CONTROLLED RELEASE FORMULATION APPROACHES AND CASE STUDY

Solubilization and Bioavailability Enhancement: Product Development Strategies for Classic Challenges

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DEVELOPMENT PIPELINES ARE COMPLEX

- Industry wide it is estimated that more than 70% of NME entering development present challenges for formulation development
  - High molecular weight
  - High lipophilicity
  - Poorly soluble and poorly permeable
- This translates into significant challenges with regard to formulation development
  - Opportunity for innovative drug delivery solutions
  - Successful introduction of oral products utilizing solubility enhancing techniques
    - e.g.: Rapamune®, Megace® ES, Sporanox®

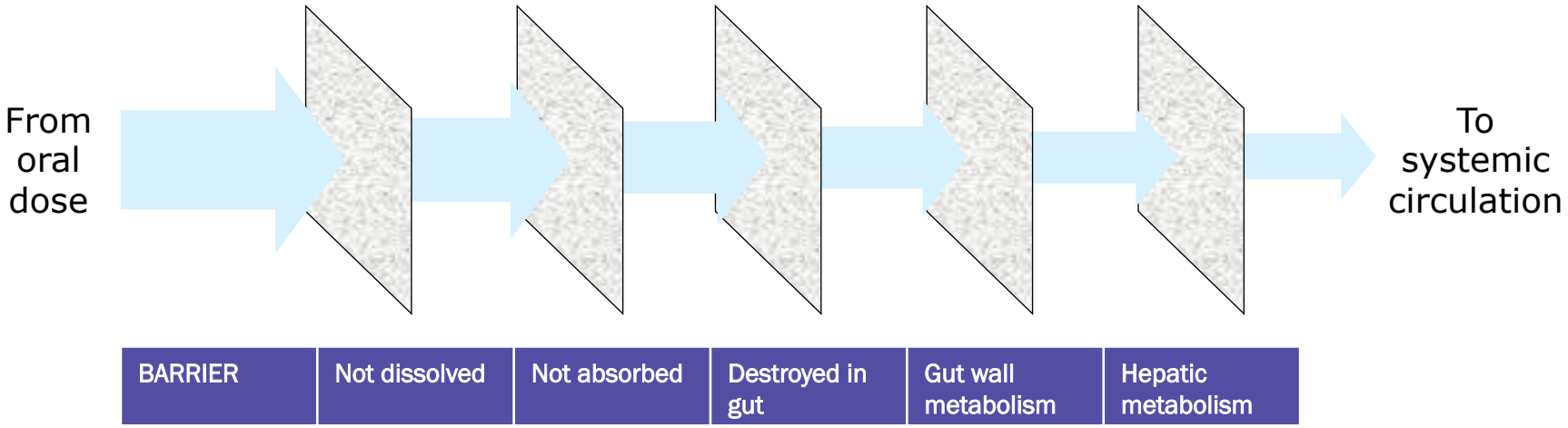
REVIEW BCS CLASSIFICATION GUIDELINES

	High Solubility	Low Solubility
High Permeability	Class I	Class II
Low Permeability	Class III	Class IV

- Solubility classification
  - For highly soluble compounds, dose solubility volume is ≤ 250 mL
  - For poorly soluble compounds, dose solubility volume is ≥ 250 mL, where dose solubility volume is the volume needed to dissolve highest strength (dose) across pH range of 1.0 to 7.5 at 37°C.
- Permeability classification
  - For highly permeable compounds, extent of intestinal absorption is > 90% (based on *in vivo* or *in vitro* studies)
- Bioavailability of Class II compounds are limited by their solubility and dissolution rate

Sathe, P, *et al* (2008). "Regulatory Aspects of Dissolution for Low Solubility Drug Products" In: Liu, R *Water Insoluble Drug Formulation*. 2nd ed. Boca Raton, FL: CRC Press. 101-112

THE SOLUBILITY CHALLENGE IS THE FIRST OBSTACLE TO COMPLETE ABSORPTION



- Low and variable bioavailability
- Food effect on bioavailability
- Potential for suboptimal dosing and exposure (also in non clinical studies)
- Potential for failure of dose-response proportionality
- High rate of clinical failures

NOYES - WHITNEY EQUATION

$$\frac{dC}{dt} = \frac{D * A * (Cs - Ct)}{h * V}$$

Where

- dC/dt = dissolution rate
- D = diffusion coefficient
- A= surface area of the drug
- C_s = saturation solubility of the drug
- C_t = concentration at time t
- h=diffusion layer thickness
- V=volume

Factors that can be influenced to impact dissolution rate

- Surface area of the drug
- Saturation solubility of the drug
- Diffusion layer thickness

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APPROACHES TO INCREASE SOLUBILITY AND DISSOLUTION RATE

- Critical to understand the underlying reason for the solubility behavior
  - "brick dust" or "grease ball"
- Success of solubilization technique in increasing saturation solubility and dissolution rate of compound depends on molecular characteristics

APPROACHES TO INCREASE SOLUBILITY AND DISSOLUTION

- pH adjustment
- Salt formation
- Size reduction
  - Micronizing
  - Nanoparticles – suspensions and solid particles
- Solubilization
  - Co-solvents
  - Complexation with cyclodextrin
  - Use of surfactants
- Emulsions, microemulsions and lipid based formulations
  - Self emulsifying drug delivery systems (SEDDS)
  - Self microemulsifying drug delivery systems (SMEDDS)

APPROACHES TO INCREASE SOLUBILITY AND DISSOLUTION

- Particle engineering technologies
  - Controlled precipitation techniques utilizing cryo-procedures or SCF
- Amorphous dispersions
  - Solid dispersions and solid solutions
    - Solvent based methods: Spray drying
    - Thermal : Hot melt extrusion

CONSIDERATIONS FOR CHOOSING A SOLUBILIZATION TECHNOLOGY

- Understand the characteristics of your drug substance and the objective of solubility enhancement
  - Brick dust or grease ball
- Evaluate multiple pathways to understand the limitations of the “solution”
- Consider the following in your choice of solubilization technology
  - Effectiveness of technology to obtain the desired enhancement
  - Drug loading and ease of formulation for the final prototype
    - IR formulation
    - CR formulation – compatibility with delivery profile options
  - Stability of “solubility enhanced API”
    - Chemical and physical stability
  - Avoidance of local effects during delivery – precipitation, crystallization, form change
  - Regulatory status of added excipients
  - Scalability of technology
  - Costs – incremental addition to COGs for final product

CHALLENGES SPECIFIC TO THE CONTROLLED DELIVERY OF POORLY SOLUBLE COMPOUNDS

- Solubilization challenge combined with engineering the release profile
- Ability to maintain the solubilized state throughout the GI tract
  - Precipitation, crystallization or form change during prolonged exposure
  - Particle size change (aggregation or ripening) of nanosized particles during prolonged exposure
  - Inability to release functional excipients concomitantly with the drug
- Compatibility of “solubilization technology” with technology platform for controlled delivery
- Scale up concerns for both solubilization technology and controlled release dosage form design

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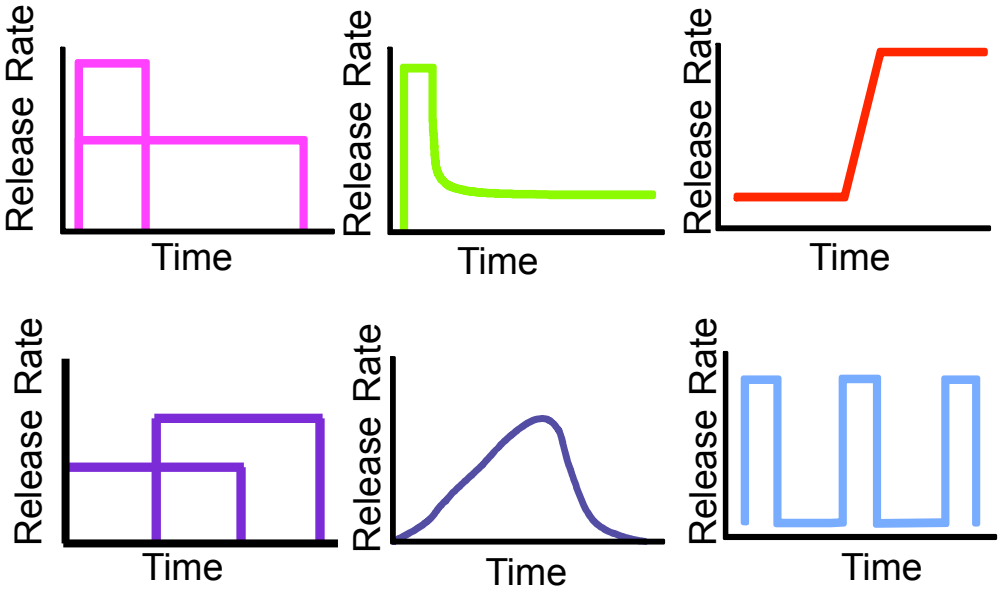
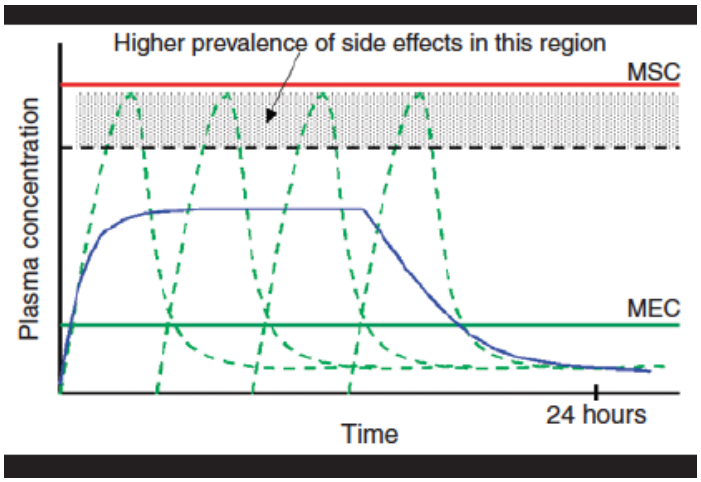
CONTROLLED RELEASE

KEY RATIONALE FOR CONTROLLED RELEASE

- Clinical benefits
  - Improved efficacy – modulate absorption, rate of absorption, site of absorption
  - Greater selectivity of activity
  - Reduced side effects
  - Potential to moderate tolerance to drug
  - Potential for new indications
  - Could be "product enabling" for drugs with narrow therapeutic windows
  - Potential for dose sparing, provided absorption is maximized
- Commercial benefits
  - Life cycle management – line extensions, product differentiation, market expansion
  - Patent protection
  - Potential for reduced COGs
- Patient benefits
  - Compliance (reduced dosing frequency) and
  - Clinical benefits leads to improved quality of life

ORAL CONTROLLED RELEASE: MEETING THERAPEUTIC NEEDS WITH DIFFERENTIATING IN VITRO RELEASE PROFILES





Identify the clinical rationale and define the target profile

Das, N.G. and Das, S.G. Formulation, Fill and Finish. 2003, 10-16

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WHAT DO WE NEED TO KNOW ABOUT THE DISEASE AND PATIENTS?

- Disease condition and patients
  - Acute or chronic
  - Patient factors – age, progression of disease, organs and functions impacted by disease condition
  - How will the product be used?
  - What is the unmet medical need to the patient?

