Engineering Drug Delivery

– **Aron Deen**
– **Michael Matlock**
– **Brian Copeland**
– **Brett Covey**
– **Jenny Oberlag**

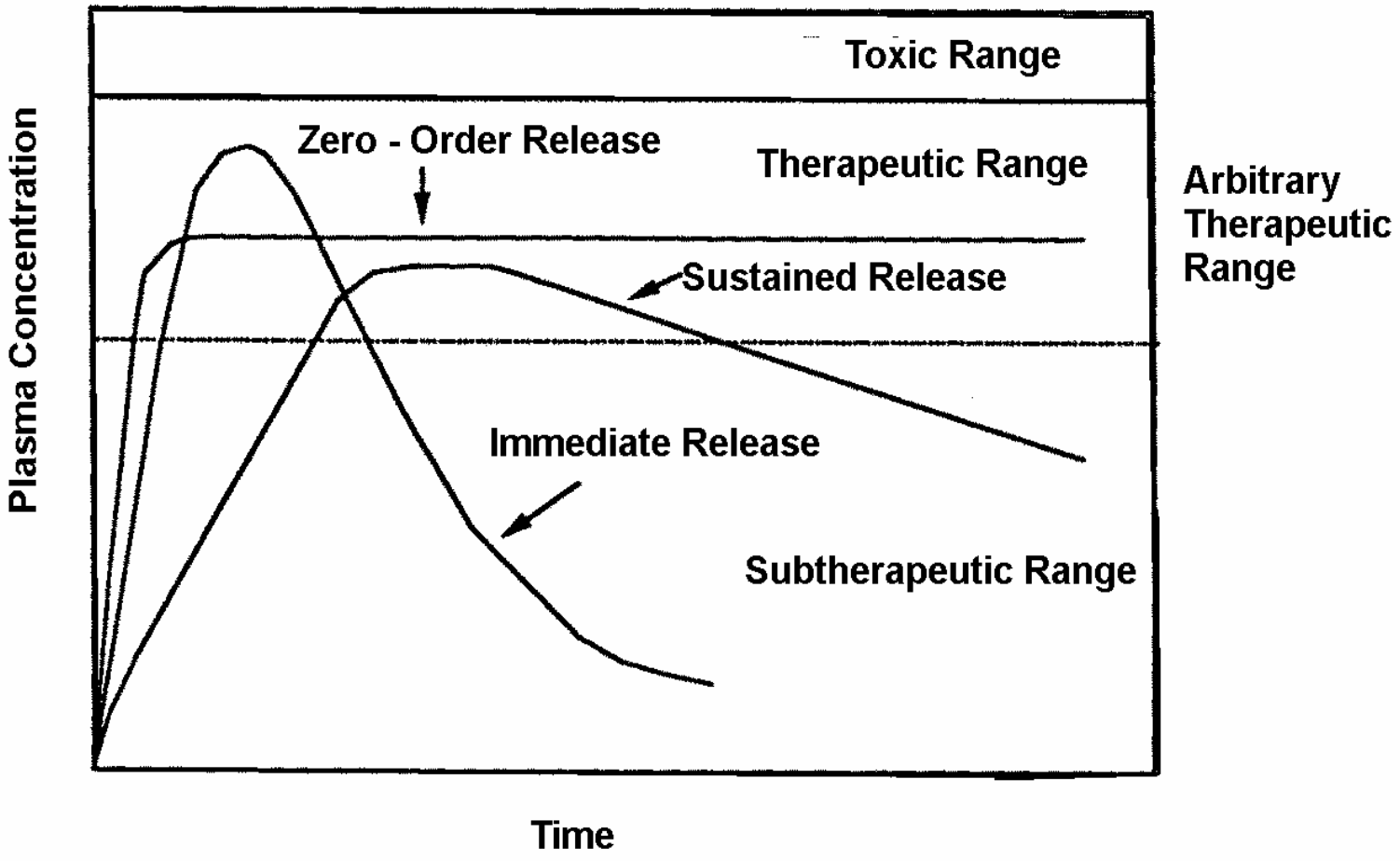
Purpose of This Project

- **Design a slow release pill to deliver medicine**
- **Analyze the Market**
- **Propose a fabrication process and a business plan.**

Types of Dosage Forms

- Immediate release:
  - Dosage delivery begins as soon as pill is ingested
- Sustained release:
  - Any dosage form that provides medication over an extended time
  - Zero-order release
    - Rate of drug release is independent of the amount of drug remaining in capsule or tablet

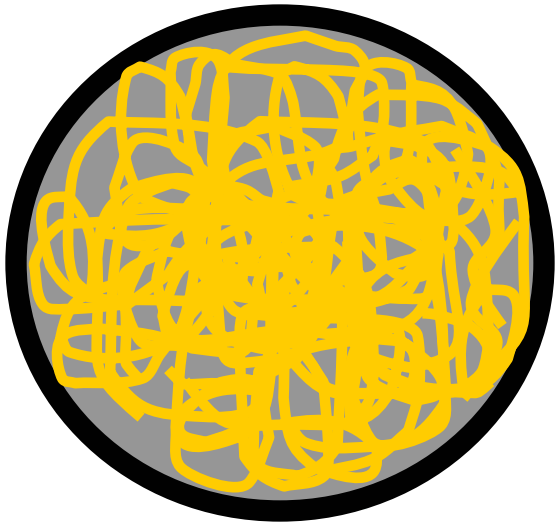
Release Profiles



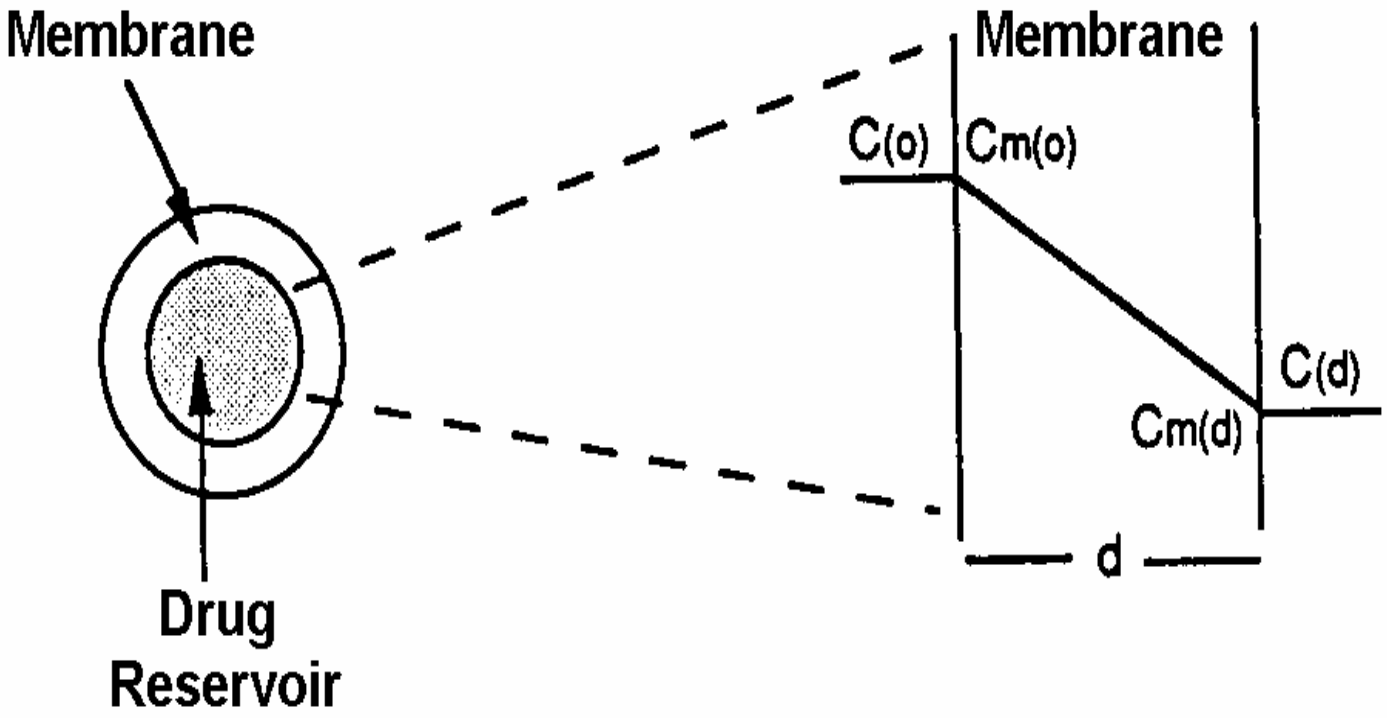
Types of Sustained Release Delivery Systems

- Matrix
  - drug dispersed homogeneously throughout a polymer matrix. Drug in the outside layer is exposed to the bathing solution is dissolved and diffuses out of the matrix
- Reservoir
  - drug core surrounded/coated by a rate controlling membrane
- Osmotic
  - utilize the principles of osmotic pressure for the delivery of drugs

Matrix Release System

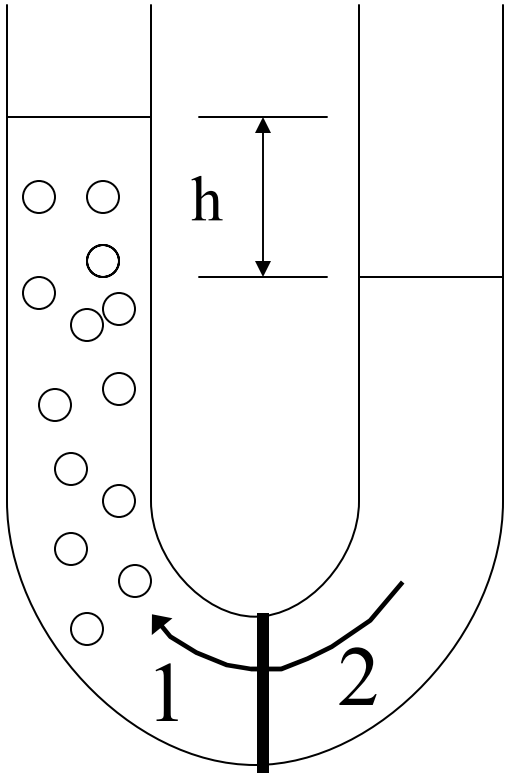


Reservoir Diffusion Device

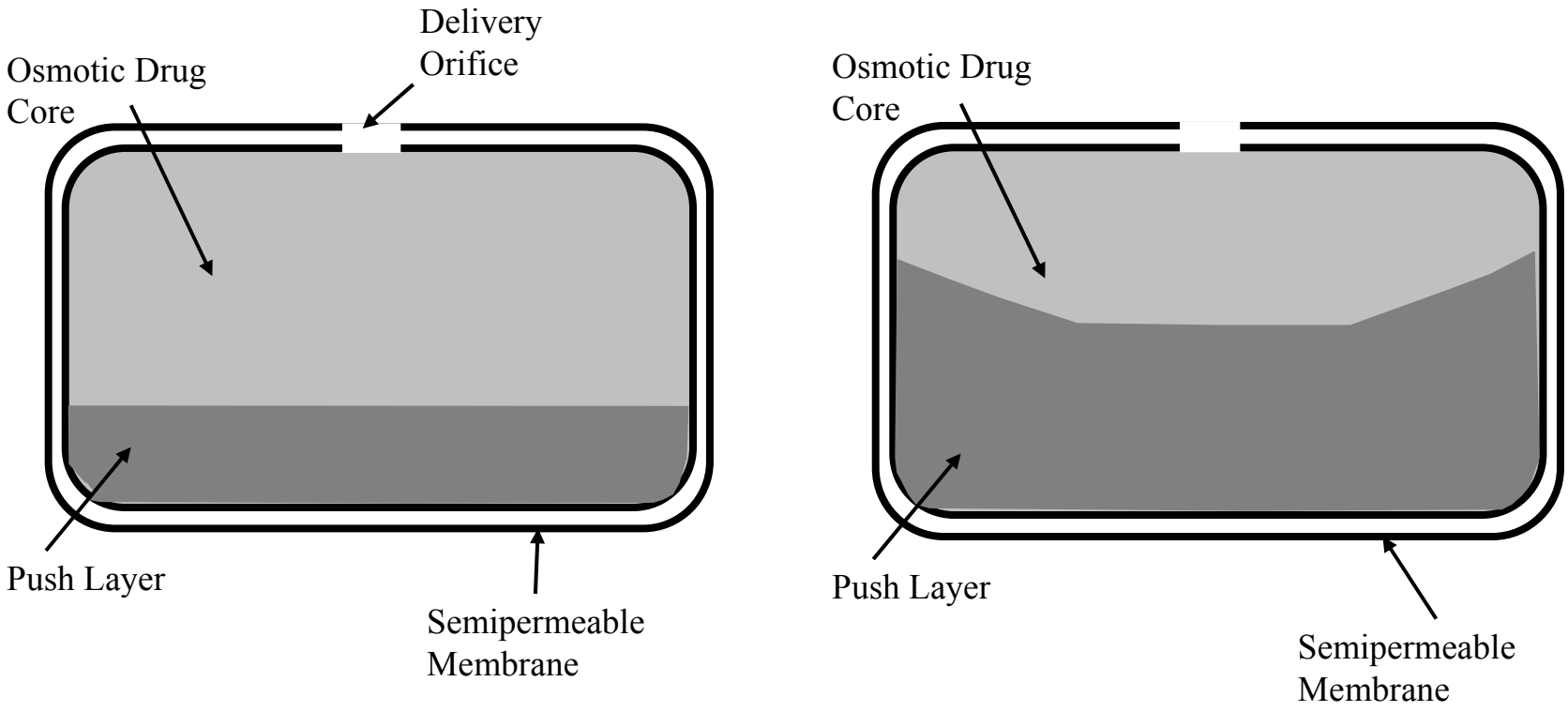


Osmotic Pressure

Chemical potential of solvent in a solution and a pure liquid must be the same if they are in contact through a semi-permeable membrane at the same pressure.



