	47
24	25	26	27	28	29	30	48

2.0.03 WEDNESDAY OCTOBER 22

Types of osmotic pumps drug delivery system :-



It consists of an osmotic core (containing drug with or without an osmogent) coated with a semipermeable membrane.

The dosage form after coming in contact with the aq. fluids imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulations.

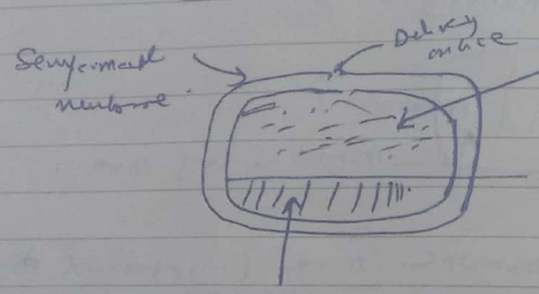
The osmotic imbibition of water results in a formation of saturated solution of drug within the core which is dispensed at a controlled rate from the delivery orifice in the membrane.

* Though 60-80% of drug is delivered at a constant rate from pump a lag time of 30-60 min is observed in most of cases as the system hydrates before zero order deliver from the systems begins.
* Systems are suitable for delivery of drugs having

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

moderate water solubility

2) Push pull osmotic pump (PPOP)



* can be used for delivery of drugs having extremes of water solubility.
* It is bilayer tablet created with semipermeable membrane.
* Drug along with osmogents is present in the upper compartment whereas lower compartment consist of polymeric osmotic agents.
* The drug compartment is connected to the outside environment via a delivery orifice. After coming in contact with the aq. environment polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of fine dispersion via the orifice.

A number of modification are available.

* delayed push pull systems ex extended release of verapamil.
* Multilayer push-pull system. (for pulsatile or delayed drug.
* Push-stick system for delivery of insoluble drugs requiring high loading with an optional delayed, patterned or pulsatile release profile.

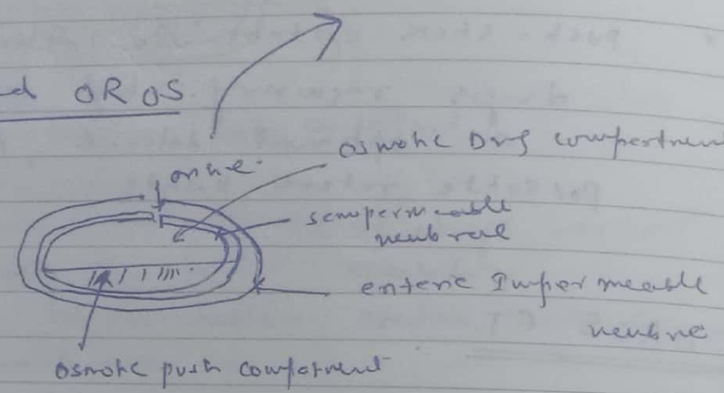
3 OROS CT.

It is used as once or twice a day formulation for targeted delivery to the colon.

* It can be single unit or It can comprise of as many as five to six pull osmotic units filled in a hard gelatin capsule.
* After coming in contact with GIT fluids, gelatin capsule dissolves and the enteric coating prevents entry of fluids from stomach to the system.
* As the system enters into the small intestine the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell

* At the some time flowable gel is formed in the drug compartment which is pushed out of the orifice at a rate which is precisely controlled by the rate of water transport across semipermeable membrane.

3- Liquid ORAS

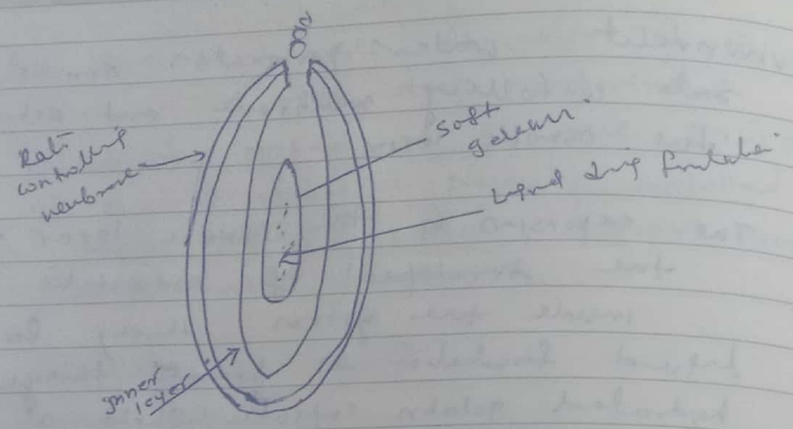


It is designed to deliver drug as liquid formulations and combine the benefits of extended release with high bioavailability.

