

Dane O. Kildsig Center for Pharmaceutical Processing Research - CPPR

- Background
- Mission
- Research
- Organization

BACKGROUND

- Administered by Engineering Education and Centers Division of NSF's Engineering Directorate
- Alex Schwarzkopf, Director
- First Industry/University Cooperative Research Center (I/UCRC) established in 1981
- CPPR was funded a NSF I/UCRC from 1995-2005
- Renamed by the NSF to the ***Dane O. Kildsig Center for Pharmaceutical Processing Research*** prior to graduation in 2005
- Currently more than 50 Centers in diverse areas of science and engineering

PURPOSE OF I/UCRC's

- Promote closer interaction between industry and universities
- Provide support for university research
- Promote interactions between development and manufacturing within member companies
- Industry participation in selection and planning of university research projects

MISSION STATEMENT

The Dane O. Kildsig Center for Pharmaceutical Processing Research has it as a mission to foster an interdisciplinary approach to pharmaceutical processing-related research, to catalyze interaction between industrial and academic scientists, and to make the application of a basic science approach to formulation and manufacture of drug products an integral part of graduate pharmaceutical education

CENTER RESEARCH OBJECTIVES

- Center research is focused on the didactic training of graduate students and postdocs in the pharmaceutical processing area
- Accomplished by research aimed at elucidating the scientific principles underlying the processes and the application of this knowledge for product development
- CPPR also sponsors a symposium on freeze drying of pharmaceuticals and biologicals

CENTER RESEARCH OBJECTIVES

- Explore and develop new technology for pharmaceutical and biological processing
- Study the interaction between physical and mechanical properties of pharmaceutical materials and processing conditions
- Explore Process Analytical Technology for process monitoring and control



PROCESS ANALYTICAL TECHNOLOGY (PAT) LABORATORY



OBJECTIVES

- Develop CPPR lab for sensor evaluation and non-GMP experiments
 - Member and Academic use for experimentation and training
 - Platform for other center
-
- Produce blending “white paper”

Processing Variability

- Regulations allow for marketing approval under Biowaivers for BCS class 1 compounds and potentially for some class 2 and 3 compounds.
- Irrespective of the BCS, the comparative bioavailability of a generic formulation becomes paramount when the active moiety exhibits poor solubility in water, a narrow therapeutic index, or non-linear kinetics.
 - Drugs exhibiting these properties could result in
 - Loss in therapeutic efficacy
 - Induce toxicity with only minor changes in blood levels

Differing Dissolution Profiles

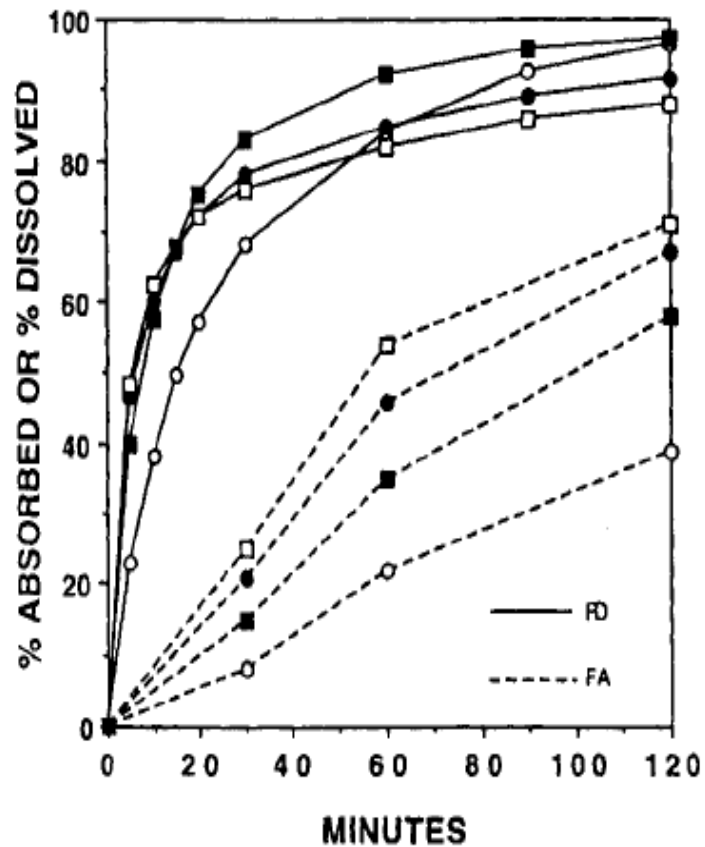


Fig. 2. Percent dissolution (——) or percent absorbed (----) versus time profiles for four different 200 mg carbamazepine tablet Products. (○, Product 1; ●, Product 2; □, Product 3; ■, Product 4).