- Delivery platform and technology
  - Choose technology and platform based on intellectual property, cost, preferred route of delivery, suitability for drug and product

PHYSIOLOGICAL CONSIDERATIONS

KEY CONSIDERATIONS FOR VIABILITY OF ORAL CONTROLLED RELEASE

- Dose
  - Multiple units may be needed if dose > 250 to 300 mg
  - Dose/unit system is dependent on
    - Drug solubility
    - Dissolution rate of drug
    - Impact of excipients
    - Type of release profile needed (choice of technology)
- Transport mechanism
  - Drugs transported by passive diffusion are ideal
  - Active transport and efflux mechanisms add to complexity of delivery
- Regional permeability
  - Permeability across GI tract
  - Colonic permeability is critical for once a day dosage forms
- Half life of drug
  - What is too short or too long?
- Metabolism
  - High first pass metabolism or pre systemic metabolism is undesirable
  - Substrates for P-gp or CYP 3A4 add to complexity of delivery

Thombre, A.G. Drug Discovery Today. 2005; 17(10): 1159-1166

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KEY CONSIDERATIONS FOR VIABILITY OF ORAL CONTROLLED RELEASE

- Physiological factors
  - Site of delivery in the GI tract
  - Composition of GI fluids at site of delivery
    - pH, Ionic strength, osmolarity, presence of bile salts, presence of mucus, surfactants and other digestive material
  - Dosage form transit time
    - Inter and intra individual variability

FACTORS INFLUENCING ORAL CONTROLLED RELEASE

- Physiological factors
  - Site of delivery in the GI tract
  - Composition of GI fluids at site of delivery
    - pH, Ionic strength, osmolarity, presence of bile salts, presence of mucus, surfactants and other digestive material
  - Dosage form transit time
    - Inter and intra individual variability
- Pharmacokinetic factors
  - Dose
  - Biological half life ($t_{1/2}$) of the compound
  - Metabolism
    - Presystemic metabolism
    - First pass metabolism
  - Therapeutic window

FACTORS INFLUENCING ORAL CONTROLLED RELEASE

- Physicochemical properties
  - pKa
    - Precipitation in GI tract
  - Aqueous solubility
    - BCS classification
    - pH solubility profile
    - pH stability profile
  - Partition coefficient
  - Chemical stability
- Biopharmaceutical properties
  - Mechanism of absorption
    - Passive vs. Active
    - Efflux transport
  - Permeability
    - Overall permeability
    - Site specificity in GI tract

DOSAGE FORM TRANSIT TIMES THROUGH THE GI TRACT

- Gut physiology is complex and varied and often an underestimated challenge for dosage form design
- Dosage form behavior is influenced by
  - Intestinal motility
  - Presence or absence of food
  - Fluid volume and fluid composition
  - Disease state of the gut
  - Inter- and intra- individual variability
  - Circadian aspects
  - Type of dosage form and time of administration
  - Gender effects?
- Significant gaps exist in our understanding of the interaction between dosage form and physiological factors

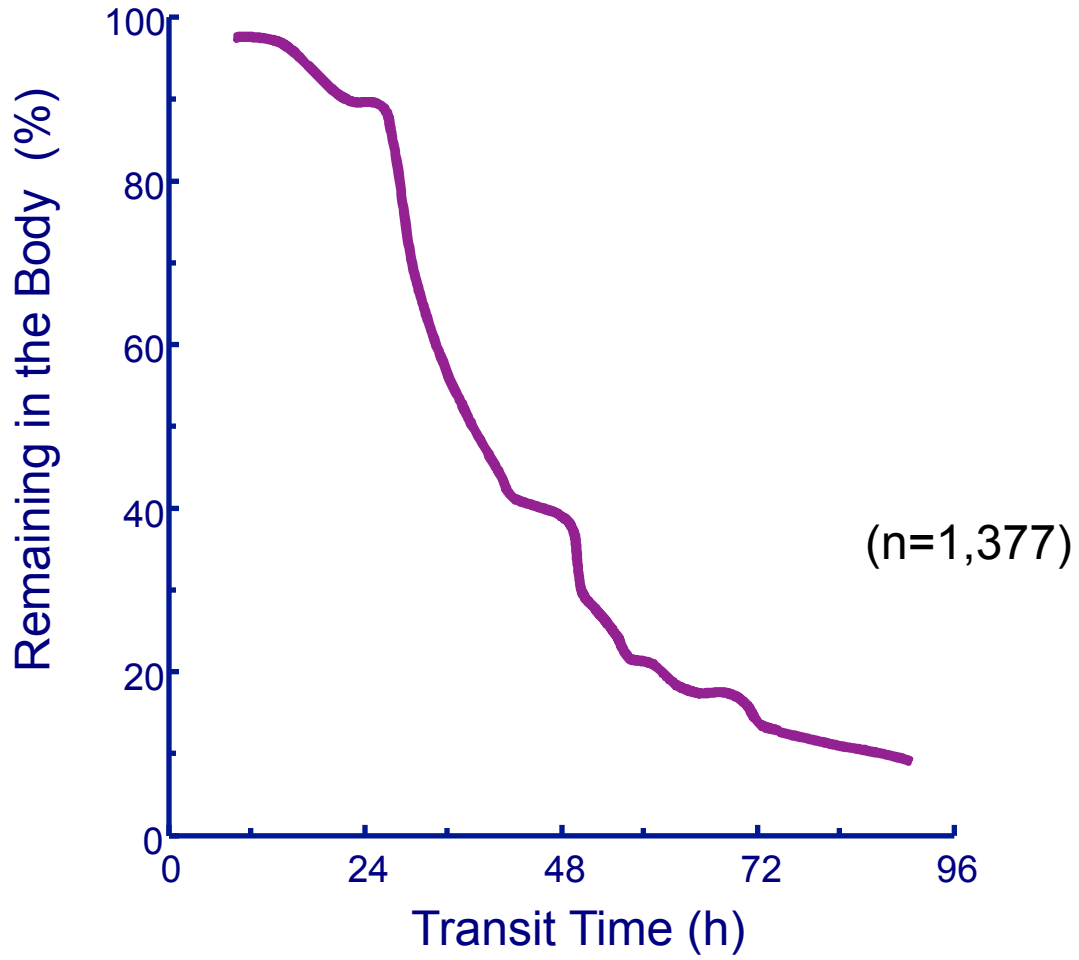
HOW VARIABLE ARE THE GI TRANSIT TIMES?

Location	Typical range (hr)
Stomach	0.25 – 10*
Small Intestine	3 - 4
Colon	4 – 70**

- *Variability dependent on fed/fasted state and size and type of dosage form
- **Upto 96 h has been reported

McConnell *et al*., Int. J. Pharm. 2008; 364: 213-226
Karlarli, T.T:. Biopharm & Drug Disp. 1995; 16: 351-380
Dressman *et al*., Pharm. Res. 1998; 15(1): 11-22

FREQUENCY OF SYSTEM SURVIVAL IN THE GI TRACT FOLLOWING OROS® ADMINISTRATION IN THE MORNING



Theeuwes, F. et al., "Osmotic Systems for Colon-Targeted Drug Delivery".
In Colonic Drug Absorption and Metabolism. Ed. Peter R. Bieck, Marcel Dekker, Inc. (1993).

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REVIEW OF KEY CHARACTERISTICS OF HUMAN GI TRACT

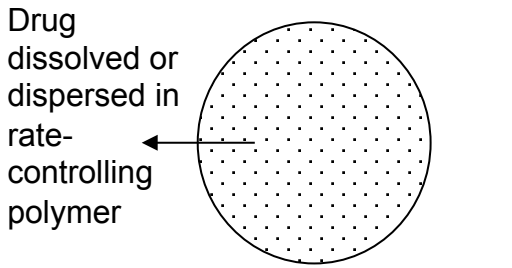
Segment	Average length (cm)	Average dia (cm)	Average absorbing area (cm^2)	pH
Stomach	20	15	~11	1.5 to 3.5
Duodenum	25	5	~0.09	5 to 7
Jejunum	300	5	~60	6 to 7
Ileum	300	5	~60	7
Colon	150	5	~0.25	5.5 to 7.0
Rectum	15-19	2.5	~0.015	7

Karlarli, T.T:. Biopharm & Drug Disp. 1995; 16: 351-380

CONTROLLED RELEASE DOSAGE FORMS

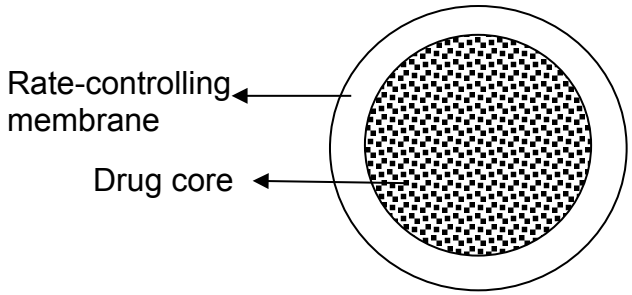
ORAL CONTROLLED RELEASE SYSTEMS – MAJOR DESIGN TYPES FOR COMMERCIALIZED PRODUCTS

- **Matrix systems**
  - Fickian diffusion and polymer relaxation



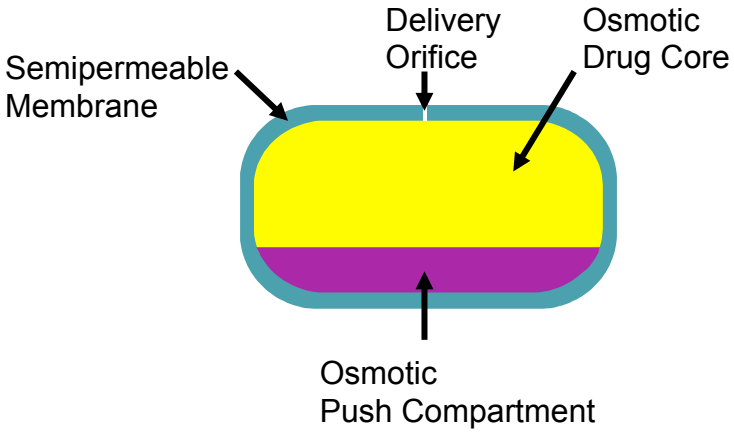
Monolithic matrix system

- **Reservoir systems**
  - Diffusion controlled release



Reservoir system

- **Osmotic systems**
  - Osmotic activity controlled



MATRIX SYSTEMS

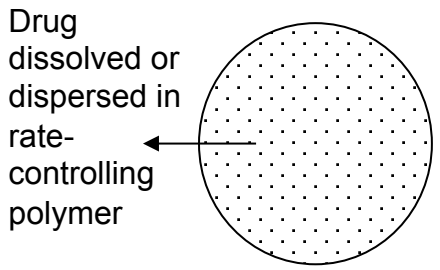
- Drug substance is homogenously mixed with the rate controlling materials and other inactive materials to form tablets or other solid dosage forms
- Depending on polymeric composition,
  - Non erodible matrix governed by Fickian diffusion
  - Erodible matrix governed by Fickian diffusion and polymer relaxation
- Examples of commonly used polymeric materials
  - Non ionic soluble cellulose ethers (HPMC, HPC, HEC etc)
  - Polyethylene oxide polymers (Polyox)
  - Water soluble polysaccharides – Xanthan gum, Alginates
  - Polyvinyl acetate and Polyvinyl pyrrolidone

