Solvent-Activated Controlled Release Systems

Swelling and Osmotic Systems and the Use of Hydrogels in Controlled Release

Nicholas A. Peppas
Departments of Chemical and Biomedical Engineering, and Pharmaceutics
The University of Texas at Austin
Austin, Texas 78712, USA
Swelling-Controlled Release Systems

- Controlled Release Devices Based on Hydrophilic, Glassy Polymers that Swell in Water or Biological Fluids

- Devices Based on Neutral or Ionic Hydrogels that may be Dependent on Physiological Changes
Hydrophilic Polymers and Hydrogels

- Crosslinked Polymer Structures (Networks) Swollen in Water or Biological Fluids to Equilibrium
- Hydroxylated poly(alkyl methacrylates)
- Poly((meth)acrylic acid)
- Poly(vinyl alcohol)
- Poly(N-vinyl-2-pyrrolidone)
- Poly(ethylene oxide) and poly(ethylene glycol)
- Cellulose derivatives
  
  N.A. Peppas, "Hydrogels and Drug Delivery,"  
Basic Mechanism of Swelling-Controlled Release Systems: Carrier Swelling

- The Solvent Penetration Front Controls the Drug Release
- Glassy/Rubbery Transition due to Water Transport
- Often Relaxation-Dependent Diffusion
Basic Mechanism of Swelling-Controlled Release Systems

Schematic Representation of the Action of a Swelling-Controlled Release System. The Penetrant (A) enters the Initially Glassy Polymer (B) with Velocity $u$ and forms a Gel-Like Material of Thickness $\delta(t)$. The Previously Incorporated Drug (C) can Diffuse through the Swollen Polymer Layer.
Oral Dosage Form Classifications

- **Membrane Systems** - Drug core surrounded by a rate-controlling membrane (e.g., microcapsules & coated drug pellets, granules or beads)
- **Matrix Systems** - Drug dissolved or dispersed in a carrier matrix (e.g., microspheres, beads, pellets, granules & tablets)
- **Hybrid Systems** - A combination of membrane and matrix systems (e.g., coated pellets or beads imbeded in a tablet matrix, coated matrix beads, press-coated matrix tablets)
Oral Mechanisms: Swellable Matrix Systems

- Diffusion controlled
- Dissolution controlled
- Swelling and erosion controlled
- Geometry/area changes
- Non-uniform drug distribution
Factors Affecting Oral Absorption

Drug Substance

- pKa
- Solubility
- Permeability

Formulation

- GI Transit
  - Disintegrating vs. Non-disintegrating
  - Single-unit vs. Multiple-unit
  - Gastric Retentive Systems
- In-vivo Drug Release

Achievable Release Profiles

- First Order (including $t^{\frac{1}{2}}$ dependence)
- Zero-Order
- Bimodal
- Pulsatile (including delayed release)
# Partial List of Oral Products

(Source: PDR, 2003)

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adalat CC</td>
<td>• Cardizem CD</td>
</tr>
<tr>
<td>• Calan SR</td>
<td>• Inderal LA</td>
</tr>
<tr>
<td>• Imdur</td>
<td>• Micro-K</td>
</tr>
<tr>
<td>• Sinemet CR</td>
<td>• Verelan</td>
</tr>
<tr>
<td>• Voltaren XR</td>
<td>• Cardene SR</td>
</tr>
<tr>
<td>• Volmax</td>
<td>• Theo-24</td>
</tr>
<tr>
<td>• Isoptin SR</td>
<td>• Kadian</td>
</tr>
<tr>
<td>• Procardia XL</td>
<td>• Dilatrate SR</td>
</tr>
<tr>
<td>• Effidac 24</td>
<td>• Oruvail</td>
</tr>
<tr>
<td>• DynaCirc CR</td>
<td>• Dilacor XR</td>
</tr>
<tr>
<td>• Glucotrol XL</td>
<td>• Indocin SR</td>
</tr>
</tbody>
</table>
Gastric Retentive Dosage Forms

**Rationale:**
To increase gastric residence time for drugs mainly absorbed in the upper GI tract.

**Proposed Approaches:**
- Floating dosage forms
- Expanding dosage
- High density pellets
- Bioadhesives
- Co-administration of drugs which delay gastric emptying