Push-pull Osmotic Pumps



Before Ingestion

After Ingestion

Design Options

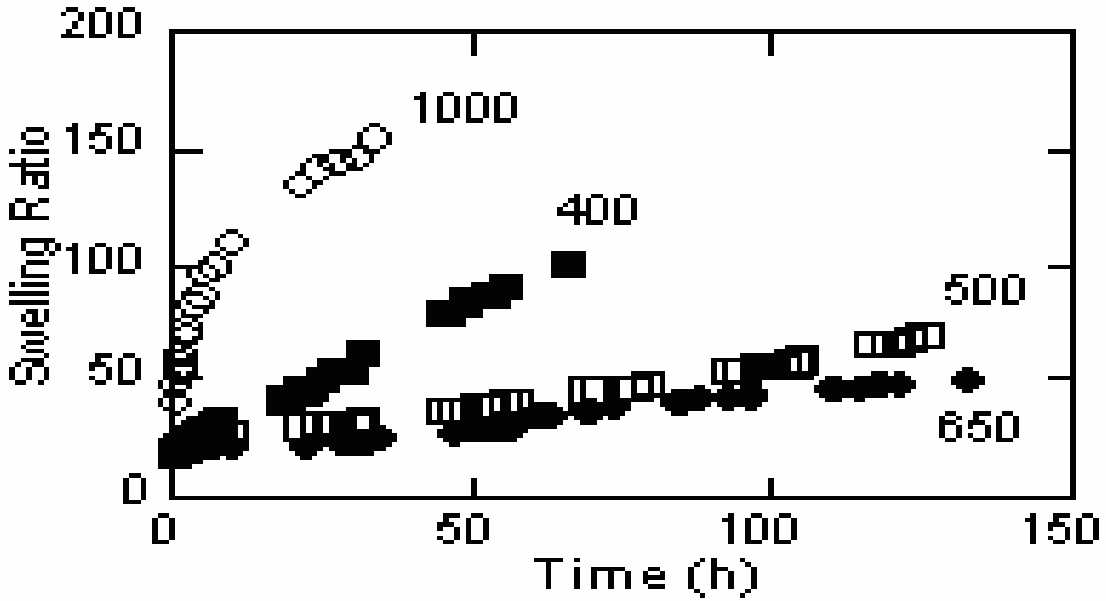
- Push layer polymer
- Semi-permeable membrane
- Size of delivery orifice
- Contents of drug layer
- Dimensions of tablet
- Thickness of semi-permeable membrane

Push Layer Polymer

- Hydrogel

Hydrophilic materials that swell in water due to presence of hydrophilic groups (like -OH, COOH, NH2, etc) or due to presence of ionic groups (like COO-, NR4+, etc).

Swelling Ratio



Φ = volume of water absorbed/volume of dry polymer

- Constant Delivery Profile

$$v(t) = \beta t$$

Materials present in the push layer

18.4 mg polyacrylic acid (PAA) hydrogel crosslinked with ethylene glycol dimethacrylate (EGDMA)

- swelling is linear with time
- cheap material to purchase
- does not react with the active ingredient

Semi-permeable Membane Criteria

- High Water Permeability
- High degree of Semipermeabilily to solute
- Stability over a wide range of pH and temperatures
- Good mechanical integrity
- Life span of 3-5 years
- Biocompatible
- Low cost

Membrane-forming Polymer

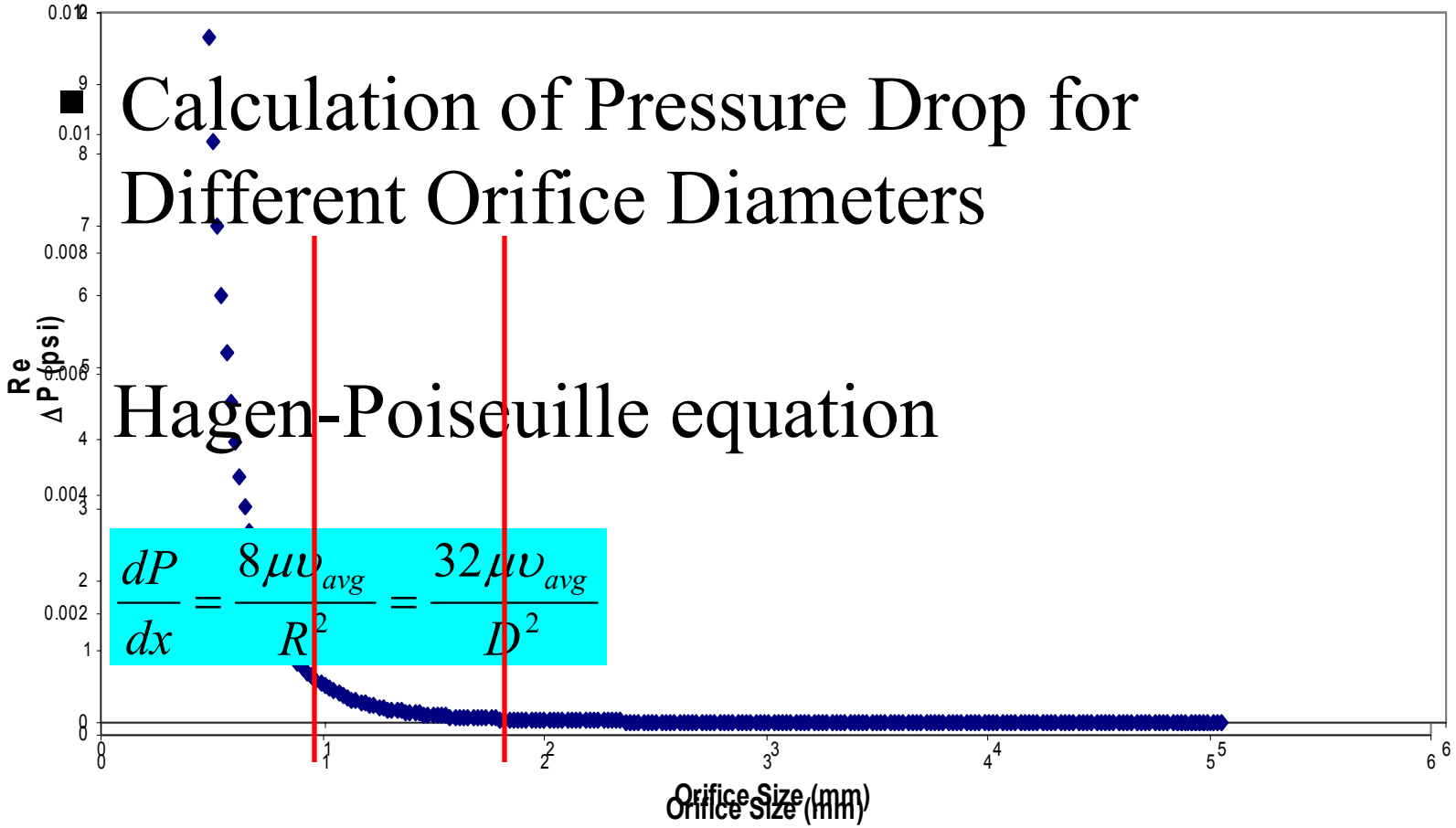
Two major groups of polymeric materials have the right qualifications to produce satisfactory membranes for osmosis.

- **Cellulose Acetate (CA)**
  - **Ease of FDA approval**

Size of delivery orifice

- Smaller Diameters
  - Development of Hydrostatic Pressure Inside the pill
- Larger Diameters
  - Significant Diffusion

Size of delivery orifice



Calculation of Pressure Drop for Different Orifice Diameters

Hagen-Poiseuille equation

$$\frac{dP}{dx} = \frac{8\mu\upsilon_{avg}}{R^2} = \frac{32\mu\upsilon_{avg}}{D^2}$$

$$\mathrm{Re} = \frac{\rho D\,\upsilon}{\mu}$$

Contents of drug layer

- Active pharmaceutical ingredient (API)
  - 0.4mg Tamsulosin Hydrochloride
- Inactive ingredient
  - 112mg Microcrystalline Cellulose
- Osmotic Agent
  - 0.1mg Sodium Chloride

Thickness of semipermeable membrane

$$\left.\frac{dv}{dt}\right|_{TOP} = \left.\frac{dv}{dt}\right|_{BOTTOM} \Rightarrow \frac{A_S}{h} KRTc_B = \beta$$

$$h = 250\ \mu m$$

- To ensure that the coating is able to resist the pressure within the device, thickness of membrane is usually kept between 200 and 300 μm

Dimensions of Pill

$$1cm \times 0.5cm$$

Fabrication Process

- Batch Size/Cycle Time
- Drug Layer Fabrication
- Osmotic Layer Fabrication
- Overall Tablet Fabrication
- Explanation of Required Utilities for Plant
- Plant Layout

Selection of Batch Size and Cycle Time

Batch Size dependent on:

- Volume of Pill/Density of Components
- Degree of Uniformity
- Thickness
- Rate Limiting Machine

Cycle Time dependent on:

- Batch Size
- Parameters Chosen for Each Process Machine
- Rate Limiting Machine

Selection of Batch Size and Cycle Time

Drug Layer Component Weights-determined from volume and density:

Tamsulosin Hydrochloride: 0.4 mg/pill = 0.4 kg/batch*

Microcrystalline Cellulose: 0.112 g/pill = 112 kg/batch*

NaCl: 0.1 mg/pill = 0.1 kg/batch*

Osmotic Layer Weight-determined from volume and density:

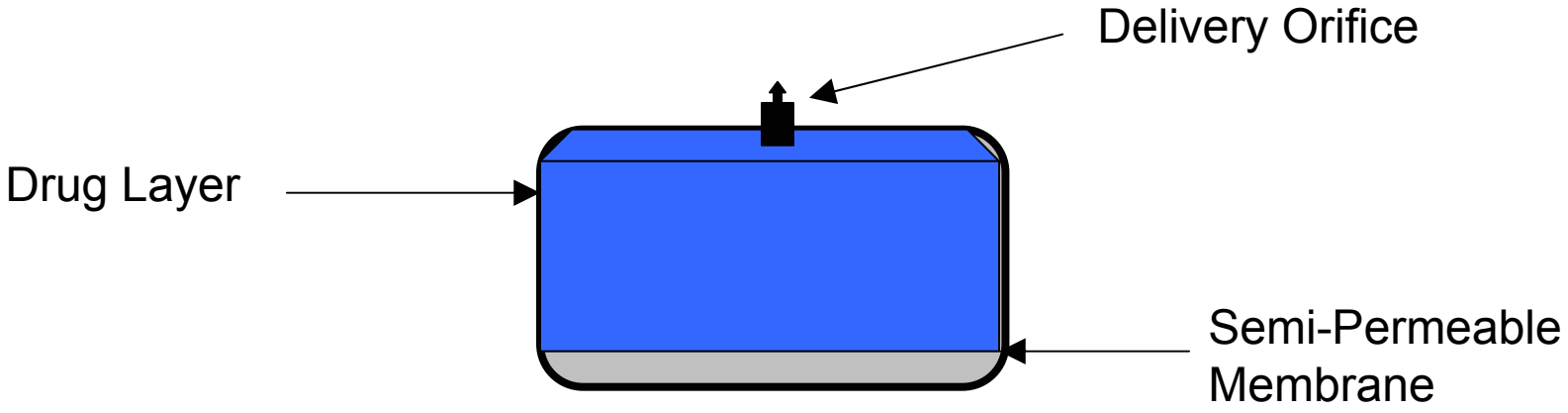
Polyacrylic Acid (hydrogel): 0.0184 g/pill = 18.4 kg/batch*

Semi-permeable Membrane-determined from thickness (250 μm)

