

**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**

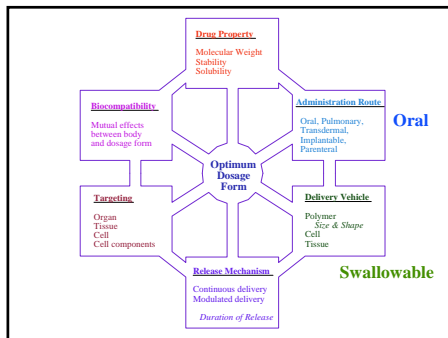
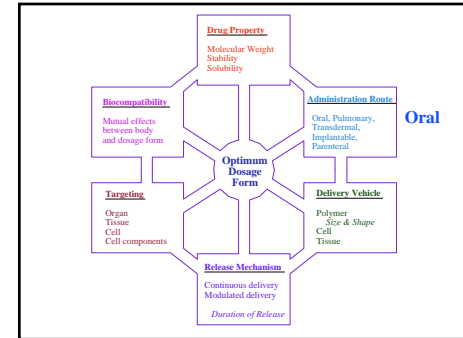
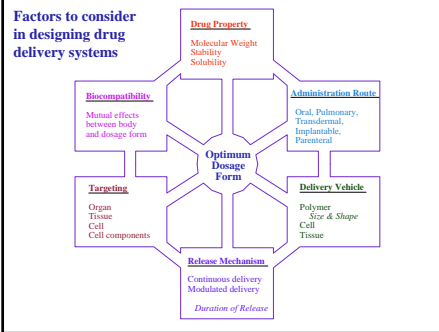
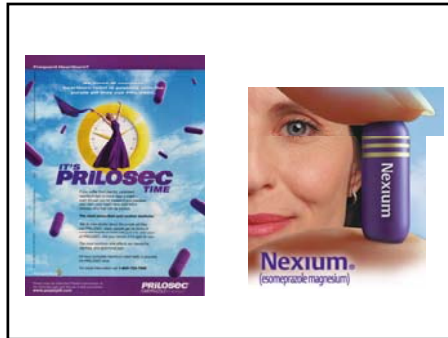
**ONCE-A-DAY ORAL DOSAGE FORMS**

**2. DRUGS WITH SHORT HALF-LIVES**

**PRILOSEC (OMEPRAZOLE)**

**HALF-LIFE OF 0.5-1 HOUR**

**INHIBITION OF H<sup>+</sup>/K<sup>+</sup> ATPase ENZYME SYSTEM LASTS 24-72 HOURS**

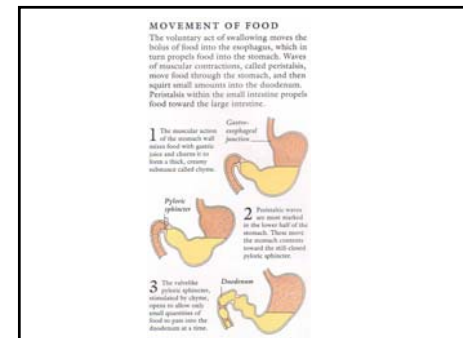


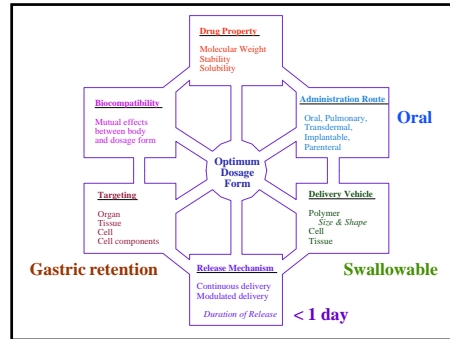
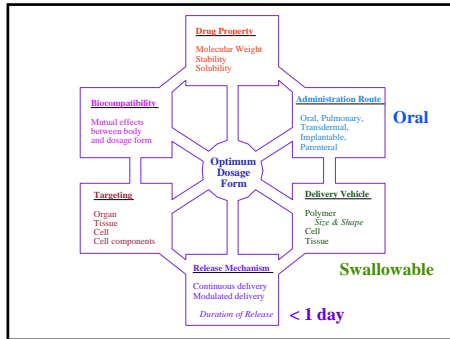
**ORAL DRUG DELIVERY**

