

The Cost of Optimal Drug Delivery Reducing and Preventing the Burst Effect in Matrix Systems

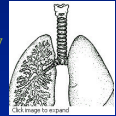
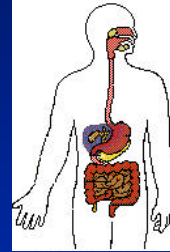


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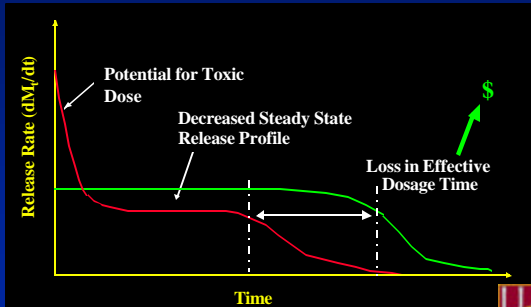
Potential Delivery Routes

implantable
oral
transdermal
intramuscular
intravenous

ocular
nasal
buccal
pulmonary
rectal
intravaginal



Potential Disadvantages due to Burst Release



Significance of Burst Release

Conditions Where Burst is Desirable

- necessary high drug concentration at beginning of therapy
- delayed burst for release at specific time or triggering condition
- sudden flavor release in food

Significance of Burst Release

Conditions of Undesirable Burst

- local toxicity
- systemic toxicity
- ineffective use of drug
- lack of predictable behavior

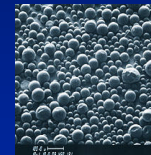
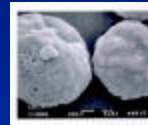
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Observed Cases of Burst Release

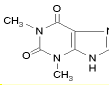
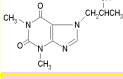
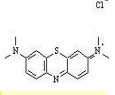
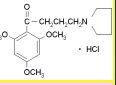
- Burst is especially prevalent in:
 - systems with small molecular weight, hydrophilic drugs
 - microsphere systems (high surface area)
 - porous systems



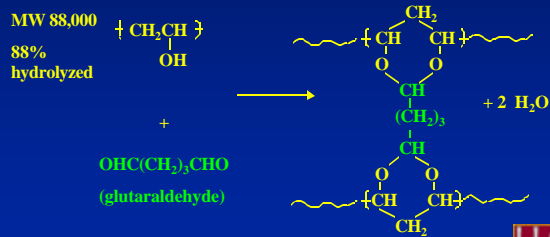
- Burst is also problematic in protein systems
 - surface desorption; incomplete encapsulation



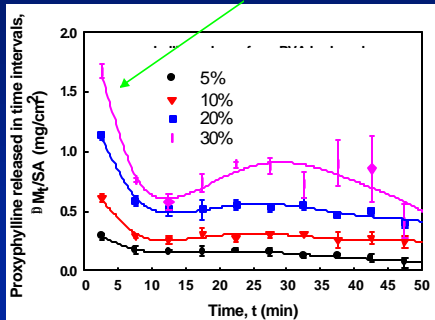
Experimental Verification: Model Drugs

Name	Theophylline	Proxiphylline	Methylene Blue	Buflomedil HCl
Structure				
Biological Function	Bronchodilator	Bronchodilator	Dye used for diagnosing kidney disorders	Vasodilator

Hydrogel System: Crosslinked Poly(Vinyl Alcohol)

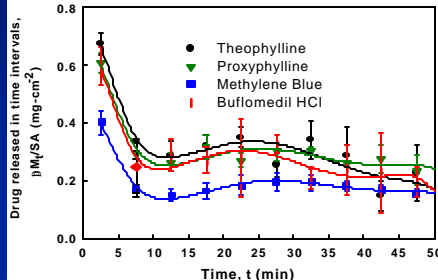


Effects of Drug Loading Concentration: Proxiphylline Burst Amplified at High Loading

