CHAPTER 10.
I. ORAL CONTROLLED RELEASE DOSAGE FORMS

ONCE-A-DAY ORAL DOSAGE FORMS
1. DRUGS BECOMING ACTIVE METABOLITE WITH LONG HALF-LIVES
   CLARITIN
   LORATADINE: HALF-LIFE OF 8 HOURS
   DESCARBOETHOXYLORATADINE: 28 H
   CLARITIN-D 24 HOUR EXTENDED RELEASE IS FOR PSEUDOEPHEDRINE

2. DRUGS WITH SHORT HALF-LIVES
   PRILOSEC (OMEPRAZOLE)
   HALF-LIFE OF 0.5-1 HOUR
   INHIBITION OF H+/K+ ATPase ENZYME SYSTEM LASTS 24-72 HOURS
LIMITING FACTORS FOR ORAL CONTROLLED RELEASE DOSAGE FORMS

1. RELATIVELY SHORT GASTRIC EMPTYING TIME AND INTESTINAL TRANSIT TIME
2. NON-UNIFORM ABSORPTION ABILITIES OF DIFFERENT SEGMENTS OF THE GI TRACT
3. PRESHYSTEMIC CLEARANCE
### Biocompatibility and Mutual Effects Between Body and Dosage Form

<table>
<thead>
<tr>
<th>Drug Property</th>
<th>Molecular Weight</th>
<th>Stability</th>
<th>Solubility</th>
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</table>

| Administration Route | Oral, Pulmonary, Transdermal, Implantable, Parenteral |

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<tr>
<th>Optimum Dosage</th>
<th>Oral</th>
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Most polymers have high molecular weight (High Mol. Wt.) and high permeability.

### Targeting

<table>
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<tr>
<th>Organ</th>
<th>Tissue</th>
<th>Cell</th>
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</table>

| Cell Components | |

### Release Mechanism

- Continuous delivery
- Modulated delivery

### Duration of Release

- Delivery Vehicle: Polymer
- Size & Shape: Cell, Tissue

### Dosage Form

- Swallowable: < 1 day
- Gastric retention
- Colon targeting

### LIMITING FACTORS FOR ORAL CONTROLLED RELEASE DOSAGE FORMS

1. Relatively short gastric emptying time and intestinal transit time
2. Non-uniform absorption abilities of different segments of the GI tract
3. Presystemic clearance
4. Poor absorption of peptides and protein drugs
5. Poor in vitro-in vivo correlation

### Oral Drug Delivery Technologies

**Extension of Gastric Retention Time**

A number of approaches are used to extend gastric retention time, which are relatively more difficult compared to extending intestinal transit time. The focus is on the development of gastric retention devices.

**Intragastric Floating Systems (Low Density Systems)**

- Intragastric floating systems (low density systems)
- High density dosage forms
- Mucosadhesive dosage forms
- Unfoldable, extendible, or expandable systems
- Superporous hydrogel systems

**Hydrodynamically Balanced Intragastric Delivery Systems**

- Extends gastric retention time
- Dry mass reduction
- Hydration
- Drug diffusion

![Image of oral drug delivery technologies](Image from Leon Shargel & Andrew B.C. Yu, Applied Biopharmaceutics & Pharmacokinetics. 4th Edn. 1999, Appleton & Lange, Stamford, CT)
**GAS GENERATING FLOATING SYSTEMS**

- Swellable membrane
- Effervescent layer
- CO₂ gas
- Drug diffusion
- Water penetration

**LOW DENSITY MUCOADHESIVE MICROPARTICLES**

- Conventional sustained-release pill
- Water penetration
- Drug diffusion
- (e.g., CaCO₃ + Citric Acid)

**MUCOADHESIVES**

- Poly(acrylic acid) at pH 1–4
- H H
- COOH

**SYSTEMS UNFOLDING IN THE STOMACH**

- Biodegradable polymer
- Failure in unfolding of arms
- Premature degradation of polymers during storage
- Useful in veterinary applications

**SYSTEMS EXTENDING TO COMPLEX GEOMETRIC SHAPES**

- Not easy for drug loading

**SYSTEMS EXPANDING TO LARGER SIZES**

- Biodegradable plug (gas outlet)
- Gas chamber
- Collapsed state
- Expanded state
- The size of expanded system is not large enough for gastric retention

**Gastric Emptying Following a Light Breakfast**

**FAST SWELLING SUPERPOROUS HYDROGEL SYSTEMS**

- Fast swelling with high swelling ratios
- Can be degradable by pepsin and acid
- Currently under development for human study
Development of gastric retention devices

Commercial Technologies
- Superporous Hydrogel Systems (Kos Pharmaceuticals, Inc.)
- Gastric Retention System (DepoMed)
- West Gastroretentive System (West Pharm. Services)
- OraSert™, OraSite® (KV Pharmaceutical)

Practical Considerations
- Optimum gastric retention time?
- Control of exact gastric retention time?