Dissolution rates during the first 30 minutes and corresponding *in vivo* absorption rates of each generic product exceeded those of the innovator product.

Indicates a potential issue with repeated dosing

Meyer et al. (1998). Pharm. Res. 15(11):1787-1791.

Pharmacokinetic Data

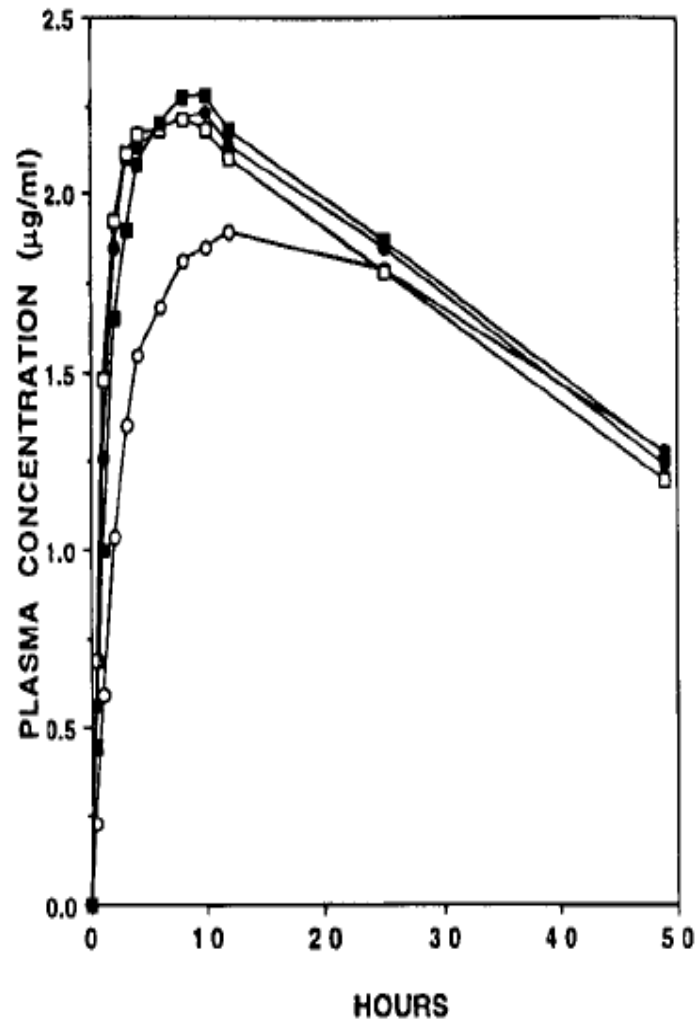


Fig. 1. Mean carbamazepine plasma concentrations. (○, Product 1; ●, Product 2; □, Product 3; ■, Product 4).

Table II. Statistical Analysis Ratio and 90% Confidence Limits (Two, One-Sided Test)

Parameter	Product comparison	LS mean ratio	90% Confidence interval
C_{max}	2 vrs 1	1.19	113% to 125%
	3 vrs 1	1.17	111% to 123%
	4 vrs 1	1.19	114% to 126%
AUC (0-∞)	2 vrs 1	1.04	100% to 108%
	3 vrs 1	1.01	97% to 105%
	4 vrs 1	1.03	99% to 108%

Meyer et al. (1998). *Pharm. Res.*
15(11):1787-1791.

IVIVC ??