**Potential Issues:**
- Several approaches have inherent limitations
- Controversial in-vivo results with floating dosage forms

**Challenges:**
- Reproducibility
- Conclusive evidence of clinical benefit
Examples of Excipients Used in Floating Oral Dosage Forms

- HPMC
- HPC
- Methyl Cellulose
- Fatty Acid Glycerides
- Sodium Alginate
- Sodium Bicarbonate
PHEMA-based Carriers

- Poly(2-Hydroxyethyl Methacrylate) (PHEMA) Crosslinked and Copolymerized with Ethylene Dimethacrylate (EGDMA) and Other Monomers with Two Double Bonds

- Copolymers of HEMA with Hydrophilic Monomers Crosslinked Copolymers of HEMA with N-Vinyl-Pyrrolidone, Acrylamide, PVA, etc.

- Copolymers of HEMA with Hydrophobic Monomers Crosslinked Copolymers of HEMA with MMA and Other Acrylates
Poly(methacrylic acid)
Poly(acrylic acid) Carriers

- **Eudragit®** (Degussa-Huls, Darmstadt, Germany.)
  - Available in many Forms, Swellable or Hydrophobic
  - Mainly a Chemical Copolymer of Methacrylic and Acrylic Esters with or without Quaternary Ammonium Ions
  - Excellent as Tablet Coating Material

- **Carbopol®** (Noveon Pharmaceuticals, Cleveland, OH)
  - Used as Excipients
  - Successful Bioadhesives (Carbopol ®)
PVA and PNVP Carriers

- Homo- and Copolymers of Poly(Vinyl Alcohol) (PVA) (Elvanol, duPont; Airviol; Celanese; Mowiol and Poval; Kuraray)

- Crosslinked Homopolymers of PVA and its Copolymer with NVP, Acrylamides, etc.

- Homo- and Copolymer of Poly(N-Vinyl Pyrrolidone) (PNVP) Crosslinked Homopolymers and Copolymers of NVP
Simplified Analysis of Release Kinetics

Power Law Model for Solvent Uptake or Drug Release

\[
\frac{M_t}{M_\infty} = k \ t^n
\]

Fickian Diffusion

\( n = 0.5 \)

Case II Diffusion

\( n = 1.0 \)

P.L. Ritger and N.A. Peppas: "A Simple Equation for Description of Solute Release. II."

*J. Controlled Release, 5, 37-42 (1987).*
## Experimental Approach

**Study Swelling and Drug Release from Two Hydrogel Systems**

<table>
<thead>
<tr>
<th>Hydrogels</th>
<th>*P(HEMA-co-MMA)</th>
<th>Poly(vinyl alcohol), PVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>0 - 100 % HEMA</td>
<td>0 - 15 % poly(vinyl acetate)</td>
</tr>
<tr>
<td>Crosslinking Ratios</td>
<td>0.5, 1.0 and 2.0 %</td>
<td>1 and 10 %</td>
</tr>
<tr>
<td>Initiation Mechanism</td>
<td>redox, thermal, photo</td>
<td>acid-catalyzed</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>$M_n$ from monomer</td>
<td>15,000 to 48,000</td>
</tr>
</tbody>
</table>

Drug Loading: equilibrium partitioning or during crosslinking
## Bioactive Agents