STEADY-STATE DRUG RELEASE FROM MATRICES: THE HIGUCHI EQUATION

- For a homogenous, monolithic matrix the release behavior can be described by Higuchi equation

$$M_t = \sqrt{[DC_s(2A - C_s)t]}$$

Where
M_t = drug released per unit area at time t
A = drug loading per unit volume
Cs= drug solubility
D=diffusion coefficient in the matrix



Monolithic matrix system

Higuchi, T. J. Pharm. Sci. 1961; 50: 874-875

STEADY-STATE DRUG RELEASE FROM MATRICES: THE HIGUCHI EQUATION

- Assumptions for the Higuchi equation
  - Drug is homogeneously dispersed in matrix
  - Drug release is dictated by diffusion through polymer matrix (matrix does not erode before drug released)
  - Pseudosteady-state exists
  - Surface area is constant over release time and system is planar
  - Sink conditions exist
    - Drug load >> drug solubility
  - Diffusion is not dissolution limited
  - Drug particles are small compared to the average distance of diffusion

Higuchi, T. J. Pharm. Sci. 1961; 50: 874-875

RELEASE FROM POROUS GRANULAR MATRICES

- The Higuchi equation can be modified to describe diffusion through porous matrices by including porosity (ø) and tortuosity (τ) terms.

$$M_t = \sqrt{D_{eff} C_s \left(2A - \phi C_s\right) t}$$

- The diffusion coefficient is modified

$$D_{eff} = \frac{D\phi}{\tau}$$

- where D_{eff} is the effective diffusion coefficient (D corrected for transport through a porous pathway).
- Porosity, ϕ, is the total porosity of the matrix after all the drug has been leached.

$$\phi = \phi_0 + \frac{A}{\rho}$$

- where ρ is the density of the drug and A is drug load expressed in terms of g/cm^3.
- Tortuosity, τ, is defined as the increase in path length of diffusion due to the presence of branching and bending of the pore structure compared to linear pores.
- A straight pore has a tortuosity value of 1 and values of τ can range from 2 up to 1000.

Higuchi, T. J. Pharm. Sci. 1963; 50: 1145-1149

RELEASE KINETICS FROM ERODIBLE MATRICES

- Two mechanisms for drug release
  - Fickian diffusion
  - Swelling and erosion of polymeric matrix
- Release is generally described using the semi-empirical equation

$$\frac{Mt}{M_\infty} = kt^n$$

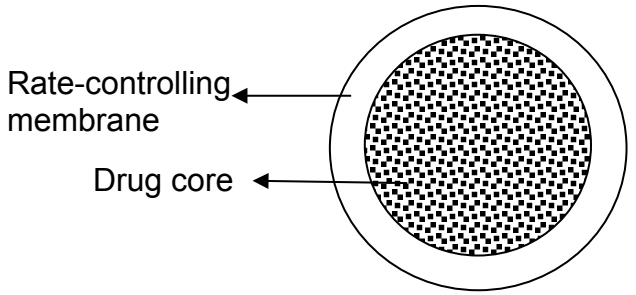
K = rate constant incorporating characteristics of the macromolecular network and drug

n=diffusional exponent (n ranges from 0.5 to 1 indicating predominant release mechanism)

Korsmeyer R.W and Peppas, N.A. J.Controlled Rel. 1(2), 1984, pp89

RESERVOIR SYSTEMS

- Core containing a solid drug or a highly concentrated drug core, coated with a film of rate controlling membrane
  - Release controlled by concentration gradient between reservoir and core
  - Leachable additives added to the rate controlling membrane can influence rate
  - Drug transport can be diffusion controlled through the film, through a hydrated film, or through a capillary network within the film
- Microparticles, microspheres, and nanoparticles are common examples of reservoir systems



Reservoir system

RELEASE KINETICS FROM RESERVOIR SYSTEMS

- Based on Fick's first law, the one dimensional release rate from a reservoir is described by

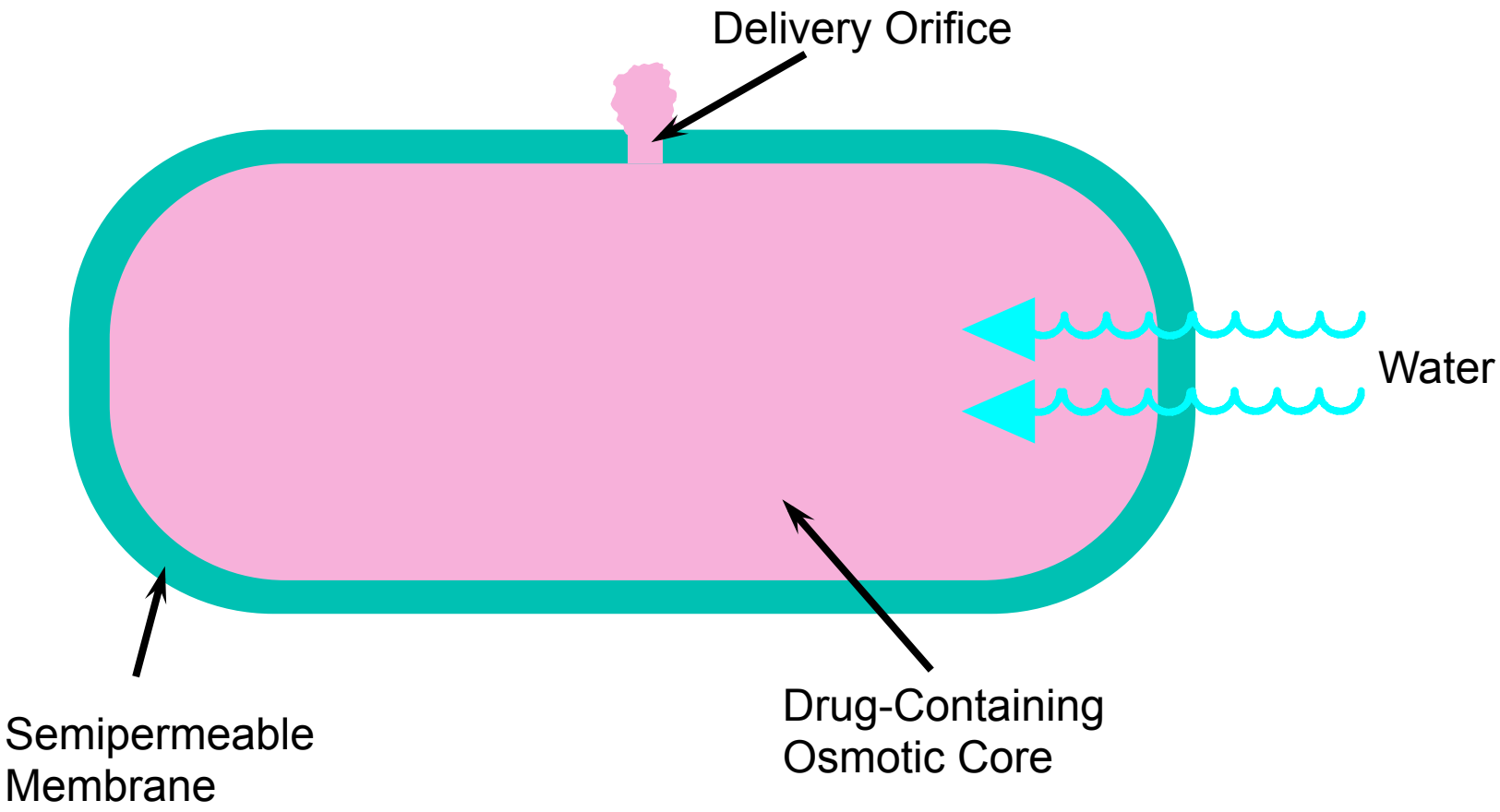
$$\frac{dMt}{dt} = \frac{DSK}{l}(Cs - Ct)$$

Where
Mt= amount of drug released at time t
D=diffusion coefficient of the drug
S=surface area for drug diffusion
K=partition coefficient of the drug between membrane and external phase
l=diffusional pathlength

Under sink conditions,

$$Mt = (\frac{DSK\Delta C}{l})t = kt$$

OSMOTIC SYSTEMS: ELEMENTARY OSMOTIC PUMP



Theeuwes, F. J. Pharm. Sci. 1975; 64 (12): 1987-1991

DESIGN PRINCIPLES FOR ELEMENTARY OSMOTIC PUMP

- The release rate of drug from an EOP (Elementary Osmotic Pump) can be predicted from the following –

$$\frac{dm}{dt} = \frac{(k)}{h} * A * (\delta\pi C_s)$$

- Where
  - dm/dt = release rate of drug;
  - k = membrane permeability;
  - h = membrane thickness;
  - A = core surface area;
  - $\delta\pi$ = osmotic pressure differential across the membrane;
  - C_S = drug concentration at saturation (ie solubility)

- EOP design is the basic, simplest design based on osmotic driving principles
- EOP is limited in application to soluble drugs

Theeuwes, F. J. Pharm. Sci. 1975; 64 (12): 1987-1991

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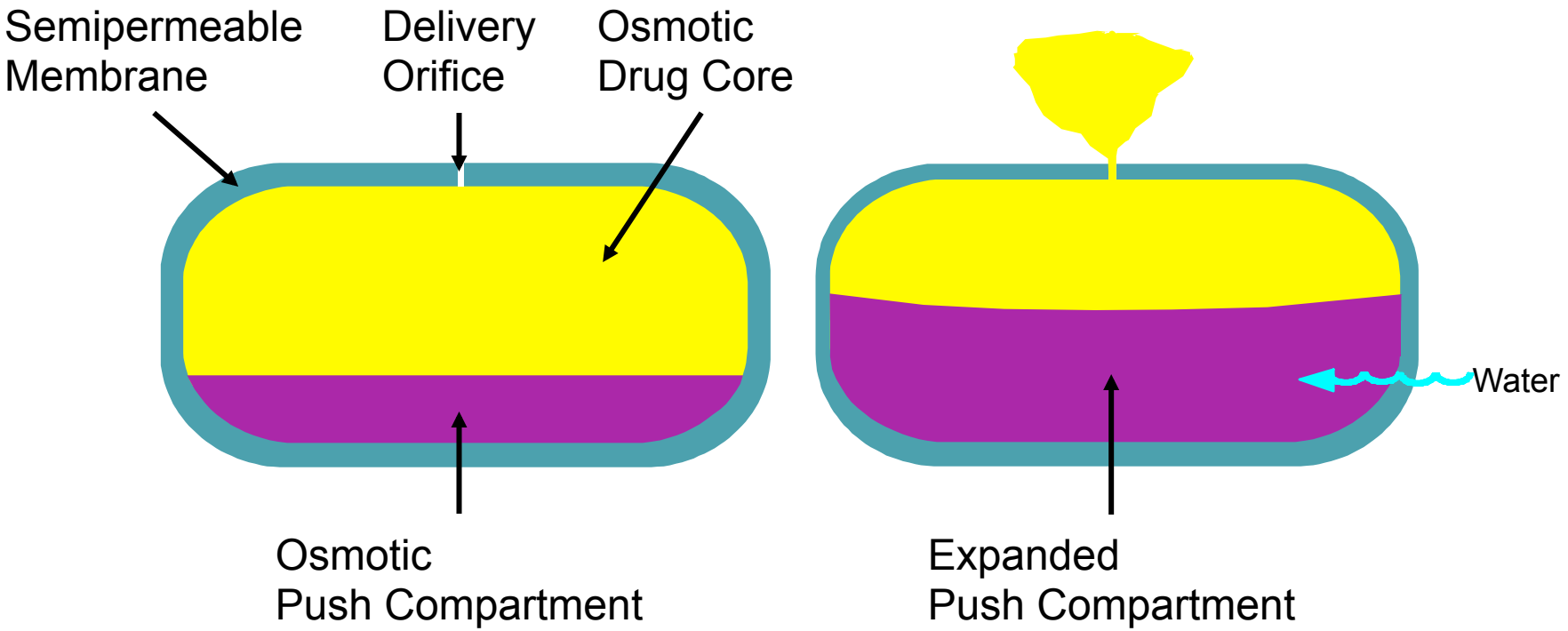
OSMOTIC SYSTEMS: PUSH PULL™ PLATFORM



$$\frac{dm}{dt} = \frac{k}{h}\left(A_D \delta\pi_D + A_p \delta\pi_P\right)C$$

Theeuwes, F. Osmotic system for the controlled and delivery of agent over time. United States Patent 4,111,202. September 5, 1978

