

**Case Study:
Matching Up Material Properties and
Process in Product Design -
Starting with the End in Mind**

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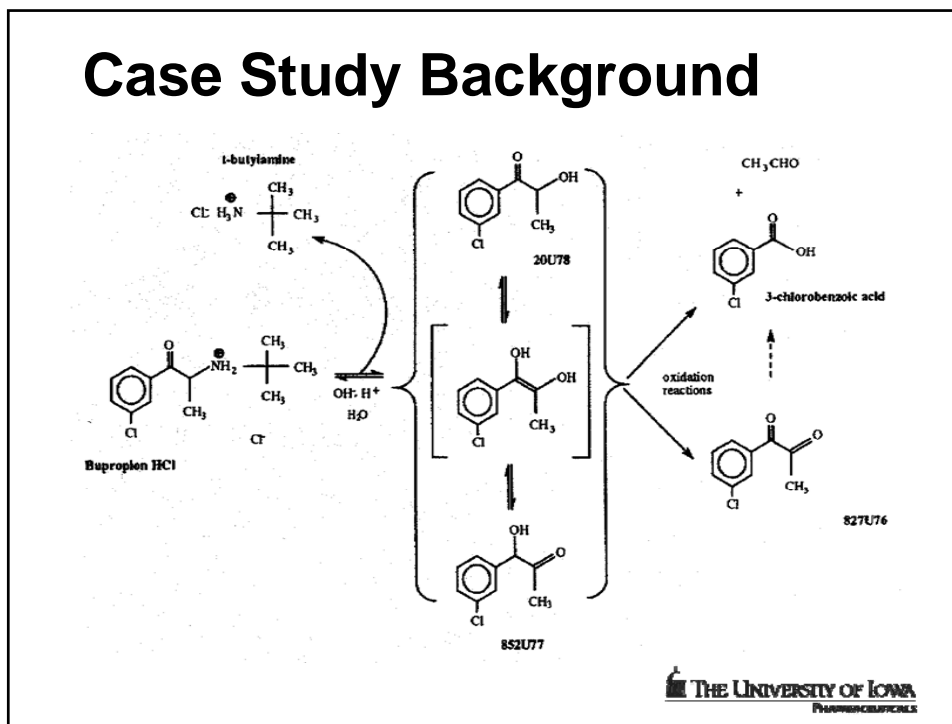


Presentation Outline

- Case study background
- *“Starting with the End in Mind”*
 - Material properties
 - Process
 - Desired attributes of the reformulated drug product
- Summary of investigations
- Final outcome
- Acknowledgments



Case Study Background



Case Study Background

RX GLAXO WELLCOME INC P. 1304



100 mg



150 mg

Wellbutrin SR®
Sustained-Release Tablets
(bupropion HCl)

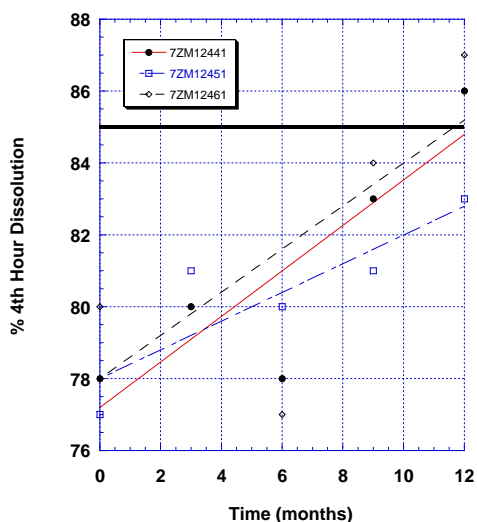
- Wellbutrin SR: FDA approved on October 4, 1996.
- U.S. Patent Nos.