<table>
<thead>
<tr>
<th>NAME</th>
<th>MOLECULAR WEIGHT</th>
<th>EFFECTIVE RADIUS (Å)</th>
<th>PHARMACOLOGICAL FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>180</td>
<td>3.03</td>
<td>Bronchodilator, anti-asthma</td>
</tr>
<tr>
<td>Proxyphylline</td>
<td>238.2</td>
<td>3.53</td>
<td>Bronchodilator, vasodilator</td>
</tr>
<tr>
<td>Triamterene</td>
<td>253.3</td>
<td>3.43</td>
<td>Diuretic</td>
</tr>
<tr>
<td>Oxprenolol HCl</td>
<td>302</td>
<td>3.92</td>
<td>β-Blocker, anti-arrhythmia</td>
</tr>
<tr>
<td>Buflomedil HCl</td>
<td>343.8</td>
<td>4.05</td>
<td>Peripheral vasodilator</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>451</td>
<td>4.24</td>
<td>Anti-anginal</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>1,355</td>
<td>8.5</td>
<td>Formation of blood</td>
</tr>
<tr>
<td>Dextran (FITC)</td>
<td>4,400, 16,000, 150,000</td>
<td>22.1, 247</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>Inulin</td>
<td>5,200</td>
<td>11.1</td>
<td>Diagnostic aid</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>14,100</td>
<td>~18</td>
<td>Mucolytic Enzyme</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17,200</td>
<td>~19</td>
<td>Model globular protein</td>
</tr>
<tr>
<td>Ovalbumin</td>
<td>45,000</td>
<td>~30</td>
<td>Model globular protein</td>
</tr>
<tr>
<td>Albumin</td>
<td>66,000</td>
<td>~32</td>
<td>Model globular protein</td>
</tr>
</tbody>
</table>
Water Uptake:
Effect of Hydrogel Composition
Drug Release:
Effect of Hydrogel Structure on Theophylline Release
Drug Release:
Effect of Drug Size and Type

Hydrogel formed from 35,700 MW PVA, Crosslinked 1 mol % in 15 % aqueous solution. Drug loaded by partitioning.
Poly(hydroxyethyl Methacrylate) Based Carriers

A Wide Range of Synthetic Techniques for Preparation of Hydrogel Microparticles Using HEMA and Other Monomers. Results with Oxprenolol Release over 20 hours.

Cumulative Release of Oxprenolol HCl (Ox) from Polymer 3 Monolith and IPN-Modified Samples.

[W.R. Good and K.F. Mueller, AIChE Symp. Ser., 77, 42 (1981)]
Partially-Coated Swelling Systems

- Geomatrix® (SkyePharma PLC, London, UK and Muttenz, Switzerland): A Simple Swellable System, Partially Covered with Impermeable Coatings

  - Release is Controlled by the Uncoated Area and (Probably) by Molecular Changes During Swelling.

P. Colombo et al., Intern. J. Pharmac., 63, 43 (1990); many Patents
• Release of Diltiazem HCl from HPMC-Based Geomatrix® Systems (P. Colombo et al., Proceed. APGI, 5, 261 (1989)).
• Impermeable Coating with Cellulose Acetate Propionate (CAP)

Drug Release from the Most Common Type of Hydrophilic Carriers and Devices: Swellable Matrices That Dissolve

- Water diffusion in glassy matrix
- Glassy/rubbery polymer transition
- Polymer relaxation, swelling, dissolution
- Drug transport across polymer gel layer
Moving Fronts in Swellable Matrices

Water penetration into matrix creates sharp moving boundaries defining different regions inside the matrix (dry core, gel layer, undissolved drug gel layer):

Swelling front
Erosion front
Diffusion front
Moving Fronts in Swellable Matrices

- **Swelling Front**
- **Diffusion Front**
- **Erosion Front**

- $C_d$ = Drug Loading
- $C_s$ = Drug Solubility in Water

Thickness: Initial radius of the matrix
Device for Front Position Measurement
Relevant Front Movement During BPP Release
BPP Release Kinetics

Fraction Released vs Time (min) for different concentrations:
- 10%
- 20%
- 30%
- 40%
- 60%
- 80%

The graph shows the fraction released over time for various concentrations of BPP, with time in minutes on the x-axis and fraction released on the y-axis.
Loading 30%
Loading 60%

30 min

120 min

240 min

360 min
Dome Matrix® Geometry

Compressed matrices made with special shaped punches
Dome Matrix®

DELIERY MODULE
• dose split
• geometry flexibility
• assembly

• delivery mechanism
• time and site target
• carrier
Dome Matrix and Flat Base Disc

![Graph showing the fraction released over time for dome matrix and flat base disc](image)

- **Fraction Released**
- **Time (min)**

Legend:
- □ dome matrix
- ○ flat base disc
- Fitted line
Release Surfaces

Figure 2b
BPP Release from Side Surface

Fraction Released vs. Time (min)

- Flat base matrix
- Dome matrix
- Fitted line
BPP Release from Different Bases

Same release surface of curved surfaces

Fraction Released

Time (min)

convex
one base (flat base disc)
concave
fitted line
Different Shaped Surfaces

convex

flat

concave

300 minutes
We have developed an advanced experimental technique that can be applied on dry and slowly swelling tablets in situ (without moving them out of the dissolution vessel during swelling and release) and can be used to identify the swelling and dissolution process.

