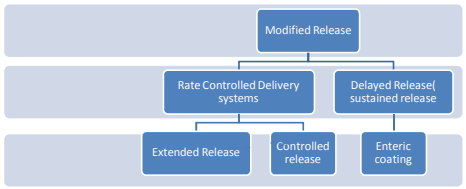
Modified Release Dosage Form

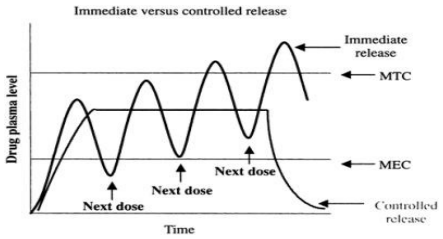
Conventional Drug Delivery

- Conventional Drug Delivery systems such as tablets, capsules, elixiris and syrups.

Modified Release

- Extended Release
- Delayed Release (sustained release
- Enteric coated tablets

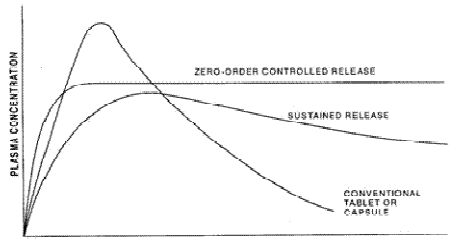




http://aragec.com/controlled+release.html

Delayed Release Dosage form

- Need for a more efficient drug delivery system and improve upon the performance of conventional Dosage form. These were the Delayed Release(sustained Release)
  - Protect drugs against hostile condition in GI.
  - Prolong their action.
  - Improving their bioavailability
  - Provide some degree of control
  - Example Enteric coated.
  - Include polymers, waxes
- Drawbacks:
  - Release of the drug is subject to environmental conditions at the site of drug release.
  - Do not provide long term drug release
  - No constant blood-drug concentration.



Plasma drug concentration profile for conventional release (immediate release), a sustained release and a controlled release formulation.

http://www.pharmatutor.org/articles/review-sustained-release-dosage-forms

Rate-Controlled Drug Delivery Systems

- The rate of drug release from the delivery system is controlled.
- Drug release is Independent on the environmental conditions at the site of administration.
- Drug release is dependent on the properties of the device and the characteristics of the drug and delivery system.
- Involves the use of polymers (permeable barrier the drug must cross before reaching body fluids)

Rate-Controlled Drug Delivery Systems

1. Osmotically Controlled Systems.
2. Ion-Exchange Resins.
3. Diffusion Controlled Systems
   I. Reservoir Devices
   II. Matrix Devices
4. Dissolution Controlled Systems

Advantages

1. Frequency of dosing is reduced.
2. Enhanced patient compliance.
3. Drug administration can be made more convenient. bid vs qid.
4. Total amount of dose administered is low in some cases.
5. Better control of drug absorption can be attained. i.e less fluctuation in drug blood levels.
6. Systemic adverse side effects can be reduced. How?
7. Reduction in overall health care costs. How?

Disadvantage

1. No prompt termination of therapy.
2. Risk of toxicity in the event of dose dumping due to failure of the technology.
3. Loss of flexibility in adjusting dosage regimens or drug dose.
4. Economic factors – Manufacturing is costly

A Successful Extended Release product

1. Release of drug from dosage form at predetermined rate.
2. Dissolves in the gastrointestinal fluids.
3. Maintained at a sufficient gastrointestinal residence time.
4. Absorbed at a rate that replaces the amount being metabolized and excreted.

Drug Candidates for Extended-Release Products

1. Exhibit neither very slow nor very fast rates of absorption and excretion.
2. Uniformly absorbed from GI tract at a predictable rate.
3. Administered in relatively small amounts.
4. Posses a good margin of safety. Is it large or narrow therapeutic window?
5. Used to treat chronic diseases rather than acute.