5,358,970	Aug. 12, 2013
5,427,798	Aug. 12, 2013
5,731,000	Aug. 12, 2013
5,763,493	Aug. 12, 2013
RE33994	Aug. 18, 2004
- 50 mg strength developed and approved, but with dissolution specification changes - never launched
- May 7, 1998 - FDA asks for "long term" solution for the 100 mg SR strength by reformulating the product

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Wellbutrin SR 100 mg Tablets

- Hydrophilic Matrix
- USP Apparatus II
Water, 37°C
50 rpms
- Dissolution Specifications:
 - 1 h = 25-45%
 - 4 h = 60-85%
 - 8 h = NLT 80%



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Material Properties

<u>Ingredient</u>	<u>Original Wellbutrin SR 100 mg Tablet (%)</u>	<u>Function</u>
Bupropion HCl	37.0	API
Methocel E4M Prem. CR	20.0	Release Controlling Excipient
Avicel PH 102	36.0	Binder/ Disintegrant
Cysteine HCl, monohydrate	6.0	Stabilizer
Mg stearate	1.0	Lubricant



100 mg

Total Core
Tablet Weight = 270 mg

Core Tablet
Diameter = 9.4 mm

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Process

- Dispensing/Sieving - bupropion HCl/MCC/HPMC
- Blending
- Top Spray Fluid Bed Granulation - cysteine HCl
- Lubrication Addition/Milling - magnesium stearate
- Lubrication Blending
- Compression
- Film-Coating
- Polishing - carnauba wax
- Printing
- Packaging



Desired Attributes of the Reformulated Drug Product

- Do no harm
- 18 months shelf-life at 25°C/60%RH
- Adhere to and/or create new intellectual property
- Maintain product line image
 - round, biconvex tablets
 - no greater in size than 150 mg strength
- Minimize compositional changes
- Minimize unit process changes



Summary of Investigations

- Early attempts:
 max of allowed formulation parameters (lube, film coating, carnauba wax, high end of MW for HPMC)
 sieve for finer particle size HPMC
 blend drug with portion of lubricant
 increased blending lubrication
 compression force
 reduced lubricant (harder tablets)
 intra vs. extra-granular HPMC (same and higher MW)
 intra vs. extra-granular MCC
 higher MW/viscosity of HPMC
 higher MW/viscosity and different grade of HPMC
 replace MCC with lactose
 replace MCC with ProSolv SMCC50
 replace MCC with Avicel CE-15
 synergism with HPC
 addition of SLS
 coat tablet with ethycellulose functional coating



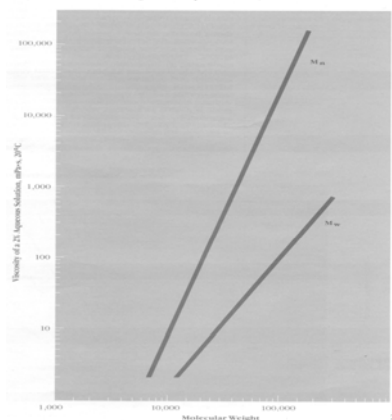
Summary of Investigations

	<u>Orig. 50s</u>	<u>Orig. 100s</u>	<u>150s</u>
<u>Ingredient</u>	%	%	%
Bupropion HCl	37.0	37.0	37.5
Methocel E4M Prem. CR	25.2	20.0	10.0
Avicel PH 102	30.8	36.0	49.6
Cysteine HCl, monohydrate	6.0	6.0	1.9
Mg stearate	1.0	1.0	1.0
Total Tablet Weight (mg)	135	270	400
Tablet diameter (mm)	7.4	9.4	11
<i>HPMC/ Cysteine HCl</i>	4.2	3.3	5.3

Summary of Investigations

- Viscosity measurements are an effective means of monitoring changes in HPMC with your dosage form.

Figure 7: Molecular weight/viscosity correlation, 20°C



"METHOCEL Cellulose Ethers – Technical Handbook" Form No. 192-1062-791-JB, p. 21, The Dow Chemical Co., April 1988.