Cellulose Acetate: 7.85 L/batch*

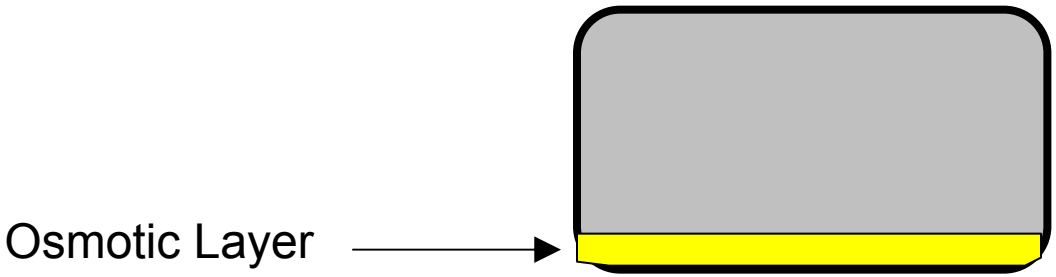
*Value based on production capacity of 1 million tablets per batch (1 batch/day)

Drug Layer (Top Layer of Tablet)



- Weigh System
- Blending
- Binding
- High Shear Granulation
- Fluidized Bed Drying
- Milling

Osmotic Layer (Bottom Layer of Tablet):



- Weigh System
- Milling

Overall Tablet Fabrication:

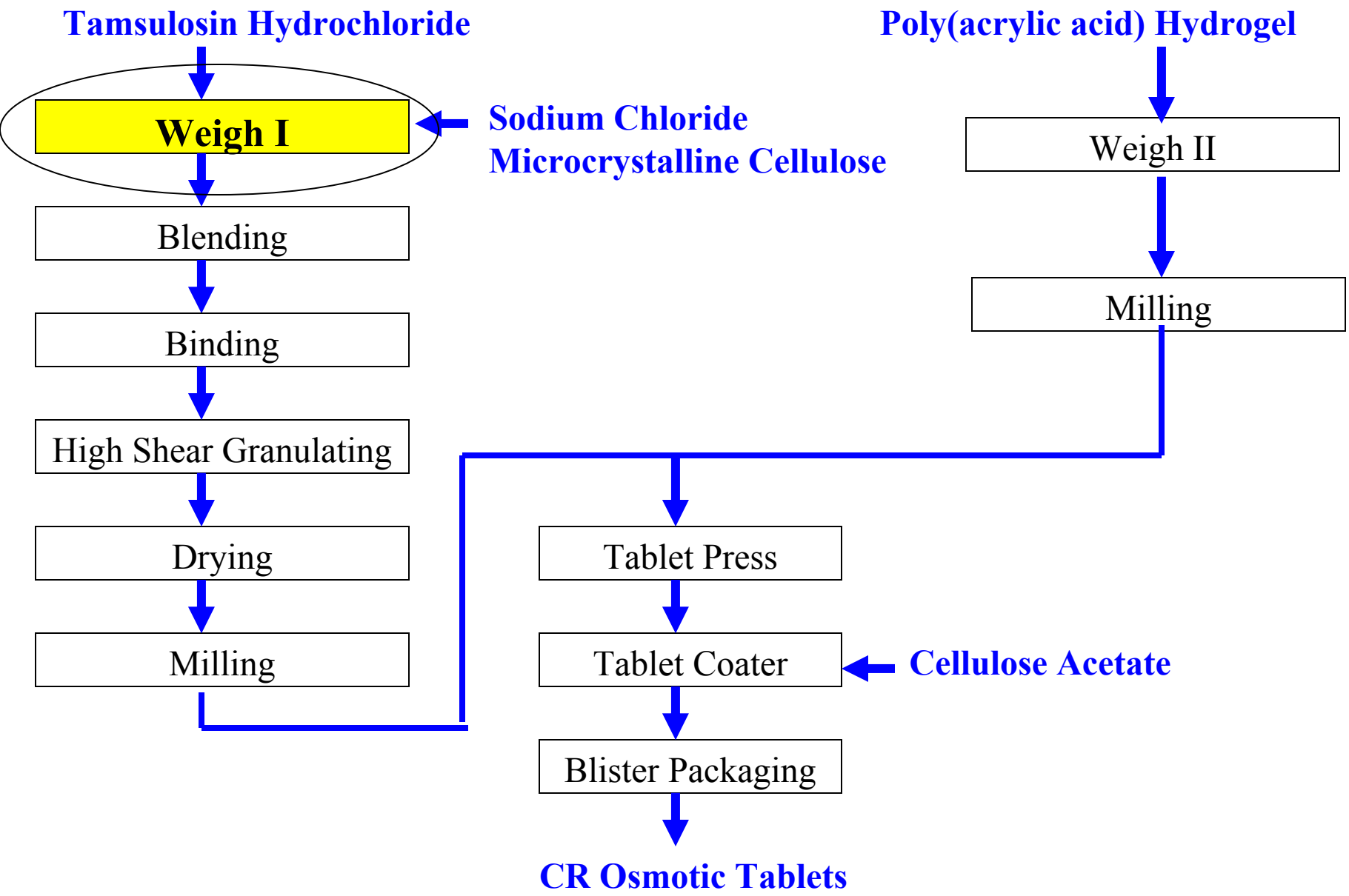
- Tablet Press
- Tablet Coater
- Laser Drilling and Packaging

Selection of Process Machines

Process Machines Chosen on the Basis of:

- Design Parameters
- Dependability
- Reliability
- Consistency
- Cost

Process Flow Diagram

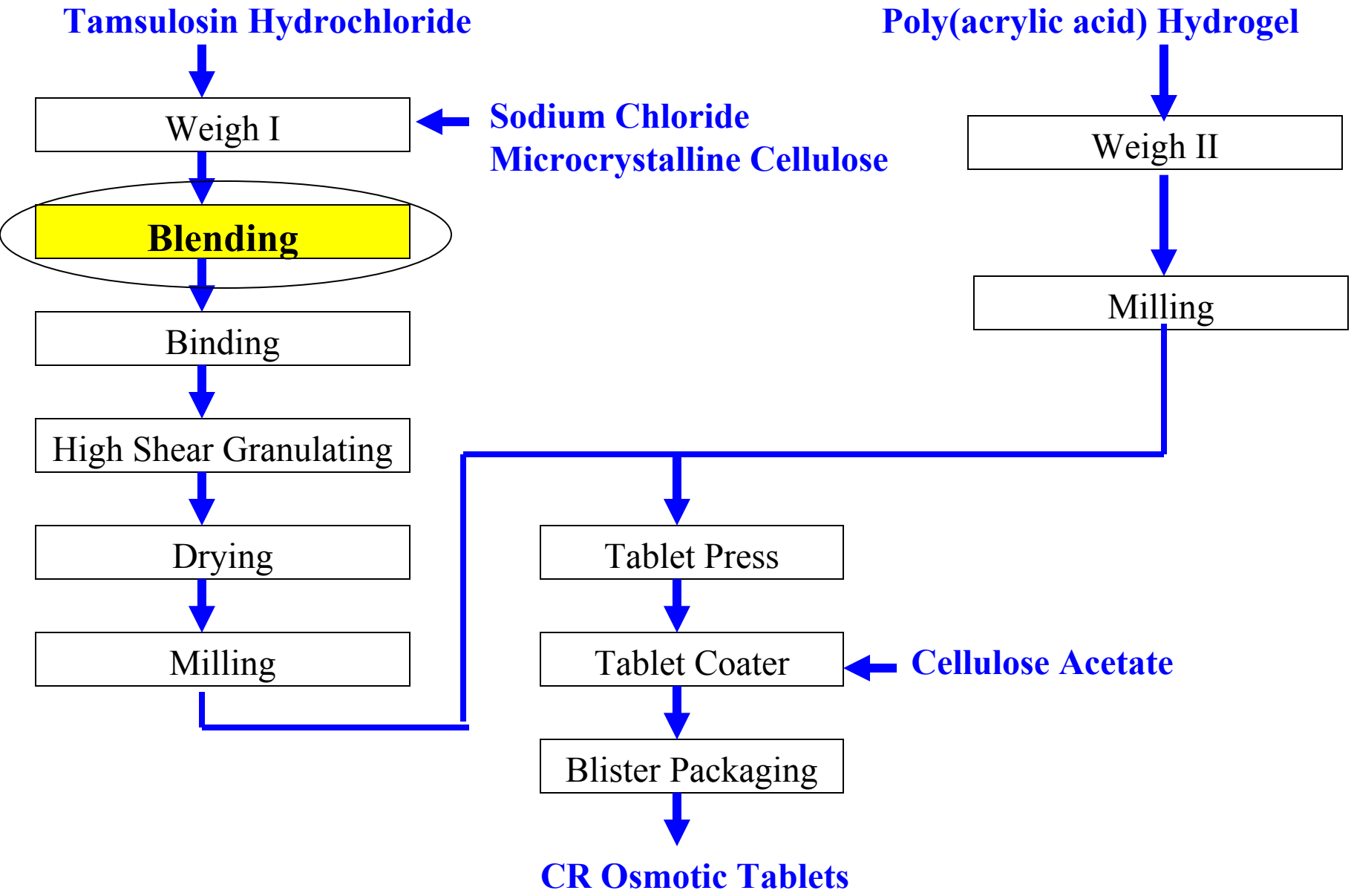


All components that come into direct contact with product are made out of 316L Stainless Steel – FDA Standard/Requirement

WEIGH SYSTEM

- Accurately Weighs Out API, Microcrystalline Cellulose, and NaCl
- Maximum Capacity of 900 kg