Unsuitable drugs for Extended Release

1. Not effectively absorbed in the lower intestine.
   - Riboflavin, ferrous salts
2. Absorbed and excreted rapidly; short biological t1/2(<1 hr).
   - Furosemide
3. Long biologic half-lives (>12 hr)
   - Diazepam, phenytoin
4. Large doses required (>1gm)
   - Sulfonamides

5. Drugs with low therapeutic indices.
   - Phenobarbital, Digitoxin
6. Precise dose titration to individual is required.
   - Anticoagulants, cardiac glycosides
7. No clear advantage for SR formulation
   - Griseofulvin

Loading dose vs Maintenance dose

1. Loading dose
- immediately available portion of the SR dosage form
- Minimizes lag time
- Responsible for initial part of plasma-conc time profile

2. Maintenance dose
- Slow available portion of the drug
- Responsible for maintaining constant plasma levels
- Depends on length of therapy required

Extended Release Technology

- Extended drug action is achieved by either or:

1. Affecting the rate at which the drug is released by the following technologies
   I. Modifying drug dissolution by controlling access of biologic fluids to the drug by using barrier coatings.
   II. Controlling diffusion rates from dosage forms.
   III. Chemical reaction between the drug or its pharmaceutical barrier and site specific biologic fluids.
2. Slowing the transient time of the dosage form through the GI tract.

Classification of polymers based on Matrix characteristics

1. Insoluble (eroding)
   i. Plastic Matrix : Methacrylate copolymer, polyvinyl acetate.
   ii. Carnauba wax, Stearyl alcohol, Stearic acid, Polyethylene glycol, Castor wax, Polyethylene glycol monostearate, Triglycerides, Cetyl alcohol, Glyceryl monosterate

2. Hydrophilic Matrix:
   i. Methylcellulose, ethyl cellulose Hydroxyethylcellulose, Hydroxypropylmethylcellulose), Sodium carboxymethylcellulose, Carboxypolymethylene, Galactomannose, Sodium alginate

1. Barrier coatings:
Coated Beads, Granules and Microspheres

- Drug is distributed onto beads, pellets, granules or particulate systems.
- Using conventional pan coating or air suspension coating.
- A solution of the drug substance is placed on small inert seeds or beads made of sugar or starch or microcrystalline cellulose spheres.
- Microcrystalline cellulose beads are more durable.

- Some of the beads are kept uncoated. Why?
- 2/3 to ¾ of the beads/granules receive varying coats of a lipid or cellulosic material such as
  1. Beeswax
  2. Carnuba wax
  3. Cetyl alcohol
  4. Glyceryl monosterate
  5. Ethyl cellulose
- Granules of different coatings thicknesses (color coded) are blended to achieve a mix having the desired drug release characteristics.
- Granules are placed in a capsule or compressed into tablets. (combining 3-4 release groups) about 100 beads.
- E.g Spansule

Spansule

2. Multitablet systems

- Small compressed tablets (mini tablets) with varying drug-release profile.
- Mini tablets receive varying coats of a lipid material.
- Placed in a gelatin capsule.
- Each capsule contain 8-10 tablets some uncoated and some coated. Why uncoated?

http://www.pharmatutor.org/articles/recent-advance-pulsatile-drug-delivery-system?page=0,1

3. Microencapsulated Drug

- Microencapsulation is a process by which a drug(solid or liquid) maybe enclosed in microscopic particles by formation of thin coatings of wall material around the substance.
- Wall forming material include:
  - Gelatin
  - Polyvinyl alcohol
  - Ethylcellulose
- Use of two solutions one constitutes the wall forming and drug the second e.g acacia lowers the interfacial tension, and concentrate or disperse the gelatin(wall forming polymer) into tiny liquid droplets forming a film around the drug particle i.e encapsulating it.
- E.g Potassium Chloride ER(Micr-K Extencaps)