**MOST PREFERRED ROUTE OF DELIVERY**

**LIMITING FACTORS FOR ORAL CONTROLLED RELEASE DOSAGE FORMS**

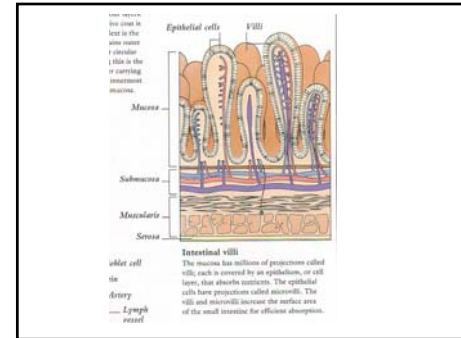
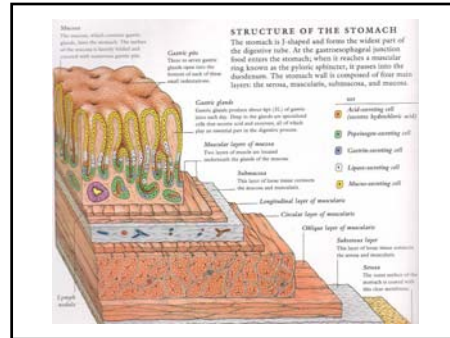
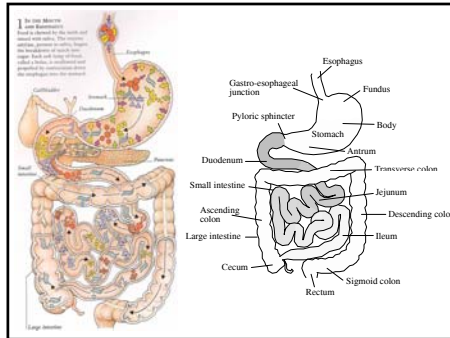
**1. RELATIVELY SHORT GASTRIC EMPTYING TIME AND INTESTINAL TRANSIT TIME**





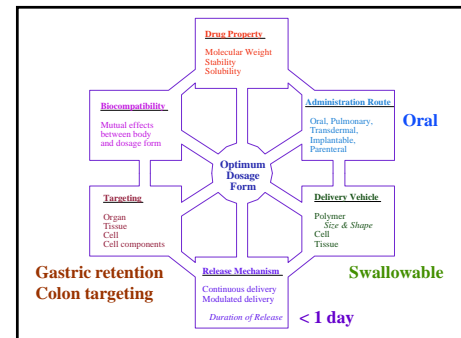
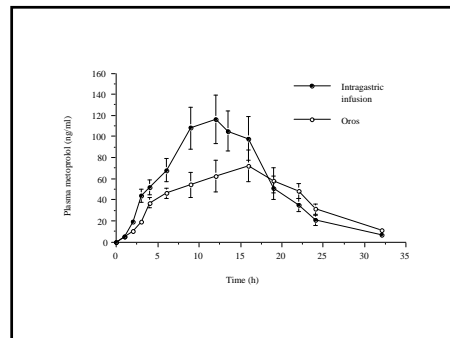
**LIMITING FACTORS FOR ORAL CONTROLLED RELEASE DOSAGE FORMS**