Process Flow Diagram



BLENDING

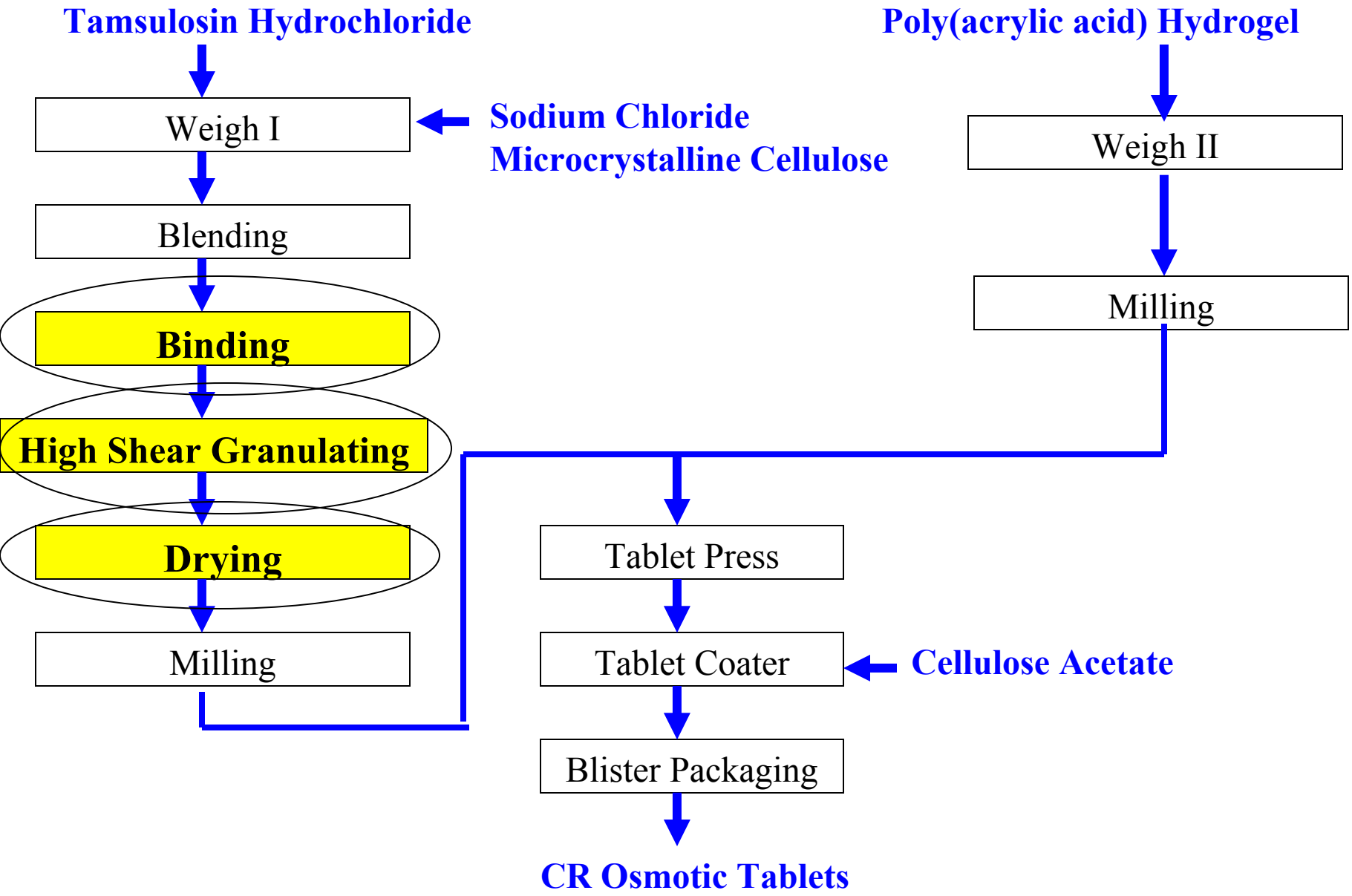
IBC Blending-IEDCO Blender

- Mixing of API, Microcrystalline Cellulose and NaCl

Intermediate Bulk Containers

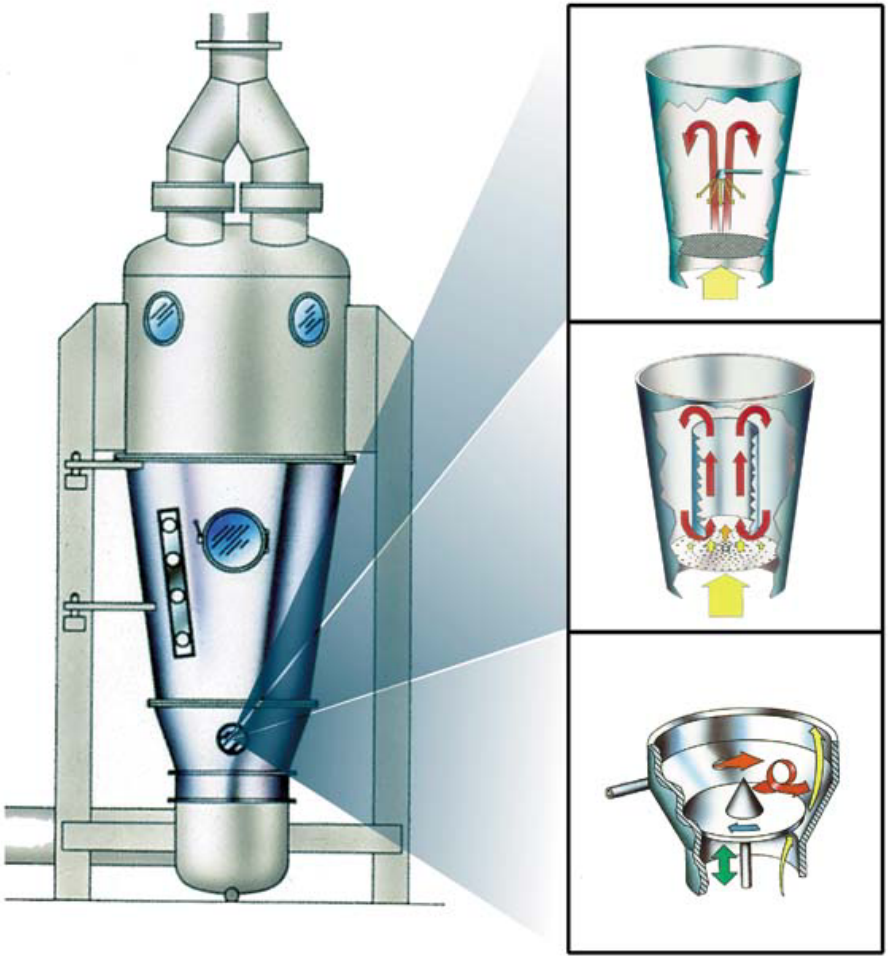
IBC Blender

Process Flow Diagram



BINDING, HIGH SHEAR GRANULATING, AND DRYING

GLATT GPCG 120-Top Spray Processing

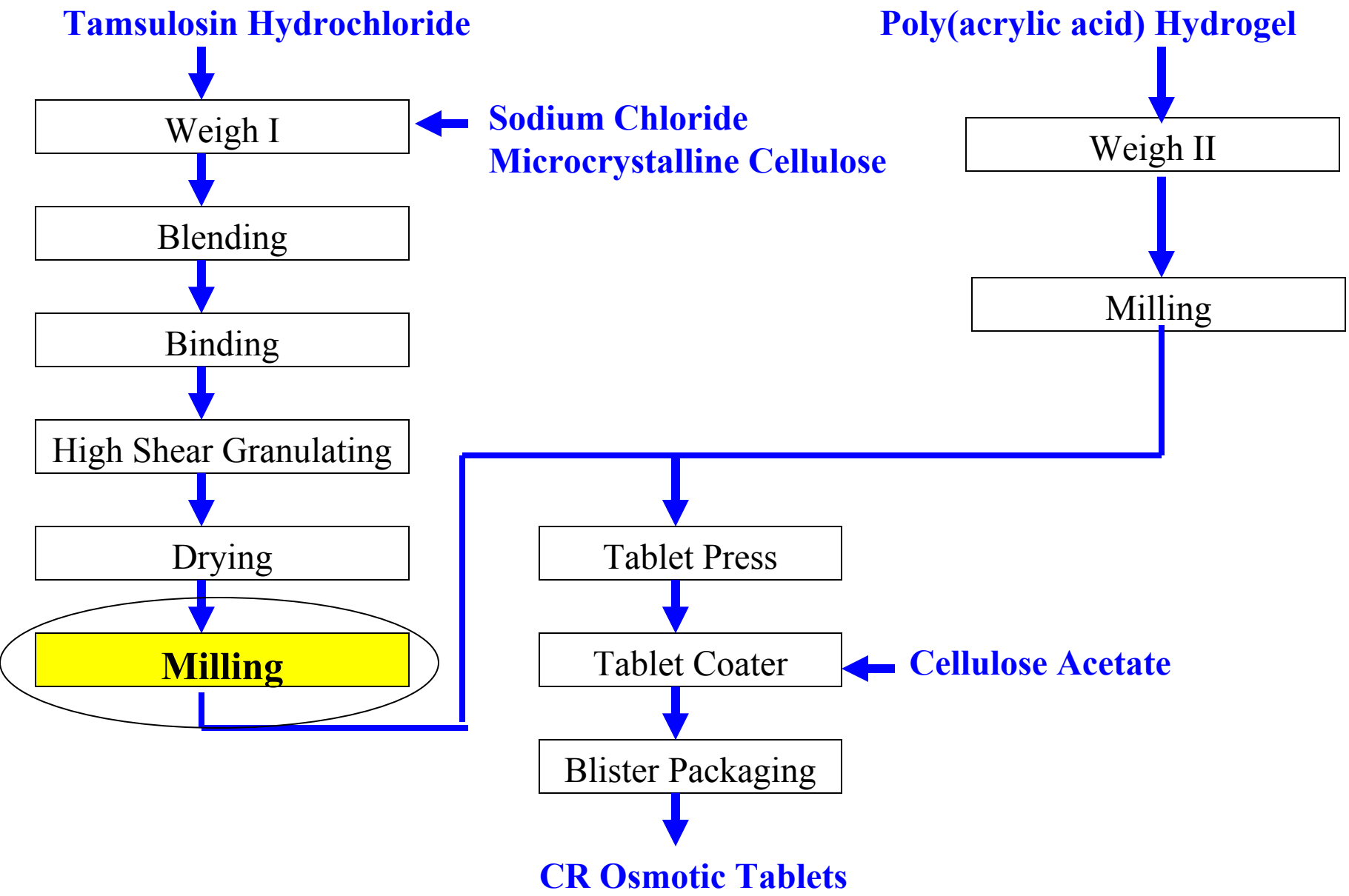


Utilities Required:

Plant Steam, Electrical, Compressed Air/CDA (Clean Dry Air), USP Water, Chilled Water

*Rate Limiting Machine at 420L

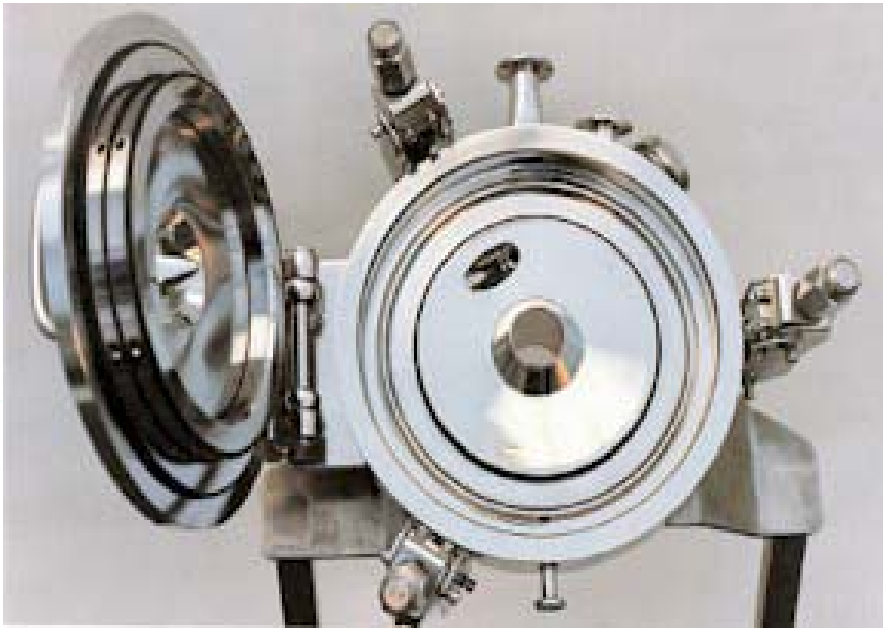
Process Flow Diagram



MILLING

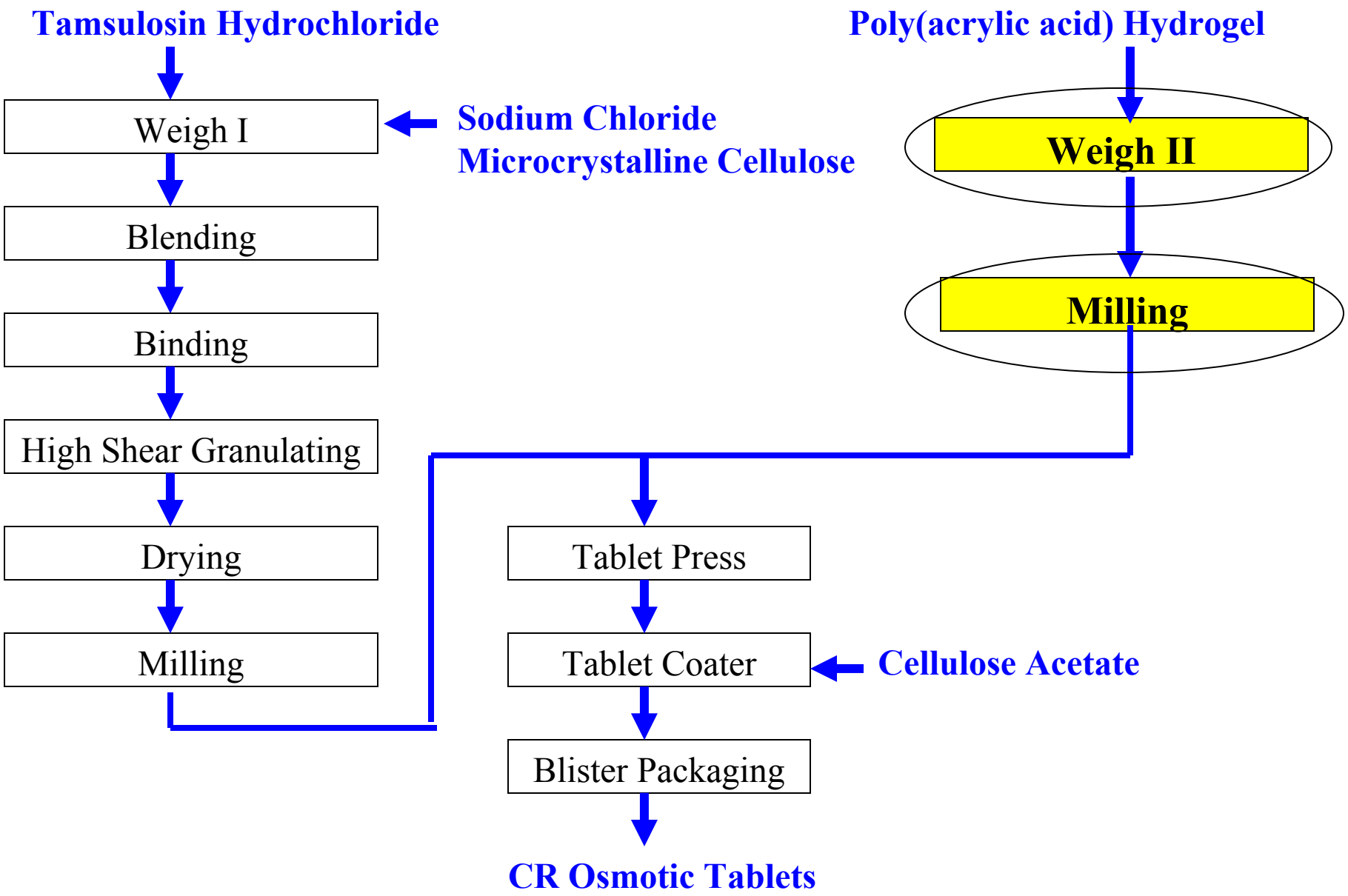
Hosokawa Alpine AS Spiral Jet Mill

- Mills Pellets into Uniform Size Throughout
- Ultra Fine Size Reduction between 0.5 to 10 microns