High-Resolution X-ray Computed Tomography
High-Resolution X-ray Computed Tomography

1. A technique for digitally slicing a swelling sample in real time using X-rays

2. Acquisition of multiple data on “slices” of a sample over a range of angular orientations

3. CT image is called a slice and corresponds to thin section of specified thickness of the sample scanned
High-Resolution X-ray Computed Tomography

- Rapid acquisition, nondestructive technique
- Provides cross-sectional images in different planes through a sample
- Allows visualization of features in the interior of opaque and solid sample
- Allows continuous collection of digital information on 3-D geometries and properties of a wide range of materials
- Applied to the pharmaceutical field for the first time
Dome Matrix® Swelling

Fronts not as distinct
As originally believed

$t = 0$  $t = 15$ min  $t = 55$ min
Dome Matrix® Swelling

Time = 30 min
Dome Matrix® Swelling

Time = 45 min
Modules Assemblage Stacked Configuration

- 2-6 modules stacked in capsule with convex face inserted in concave face
- dose and release flexibility (different modules)
- increasing length cylinder due to module sticking (geometric effect on release kinetics)
Modules Assemblage Void Configuration

- capsule contains four modules soldered two by two with concave bases facing
- the soldered modules immediately float (stomach targeting)
- void chamber can be filled with additional drugs (carrier concept)
Intelligent Carriers for Drug Delivery

• Crosslinked polymer structures (networks) swollen in water or biological fluids to equilibrium, and responsive to external conditions.

• Poly((meth)acrylic acid)

• Hydrogen-bonding copolymers
Critical Phenomena

- Temperature sensitivity
- pH-Sensitivity
- Ionic strength
- Solvent composition
Swelling of Ionic Gels

Each fixed ion has an associated mobile counterion which is restricted to remain in the gel. Osmotic pressure gives rise to swelling when these ions are dissociated.
pH-Sensitive Release System
Influence of mol% MAA on Equilibrium Swelling

![Graph showing the influence of mol% MAA on equilibrium swelling. The x-axis represents pH of swelling medium, ranging from 0 to 12. The y-axis represents equilibrium swelling ratio (Q), ranging from 0 to 8. The graph compares 10 mol% MAA (circles), 40 mol% MAA (squares), and 80 mol% MAA (triangles).]
Factors Affecting the Swelling Properties of Polymer Networks

- Nature of polymer
- Polymer-solvent interaction
- Degree of crosslinking
- Viscoelastic properties of polymer
Dynamic Swelling vs. pH
T=37°C, I=0.1M, V=100 ml
P(HEMA-co-MAA) (50:50 mol%) Glutaric Acid Buffer

![Graph showing dynamic water uptake vs. time for different pH values.](image-url)
Cationic Carriers

Monomers: 2-hydroxyethyl methacrylate (HEMA)

\[
\text{CH}_3 \\
\text{CH}_2=\text{C-C-O}_2\text{CH}_2\text{CH}_2\text{OH}
\]

Diethyl aminoethyl methacrylate (DEAEMA)

\[
\text{CH}_3 \\
\text{CH}_2=\text{C-C-O}_2\text{CH}_2\text{CH}_2\text{N} \left(\text{C}_2\text{H}_5\right) \text{C}_2\text{H}_5
\]

Diethyl aminoethyl acrylate (DEAEA)

\[
\text{CH}_2=\text{CH-C-O}_2\text{CH}_2\text{CH}_2\text{N} \left(\text{C}_2\text{H}_5\right) \text{C}_2\text{H}_5
\]