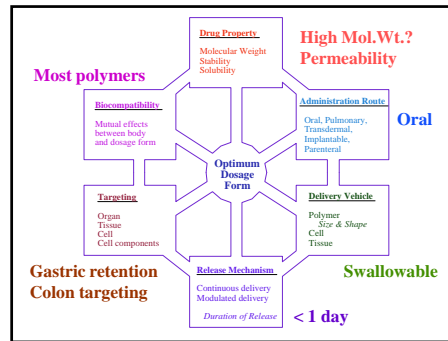
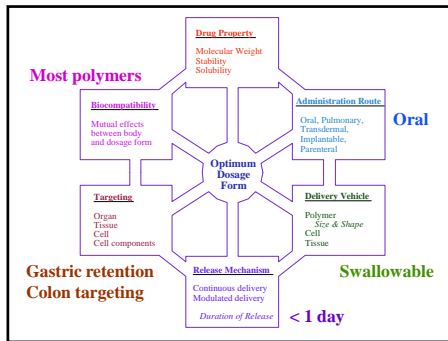
1. RELATIVELY SHORT GASTRIC EMPTYING TIME AND INTESTINAL TRANSIT TIME
2. NON-UNIFORM ABSORPTION ABILITIES OF DIFFERENT SEGMENTS OF THE GI TRACT



**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



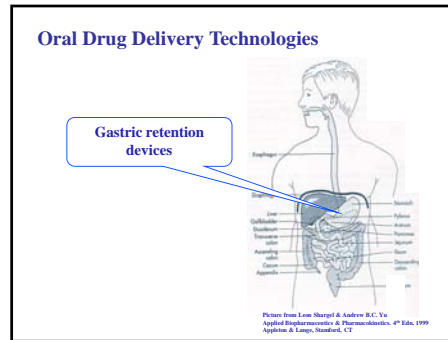


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4. POOR ABSORPTION OF PEPTIDES AND PROTEIN DRUGS

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5. POOR IN VITRO-IN VIVO CORRELATION



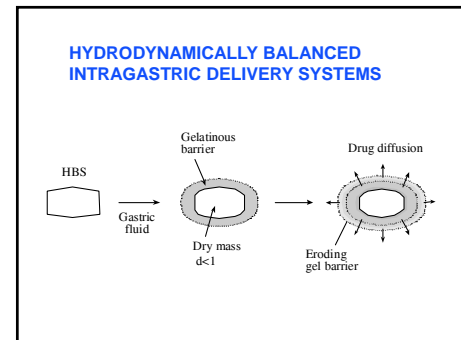
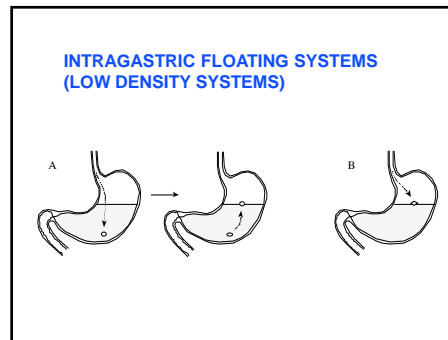
**EXTENSION OF GASTRIC RETENTION TIME A NUMBER OF APPROACHES**