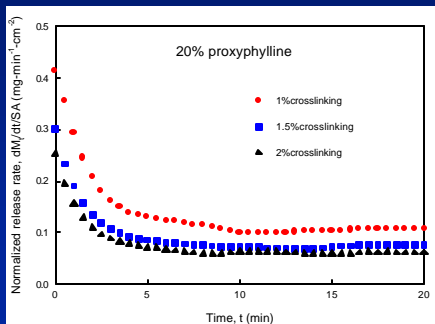


Burst Effect Lower for Methylene Blue, due to combined effect of

high partition coefficient, low water solubility, and higher molecular weight

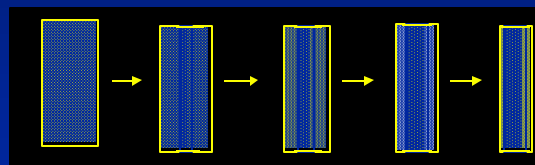


Crosslinking Reduces Burst... but also reduces long-term release rate



Potential Causes for the Burst Effect

- Adsorption of drug to matrix surface
- Drug migration to surface during drying



Drying process →

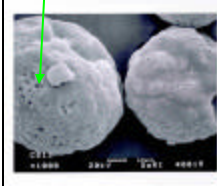
Potential Causes for the Burst Effect

- Adsorption of drug to surface
- Drug migration to surface during drying
- Device geometry
- Development of gel layer
- Heterogeneous nature of hydrogels
- Pore space vs. mesh space

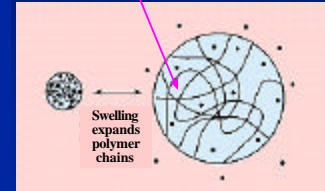


Potential Causes for the Burst Effect

Pore Diffusion Allows Rapid Release



Mesh Space is Much Smaller and is a Bigger Hindrance to Diffusion



Can the Burst Effect be Predicted and Controlled?



Some Attempts to Model the Burst Effect

- ❖ $\frac{M_t}{M_\infty} = kt^n + \alpha$
 - M_t = amount of drug released at time t
 - M_∞ = amount of drug released at infinity
 - α = burst quantity
- ❖ $\frac{dC^s}{dt} = -k_d C^s$
 - C^s = drug concentration on the surface
 - k_d = desorption constant

These models separate the burst effect ENTIRELY from the release behavior



Redefining Hydrogels: Two Simultaneous Diffusion Processes

- Patil et al. - poly(sucrose acrylate)
- Separated diffusion coefficients for macropores and polymer mesh-
 - $D_{3,21}$ = diffusion through mesh
 - $D_{3,p}$ = pore diffusion

$$\frac{\partial C_3}{\partial t} = \frac{\partial}{\partial x} \left(D_{3,21} \frac{\partial C_3}{\partial x} \right) + \frac{\partial}{\partial x} \left(D_{3,p} \frac{\partial C_3}{\partial x} \right)$$



A Starting Point: The Diffusion-Convection Model for Water and Drug Transport

Water Diffusion	$\frac{\partial C_1}{\partial t} = \frac{\partial}{\partial x} \left(D_{1,2} \frac{\partial C_1}{\partial x} - v C_1 \right)$
Drug Diffusion	$\frac{\partial C_3}{\partial t} = \frac{\partial}{\partial x} \left(D_{3,21} \frac{\partial C_3}{\partial x} \right)$



Developing a Model to Better Predict the Burst Effect

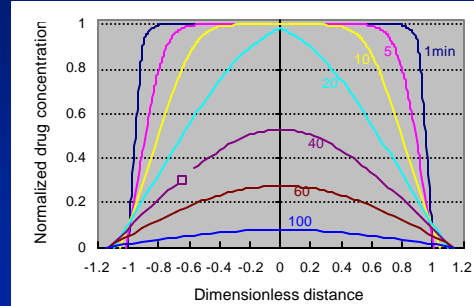
To account for the burst effect:

- Incorporate New Desorption Boundary Conditions
- Non-constant convective term, m