Colon-targeted Drug Delivery Systems

Advantages of colonic drug delivery
- pH
- Enzyme activity
- Transit Time
- Colon segment

Colon-targeted Drug Delivery Systems
- Enteric coating
- pH-sensitive polymers (Enteric coating)
- Redox-sensitive polymers
- Embedding in matrices
- Biodegradable matrices and hydrogels
- pH-sensitive matrices
- Time-dependent systems

Challenges for colonic targeting
- Protection of the incorporated drugs from chemical and enzymatic degradation while traveling through the upper GI tract.
- Release of the incorporated drugs at the colon segment
- Systemic absorption of the released drug at an efficient rate from the colon to be therapeutically effective.

Protection of the incorporated drug
- Coating with polymers
  - pH-sensitive polymers (Enteric coating)
  - Redox-sensitive polymers
- Embedding in matrices
  - Biodegradable matrices and hydrogels
- pH-sensitive matrices
- Time-dependent systems

Protection of the incorporated drug by enteric coating
- Eudragit® enteric coating polymers
  - Copolymer of methacrylic acid and methyl methacrylate
  - Dissolves at pH=6 (Eudragit® L) and pH=7 (Eudragit® S)
- Copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate
  - Dissolves at pH=6 (Eudragit® S 30 D)

Protection of the incorporated drug by conjugation
- Conjugation to:
  - Cyclodextrin
  - Azon
  - Glycoside
  - Glucuronate
  - Dextran
  - Polypeptide
  - Polymers (as pendant chains)

Enteric coating materials

Eudragit®

Eudragit E
Eudragit S
Eudragit RL & RS
Eudragit NE 30 D

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- Conjugation to:
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**Release of the incorporated drug**

**Specific**
- Coating with pH-sensitive polymers
- Coating with azoreductive (\(-\text{N=N}-\)) polymers (azoreductase)
- Exploitation of carriers that are degradable specifically by colonic bacteria (esterases, amidases, glucosidase, glucuronidase, sulfatase)

**Nonspecific**
- Enteric coating + time-dependent barrier coat dissolution
- Swelling, ejectable hydrogel system
- Erodible system

**Time-Dependent Systems**
- Control of lag time
- Control of coating layer thickness
- A hydrophobic coat (glycerol monostearate or hydrogenated castor oil)
- A layer of hydrophilic polymer (hydroxypropyl methylcellulose)
- Timed removal of a hydrogel plug
- Enteric coating to avoid influence of gastric emptying
- Osmotic-controlled delivery systems

**Limitation**
- Poor reliability: No control on individual’s transit time
- Drug release can occur in the small intestine or the terminal colon

**Improvement**
- Use of enzymatically degradable coating or a hydrogel plug

**CODESTM**
- Enteric coating
- Cationic polymer

**Erosion at pH 7**
- Lactulose core
- Degradation by bacteria in the colon

**Egalet Technology (Eroding system)**

**Intelisite Delivery System**

**Small bowel drug delivery**

**Enterion Capsule**

**Pulsincap Delivery System**
Swellable Video Pills

Given Imaging has released the results of a 100-patient multicenter study testing the sensitivity of its M2A(R) Capsule Endoscopy device, which was accurate in detecting patient's gastrointestinal bleeding 91 percent of the time. The M2A was found to be well-tolerated by patients and provided information that changed the course of patient management in 86 percent of patients diagnosed. The M2A endoscopy is an ingested device for use in the gastrointestinal tract that transmits color video images as it passes.

COMBINING ENDOSCOPE AND INTELISITE DELIVERY CAPABILITIES

Absorption of the released drug

Advantages of using polysaccharides
- Wide availability
- Various structures with various properties
- Low cost
- Easy chemical modification
- High stability
- Safe and nontoxic property
- Biodegradation
- Absorption of water to form gels

Polysaccharides for colon delivery
- Chitosan
- Pectins
- Guar gum
- Dextran
- Inulin
- Chondroitin sulphate
- Amylose
- Alginates

Polysaccharides useful for colon delivery
- Calcium ion chelating agents (EDTA, citrate)
- Surfactants
- Bile salts (taurocholate, glycocholate)
- Fatty acids (sodium caprate, caprylate, laurate, oleate)
- Mixed micelles (oleic acid-taurocholate)

Enzyme inhibitors
- Antibody-mediated absorption
- Syntonix approach
Human Colonic Bioavailability Findings

<table>
<thead>
<tr>
<th>Colonic Bioavailability</th>
<th>% of Compounds</th>
<th>Formulation</th>
</tr>
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<tbody>
<tr>
<td>0-30%</td>
<td>40</td>
<td>Difficult</td>
</tr>
<tr>
<td>30-60%</td>
<td>20</td>
<td>Easy</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>40</td>
<td>Easy</td>
</tr>
</tbody>
</table>