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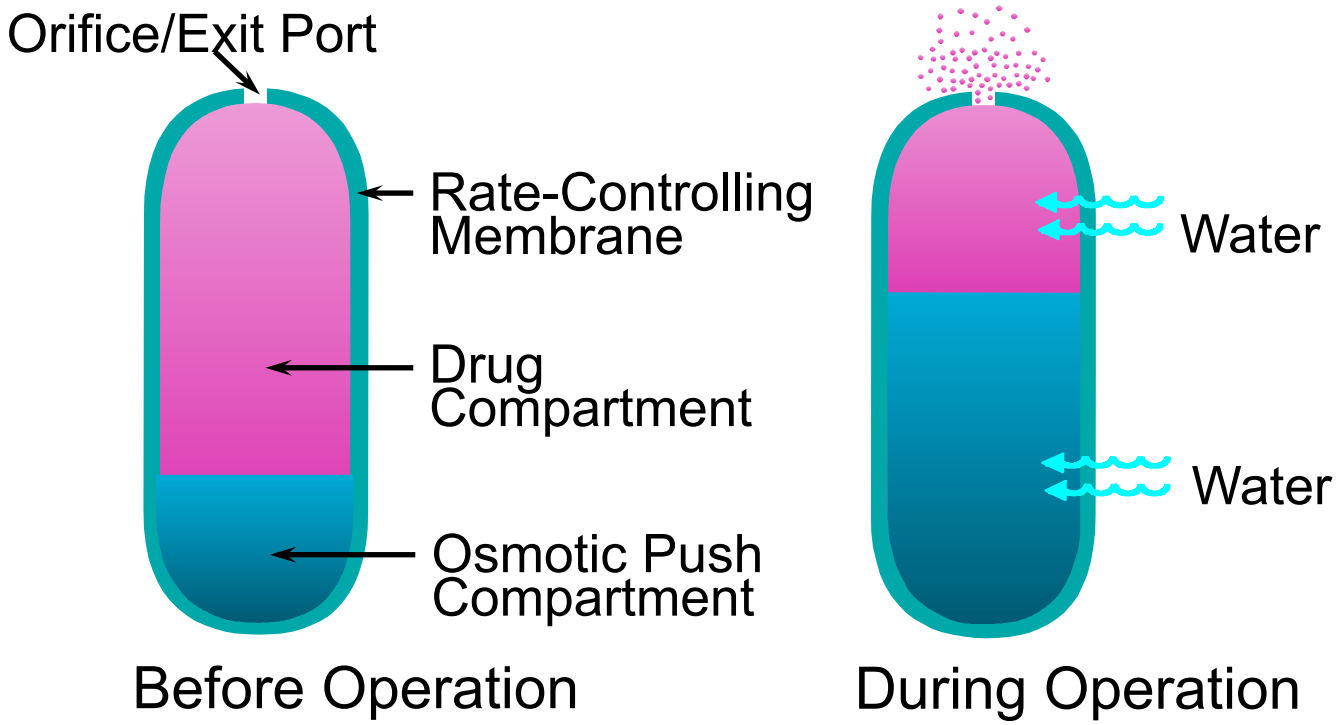
OROS® CAPSULE-SHAPED PUSH-PULL™ SYSTEM (LONGITUDINALLY COMPRESSED TABLET)



Drug layer can be single or bilayer configuration (e.g: Concerta™, Invega™)

Conley *et al*. Curr. Med. Res. Opin. 2006; 22(10): 1879-1892

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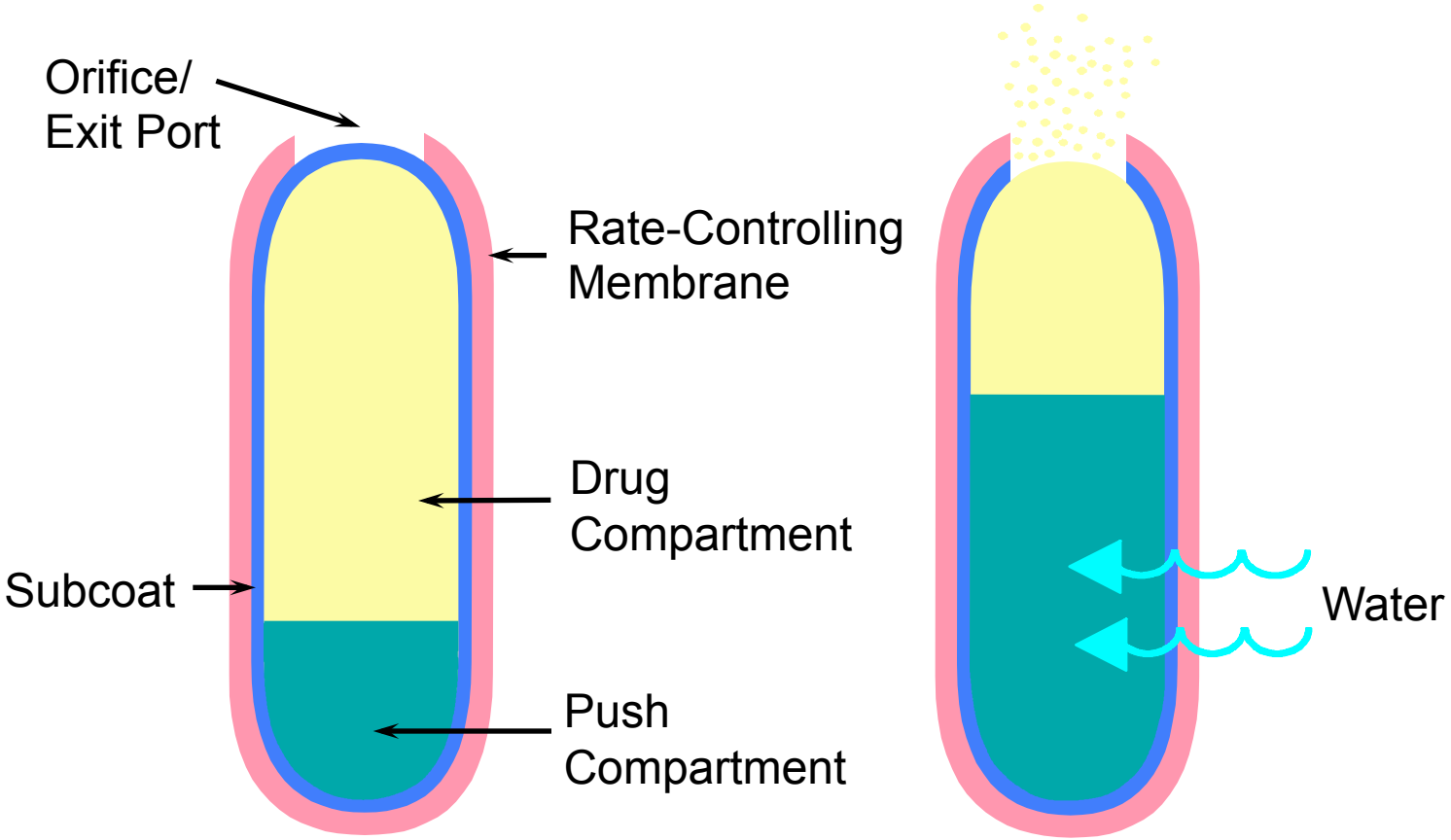
OROS® PUSH-STICK™ DESIGN FOR HIGH LOADING OF POORLY SOLUBLE DRUGS



Cruz, E. *et al*. OROS Push Stick for controlled delivery of active agents. US Patent Application 2005/0089570. April 28, 2005

OROS® PUSH-STICK™ DESIGN FOR HIGH LOADING OF POORLY SOLUBLE DRUGS

- Dual mechanisms in establishing dissolution rate –
  - > osmotic contribution:

$$(dm/dt)_P = (k/h)\, A_P\, \delta\pi_P\, C$$

  - > dissolution contribution:

$$(dm/dt)_D = A_D\, (D/h)\, \delta C$$

- The osmotic and dissolution contributions must be balanced.

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DESIGN ADVANTAGES OF PUSH PULL™ PLATFORM

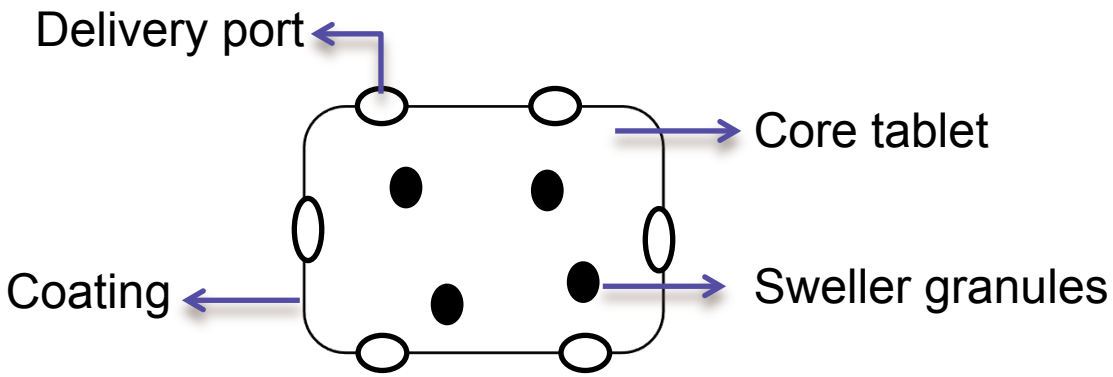
- Ability to deliver payload in a suspension form
  - Moderately soluble and insoluble drugs
- Drug layer and osmotic layer are separate compartments
  - Formulation of drug layer compartment with "solubilized API" or other functional excipients
- Ability to engineer release profile based on geometry differences

OSMOTIC SYSTEMS: ADDITIONAL DESIGNS AND MODIFICATIONS

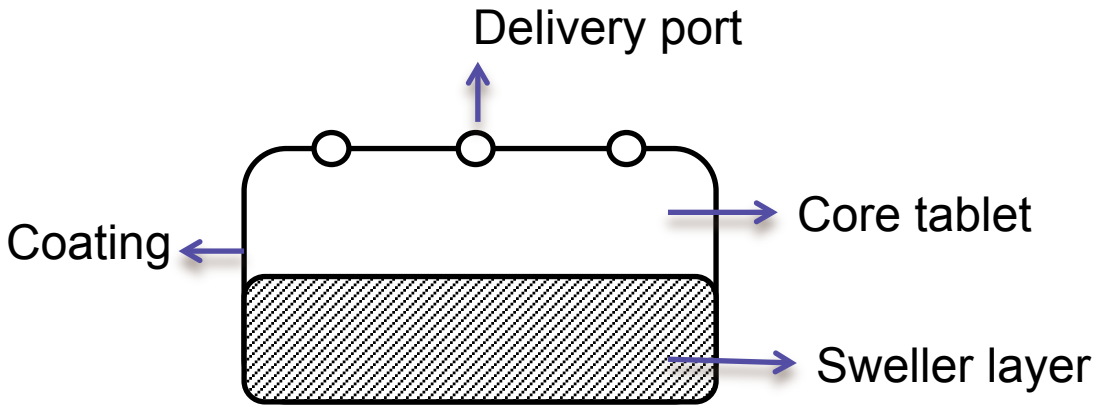
- Single layer design –
  - Asymmetric Membrane Tablet (insoluble, asymmetric, microporous coating)
  - Controlled Porosity Films
  - Addition of solubilizing agents, wicking agents and other functional excipients within the core
    - EnSoTrol™ (Supernus Pharmaceuticals)
- Multi-layer design
  - Swellable Core Technology (SCT – developed by Pfizer and Bend Research Inc.)