4. Drug embedding in Slowly Eroding or Hydrophilic Matrix

- Drug + slowly eroding excipients formed into granules.(provide extended release)
- Granules of Drug without slowly eroding excipients.(provide immediate release).
- Commonly used excipient is Hydrophilic cellulose polymers e.g HPMC (hydroxy propyl methyl cellulose).
- Steps:

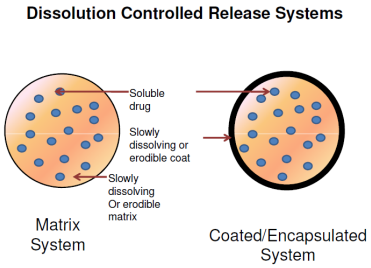
1. Hydration of cellulosic polymer.
2. Gel formation on the polymer surface.
3. Tablet erosion.
4. Continuous release of drug.

Hydrophilic Matrix System

- Granules are prepared of drug + excipients + HPMC (hydrophilic matrix)
- Tablets compressed.
- In GI, tablet is wetted by _____ _____ and polymer begins to _____.
- A gel layer forms on surface of the tablet where initial amount of drug is exposed and released.
- Fluid permeates further into tablet, gel layer thickness increases and soluble drug diffuses through the gel layer.
- As the other layer fully hydrates it erodes from the tablet core.
- Rate of drug release is controlled by diffusion and tablet erosion.

Successful hydrophilic matrix system

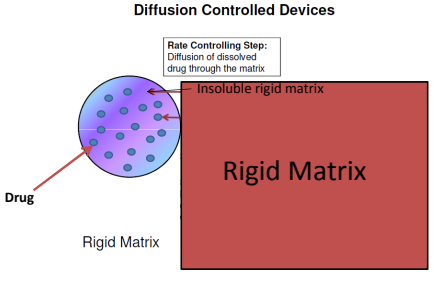
- Polymer must form a gel layer rapidly. Why?
- 20% of HPMC result in satisfactory rates of drug release thus a successful extended release tablet formulation.
- Can also be used to form extended release capsules.
- Or multilayered tablets. Inner core extended release, outer shell for immediate release.



5. Drug embedding in Inert Plastic Matrix

- Drug + inert plastic matrix material formed into granules.(provide extended release).
- Granules of Drug without slowly eroding excipients.(provide immediate release).
- Commonly used excipient is polyvinyl acetate, polymethacrylate.
- Matrix or plastic form is created by compression of the granules and will retain its shape during leaching of the drug and exiting from the GI tract. (excreted unchanged in feces)
- Steps:

1. Hydration of cellulosic polymer.
2. Gel formation on the polymer surface.
3. Tablet erosion.
4. Continuous release of drug by diffusion.



6. Slow dissolving salts or Complex

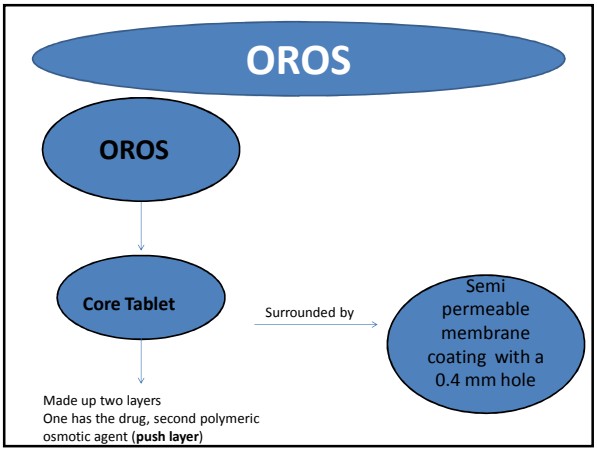
- Drug forms complex with certain chemicals that is slowly soluble in body fluids depending on the pH of the environment.
- This slow-dissolution rate provides the Extended release characteristic for the drug in the complex.
- Salt of Tannic acid provide this mechanism.
- Amine drugs and Tannic acid
- Penicillin G + N, N' Dibenzyl ethylenediamine.