Initiator: 2,2 azobis 2-methylpropionitrile (AIBN)

Crosslinking agent: ethylene glycol dimethacrylate (EGDMA)
P(DEAEM-co-HEMA) 30% DEAEM
X=0.001 mol EGDMA/mol monomer
T=37°C  I=0.1M  V=100 ml
Carriers that are Temperature-Sensitive

Upper critical miscibility temperature (UCST)

Lower critical miscibility temperature (LCST)

\[
\frac{\partial \mu_1}{\partial \nu_2}_{T,P} = 0 \quad \frac{\partial^2 \mu_1}{\partial \nu_2^2}_{T,P} = 0
\]

Mathematically, we seek conditions for which

Conditions of incipient separation
Poly(N-isopropyl acrylamide)-based Carriers
Synthesis of Environmentally Sensitive Hydrogels: Complexation Approach
Effect of Complexation on Hydrogel Structure

Uncomplexed State

Complexed State

PEG graft

PMAA network

decrease pH
Equilibrium Mesh Size as a Function of pH for Samples Containing PEG Grafts of Molecular Weight 1000 with the Ratio of MAA:PEG being (○) 60:40, (□) 50:50, (△) 40:60.
Oscillatory Swelling Behavior as a Function of Time and pH for a Sample Containing 50% PMAA and 50% PEG with the Molecular Weight of the PEG Grafts being (○) 200, (□) 400, (△) 1000.
Simple Model of Glucose-Insulin System

Insulin → Plasma Insulin → Effective Insulin

Liver ← Plasma Glucose ← Tissue

Exercise, Meals

Controlled Drug Delivery System

Pancreas

Target Glucose Level
Mechanism of Intelligent Hydrogels

Expanding Gels

Empty hydrogel absorbs glucose leading to gluconic acid production.

Decrease in pH leads to gel expansion which releases insulin.
Polymer Synthesis Details

• Expanding Gels
  – pH sensitivity - Diethylaminoethyl methacrylate (DEAEM)
  – biocompatibility - Poly(ethylene glycol) monomethacrylate (PEGMA)
  – crosslinking agent - Tetra(ethylene glycol) dimethacrylate (TEGDMA)
  – glucose sensitivity - Glucose oxidase
  – increased oxygen permeability - Catalase

• Squeezing Gels
  – pH sensitivity - methacrylic acid (MAA)
  – biocompatibility - Poly(ethylene glycol) monomethacrylate (PEGMA)
  – crosslinking agent - Tetra(ethylene glycol) dimethacrylate (TEGDMA)
  – glucose sensitivity - Glucose oxidase
  – increased oxygen permeability - Catalase
Hydrogels

Glucose + Oxygen $\rightarrow$ Gluconic Acid + H$_2$O$_2$

- Weight Swelling Ratios were Determined for the Hydrogels.

- Concentration of the Released Insulin was Determined Using Radioimmune Assay
Swelling/Deswelling of Glucose Oxidase-Containing Microparticles of a Cationic Hydrogel [K. Podual and N. Peppas, Unpublished].
Insulin Release Study
(P(DEAEM-g-EG) Hydrogels)

Concentration of insulin
(μ IU/ml)

Time (min)
Glucose-Dependent Gel Swelling
(P(DEAEM-g-EG) Hydrogels)

\[ \frac{q \text{ swollen polymer}}{g \text{ dry polymer}} \]
Polymer Therapeutics

- Use of specific polymers to target specific cells of sites
- Copolymerization for incorporation of selected functional groups.
- Use of dendrimers and star polymers
Dendrimers: Convergent Approach

Reactive Group

Wedge  Central Core

Dendrimer
Dendrimers: Divergent Approach

Monomer → Central Core → Intermediate (IG) → Final Dendrimer (II G) → Final Dendrimer (n G)
Chemical Activation of Star Polymer Followed by Immobilization of Biomolecules

* : Active End

: Biomolecule
“Smart” Drug Delivery
Helps Patients Stay on Treatment!