Wald, R. Modern Oral Osmotic Technology. Tablets & Capsules. Oct 2009

OSMOTIC SYSTEMS: PICTORIAL DEPICTIONS OF SWELLABLE CORE TECHNOLOGY (SCT)



Granular core



Bi-layer core

For additional examples and designs for SCT dosage form designs, please refer to US Patents 6,706,283 and 7,550,158

Figure adapted from U.S. Patents 6,706,283 and 7,550,158

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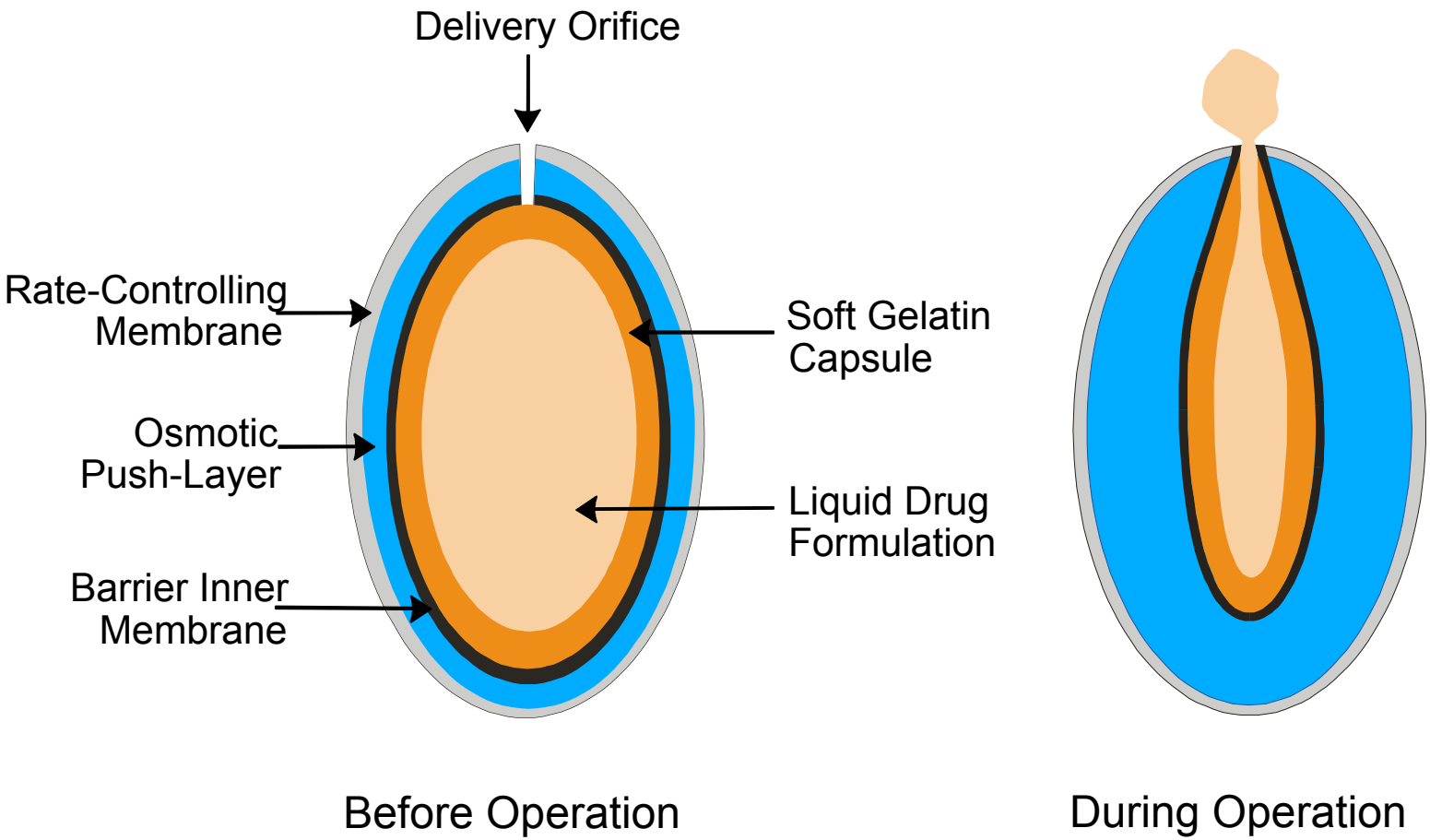
CONTROLLED RELEASE SYSTEMS FOR DELIVERY OF LIQUID FORMULATIONS

- Combine drug solubilization technologies with controlled release applications
- Delivery of liquid formulations
  - L-OROS™ technology platform
- Delivery of lipid formulations in a solid dosage form
  - "Liquisolids" – lipid formulations or SEDDS adsorbed on solid carriers

Dong, L. *et al*. Drug Development and Delivery. 2002; 2(1)
Nazzal, S. and Khan, M.A. Int. J. Pharm. 2006; 315: 110-121

L-OROS® SOFTCAP™ DELIVERY SYSTEM



Dong, L. *et al*. Drug Development and Delivery. 2002

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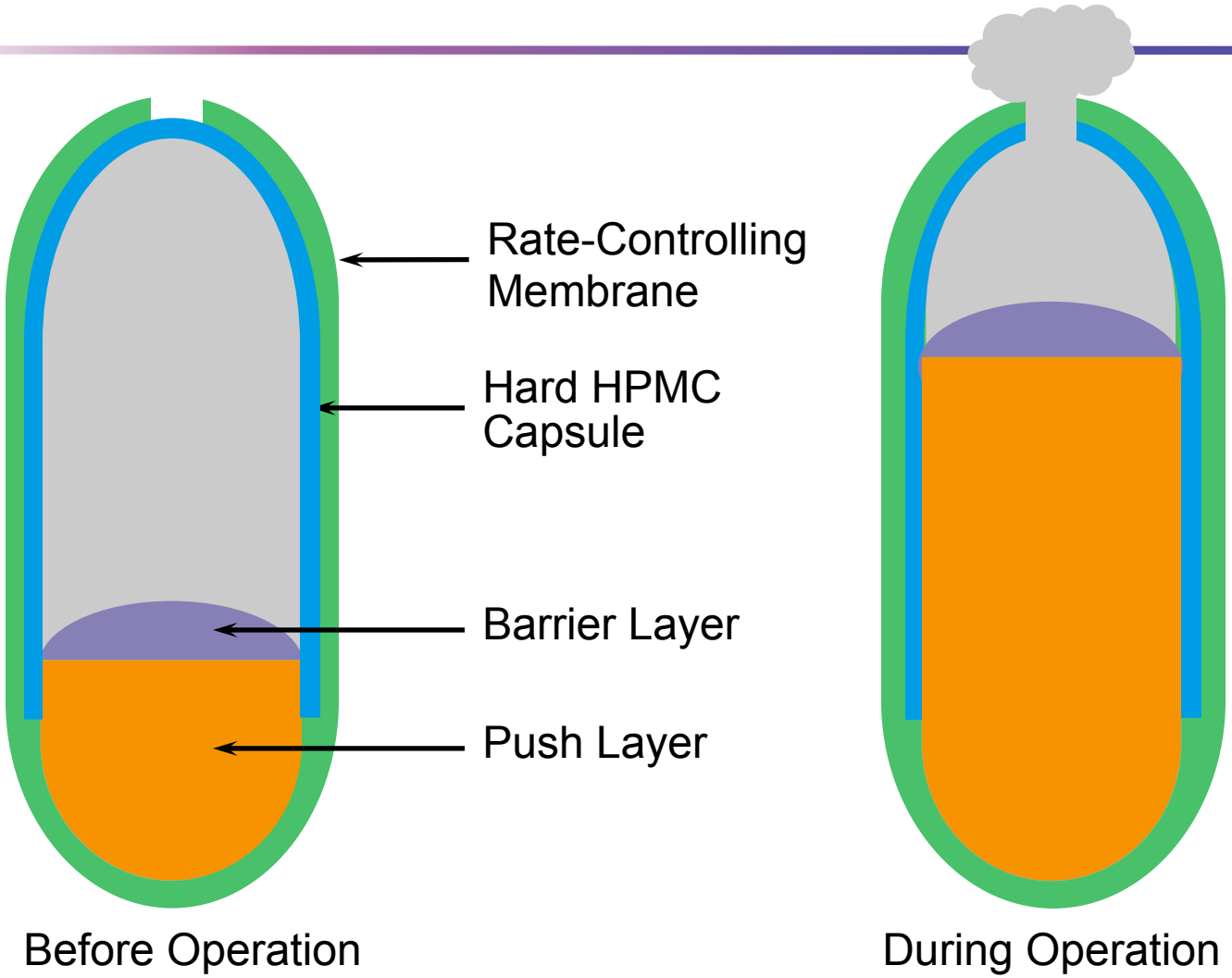
L-OROS® HARDCAP™ DELIVERY SYSTEM



Li, S. *et al* (2008)."Oral Modified Release Drug Delivery for Water Insoluble Drugs".
In: Liu, R *Water Insoluble Drug Formulation*. 2nd ed. Boca Raton, FL: CRC Press. 609-636

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FEATURES OF OSMOTIC DELIVERY SYSTEMS

- Applicability to a wide variety of drug characteristics esp. solubility range
- Ability to obtain patterned delivery
- Release Rate Independent of:
  - Food
  - Stirring
  - Gastric motility
  - pH of the environment
- Release rate proportionality between dosage strengths
- Likelihood of obtaining IVIVC