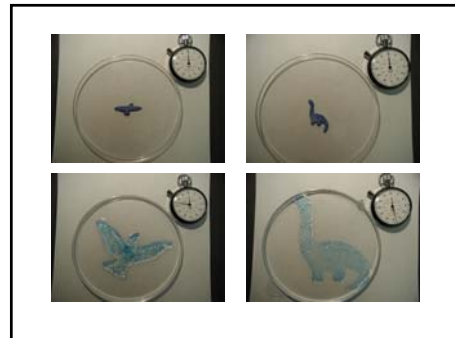
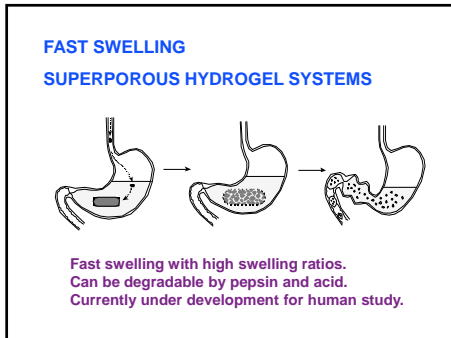
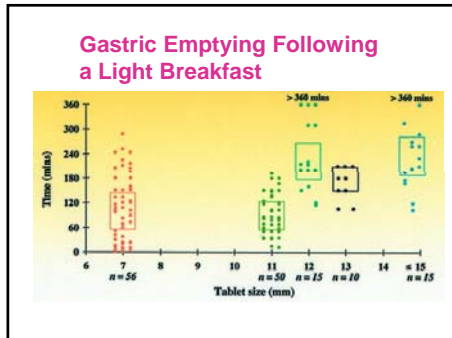
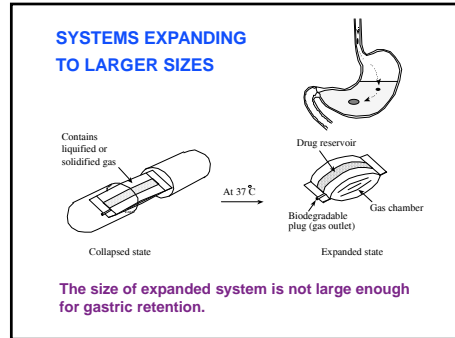
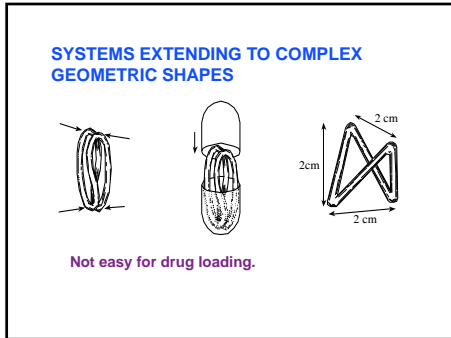
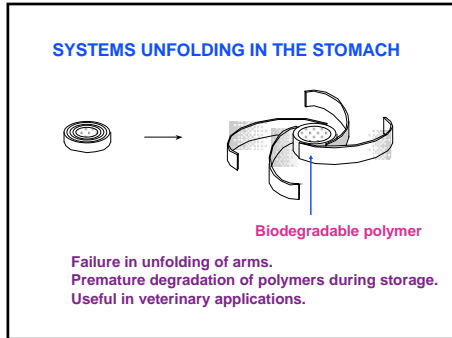
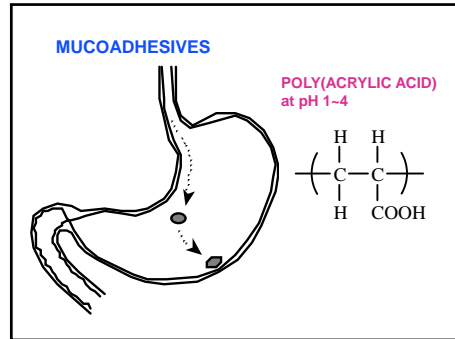
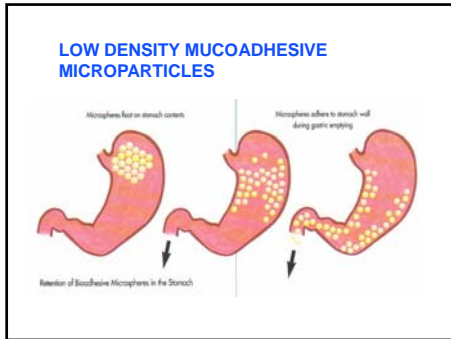
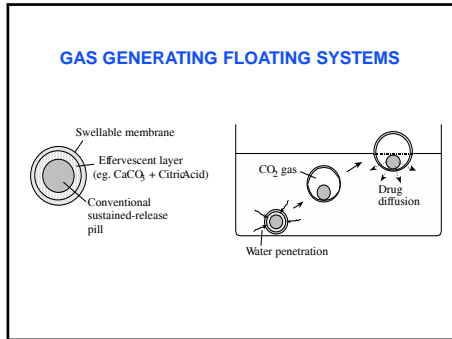
**EXTENSION OF INTESTINAL TRANSIT TIME RELATIVELY MORE DIFFICULT**