40 tablets/100 mL water

“fresh” tablets: 2890 cps

“aged” tablets: 75 cps



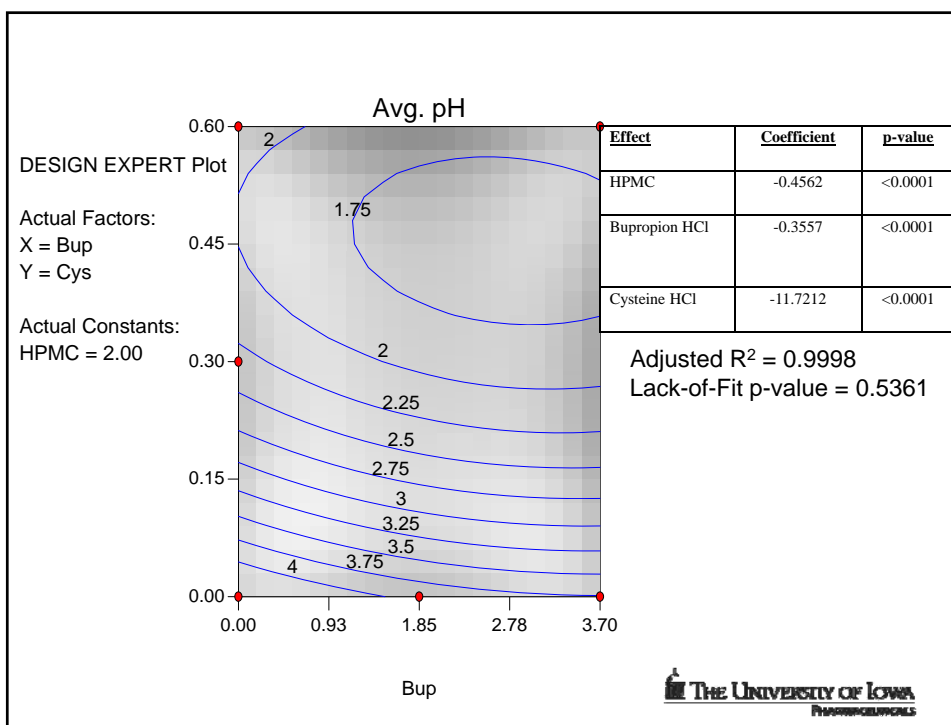
Summary of Investigations

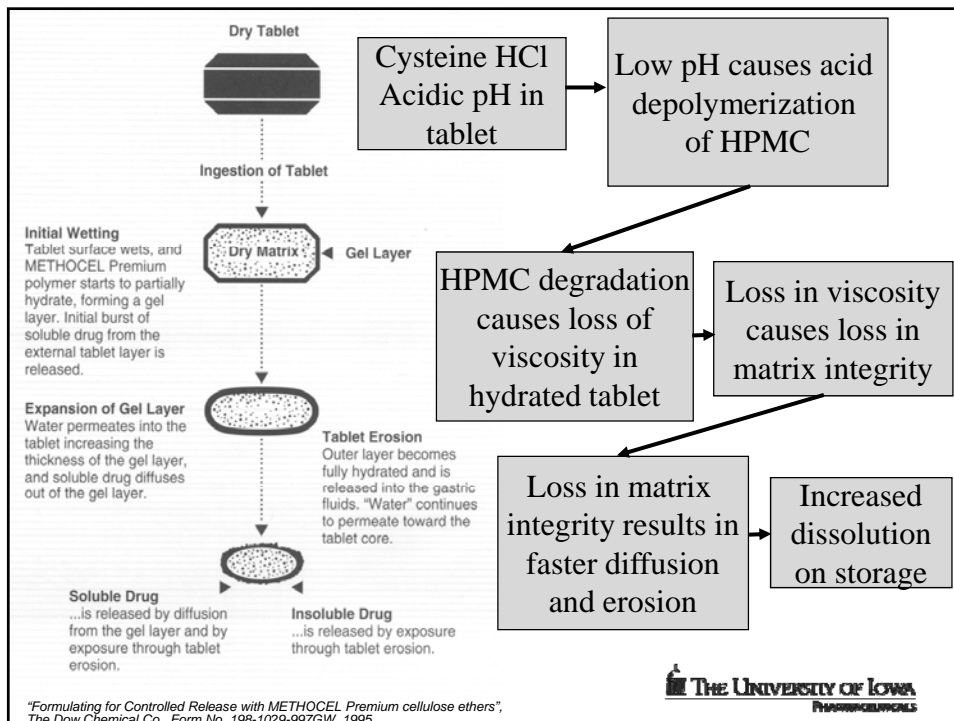
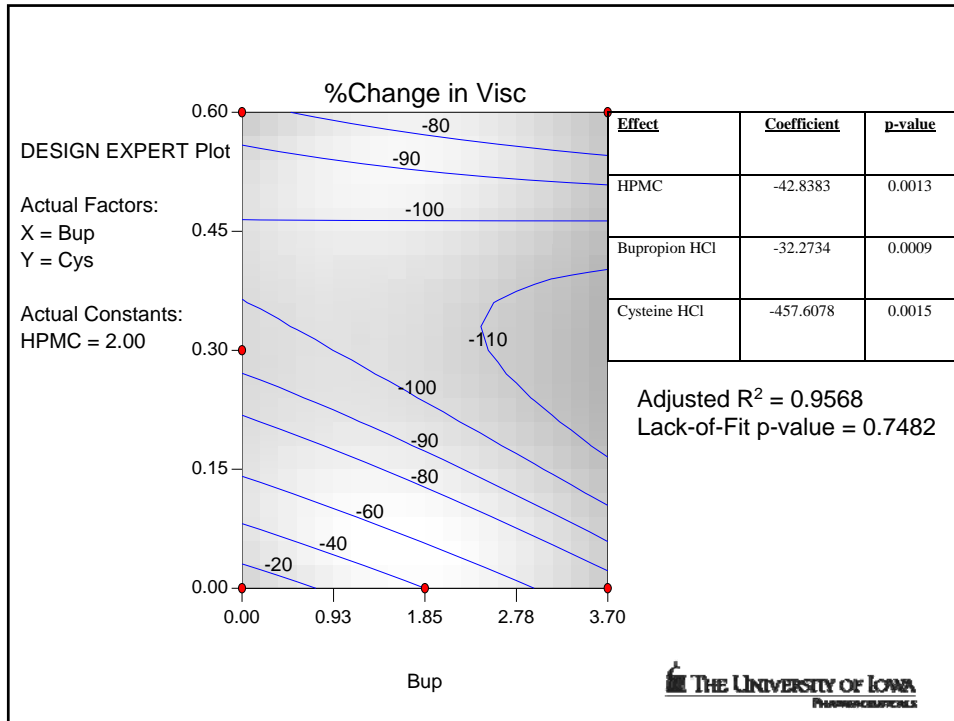
- Needed a quick “measuring stick” to confirm impact
- Designed study using aqueous, colloidal solution of HPMC with dissolved bupropion HCl and/or cysteine HCl at appropriate ratios
- Solutions stored in 8 oz. PP cups at 30°C for up to 14 days.
- A D-Optimal design was chosen for this study
- A number of responses were monitored, most importantly pH and viscosity