POWDER NOW READY FOR TABLET COMPRESSION

Process Flow Diagram



Osmotic Layer Fabrication Process

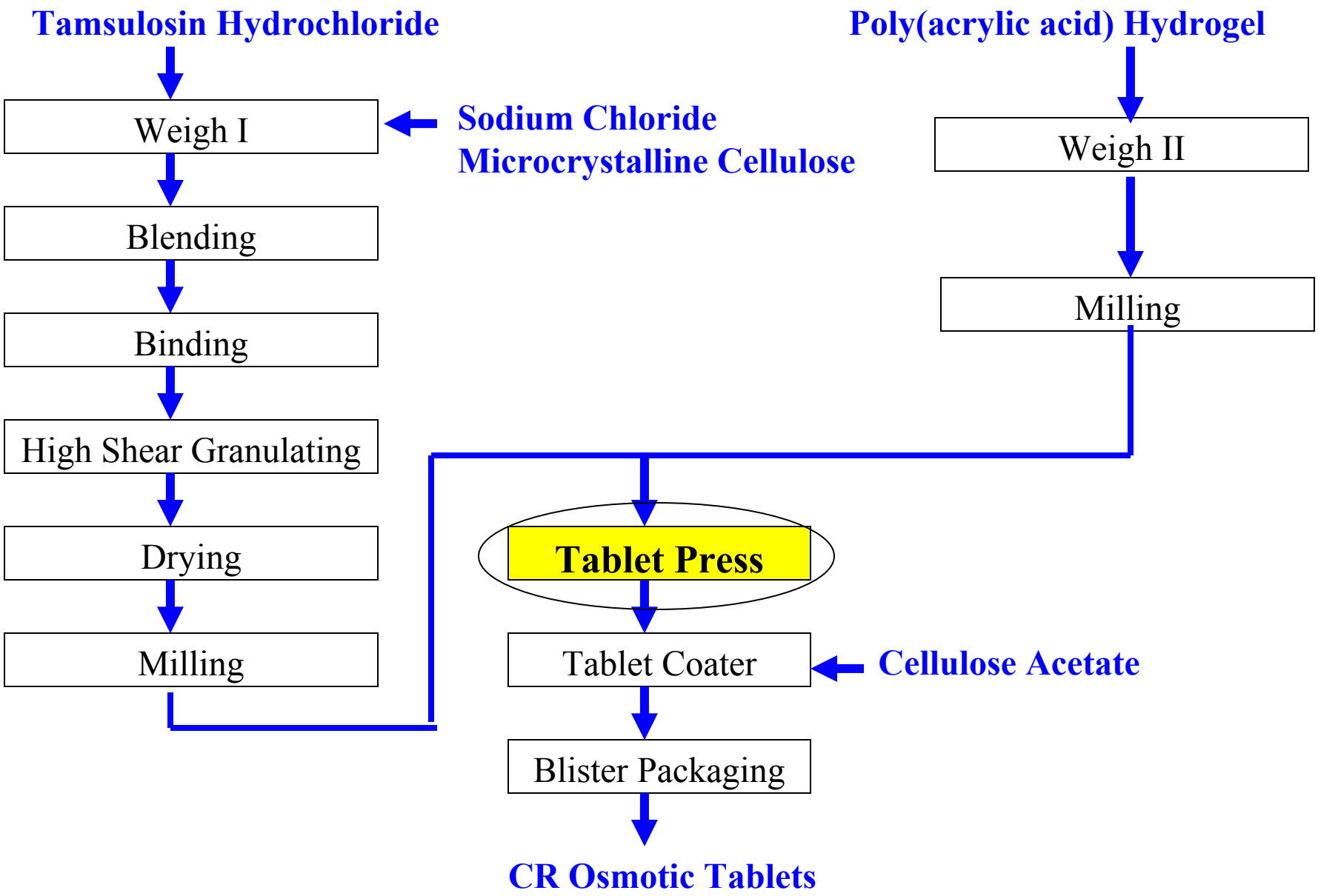
- ***WEIGH SYSTEM***

Polyacrylic acid (hydrogel): 18.4 kg/batch

- ***MILLING***

OSMOTIC LAYER NOW READY FOR TABLET COMPRESSION

Process Flow Diagram



TABLET COMPRESSION

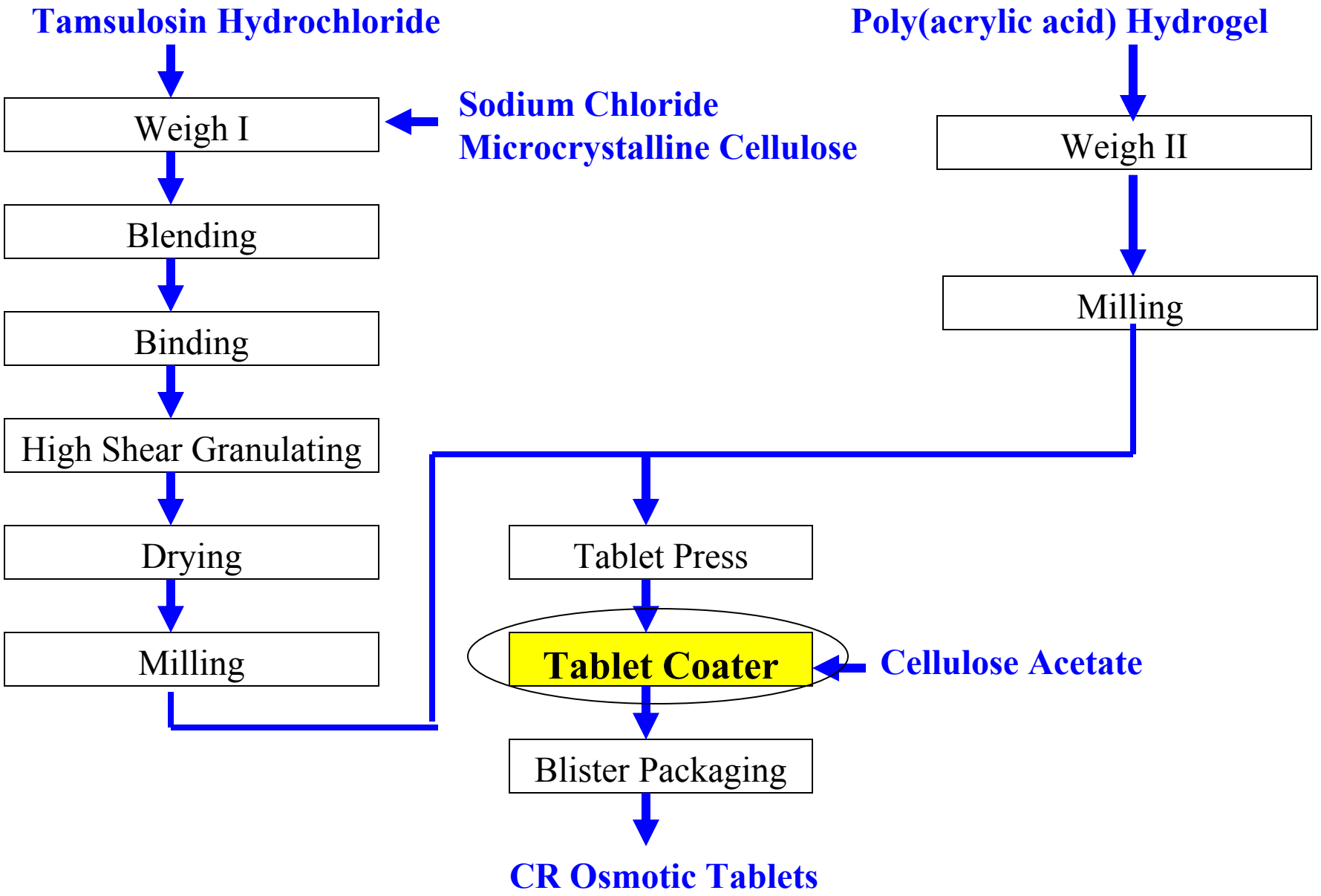
Courtoy Rotary Tablet Press Model R290

Production Cycle: 7,000 tablets/min

Utilities Required: Electrical, Compressed Air/CDA (Clean Dry Air), Dust Collection

- Weight control based on displacement measurement
- Special punch-tip and in-die lubrication systems
- State-of-the-art double layer press
- Closed system, no contamination of the room
- No cleaning of the machine

Process Flow Diagram



TABLET COATING SYSTEM

O'Hara Tablet Coater

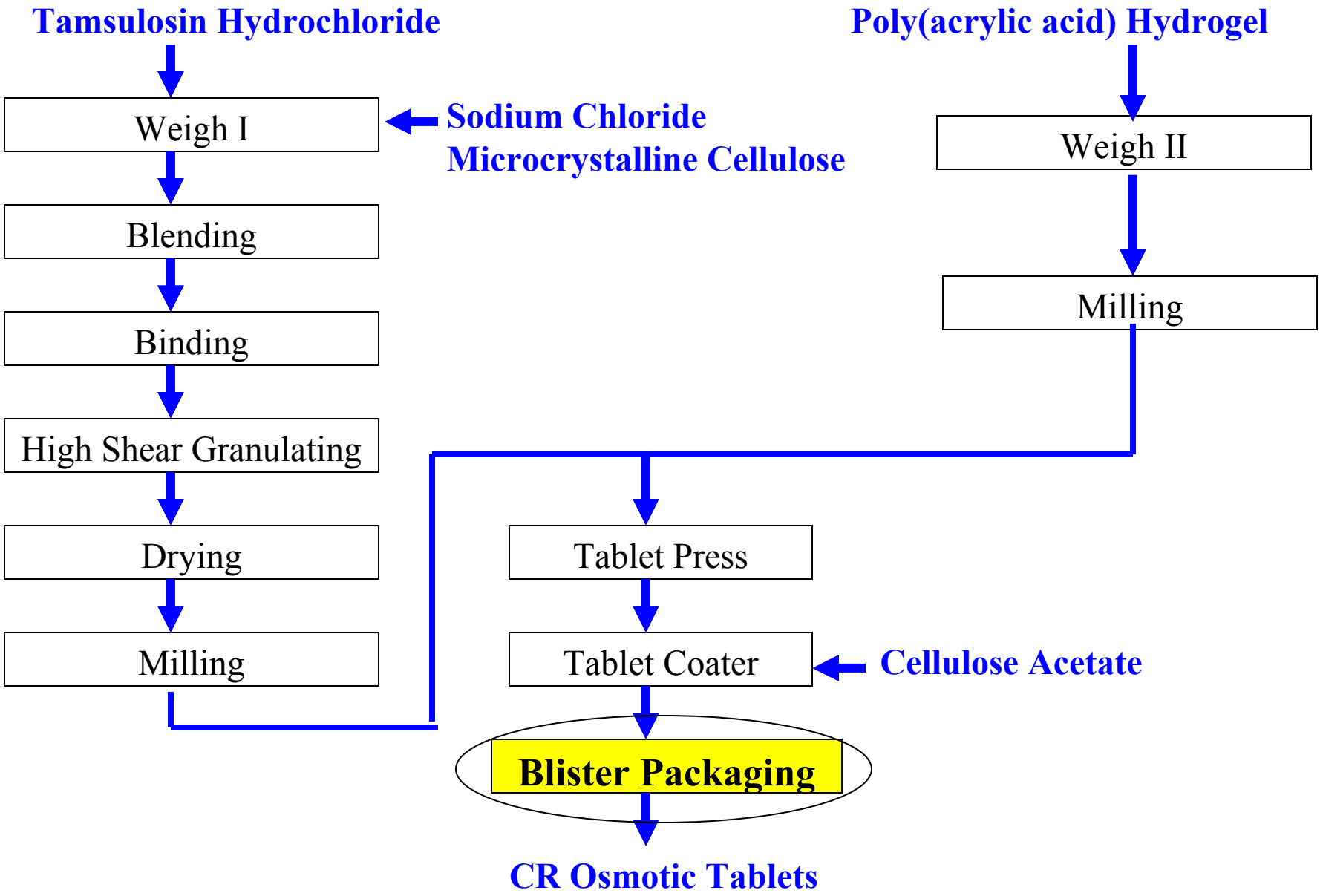
Spray for coating of cellulose acetate

Production Cycle Time ~ 5 hours/batch

Utilities Required:

- **Electrical**
- **USP Water**
- **Plant Steam**
- **Dust Collection**
- **CDA**
- **Nitrogen**