Water Diffusion	$\frac{\partial C_1}{\partial t} = \frac{\partial}{\partial x} \left(D_{1,2} \frac{\partial C_1}{\partial x} - v C_1 \right)$
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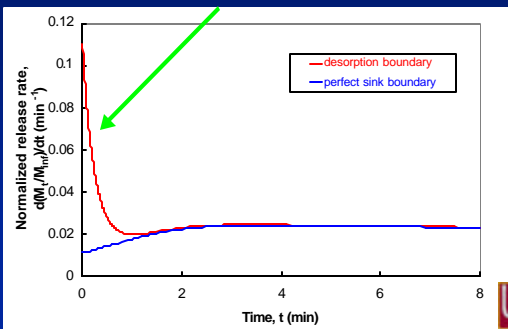


Model-predicted drug distribution in matrix during release



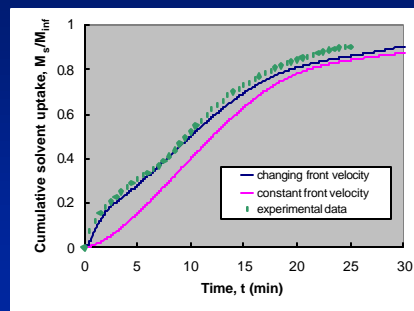
Model of Release Rate

Burst behavior better predicted using desorption boundary





Model fit of solvent uptake data

Improved fit with initial rapid front velocity

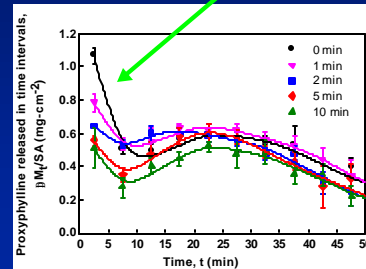


How Can the Burst Effect be Prevented?

- Non-uniform drug loading 
- Reduced Surface Concentration
- surface extraction
- Coating Layer 
- Surface Treatment to reduce porosity
- surface crosslinking



Surface Extraction of Dry PVA Samples Longer Extraction Times Decrease the Burst Effect



... But Economic Problems ...
Much of the Drug is Lost during Extraction

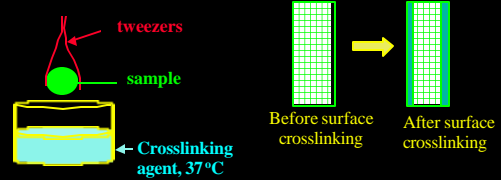
Extraction Time	1 min	2 min	5 min	10 min
Proxyphylline Removed during Extraction (wt %)	4.74 ± 0.47	8.13 ± 0.26	14.08 ± 0.93	22.33 ± 1.91

Amount lost depends on geometry and size factors, as well as drug diffusivity

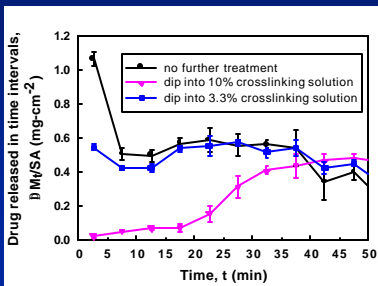


**Reducing the Burst Effect:
 Surface Preferential Crosslinking**

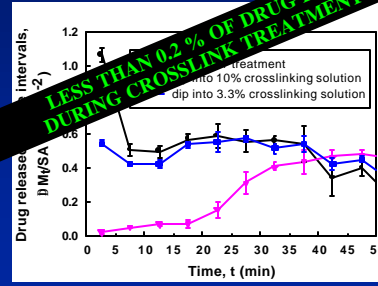
- Dip dry sample into crosslinking agent briefly and re-dry



**Proxyphylline Release from
 Surface Crosslinked PVA:**
Significant reduction in burst release



**Proxyphylline Release from
 Surface Crosslinked PVA**



Conclusions

- Conditions where Burst is Prevalent in Hydrogels
- Model Developed to Predict Burst Release and understand important parameters
- Methods developed to Control Burst Effect



Acknowledgments

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Accounting for Reduced Burst in Methylene Blue Systems: Drug Properties

Drug	M.W.	Solubility in water (g/l)	Partition coefficient in PVA gel
Theophylline	180	8.3	2.08
Proxyphylline	238.2	1000	2.28
Methylene blue	319.86	40	5.32
Buflomedil HCl	343.8	650	0.73