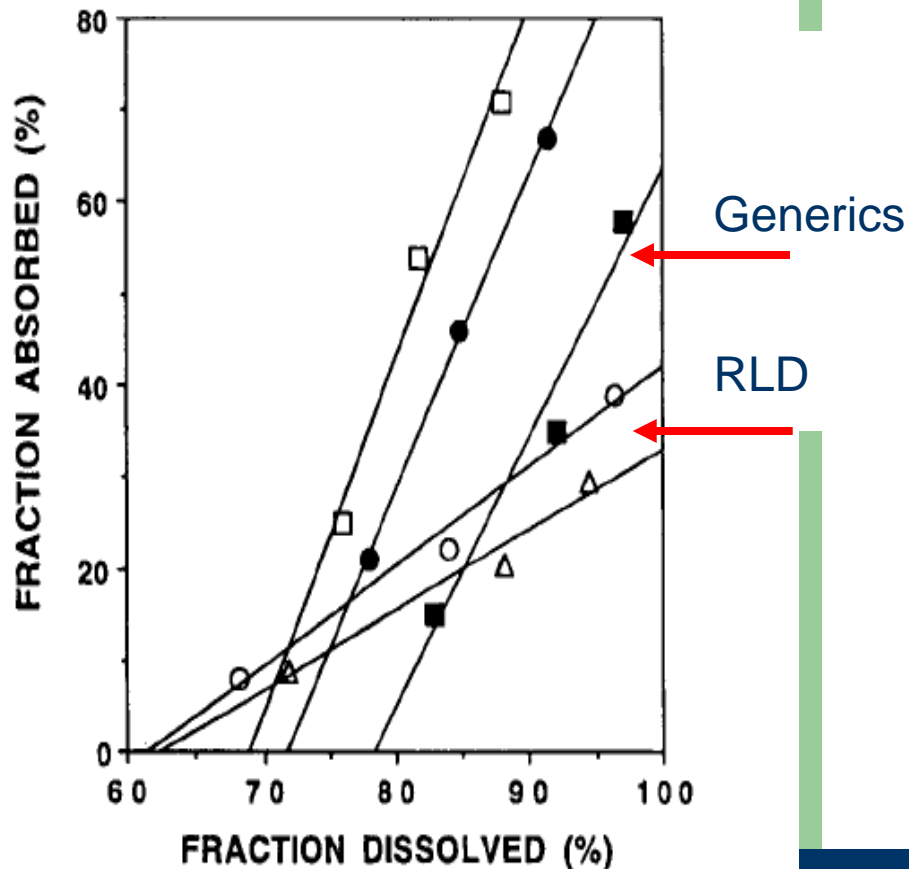


Fig. 3. Relationship between the mean percent absorbed *in vivo* and the percent dissolved *in vitro* at 30, 60 and 90 or 120 min for two lots of the innovator 200mg carbamazepine tablet and three generic tablets. (○, product 1, present study, $R^2 = 0.98$, $y = -67.1 + 1.09x$; △, Product 1, previous study, $R^2 = 0.97$, $y = -54.4 + 0.87x$; ●, Product 2; $R^2 = 0.99$, $y = -246 + 3.43x$; □, Product 3, $R^2 = 0.97$, $y = -261 + 3.79x$; ■, Product 4, $R^2 = 0.95$, $y = -235 + 2.98x$).

Even though all four products demonstrate a linear relationship between the percent dissolved and the percent absorbed, no single correlation could be established to predict the bioavailability of all four products

no correlation was possible between dissolution rate and AUC

definitely an issue in the interchangeability of these products.

Meyer et al. (1998). Pharm. Res. 15(11):1787-1791.

Processing Variables and Clinical Performance?

Surfactants and Efflux-Improving Oral Bioavailability by Reducing Efflux Liability-
(Borgman et al., *Clinical Pharmacology & Therapeutics* (2005) 77, 24–32)

Table I. Talinolol permeability across Caco-2 cell monolayers in presence of TPGS or Poloxamer 188

Surfactant (%)	Permeability coefficient (cm/s) ($\times 10^{-6}$)		
	Apical to basolateral	Basolateral to apical	
Buffer	0	0.4 \pm 0.3	4.0 \pm 1.7
Talinolol plus TPGS	0.005	1.7 \pm 0.9	4.5 \pm 1.5
	0.01	2.5 \pm 1.1	1.7 \pm 1.2
	0.02	2.7 \pm 1.2	1.6 \pm 1.0
Talinolol plus Poloxamer 188	0.1	0.5 \pm 0.3	3.9 \pm 0.9
	0.2	0.3 \pm 0.2	4.5 \pm 0.9
	0.4	0.2 \pm 0.1	3.7 \pm 1.3

Permeability assays were performed in triplicate at pH 7.4 with 300- μ mol/L talinolol solutions. Talinolol alone or in the presence of varying concentrations of surfactant was added to either the apical or basolateral chamber of Caco-2 cells, and its appearance in the receiver compartment was determined. Values represent mean permeability coefficient values (\pm SD).