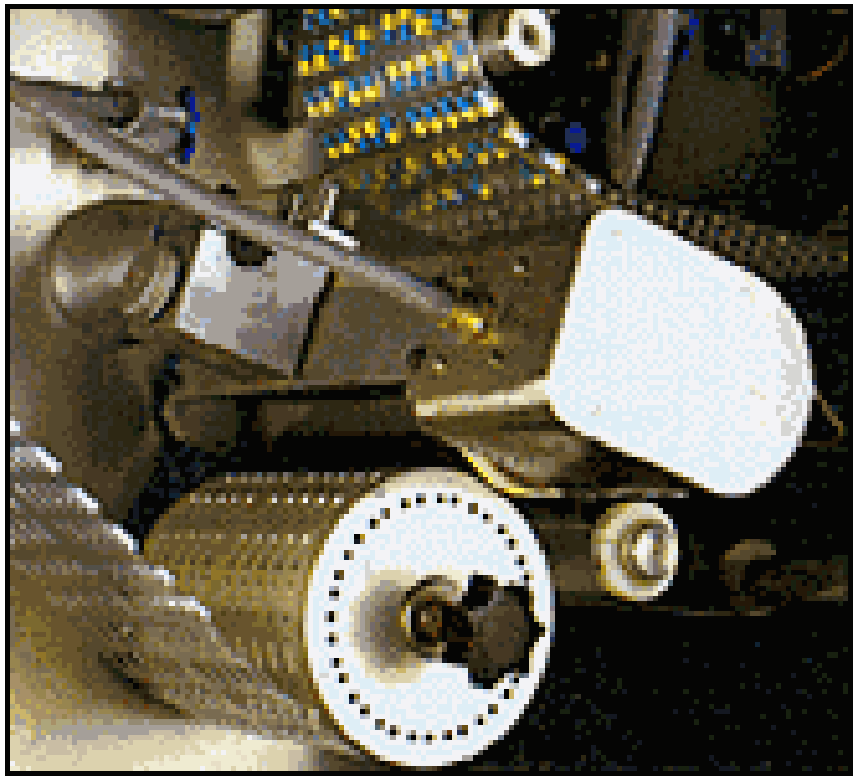
Process Flow Diagram



LASER DRILLING AND PACKAGING

IMA Blister Packaging

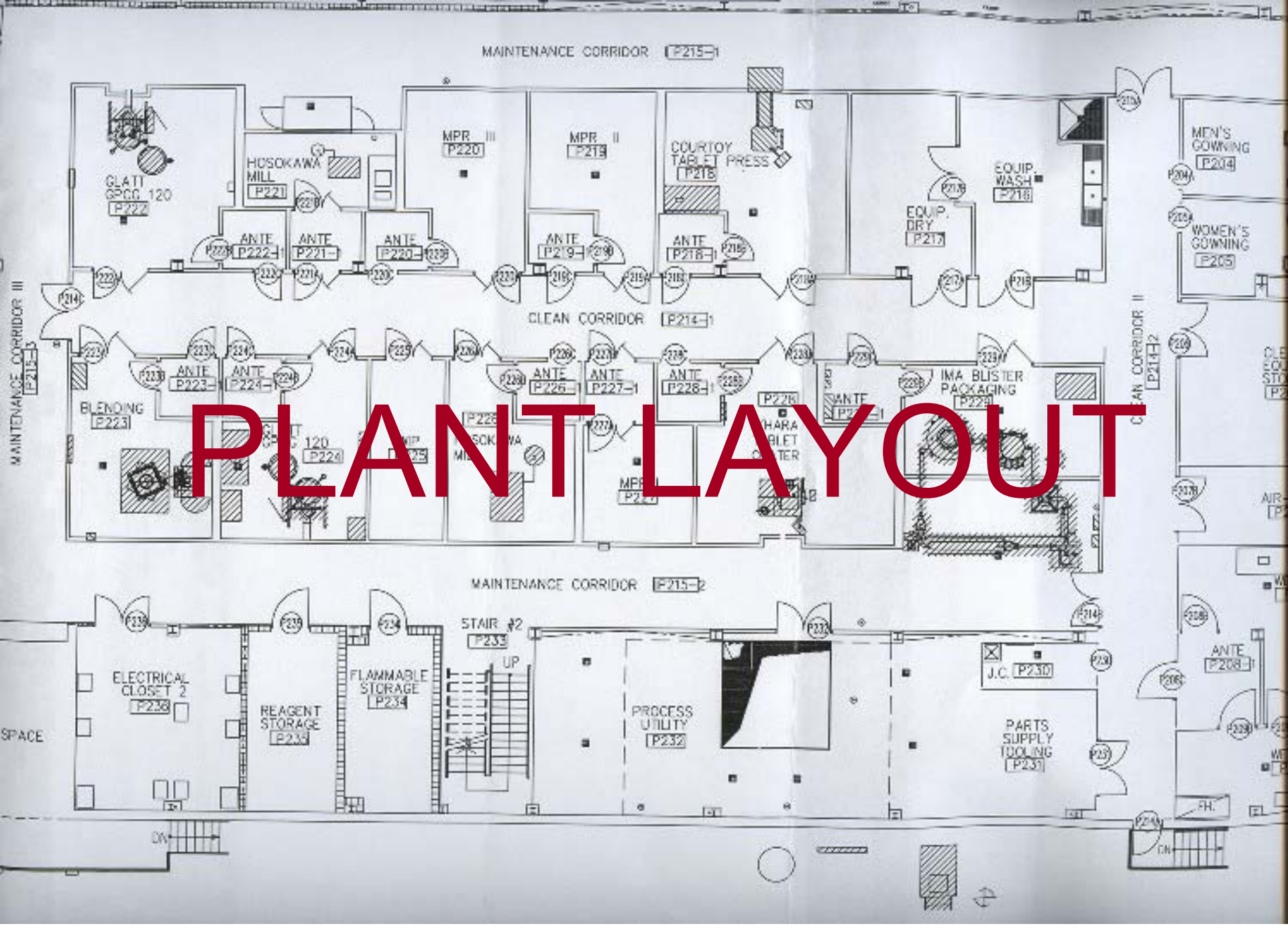
Production Cycle: 3000 tablets/min



*Most Expensive Machine at $1.7 million

Process Utilities Required for Plant

UTILITY	COST
Electrical	$2,300,000
HVAC	$1,400,000
Waste Water Treatment	$641,000
USP Water	$613,000
Chilled Water	$467,000
Clean Dry Air	$406,500
Plant Steam	$304,000
Dust Collection	$188,000



PLANT LAYOUT

FDA Approval

- Why is it Important?
- Cost
- Drug and Pill Design
- Plant and Fabrication Approval

Cost

- Novel Drug Delivery Systems (NDDS)
- Monetary Commitment
- Time Commitment
- Comparison to new chemical entity

Drug and Pill Design

- Individual Material Selection
- Active Ingredient
- Assumptions

Plant and Fabrication Approval

- Organization and Personnel
- Buildings and Facilities
- Equipment
- Control of Components and Containers
- Production and Process Controls
- Records and Reports

Validation Requirements

FDA:

Installational Qualification

Operational Qualification

Computer Systems Validation

Performance Qualification

Mission Statement

The goal of CORRN, Inc. is to provide a process to produce a time release delivery system for an orally ingested medicine commonly available on the market.

Market Strategy

Target Market
Competition
Publicity

Financial Planning

Capital Investment
Product Cost
Cumulative Position

Target Market

BPH rarely causes symptoms before age 40, but more than half of men in their sixties and as many as 90 percent in their seventies and eighties have some symptoms of BPH.[2]

Prof. Miguel J. Bagajewicz

Office Phone : (405) 325-5458

Home Phone : (405) 360-5202

(I don't mind receiving calls at home, just make sure it cannot wait.)

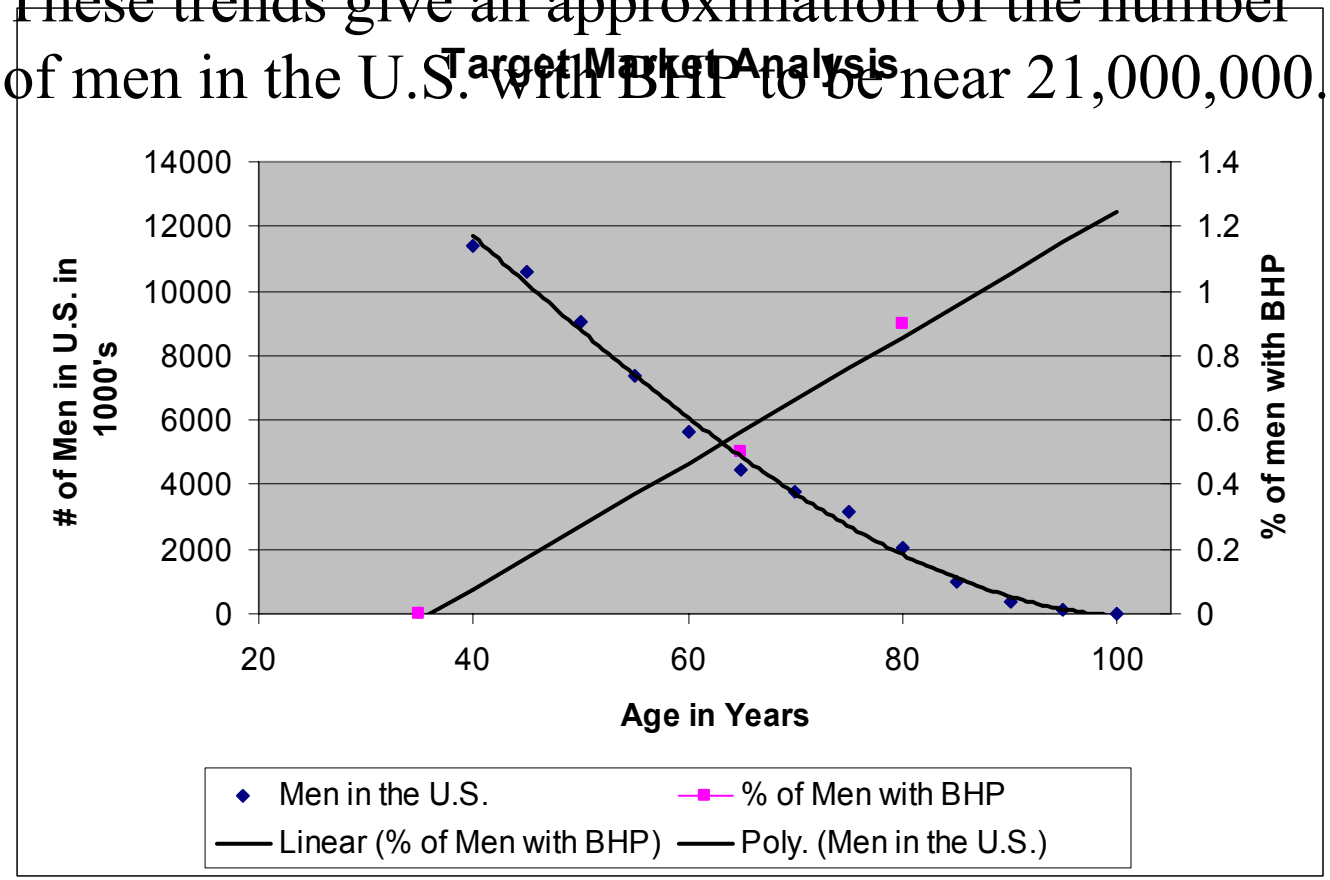
Click here to visit Web site of our Research Group

Teaching Assistant INFO

e-mail: bagajewicz@ou.edu

Target Market

These trends give an approximation of the number of men in the U.S. with BHP to be near 21,000,000.



Competition

Treatments for BHP:

- Surgery
- Drug Treatment

•Non-Selective

•Selective

Alpha blockers smooth muscles, especially in the urinary tract and prostate.

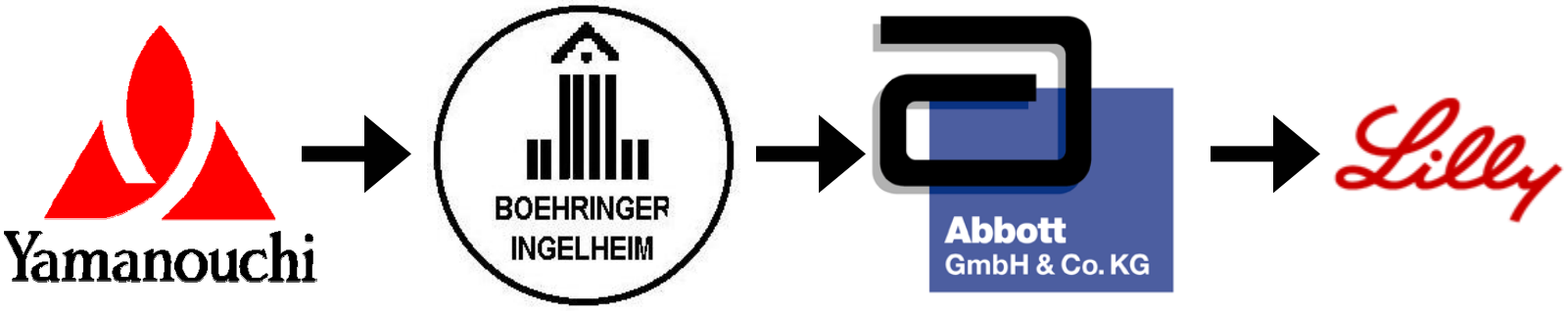
HYTRIN® TERAZOSIN HCl CAPSULES

CARDURA (doxazosin) Pfizer

They work fairly quickly, have no effect on sexual drive, and are the least expensive BPH treatment.