**FOCUS ON DEVELOPMENT OF GASTRIC RETENTION DEVICES**

**METHODS OF EXTENDING GASTRIC RETENTION TIME**

1. INTRAGASTRIC FLOATING SYSTEMS (LOW DENSITY SYSTEMS)
2. HIGH DENSITY DOSAGE FORMS
3. MUCOADHESIVE DOSAGE FORMS
4. UNFOLDABLE, EXTENDIBLE, OR EXPANDABLE SYSTEMS
5. SUPERPOROUS HYDROGEL SYSTEMS





## Development of gastric retention devices

### Commercial Technologies

- Superporous Hydrogel Systems (Kos Pharmaceuticals, Inc.)
- Gastric Retention System (DepoMed)
- West Gastroretentive System (West Pharm. Services)  
(Low density microspheres with a bioadhesive coat)
- 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

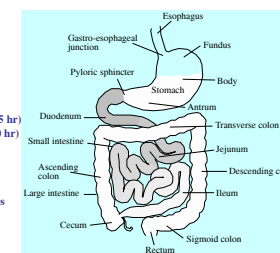
### Enzyme activity

### Transit Time

- Stomach (<3 hr)
- Small Intestine (3-5 hr)
- Large Intestine (20 hr)

### Polysaccharidases

Greater response to absorption enhancers



## 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)
- Biodegradable polymers
- Redox-sensitive polymers

### Embedding in matrices

- Biodegradable matrices and hydrogels
- pH-sensitive matrices

### Time-dependent systems

## Protection of the incorporated drug by enteric coating

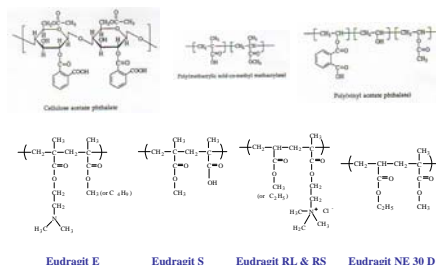
### Eudragit® enteric coating polymers

Copolymers of methacrylic acid and methyl methacrylate  
Dissolve at pH=6 (Eudragit® L) and pH=7 (Eudragit® S)

Copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate  
Dissolve at pH=7-7.5 (Eudragit® FS)  
Dissolution at a slower rate  
Superior in retarding drug release in the small intestine  
No break-up of polymer coating  
Intrasubject variability  
(marked differences in the times and sites of tablet disintegration)

Concern: Premature drug release

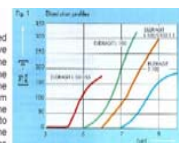
## Enteric coating materials



## Eudragit®

### Product properties

Of decisive importance for the controlled release of enteric-coated active ingredients is the dissolution profile of the EUDRAGIT® L/S film formers in the intestinal pH range from 5.5 to 7.0. The graph in Fig. 1 indicates how the film coatings dissolve in the intestine. In the duodenum, a pH range of 5.5 - 6.0 is to be expected, in the lower sections of the intestine, the pH value normally increases gradually to about pH 6.5 - 7.0 near the colon. However, the release of active ingredients also depends on the thickness of the film coatings and the solubility characteristics of the active ingredient under physiological conditions.



All polymer types in Fig. 1 can be mixed with each other in any desired ratio, thus making it possible to adjust intermediate values. The release values established in vitro must be confirmed in pharmacological and clinical tests.

<http://www.rohm.com/en/chemistry/polymers.html>

## Protection of the incorporated drug by conjugation

### Conjugation to:

- Cyclodextrin
- Azo
- Glycoside
- Glucuronate
- Dextran
- Polypeptide
- Polymers (as pendant chains)





### Human Colonic Bioavailability Findings

Colonic Bioavailability	% of Compounds	Formulation
0-30%	40	Difficult
30-60%	20	
>60%	40	Easy

Pharmaceutical Profiles Data

### SINGLE UNIT VS. MULTIPLE UNITS ORAL DOSAGE FORMS

SINGLE UNIT DOSAGE FORMS.