TPGS, D- α -Tocopheryl polyethylene glycol 1000 succinate.

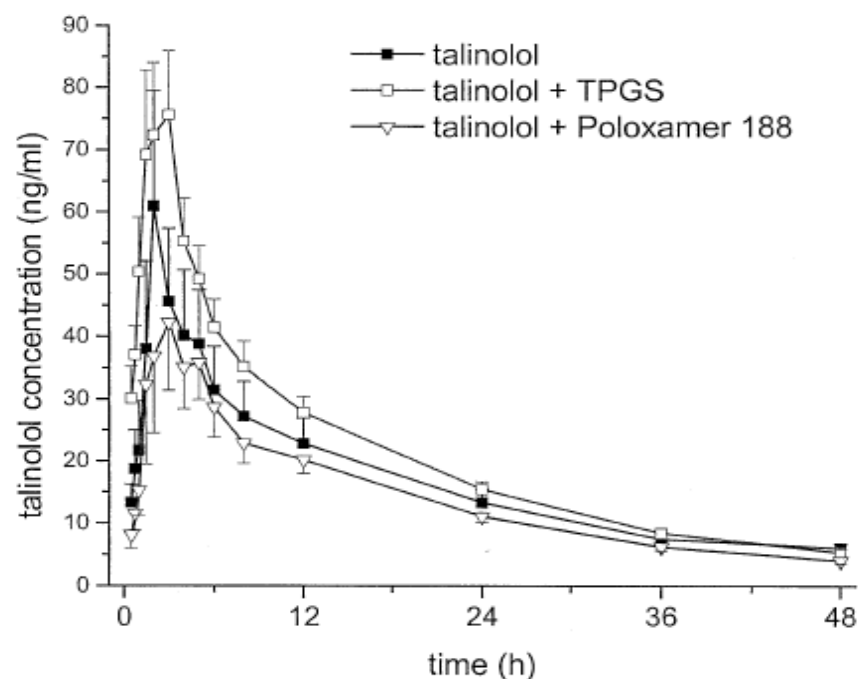


Fig 1. Plasma concentration–time profiles of talinolol (mean \pm SEM) after single intraduodenal administration of 50 mg talinolol with or without surfactants in 9 healthy individuals. Three formulations were administered: talinolol alone (*solid squares*), talinolol with 0.04% D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) (*open squares*), and talinolol with 0.8% Poloxamer 188 (*open triangles*).

TPGS enhanced the bioavailability compared to talinolol alone or in the Polaxamer 188 formulation, suggesting a **critical** concentration of TPGS is required to improve oral bioavailability.

ORGANIZATION

- Industrial Advisory Board
- Center Director
- Associate Director
- Site Directors

Center Management

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SPONSORING COMPANIES

- Abbott Laboratories
- Allergan
- Amgen
- AstraZeneca
Pharmaceuticals
- Catalent Pharma
Solutions
- GlaxoSmithKline
- Eli Lilly & Company
- Praxair
- Shionogi
- Upsher-Smith

INDUSTRIAL ADVISORY BOARD

- One member from each participating company
- Meets twice a year
- Establishes research priorities

CENTER FACULTY

- **Industrial Pharmacy** 12
- **Chemical Engineering** 2
- **Environmental Engineering** 1
- **Agricultural Engineering** 2
- **Analytical Chemistry** 2
- **Mechanical Engineering** 1
- **Materials Science** 1

INDUSTRIAL PARTNER BENEFITS

- Exploration of new technology before committing internal resources
- Leverage - Ability to benefit from substantial research funding by contributing a modest amount (\$35,000)
- Participation by company scientists in academic research projects

ACADEMIC PARTNER BENEFITS

- Support of M.S. and Ph.D. graduate student research
 - CPPR has generated over 25 Ph.D.'s with an overwhelming majority of them joining member companies. The number is even greater when you include Postdoctoral Associates.
- Scientific interaction with industrial scientists
- Graduate student interaction with industrial scientists

Industry-Academic Interactions

PROJECT MENTORS

Every project proposal by an academic scientist must have a mentor from industry

All projects must be approved by the IAB

SOMETHING TO THINK ABOUT

What you will get out of being a partner in Kildsig-CPPR will be directly proportional to what you put into it

BECOME ACTIVELY INVOLVED IN THE PROJECTS !!!

<http://www.cppr.purdue.edu>