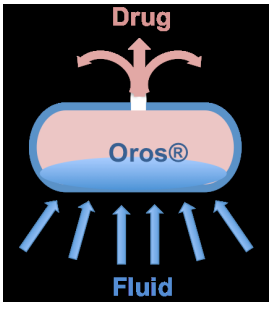
7. Ion-Exchange Resin

- A solution of cationic drug is passed on a column containing ion-exchange resin, forming a resin-drug complex.
- Complex can be formed in tablet, capsule or suspension.
- Release of drug is dependent on the pH and electrolyte concentration in the GI tract.
- Release is greater in the acidity of stomach.

8. Osmotic Pump

- OROS: oral osmotic pump drug delivery system developed by Alza.





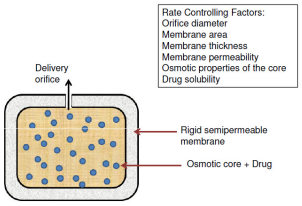
Source: google images

Mechanism of OROS

1. After ingestion, fluid enters through the semipermeable membrane into the core tablet dissolving or suspending the drug.
2. Pressure increases in the osmotic layer, drug solution is pumped out of the delivery orifice.
3. Only drug solution can leave through the hole.
4. Only few drops of water are drawn into the tablet each hour.

5. Osmotic gradient is built between the contents of the two layer core and the fluid in GI tract which controls the rate of inflow of water.
6. Drug delivery is constant as long as the osmotic gradient remains constant.
7. This system is not affected by the GI environment such as pH or motility.
8. The inert components of the tablet remain intact and are eliminated into feces as insoluble shell.

OROS



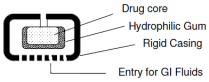
Oral Osmotic pump (oros)

9. Repeat-Action Tablets

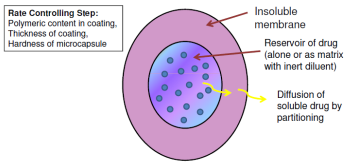
- Drug in the outer shell or coating is released immediately to provide the initial dose of drug (immediate release).
- Drug in the inner tablet core provides subsequent doses separated by a slowly permeable barrier coating.
- The drug from the inner core is released 4 to 6 hrs after administration.

Pressure Controlled System

- **Hydrodynamic Pressure controlled System**
  - Collapsible impermeable drug reservoir enclosed in a rigid housing with openings at one end
  - Other end has an orifice.
  - Space filled with swellable hydrophilic gum
  - Water imbibes – gum swells –hydrodynamic pressure – drug compartment expels the drug

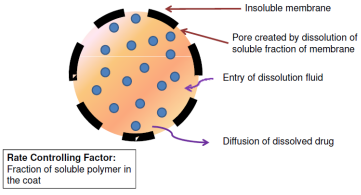


Diffusion Controlled Devices



Diffusion across the insoluble membrane of reservoir device

Dissolution and Diffusion Controlled Release



Targeted Drug Delivery

COLONIC DRUG DELIVERY

- Most drugs are absorbed from upper GIT.
- Colon a promising site for drug delivery
  - *Local disorders (ulcerative Colitis), diverticulousis*
  - *Systemic absorption*
- Drugs *unstable in upper GIT*
- Drugs poorly *absorbed from upper GIT*
- Drugs that necessitate targeting at site.

44

Rationale for colonic delivery

- Treatment of local conditions (targeted drug delivery)
  - Ulcerative colitis
  - Crohn's disease
  - Colon cancer.
- Greater responsiveness to the absorption enhancers
- Delivery protein and peptides (less peptidase activity).

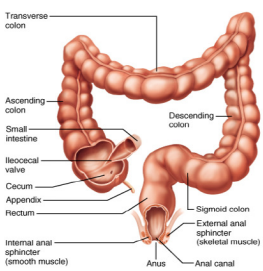
45

Advantages

- Drug is directly available at the affected site.
- Less dose can be administered.
- Decreased side effects of the drug.