CASE STUDIES

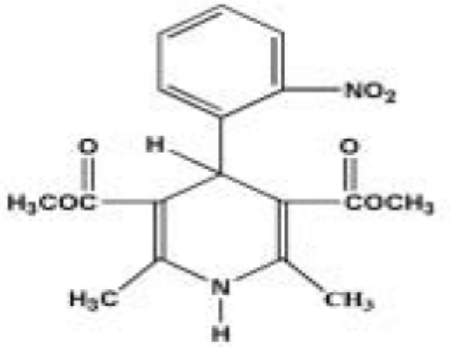
Osmotic system (OROS™ and Swellable Core Tablet)

Matrix type system

L-OROS™ for delivery of liquid formulations

NIFEDIPINE

- Solubility: 3 to 13 µg/ml; BCS Class 2
- Poor and erratic bioavailability
- Half life is ~ 2 h
- Melting point is 172-174°C

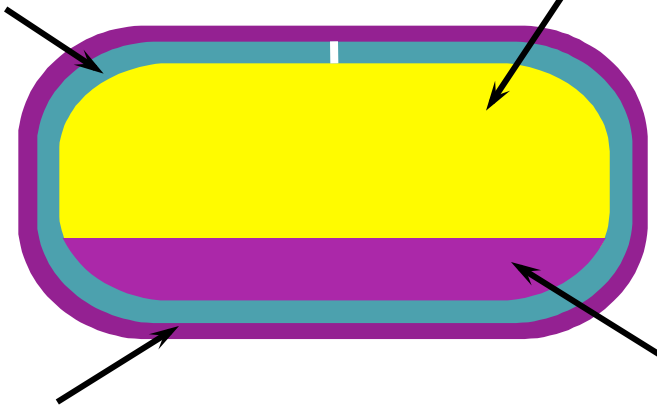


- Common side effects: headache, flushing, dizziness and palpitations
- Nifedipine has been widely studied using solid dispersions, micronization, co-crystals, and drug delivery approaches with the aim of enhancing drug dissolution, improving drug absorption, and reducing side effects

Vippagunta, S.R *et al*. Int J. Pharm. 2002, 236 (1-2), 111-123

CASE STUDY: NIFEDIPINE; OROS PUSH PULL™ PLATFORM

Membrane
- Cellulose acetate
- Polyethylene glycol



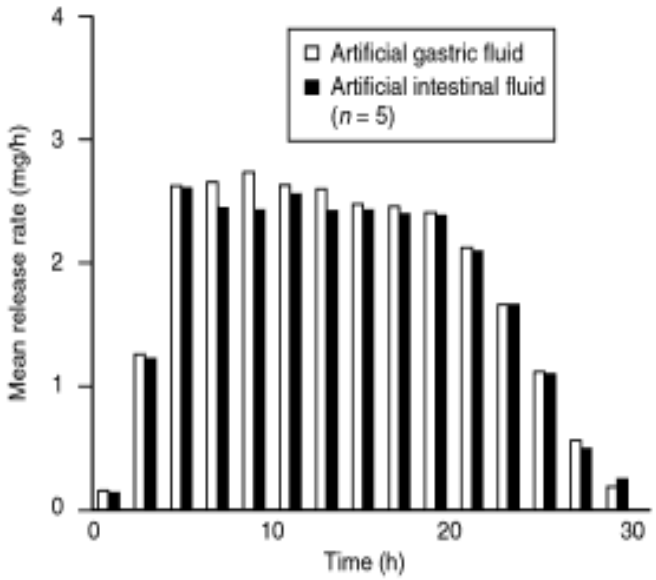
Drug Layer
- Nifedipine
- Polyox® N-80
- HPMC E-5
- Mg Stearate

Color Overcoat

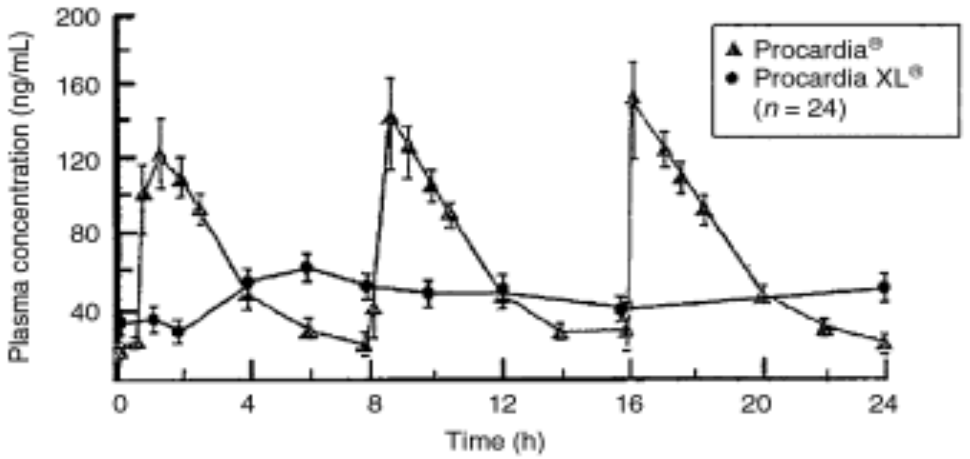
Push Layer
- Polyox®Coagulant
- NaCl
- HPMC E-5
- Mg Stearate
- Ferric Oxide

Li, S. *et al* (2008)." Oral Modified Release Drug Delivery for Water Insoluble Drugs".
In: Liu, R *Water Insoluble Drug Formulation*. 2nd ed. Boca Raton, FL: CRC Press. 609-636

OROS™ NIFEDIPINE: ZERO ORDER RELEASE OVER 24 H



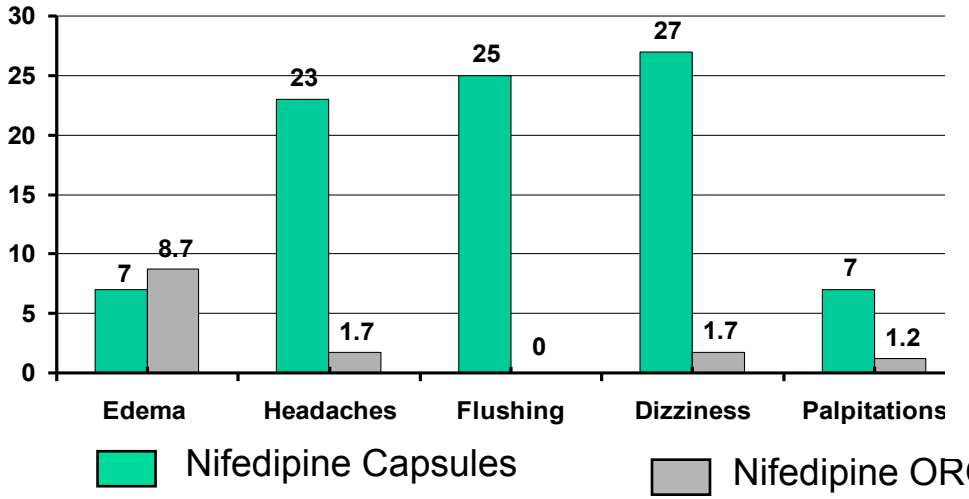
pH independent release

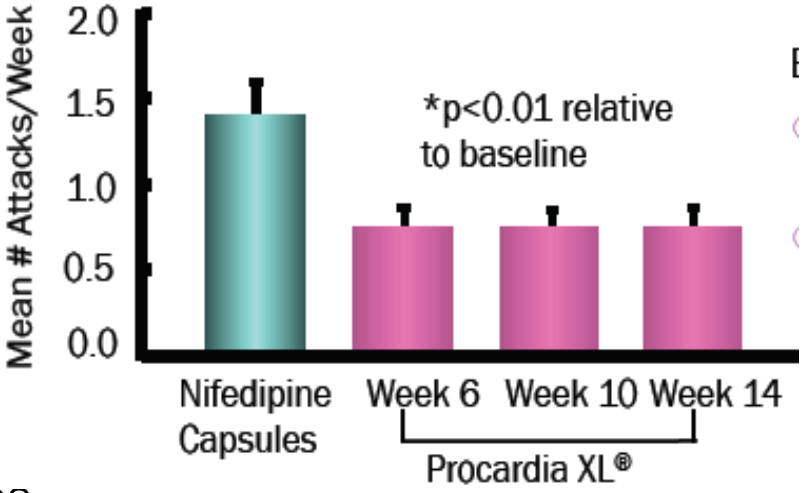


Steady state plasma profiles of Procardia® IR and Procardia XL® on Day 5

Li, S. *et al* (2008)." Oral Modified Release Drug Delivery for Water Insoluble Drugs".
In: Liu, R *Water Insoluble Drug Formulation*. 2nd ed. Boca Raton, FL: CRC Press. 609-636

INCIDENCE OF SIDE EFFECTS FOLLOWING DOSING OF OROS® AND CAPSULES OF NIFEDIPINE





- Procardia® XL was launched by Pfizer in 1989, 7 years after Procardia®
- Cardiologists recommended switching to long acting calcium channel blockers for patients with ischemic heart disease due to better safety profiles
- Product had estimated global sales of $10B until the entry of generics and other calcium channel blockers

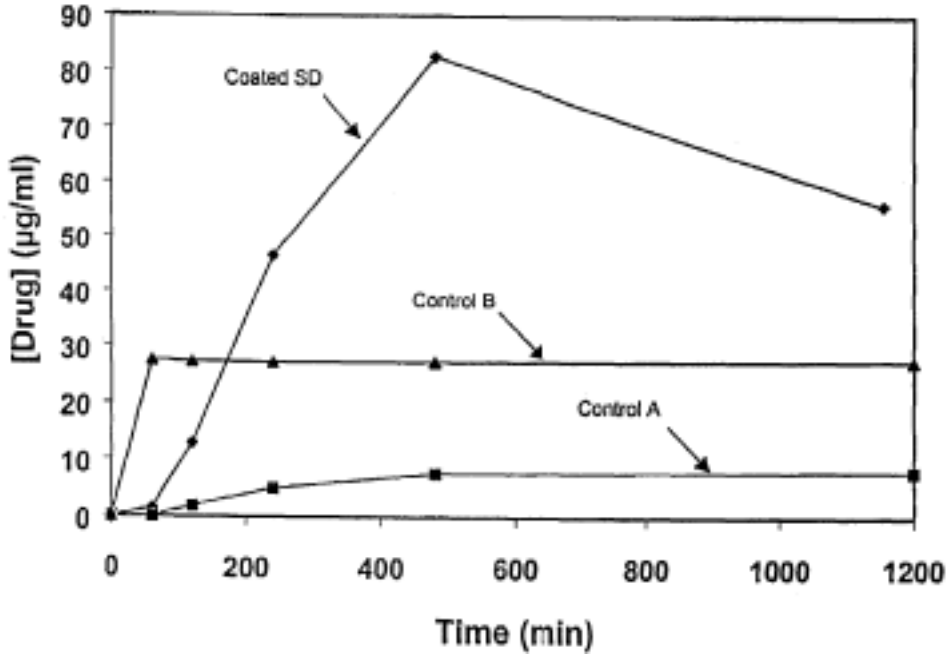
Vetrovec, GW, *et. al.*, 1987; The American Journal of Medicine, 83(6B), 24-29
Lionel and Franz. 1995; Circulation. 92: 1068-1073