• Significance and Impact

• Biosensors – Biomolecular recognition

• Intelligent Polymer Networks

• Silicon Integration

• Innovative Approaches
  – Ultrasensitive microsensors based on the integration of environmentally responsive hydrogels with silicon microcantilevers
  – Novel microdevices based on the integration of biomimetic polymer networks with silicon substrates

• Nanoparticulate Release
Figure 1 | Systems approach to drug delivery. Drug delivery lends itself to a systems approach.
Intelligent Polymer Networks

Micro-/Nanoscale Integration

Sensing/Recognition Elements

Implantable Therapeutic Device

Monitor an analyte or condition
Release a therapeutic agent to counter undesired levels of analyte

The development of microfluidic systems - integrated networks of nanometre-sized fluid channels, pumps, mixers, and sensors designed to perform a wide range of chemical processing and analytical tests. - Ed Grismer
“Smart” Drug Delivery

• The future of drug delivery systems will involve smart systems

• These will address the issue of keeping the drug at the desired therapeutic level in the body thus avoiding frequent administration
"Smart" Drug Delivery

- Systems use detection of chemical signals in the body to prompt the release of drugs.

- Microchips placed under the skin, the spinal cord or the brain to deliver drugs ranging from pain medication to chemotherapy.

- The ultimate goal is to administer drugs at the right time, at the right dose anywhere in the body with specificity and efficiency.
“Smart” Drug Delivery

- Need for *advanced intelligent materials*, more reliable devices, *miniaturized* systems

- Society asks for *improved treatment* of disease, advanced *detection* and *therapy*, and *cost effective processes*

- Improvement of *quality of life* is important
Intelligent Sensing/Therapeutic Systems: Telemedicine in Practice

- Imprinted Site
- Biodegradable Polymer
- Therapeutic Well
- Silicon Wafer
- Microchip
BioMEMS Sensor Platform

- Pattern environmentally responsive hydrogels onto silicon microcantilevers to create a BioMEMS/MEMS sensor device.

Change in pH, temperature, etc. → hydrogel swells
Osmotically Controlled Systems

- Consider Polymer with Drug Incorporated Throughout
- Presence of Highly Soluble Drug Leads to very High Osmotic Pressure
- As a Result, the Release System Starts Rupturing
Oros® Products

- First Commercial Oros® Product was the Acutrim® System (Developed for Ciba-Geigy)
  It Delivers the Appetite Suppressant Phenylpropanolamine over 16 hours
- Other Products Under Development are a Controlled Release Form for Vitamin C and a Drug Combination for Treating Symptoms of the Common Cold
Principle of Osmosis

Osmotic Pressures of Saturated Solutions of Common Drugs (in atm)

- Sodium Chloride: 356
- Fructose: 355
- Potassium Chloride: 245
- Sucrose: 150
- Dextrose: 82
- Potassium Sulfate: 39
- Monosodium Phosphate: 28
The Oros® System

Elementary Osmotic Pump Cross Section.
“Push-Pull” Osmotic Tablet

*In vitro* Release Rate of Potassium Chloride from Elementary Osmotic Pumps in Water at 37°C.

Key: 1 Range of Experimental Data Obtained from Five Systems; -, Calculated Release Rate.
Osmotic Systems

Application of the Basic Irreversible Thermodynamic Theory and the Kedem-Katchalsky Analysis (1958)

\[ J_{\nu} = L_p \Delta P + L_{pD} \Delta \Pi_s \]
\[ J_D = L_{Dp} \Delta P + L_D \Delta \Pi_s \]

\[ J_{\nu} \] Total Volume Flow

\[ J_D \] Exchange Flow

Staverman Analysis

Systems are Defined by Reflection Coefficient $\sigma$

$$\sigma = - \frac{L_{pD}}{L_p}$$

Permeability Coefficient $\omega$

and Hydraulic Permeability $L_p$
Figure 2 | Osmotic oral delivery systems. Controlled-release OROS delivery systems.
Mathematical Analysis

\[ \Delta \pi = \frac{N}{V} \text{RT} = C \text{RT} \]

\[ \frac{dV}{dt} = \frac{A}{\delta} (\sigma \Delta \pi - \Delta p) \]
Mathematical Analysis

\[ \frac{dV}{dt} = \text{Volume Flux} \]