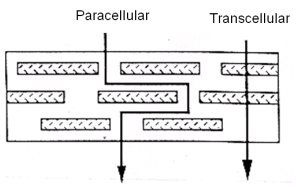
46

Anatomy



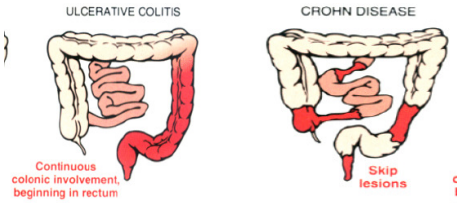
47

Routes of absorption



48

Colon Disorders



49

Strategies

- Coating with pH sensitive polymers
- Microbially/enzymatically triggered systems
- Timed release systems
- Osmotically controlled drug delivery systems
- Pressure dependent release systems.

50

Coating with pH sensitive polymers

- Insoluble in acid and soluble at higher pH
- Eudragit L, Eudragit S, polyvinyl acetate phthalate, CAP, HPMCP.
- Coated to tablets, capsules or pellets providing delayed release.
- Most often used in combination with other strategies for colon targeting

51

Microbially/enzymatically triggered systems

- Azo Bonds -N=N- bonding is taken as an advantage.
- This is cleaved by azoreductases present in the colon.
- Sulphasalazine to 5-ASA (Mesalamine) is the classical example and has been used for years
- Sulphapyridine, one of the cleavage products is responsible for side effects

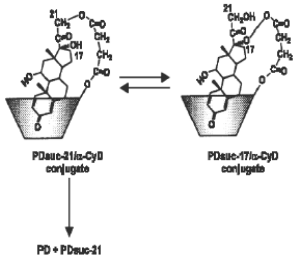
52

Microbially/enzymatically triggered systems

- Glucuronide complexes
  - Glucuronidase
- Glycoside complexes
  - Glycosidase
- Cylodextrin complexes
  - Cyclodextrinase
- Polysaccharide based formulations
  - Polysacharidase

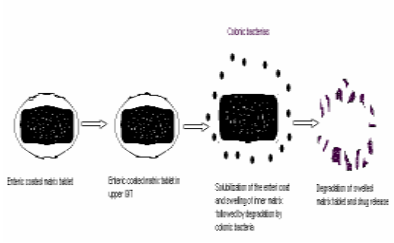
53

Cyclodextrin Conjugates



54

Polysaccharide based formulations
(e.g. pectin)



55

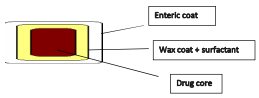
Timed Release Systems

- Transit time through small intestine (3-4 hr).
- This can be achieved by adjusting lag time for release of drug from the dosage form.
- Generally enteric coated to prevent release in stomach (Matrix + Enteric Coat)
- In addition, slow swelling or pH dependent polymers cause slow swelling and slow release

56

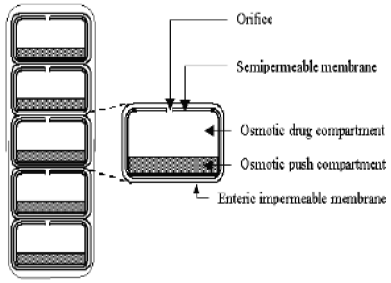
Timed Release Systems

Made of a drug core embedded in Wax coat Matrix which is enteric coated i.e bypass acidic media of the stomach.



57

Osmotically controlled Delivery

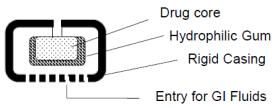


Pressure controlled delivery

- Relies on the relatively strong peristaltic waves in the colon
- Leads to an increased luminal pressure
- Raised pressure ➔ dosage form ruptures
- Releases the drug at desired site

59

Pressured Controlled Delivery



Conclusions

- Colon targeting - attractive (not fully developed)
- Diarrhea and constipation affects residence time
- Antibiotics - kill bacteria
- Administration with antacids problematic - if dosage form is enteric coated

61