AMORPHOUS DISPERSIONS IN SWELLABLE CORE TABLETS

- Drug 1
  - Glycogen phosphorylase inhibitor
  - Solubility: 1 µg/mL
  - Spray dried drug with HPMCAS (10% drug + 90% polymer) to obtain an amorphous dispersion
    - Average particle size of spray dried powder: 5 to 20 µm
  - Utilize “granular core” design of SCT
  - Core tablet:
    - 30% spray dried dispersion
    - 15% Microcrystalline cellulose
    - 30% Polyethylene oxide (600,000 Da)
    - 4% HPC
    - 20% lactose
    - 1% Mag Stearate
  - Coated with Cellulose acetate/PEG 3350 membrane and drilled with 24 delivery ports

Appel, L.E. et al. Controlled release by extrusion of solid amorphous dispersion of drugs. United States Patent 7,550,1578. June 23, 2009

RELEASE OF AMORPHOUS DISPERSION OF DRUG 1 FROM A SWELLABLE CORE TABLET DESIGN



Control A: Core containing crystalline drug
Control B: Core containing solid dispersion only
Coated SD: Solid dispersion in SCT core

Drug release in phosphate buffered media of pH 6.5

Appel, L.E. et al. Controlled release by extrusion of solid amorphous dispersion of drugs. United States Patent 7,550,1578. June 23, 2009

AMORPHOUS DISPERSIONS IN SWELLABLE CORE TABLETS

- Drug 2
  - Glycogen phosphorylase inhibitor
  - Solubility: 80 µg/mL
  - Spray dried drug with HPMCAS (50% drug + 50% polymer) to obtain an amorphous dispersion
    - Average particle size of spray dried powder: 50 µm
  - Utilize “bi-layer” design of SCT
  - Core tablet:
    - 44.4% spray dried dispersion
    - 26.1% Xylitab™ 200
    - 25.2% Polyethylene oxide (200,000 Da)
    - 3.5% Explotab™
    - 0.8% Mag Stearate
  - Sweller layer: 74.5% Explotab™, 25% Prosolv™ 90, 0.5% Magnesium stearate
  - Coated with Cellulose acetate/PEG 3350 membrane and drilled with 5 delivery ports

Appel, L.E. et al. Controlled release by extrusion of solid amorphous dispersion of drugs. United States Patent 7,550,1578. June 23, 2009

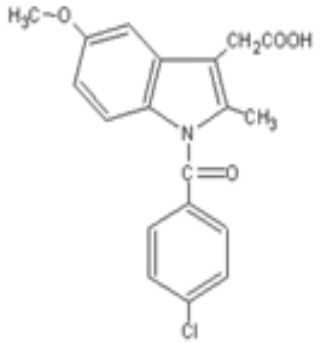
RELEASE OF AMORPHOUS DISPERSION OF DRUG 2 FROM A SWELLABLE CORE TABLET DESIGN

Time (h)	Bilayer coated Spray Dried µg/mL	Control G: Crystalline drug µg/mL
0	0	0
1	4	59
2	66	72
4	350	72
8	608	77
12	306	71
18	263	71
24	298	75

Drug release in phosphate buffered media of pH 7.2

Appel, L.E. et al. Controlled release by extrusion of solid amorphous dispersion of drugs. United States Patent 7,550,1578. June 23, 2009

CASE STUDY: DEVELOPMENT OF A MATRIX TYPE CONTROLLED RELEASE DOSAGE FORM USING HOT MELT EXTRUDATE



- Drug: Indomethacin (IDM)
  - Solubility: 4.0 to 8.8 µg/mL
  - Indomethacin (Form I) is crystalline, with a MP of 162.5°C
  - Eudragit® RL PO and Eudragit® RD 100 were used as polymers for hot melt extrusion
  - Hot melt extrudates were formed using a vertical single screw extruder. Extrudates were size reduced to 20-40 mesh and 40-60 mesh range particles.

Zhu, Y. et al., Drug Dev. Ind. Pharm. 2006; 32: 569-583

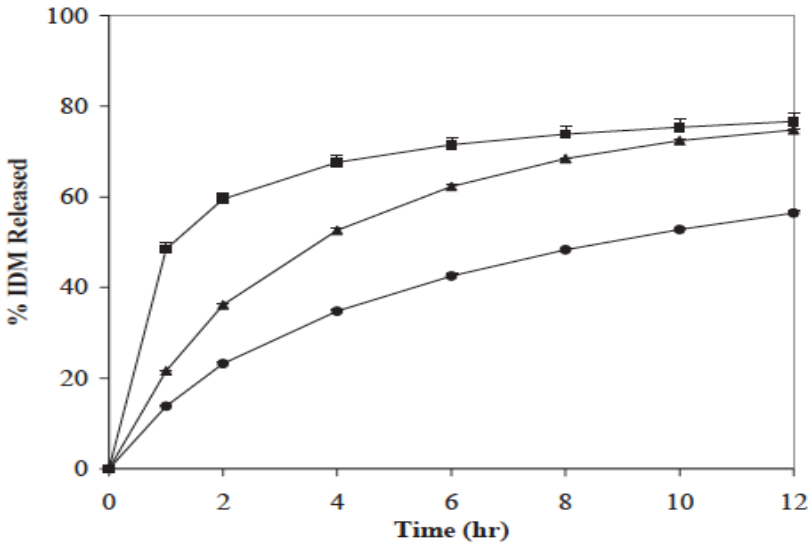
CASE STUDY: DEVELOPMENT OF A MATRIX TYPE CONTROLLED RELEASE DOSAGE FORM USING HOT MELT EXTRUDATE

- Extrudate composition
  - 30% indomethacin + 66% Eudragit® RD 100 + 4% TEC
    - 5-10% of Eudragit RD 100 replaced with Pluronic® F68
- Tablet composition
  - 50% extrudate+45% Avicel PH 101+5% L-HPC LH-21
- DSC and XRD analysis indicate indomethacin solid solution is in the amorphous state.

Zhu, Y. et al., Drug Dev. Ind. Pharm. 2006; 32: 569-583

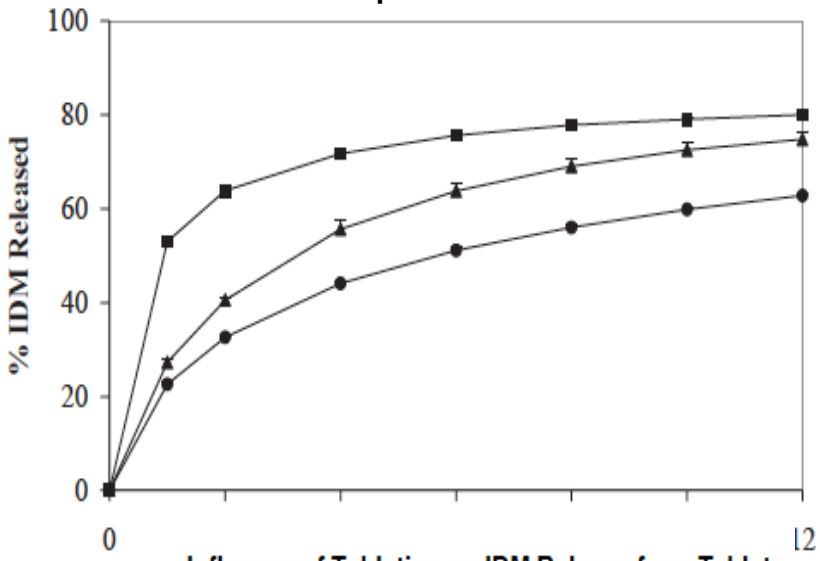
RELEASE OF INDOMETHACIN FROM EXTRUDATE GRANULES AND COMPRESSED TABLET

Extrudate granules



Influence of Pluronic® F68 on IDM Release from Hot-melt Extrudated Granules (40–60 Mesh) Containing 30% of IDM, Eudragit® RD 100, Pluronic® F68, and 4% of TEC. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C (n = 3). (●): 0% of Pluronic® F68; (▲) 5% of Pluronic® F68; (■) 10% of Pluronic® F68.

Compressed tablet



Influence of Tableting on IDM Release from Tablets Made with the Granules (40–60 Mesh) Containing 30% of IDM, Eudragit® RD 100, Pluronic® F68, and 4% of TEC Prepared by Hot-melt Extrusion. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C (n = 3). (●) 0% of Pluronic® F68; (▲) 5% of Pluronic® F68; (■): 10% of Pluronic® F68.

No influence of tablet formulation and process on release behavior of indomethacin

Zhu, Y. et al., Drug Dev. Ind. Pharm. 2006; 32: 569-583

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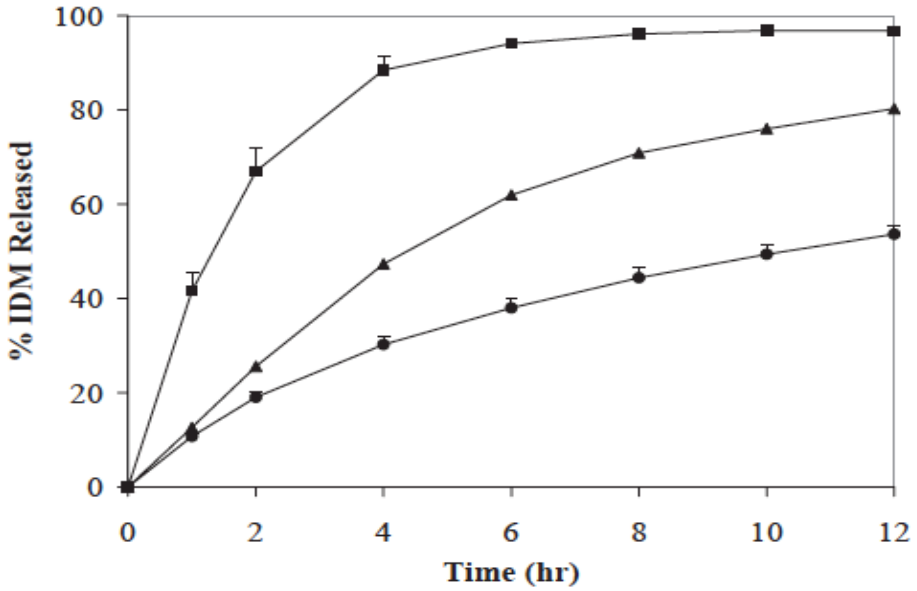
MODULATION OF INDOMETHACIN RELEASE

Incorporation of a polymer with higher water permeability at pH 6.8



Influence of Eudragit® L 100 on IDM Release from Hot-melt Extrudated Granules (20–40 Mesh) Containing 30% IDM, Eudragit® RD 100, 5% of Pluronic® F68, and 4% TEC. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C ($n = 3$). (●) 0% of Eudragit® L 100; (▲) 10% of Eudragit® L 100; (■): 20% of Eudragit® L 100.