(One big tablet)

LARGE INTERPERSONAL VARIATION

### MULTIPLE UNITS ORAL DOSAGE FORMS



### MULTIUNIT ORAL DOSAGE FORMS



The advertisement for ElixSure features the text: "ElixSure The first spill-resistant children's medicine™". It includes a website URL: <http://www.elixsure.com/>. The ad shows a child's face and several boxes of ElixSure products: ElixSure FEVERPAIN, ElixSure COUGH, and ElixSure COLIC. A headline asks "Unsure? ElixSure". A sub-headline says "Hot OTC". The main text states: "ElixSure: The first spill-resistant children's medicine. No get all the relief you need." The bottom text reads: "ElixSure: Your Pharmaceutical Innovation. A/S has announced the introduction of ElixSure products, the first spill-resistant children's medicines for children aged 2 through 12. The unique formulation does not require shaking, helping to ensure that every dose contains the full complement of active ingredients. After the next release is approved out of the safety cabinet, it will include a US ElixSure version in 3 formulations: Fever/Pain, Cough, and Colic/Constipation. Patients include parents, nurses and pediatricians. For more information, visit www.elixsure.com."

### 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

Biomacromolecules



Pictures from Leon Shargel & Andrew R.C. Yu Applied Biopharmaceutics & Pharmacokinetics, 4<sup>th</sup> Edn, 1999 Appleton & Lange, Stamford, CT

### Delivery of Biomacromolecules

Commercial Product Development

Emisphere Technologies, Inc. (Passive transcellular transport)

Oral liquid heparin: PROTECT Phase III study in 2002.

Oral insulin: Proof of concept.

(Insulin: 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

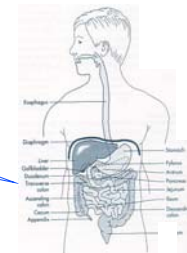
Enzymatic degradation

Chemical instability

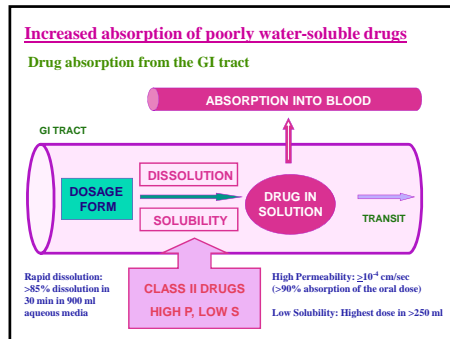
Rapid post-absorptive clearance

### Oral Drug Delivery Technologies

Poorly-soluble drugs



Pictures from Leon Shargel & Andrew R.C. Yu Applied Biopharmaceutics & Pharmacokinetics, 4<sup>th</sup> Edn, 1999 Appleton & Lange, Stamford, CT



**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

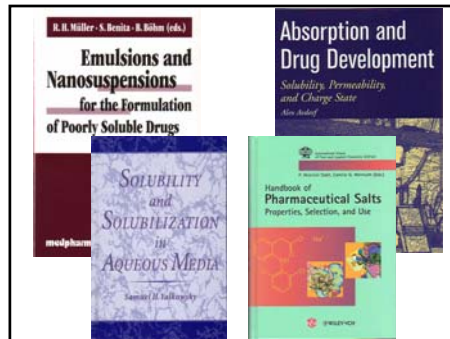
**Examples of Class IV drugs**  
Cyclosporine, furosemide, terfenadine, paclitaxel.