Flomax, or Tamsulosin HCl, is known as a selective alpha blocker

Competition



1997	1999	2002
$430 Mil. Annually for BHP	Flomax holds 30% of Market Share	Market Share increasing at 20% per year

The market share today for tamsulosin should be at least $300 million per year, or 300 million single doses at today's price.

Financial Planning

The goal of this analysis is to provide a preliminary estimate (± 20%) of the plant cost, and other economic indicators.

It will be broken down into three major sections:

- fixed and total capital investment
- total product cost
- cumulative cash position.

The following slides illustrate how these calculations are unique from those of traditional chemical processes.

Purchased Equipment

- Duplicate equipment is necessary for each layer of the tablet

- Cost indices and scaling factors cannot be used to estimate equipment cost; little or no data is available on the scaling of the equipment.

- Equipment costs include installation and instrumentation.

Direct Cost

- Some installation costs still exist for miscellaneous mechanical equipment
- Building estimates are based labor, material, and tax indices—all regional specific
- Cost for unimproved land is an average for commercially zoned property in the area

COMPONENT		BASIS FOR ESTIMATE	$
Direct Cost			
Onsite			
Purchased Equipment:			
Drug Layer Equipment		from manufacturer	1,797,000
Push Layer Equipment		from manufacturer	1,169,000
Final Process Equipment			3,706,500
Total purchased equipment			6,672,500
Installation		Installation Bid	61,000
HVAC Piping		HVAC Piping Bid	1,405,000
HVAC controls (installed)		HVAC Controls Bid	885,000
Other Mechanical		Bid	3,270,000
Offsite			
Building		M&S Building Cost Est.	1,851,300
Service facilities	8%	of TCI (P&T)	1,800,000
Yard improvements		Excavation Bid	34,000
Land	7/ft^2	Quote from Adair Realtors	210,000
Total direct cost			**16,127,800**

Indirect Cost

- The Contractor's fee is taken out of the indirect cost because it is included in the building estimate.

- Contingency is included as an investment to compensate for unpredictable events.

- In the pharmaceutical industry, equipment must be validated in order for it to be used.

COMPONENT	BASIS FOR ESTIMATE		$
Total direct cost			**16,127,800**
Indirect Cost			
Engineering & Supervision	8	% Total Direct Cost	1,290,224
Contractor's Fee		Included in Bid	0
Contingency	34	% purchased equipment cost	2,268,650
Validation**	12	% purchased equipment cost	800,700
Total indirect cost			**4,359,574**

Indirect Cost

COMPONENT	BASIS FOR ESTIMATE	$
Total direct cost		16,127,800
Total indirect cost		4,359,574
Fixed Capital Investment	**direct cost + indirect cost**	**20,487,374**
Working Capital	15 % total capital investment	3,615,419
TOTAL CAPITAL INVESTMENT		**24,102,793**
FDA Approval		20,000,000
TCI + FDA Approval		**44,102,793**

- After Working Capital is included, the TCI comes to $24 million.

However

- FDA Approval is estimated between $10 and $30 million

Financial Planning

Product Cost:

The two main categories that these expenses fall under are Manufacturing Costs and General Expenses.

Manufacturing Costs	General Expenses
Raw Materials	Administration
Labor Costs	Marketing
Utilities	R & D

Financial Planning

Product Cost:

Raw Materials:

COMPONENT	BASIS FOR ESTIMATE		Cost ($/yr)
1. Raw Materials[1]			
Tamsulosin HCl			150,000,000.00
Sodium Chloride	$30/kg	Chemical Company	900.00
Cellulose Acetate	$32/L	Chemical Company	75,360.00
Microcrystalline Cellulose	$3/kg	Avicel PH102 (using PH101)	100,800.00
		Total Raw Materials	150,177,060.00

- The cost for the active pharmaceutical ingredient was assumed based on its production rate.
- Based on 50% utilization, the proposed plant could produce one million tablets per shift.
- Costs for other materials were calculated based on the amount needed and respective market prices.
- The current market price for Tamsulosin is $1/dose.

Financial Planning

Product Cost:

Labor:

COMPONENT	BASIS FOR ESTIMATE		Cost ($/yr)
2. Labor			
Operators	14	workers at $40K per year	560,000.00
Cleaning	2	workers at $25K per year	50,000.00
Maintenance	4	workers at $40K per year	160,000.00
Quality Assurance	4	workers at $45K per year	180,000.00
Supervisory and Clerical	17	% of other operating labor	161,500.00
		Total Labor	1,111,500.00

- Labor costs were calculated based on the estimated number of staff required to operate the plant and local labor rates.

- Supervisory and clerical labor costs were calculated as a percentage of other labor costs.

Financial Planning

Product Cost:

Utilities:

COMPONENT		BASIS FOR ESTIMATE	Cost ($/yr)
3. Power and utilities[1]			
Building		WEL Networks Estimate	48,375.00
Steam		Unit requirements	1,200,000.00
Electrical		Unit requirements	2,300,000.00
Cold Water		Unit requirements	304,000.00
USP Water		Process requirements	613,000.00
		Total Power and Utilities	4,465,375.00

- Total power and utilities were calculated by the requirements of the process and the unit requirements

- The utilities for the building itself was calculated from parameters of the building size and average utility costs.

Financial Planning

Product Cost:

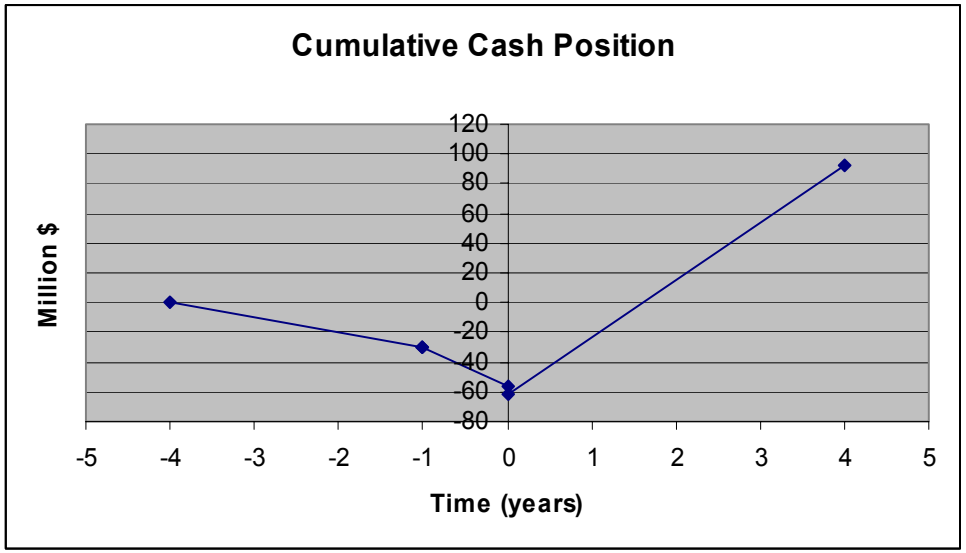
Summary

COMPONENT		BASIS FOR ESTIMATE	Cost ($/yr)
I. Manufacturing Cost			
A. Direct production costs		**Total Direct Product Cost**	**166,211,839.80**
B. Fixed Charges		**Total Fixed Charges**	**2,663,358.62**
C. Plant overhead costs	60	% of operating labor, supervision, and maintenanc	**789,824.24**
		Total Manufacturing Costs	**169,665,022.67**
II. General Expenses			
A. Administration Costs	3	% of Total Product cost	**7,104,521.14**
B. Distribution and Marketing Costs		Company Partnership	**-**
Costs	5	% of Total Product cost	**11,840,868.56**
		Total General Expenses	**18,945,389.70**
		Total Annual Product Cost	**236,817,371.29**
		Total Processing Cost ($/1000 tablets)	**789.39**

Financial Planning

Cumulative Position:

1,000,000.00	Total Tablets/Cycle
1.00	Cycle/Day
300.00	Work Days/Year
300,000,000.00	Tablets/year
166,211,839.80	Direct Production Cost per Year
0.55	Production Cost per Tablet
554.04	per 1000 Tablets
3,453,182.86	Fixed Charges
99.98	Price per 100 Tablets
999.80	Price per 1000 Tablets
7,746.72	Break Even Point (1000's of Tablets)
299,940,000.00	Gross Annual Sales
236,817,371.29	Total Annual Product Cost per Year
63,122,628.71	Gross Annual Earnings
22,092,920.05	Income Taxes (34%)
41,029,708.66	Net Annual Earnings