- \(A\) = Area of Membrane
- \(\Delta \pi\) = Osmotic Pressure
- \(\delta\) = Membrane Thickness
- \(\Delta p\) = Hydrostatic Pressure
- \(L_p\) = Permeability Coefficient
- \(\sigma\) = Reflection Coefficient

For Large Orifice, \(\Delta \pi >> \Delta p\): then

\[ \frac{dV}{dt} = \frac{A}{\delta} L_p \sigma \Delta \pi = \frac{A}{\delta} k \Delta \pi \]
Repeating

\[ \frac{dV}{dt} = \frac{A}{\delta} k \Delta \pi \]

Note

\[ \frac{dM}{dt} = \frac{dV}{dt} C \]

\[ \frac{dM}{dt} = \frac{A}{\delta} k \Delta \pi C \]
Make Saturated Solution

\[ C = S \]

\[ \frac{dM}{dt} = \frac{A}{\delta} k \Delta \pi S \]
Osmotic Pump Systems

Advantages

• Release Rates are Independent of Agent Properties
• Can Deliver Macromolecules and Ionic Species
• Relatively High Fluxes
• Release Rates are not Dependent on Environmental Conditions
Osmotic Pump Systems

Disadvantages

• Subject to Dose Dumping if Membrane Breaks [e.g. Someone Chews it]

• Slightly More Expensive to Formulate than Coating Tablets

• Possible Hole Plugging
Technical Considerations

Orifice Size

Must be Small Enough to Minimize Contributions of Solute Diffusion

Must be Large Enough to Minimize Hydrostatic Pressure. Hydrostatic Pressure can Decrease Osmotic Influx. It can also Increase System Volume.
Oral Products: Osmotic Pumping Mechanism

• Rate-Controlling Semipermeable Membrane
  – Cellulose Acetate

• Push Layer (Swellable Hydrophilic Polymers)
  – Poly(ethylene oxide)

• Selected Examples
  – Procardia XL (Nifedipine; Pfizer)
  – Covera-HS (Verapamil HCl; Searle)
  – DynaCirc CR (Isradipine; Norvartis)
Oral Products: Hybrid Systems

- **Multiple-unit System in a Single Unit**
  - Theo-Dur (Theophylline; Key)
  - Toprol XL (Metoprolol Succinate; Astra)

- **Coated Matrix Beads**
  - Delsym (Dextromethorphan; Medeva)

- **Coated Matrix Tablets**
  - Procanbid (Procainamide HCl; Monarch)
Other Oros Products

Under Joint Development by Alza and Other Companies

- Oros Albuterol to Administer Asthma-Relief Drug Ventolin® (Glaxo)
- Oros Prazosin to Deliver Antihypertensive Minipress® (Pfizer)
- Oros Nifedipine to Administer Procardia® (Pfizer) for Treatment of Angina and Hypertension
Dependence of Pilocarpine Nitrate Release Rate on the Osmotic Driving Force

Pilocarpine Nitrate Release Rate as a Function of System Area
Osmotically-Controlled, Single-Pulse Systems
Release Profile of a Single-Pulse, Osmotically-Controlled Rupturable System
Use of Osmotic Phenomenon to Achieve One-Pulse Systems


External Layer Bursts when $\Delta \pi$ is Sufficiently High
Use of Osmotic Phenomenon to Achieve One-Pulse Systems

\[ \frac{dr^*}{dt^*} \text{ versus } r^* \text{ for an } N_1 \text{ of 0.025. The ratio } N_1 \text{ of the Yield Stress to the Stiffness Determines the Dimensionless Radius } r^* \text{ at which the Spheres Burst. They Burst if the Trajectories Intersect the Dotted Line } r^* = N_1 + 1. \]

The Dimensionless Ratio

\[ N_2 = \frac{P_or_o}{2MI_o} \]

Determines the initial

Dimensionless Expansion Rate

\[ \frac{dr^*}{dt^*} \]

and also Determines Whether the Sphere would Expand Forever or Reach an Equilibrium Size if the Yield Stress were Infinite.
Other Information

See attached review articles and a number of relevant papers.