		Permeability	
		High	Low
Solubility	High	<b>Class I</b> Highly suitable for Sustained Release/Controlled Release <b>Examples:</b> Propranolol, Metoprolol, Diltiazem, Verapamil	<b>Class III</b> Problematic for Sustained Release/Controlled Release <b>Examples:</b> Acyclovir, Neomycin B, Captopril, Enalaprilate, Amilorone
	Low	<b>Class II</b> Suitable for Sustained Release/Controlled Release <b>Examples:</b> Danazol, Ketoconazole, Mefenamic acid, Nifedipine, Nifedipine, Nicardipine, Felodipine	<b>Class IV</b> Unsuitable for Sustained Release/Controlled Release <b>Examples:</b> Chlorothalidol, Furosemide, Tobramycin, Cefazolin

**Important factors that influence the absorption process:**

- Release rate from the delivery system
- Drug degradation within the GI tract; GI content, pH, enzymes, and amphipathic bile secretions
- Poor permeability across gut mucosa; preferential absorption capacity of different GI sites
- Delivery system transit time through the GI tract
- First pass metabolism and potential excretion into the GI tract
- Dose to Solubility (DS) Ratio as a function of pH under Fed & Fasted State

The biopharmaceutical classification scheme (BCS).



**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.

**Coevaporates:**  
Solid dispersion by solvent removal process.

**Coprecipitates:**  
Solid dispersion by precipitation of the drug/carrier solution with another solvent

**Solid Dispersions**

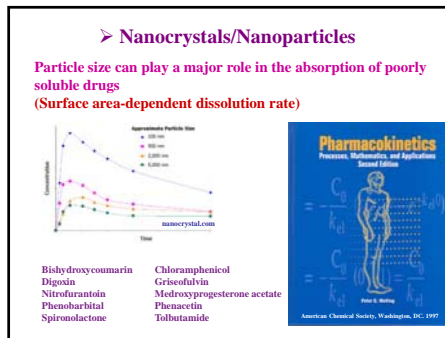
**Commercial Products**  
Gris-PEG (Griseofulvin + PEG 400, 800 + Povidone)

**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  
(Different polymorphic forms of the same drug).  
Large volume of the solvent used  
(500 ml EtOH to dissolve 5 g of 10% griseofulvin-PEG)  
Difficulty of removal of the solvent.

\* Limited number of polymeric carriers (PVP, PEG, ?)



**Nanocrystals/Nanoparticles**

**Commercial Technologies**

BioAqueous solubilization (Dow)  
Biorise (Eurand)  
Insoluble Drug Delivery Technology (SkyePharma)  
Maxsol (Vectura Drug Delivery)  
Nanocrystal® Technology (élan: Rapamune® sirolimus)

### Particle size reduction of poorly water-soluble drugs

Titration and Grinding  
Ball milling  
Fluid energy micronization  
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

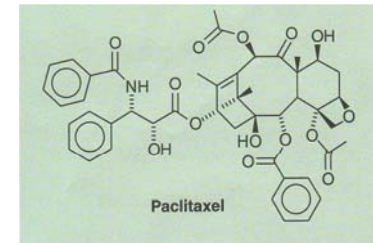
#### Commercial Products

PEG-PLGA block copolymers  
(HySoly™ & ReSoly™ 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



Water-solubility of paclitaxel: 0.3 µg/ml.  
Poor solubility, poor bioavailability  
Taxol: dissolved in cremophor EL + ethanol

### 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 involves prolonged GI intubation of subject.

Class I. High Solubility High Permeability Relationship: expected if <u>Dissolution rate is slower than Gastric emptying rate</u>	Class III. High Solubility Low Permeability Relationship: X <u>In vitro dissolution has little or no effect</u>
Class II. Low Solubility High Permeability Relationship: ⊖ <u>Feasible &amp; Useful</u>	Class IV. Low Solubility Low Permeability Relationship: Questionable <u>In vivo study required</u>

### 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

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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?



Terminator 3: Rise of the Machines. Copyright Warner Brothers



**ElixSure** The first spill-resistant children's medicine™

<http://www.elixsure.com/>

Unsure? **ElixSure**

**Hot OTC**

**ElixSure** The first spill-resistant children's medicine. Now get all the relief you need

**ElixSure** Hot OTC  
ElixSure  
ElixSure  
ElixSure