Summary of Investigations

<u>Factor</u>	<u>Low Level</u> <u>(% w/w)</u>	<u>Middle</u> <u>Level</u> <u>(% w/w)</u>	<u>High Level</u> <u>(% w/w)</u>
Methocel E4M Prem. CR	1	N/A	2
Bupropion HCl	0	1.85	3.7
Cysteine HCl	0	0.3	0.6

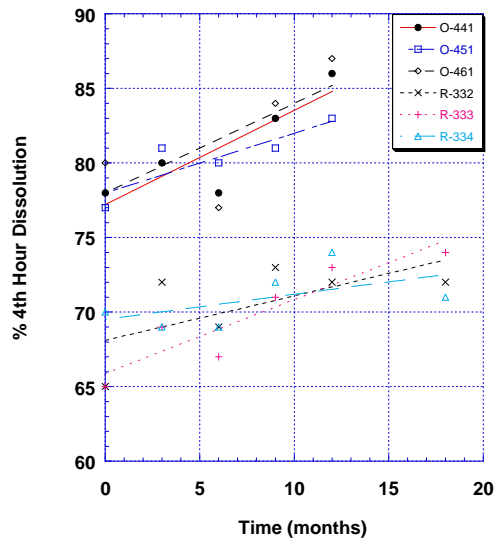




Final Outcome

- Same ingredients
- Same process

	Orig. 100s	Reform. 100s	150s
Ingredient	%	%	%
Bupropion HCl	37.0	30.8	37.5
Methocel E4M Prem. CR	20.0	33.1	10.0
Avicel PH 102	36.0	29.0	49.6
Cysteine HCl, monohydrate	6.0	6.0	1.9
Mg stearate	1.0	1.1	1.0
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Initial 4 hour dissolution for the reformulated tablet is statistically different (p-value = 0.0035).

The absolute slope of change in 4 hour dissolution vs. time is statistically different (p-value = 0.0367).



Final Outcome

- Prior Approval Supplement filed June 13, 2000 with 9 months data
- Prior Approval Supplement amended August 29, 2000 with 12 months data
- October 11, 2000 - FDA approval
18 month shelf-life achieved
- 2001 Sales: \$264,000,000
- Expiry extended to 36 months in an Annual Update to the FDA on December 1, 2005.



Acknowledgments



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- **Plus Many More!!!**