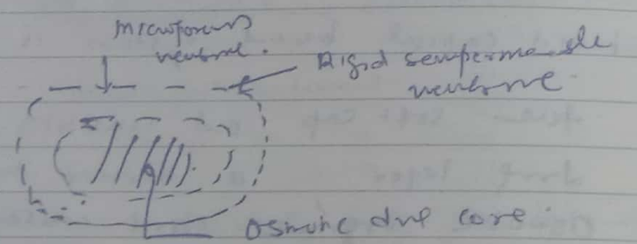
* The liquid drug formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer and the release controlling membrane.
* A delivery orifice is formed through these three layers. When the system is in contact with the aq.

environment water permeates across the rate controlling membrane and activates the osmotic layer

* The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice.
* The liquid drug formulation is pumped through the delivery orifice
* Hard capsule based system is similar to the soft cap and consists of a liquid drug layer a barrier layer and an osmotic engine, and coated with SPM.
* A delivery orifice, drilled in the membrane at the end of the drug delivery provides an outlet for the drug suspension
* After coming in contact with aq. environment water is imbibed across the SPM expanding the osmotic engine.
* The osmotic agent pushes against the barrier releasing drug through the delivery orifice



Controlled porosity osmotic pumps (CPOP)



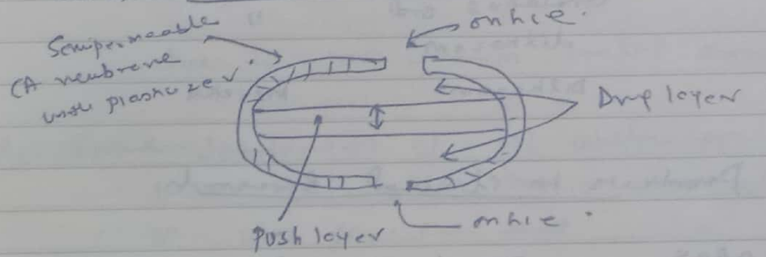
* contains water soluble additives in the coating membrane which after coming in contact with water dissolve resulting in on in situ formation of microporous membrane
* The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic with simple diffusion playing a minor role.

Do good to your friend, to keep him, and to your enemy, to make him your friend.

Multi Particulate delayed release system

* It consist of pellets of drug (with or without osmogents) coated with SPM.
* These pellets after coming in contact with the aq. environment imbibe water osmotically, which results in a rapid expansion of the membrane leading to the formation of pores and drug release

Sandwiched Osmotic Tablet :—



* A Tablet core consisting of a middle push layer and two attached drug layer is coated with SPM
* Both the drug layers are connected to the outside environment via two delivery orifice (one on each side)
* After coming in contact with the aq environment, the middle push layer contains swelling agents such

A man without patience is a lamp without oil.

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And the drug is released from the delivery device.

Some commercially marketed products.

Product	chemical	Developed by
Acutrim	Phenylpropalonnal.	Alza corp.
Calan SR	Verapamil	"
Minipress XL	Prazosin.	"
Tolzem.	Gralafral and dilhazem	"
Tiamate	Dilhazem.	Merck.

Products in clinical Research

Dilantin OROS	Phenytoin	Parke-Davis.

Advantages and Applications :-

(1) Delivery of drugs can be designed to follow zero order

* The drug release is independent of the gastric pH and hydrodynamic conditions

3) delivery rate of drug is highly predictable and can be programmed

Imagination is useful only as long as it remains practical.

2003 Friday OCTOBER 31

* Drug release exhibits significant In-vitro/ In-vivo correlation within specified limits.

* Drug release from the osmotic system is affect minimally by the presence of food.

* Better therapeutic control

Limitation and Adv. effects :-

(1) During G.I. of Nifedipine GITS tablets several batches showed different release pattern of the drug.

due to non uniform coating around the tablets.

* Some Incidences of GI obstruction in patients with pre-existing peptic ulcer disease. and It was possible that

* Indomethacin OROS show frequent Incidences of serious gastrointestinal reaction.

A man without imagination is like a bird without wings.