SINGLE UNIT VS. MULTIPLE UNITS ORAL DOSAGE FORMS

SINGLE UNIT DOSAGE FORMS.
(One big tablet)
LARGE INTERPERSONAL VARIATION

MULTIPLE UNITS ORAL DOSAGE FORMS

DESIGN PARAMETERS FOR ORAL CONTROLLED RELEASE DOSAGE FORMS
1. DOSE SIZE (500 mg MAX)
2. DRUG MOLECULAR SIZE (<750 DALTONS)
3. CHARGE & pKa OF A DRUG
4. AQUEOUS SOLUBILITY
5. PARTITION COEFFICIENT
6. STABILITY
7. HALF LIFE

Oral Drug Delivery Technologies

Delivery of Biomacromolecules
Commercial Product Development
Emisphere Technologies, Inc. (Passive transcellular transport)
Oral insulin: Proof of concept.
(Inulin: Absorption of exact amount at exact time)
R&D Stages
Oral delivery of insulin, heparin, calcitonin, interferons,
growth hormones, glucagons, vaccines
Practical Considerations
Poor absorption from the GI tract
Enzymatic degradation
Chemical instability
Rapid post-absorptive clearance
**Increased absorption of poorly water-soluble drugs**

Drug absorption from the GI tract

- GI TRACT
- ABSORPTION INTO BLOOD
- DOSAGE FORM
- DISSOLUTION
- DRUG IN SOLUTION
- TRANSIT
- CLASS II DRUGS
  - HIGH P, LOW S
  - Rapid dissolution: >85% dissolution in 30 min in 900 ml aqueous media
  - High Permeability: >10^-4 cm/sec
  - Low Solubility: Highest dose in >250 ml

**Problems with poorly water-soluble drugs**

- Difficulty in evaluations of bioactivity.
- Difficulty in producing formulations with high bioavailability.
- Special non-aqueous formulations that are not patient friendly.

**Examples of Class II drugs**

- Chloramphenicol, digoxin, griseofulvin, hydrocortisone, ketoprofen, nifedipine, phenytoin, prednisolone

**Examples of Class IV drugs**

- Cyclosporine, furosemide, terfenadine, paclitaxel.

**Absorption of poorly water-soluble drugs**

- Solubility-limited / Permeation-limited

**Scientific challenges**

- Approaches to increasing solubility
  - Solid dispersions
  - Nanocrystals/nanoparticles
  - Polymeric micelles
  - Self-emulsifying systems
  - Semi-solid formulations (liquid in hard gelatin capsules)

- Inhibition of efflux pumps by small molecules and polymers

**Solid Dispersions**

Dispersion of one or more drugs in an inert carrier at solid state prepared by melting, solvent or the melting-solvent method.

**Dispersion carriers:** PVP, PEG

- Solid dispersion: The concentration of the drug in excess of its saturation solubility.
- Solid solution: The drug remains dissolved.
- Coprecipitate: Solid dispersion by precipitation of the drug/carrier solution with another solvent

**Nanocrystals/Nanoparticles**

- Particle size can play a major role in the absorption of poorly soluble drugs
  - (Surface area-dependent dissolution rate)

**Commercial Products**

- Gris-PEG (Griseofulvin + PEG 400, 800 + Povidone)

**Practical Considerations**

- Melt method
  - Thermal degradation & sublimation in the melt method. Temperature of cooling may alter the dispersion properties.
  - (Size of the crystals, hardness of the dispersion)
- Solvent method
  - Poor selection of solvents for both drug and polymer carrier
  - Difficulty of removal of the solvent.
  - Limited number of polymeric carriers (PVP, PEG, ?)
Particle size reduction of poorly water-soluble drugs
- Titration and Grinding
- Ball milling
- Fluid energy microrization
- Controlled precipitation by change of solvents or temp.
- Spray drying

Practical Considerations
- Increased surface energy leading to particle aggregation
- Limited selection of non-toxic solvents
- High cost of production

Polymeric Micelles
- Commercial Products
  - PEG-PLGA block copolymers (HySolv™ & ReSolv™ from MacroMed, Genexol Polymeric Micelle from Samyang)
- Practical Considerations
  - Loading efficiency
    - PEG-PLGA: <20 wt%
  - Stability
    - The higher the loading efficiency, the less stable
    - Stable only for hours

Polymeric Micelles
- Practical Considerations
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Finding in vitro-in vivo correlations
- Quantitative correlations between in vitro dissolution and in vivo bioavailability parameters for drugs and dosage forms.

Incentives
- Prediction of in vivo performance from in vitro dissolution data
  - (No need for conventional in vivo bioequivalence or bioavailability studies)
- Scientific thrust
  - Differentiation of drugs and drug formulations in terms of solubility and permeability.

Finding in vitro-in vivo correlations
- Practical Considerations
  - Limited number of laboratories conducting appropriate experiments which often involve prolonged GI intubation of subject.

New oral drug delivery technologies
- Know possibilities & impossibilities
- Set the moderate goals
- Combine different technologies to meet all the needs for oral delivery
- Consider scientific value in terms of commercial value

Any Questions?
Information on a commercial product

Visit website: http://www.elixsure.com

No useful information on the mechanism.


Assignee: Taro Pharmaceuticals

21 patents
6,656,482. Spill resistant pharmaceutical system