Zhu, Y. et al., Drug Dev. Ind. Pharm. 2006; 32: 569-583

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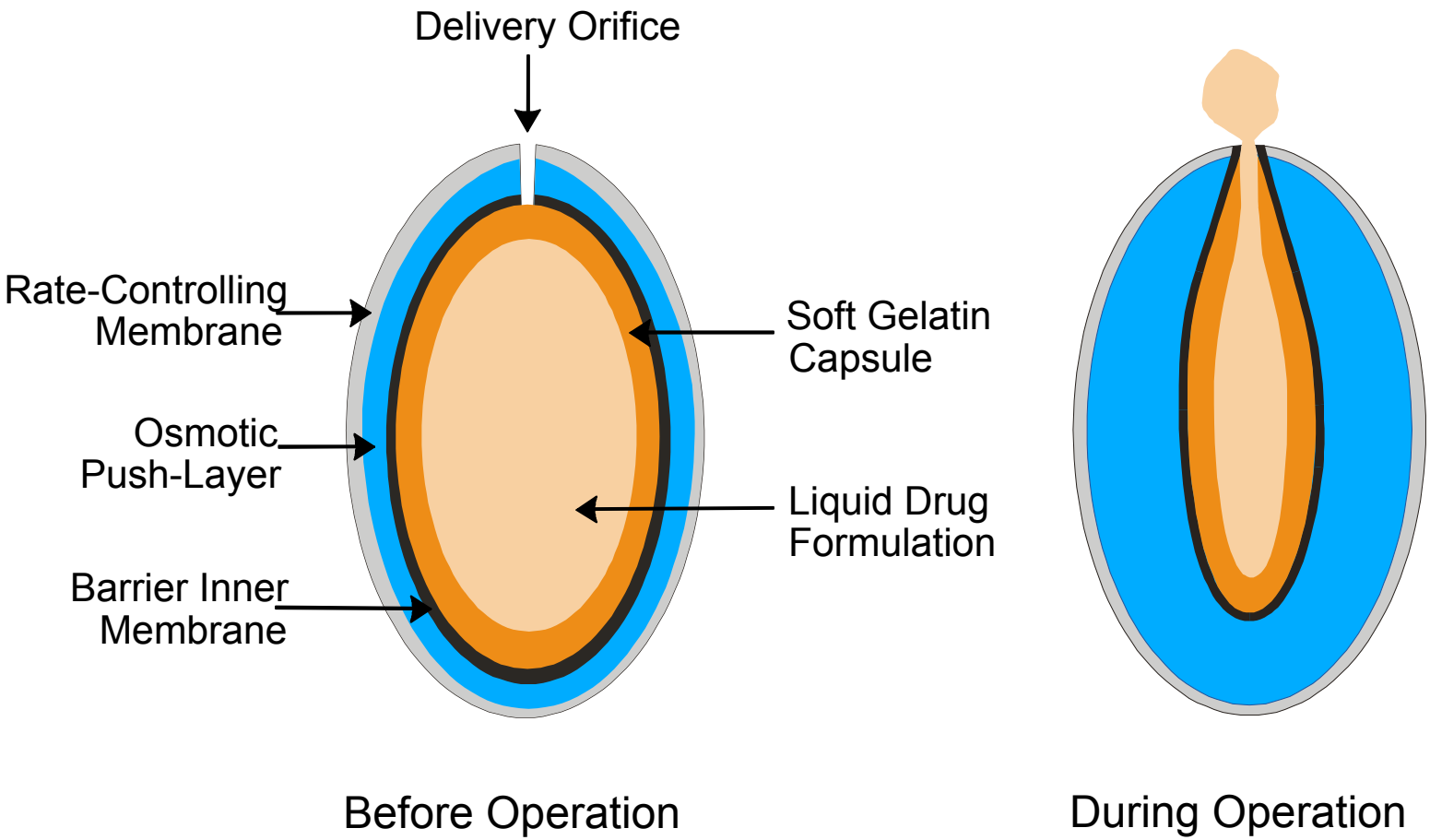
CONTROLLED RELEASE OF LIQUID FORMULATIONS

- Candidate products:
  - Night-Time® soft gel capsules
  - Neoral® capsules
- Platform: L-OROS® Soft Cap
- Formulation components
  - Barrier layer: Aqueous latex based suspension
  - Osmotic layer: Hydrophilic polymers with osmotic agents coated from a ethanol-water mix
  - Rate controlling membrane: Cellulose acetate
- All coatings are completed on traditional coating pans
- Drill orifice through coating layers

L-OROS® SOFTCAP™ DELIVERY SYSTEM



Dong, L. *et al*. Drug Development and Delivery. 2002

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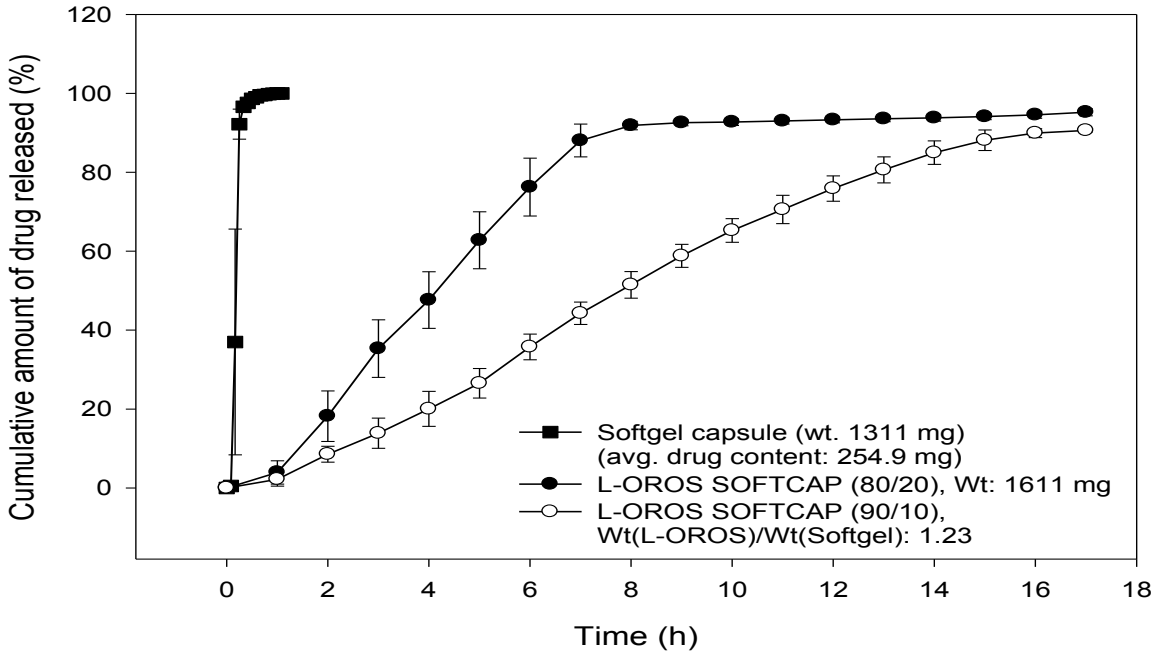
CASE STUDY: TO DEMONSTRATE FEASIBILITY FOR CONTROLLED RELEASE DELIVERY OF A LIQUID FORMULATION

- Product: Night-Time™ Soft gel capsules
- API: Acetaminophen
- Excipients:
  - Liquid formulation: Glycerin, Mannitol, PEG, Propylene glycol, Sorbitol
- Capsule size: 12 Oblong

RELEASE DURATION CAN BE TAILORED BASED ON MEMBRANE FORMULATION COMPOSITION



Drug formulation: NIGHT-TIME softgel capsules; Release in AIF, 37C, USP II method
The error bars represent the standard deviations of three runs for L-OROS and five runs for softgel.

- Consistent with osmotic delivery principles – the L-OROS™ system functionality is independent of stirring rate or pH of release media
- The values 80/20 and 90/10 refer to ratio of Cellulose acetate to flux enhancer in the rate controlling membrane

Dong, L. *et al*. Drug Development and Delivery. 2002

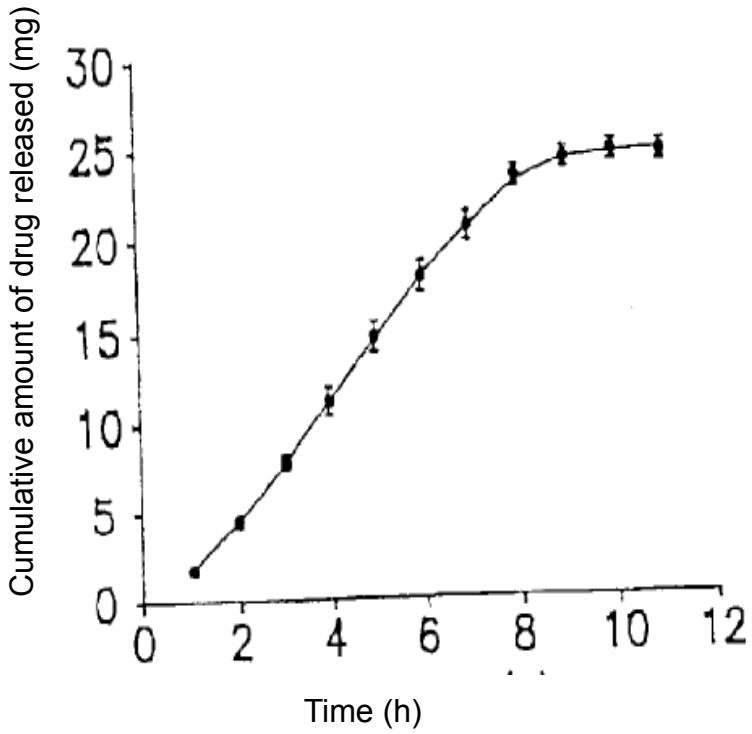
JDP Pharma Consulting, LLC . . . Connecting the Dots . . .

CASE STUDY: CONTROLLED DELIVERY OF A MICROEMULSION

- Drug: Cyclosporine
  - Cyclic polypeptide immunosuppressant agent consisting of 11 amino acids
  - MW: 1202.63
  - Marketed formulation: Neoral® soft gelatin capsules
    - Excipients: Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-α- tocopherol USP, gelatin NF, glycerol, iron oxide black, propylene glycol USP, titanium dioxide USP, carmine, and other ingredients.

Neoral Product Insert. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, October 2009

RELEASE OF CYCLOSPORINE FROM L-OROS™ SOFTCAP



Formulation components

- Barrier layer: Cellulose acetate + acetyltributyl citrate
- Osmotic layer: Sodium CMC + Methyl cellulose + NaCl (ethanol: water coating)
- Rate controlling membrane: Cellulose acetate + Pluronic F 108

US Patent 6,929,803: Conversion of liquid filled gelatin capsules into controlled release systems by mutiple coatings

PLANNING FOR SUCCESS …

- Combining solubilization technologies with dosage form design, provides a basis for controlled release of insoluble compounds.
- Development programs can be challenging…..how will we meet the challenge?
  - Discriminative analytical testing – in vitro release/dissolution testing and physical stability measurements are needed
  - Scalability and reproducibility – technical hurdles to process development and scale up, cost and efficiency of dosage form design
  - Improved ability to understand the fundamental principles of your dosage form design
- Recognize the complex interface between the GI tract and dosage form. There is much more to learn!!
- Manage the risk ….introducing a NME in a solubility enhanced state in a controlled release dosage form.

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ORAL CONTROLLED RELEASE BY THE NUMBERS

- More than 60 approved products on the market
- Global sales of ~ $30 billion in 2008 for oral CR products
- Sales are expected to rise at 10% rate for the next 2-3 years
  - Central Nervous System, Cardiovascular, and Gastrointestinal agents are the leaders in the oral CR category

Controlled Release: Higher Stakes, More Value. Pharmaceutical Commerce, Aug 2008

ACKNOWLEDGEMENTS

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Liang C. Dong

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