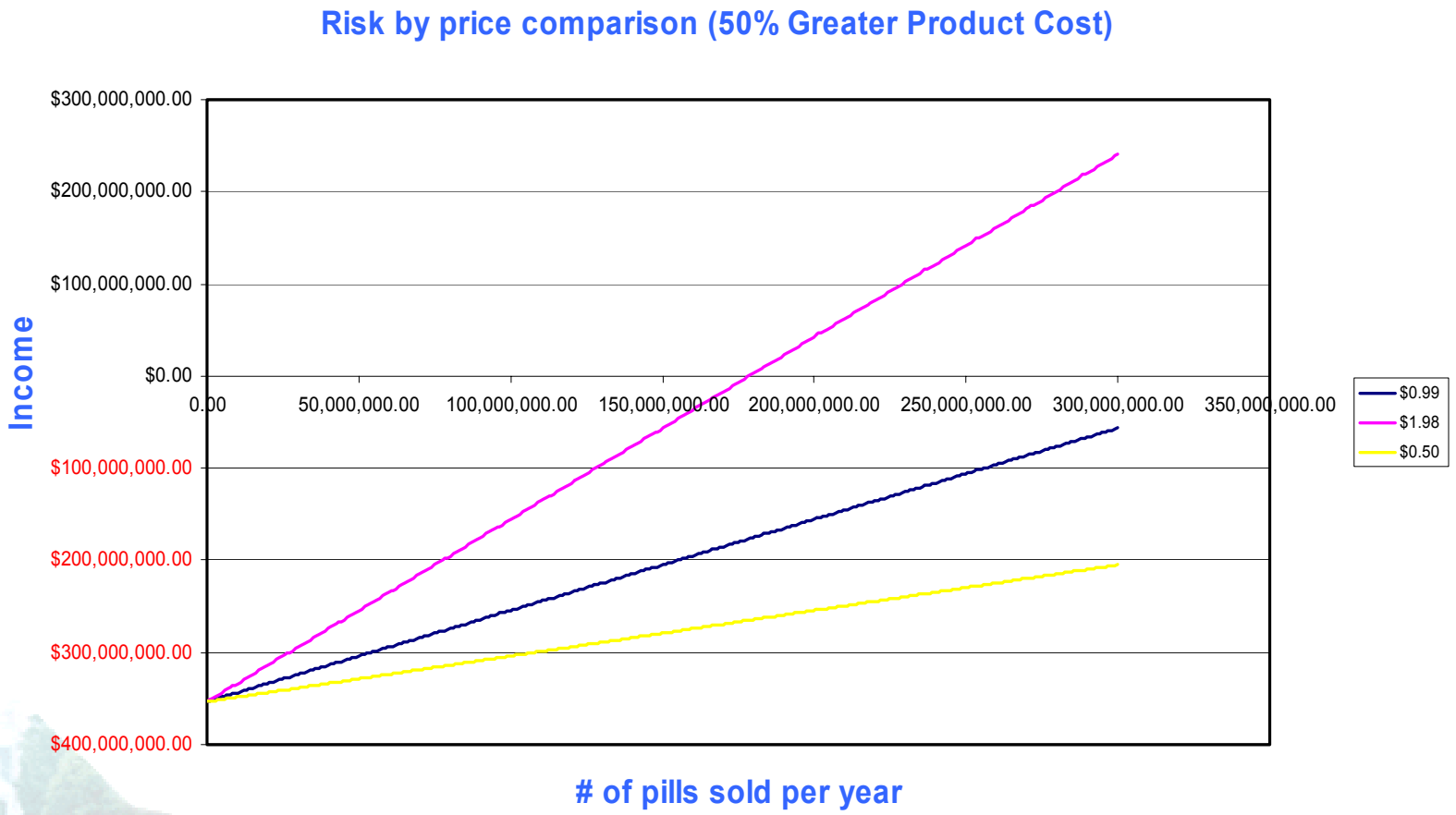
Risk Analysis

Overview

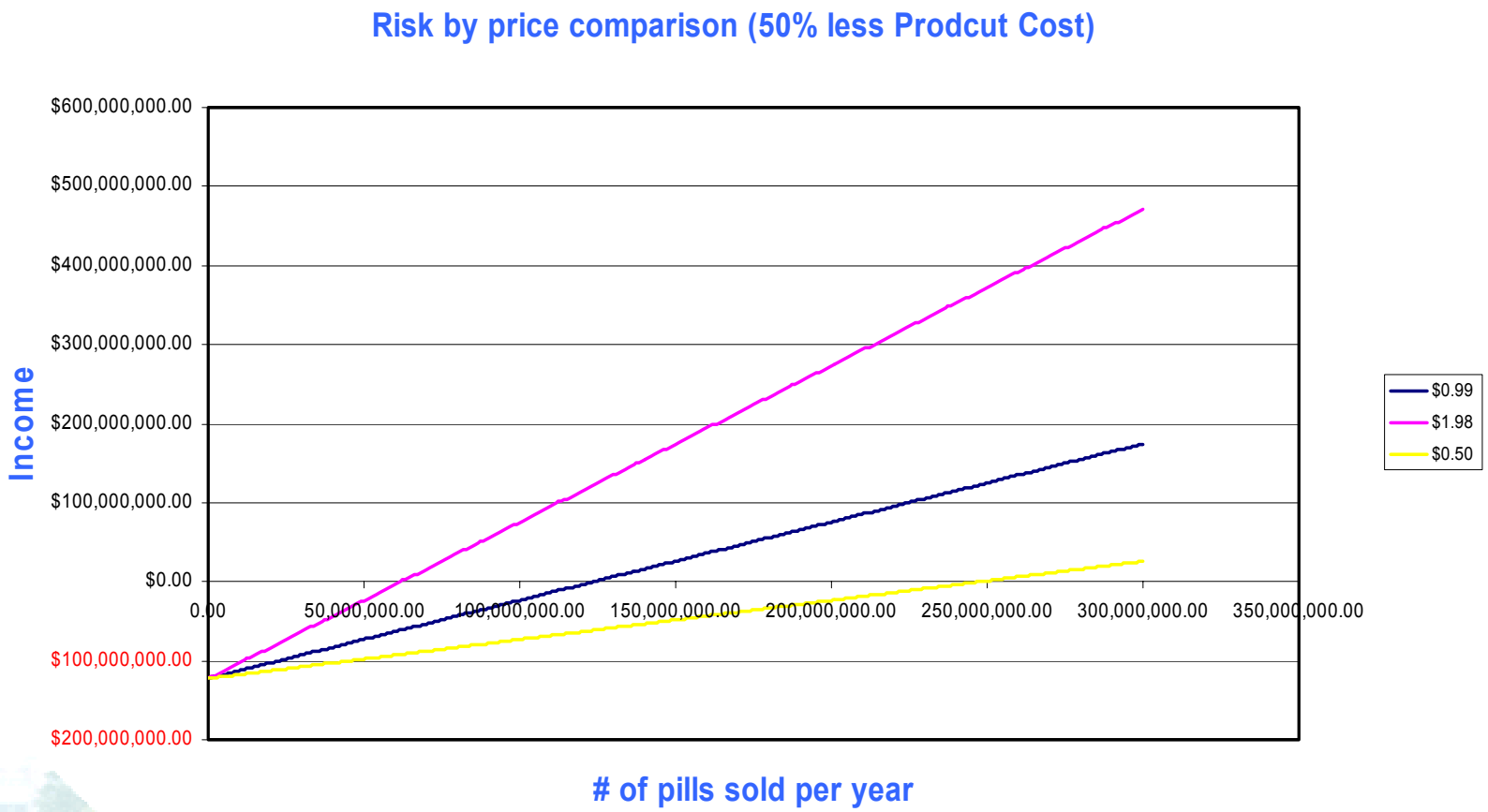
- Simple Price Breakdown
- Mathematical Formula Presentation
- Excel model
- Comparison

Simple Price Breakdown

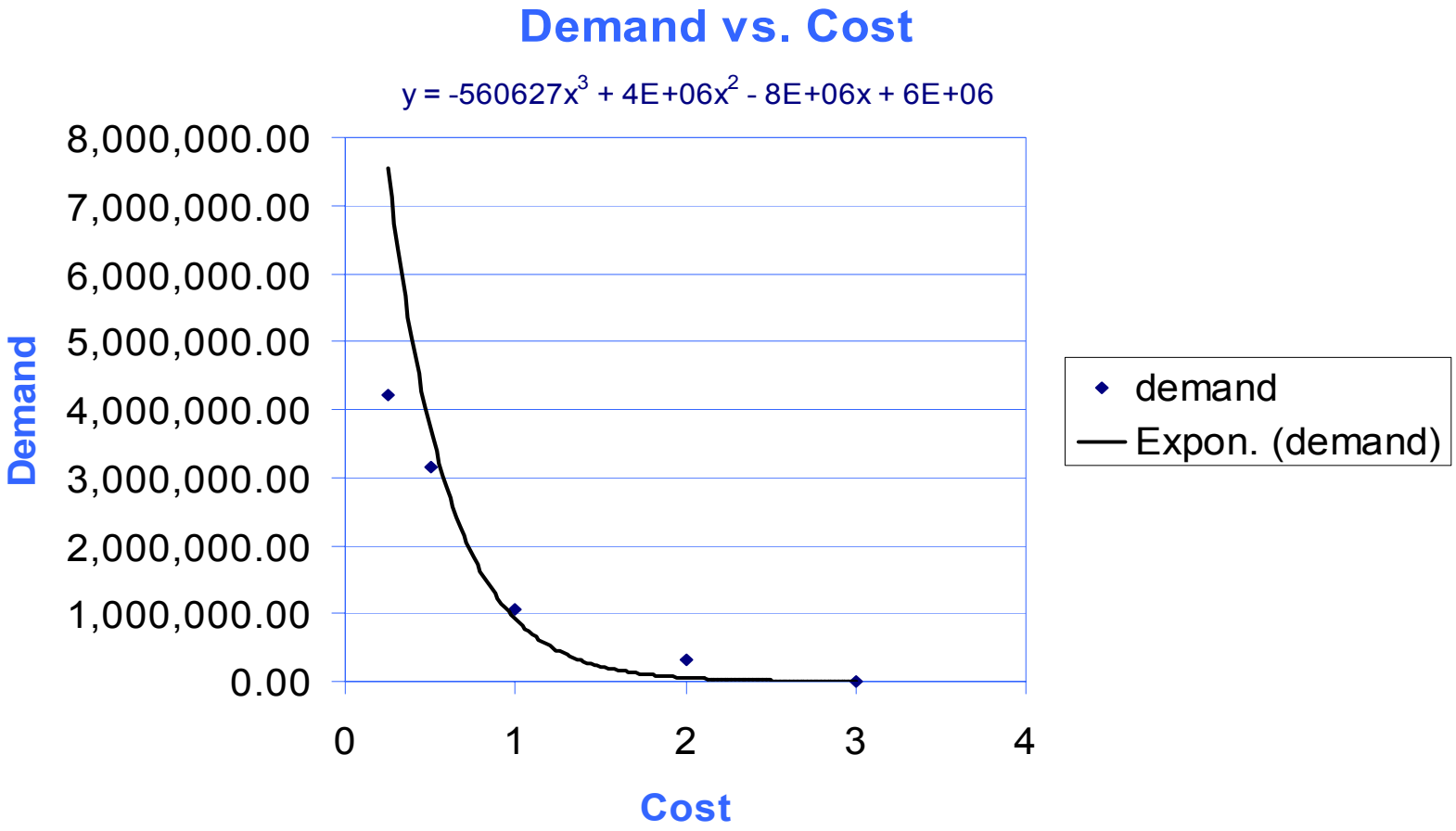
Simple Price Breakdown



Simple Price Breakdown



Simple Price Breakdown



Mathematical Formula

- Revenue: $\text{Re}\, v(t) = prod\,(t) * \sum_{i=1}^{3} y_i P_i d_i$
- Operating Cost: $OC(t) = \alpha_t + \beta_t * prod(t)$
- Capital Investment: $CI = \delta_t + \gamma_t * capacity$

Mathematical Formula

- Production:

$$prod(t) = \sum_{i=1}^{3} y_i d_i$$

- Constraints on production:

$$prod(t) \leq demand(t)$$

$$prod(t) \leq capacity$$

Mathematical Formula

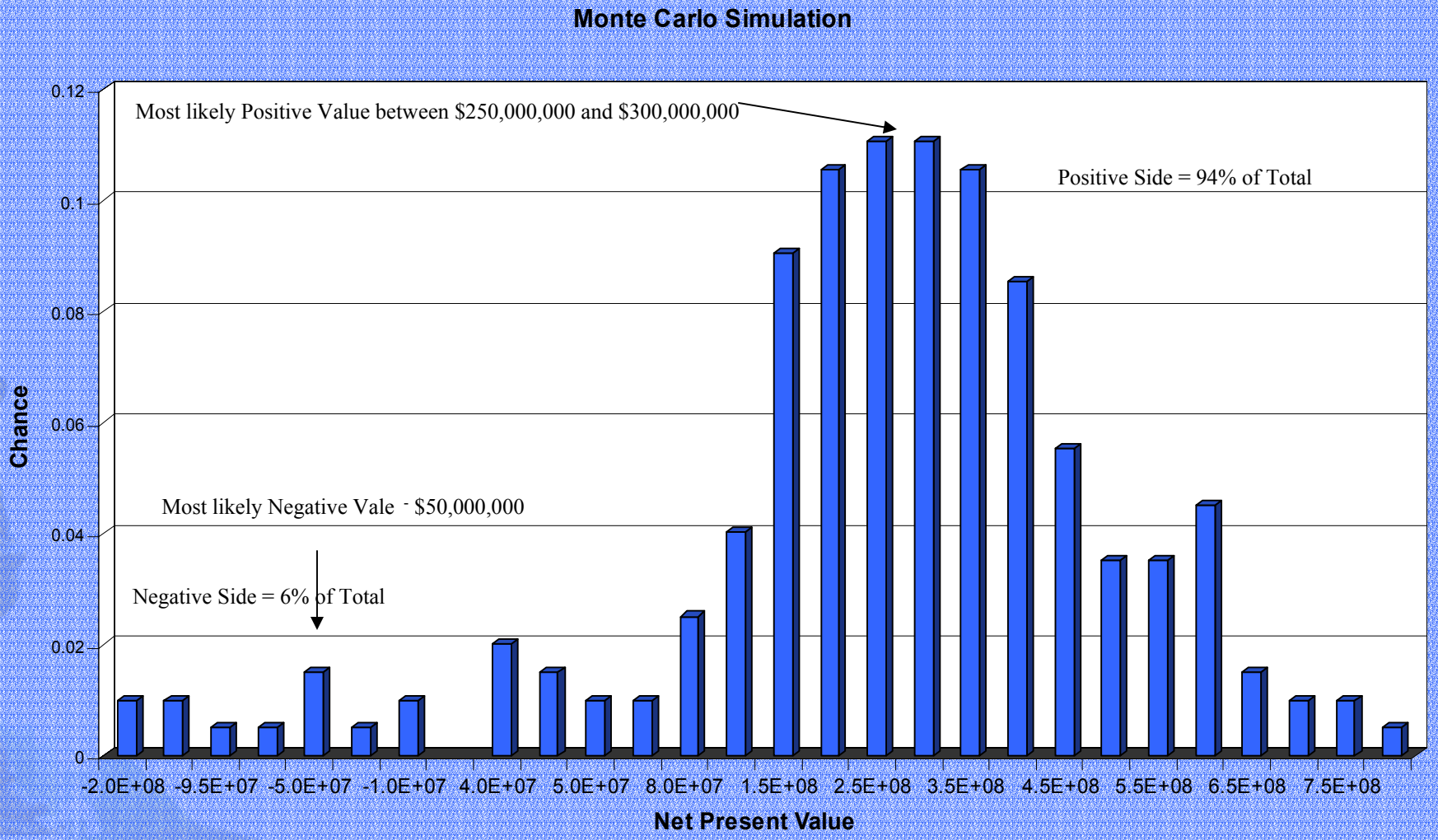
- Taxes:

$$taxes(t) = (\mathrm{Re}v(t) - OC(t) - (CI \div n)) * rate$$

- Net Present Value:

$$npv = (\sum_{t=1}^{10} \mathrm{Re}v(t) - OC(t) - taxes(t)) - CI$$

Excel Model


Monte Carlo Simulation
Most likely Positive Value between $250,000,000 and $300,000,000
Positive Side = 94% of Total
Most likely Negative Vale - $50,000,000
Negative Side = 6% of Total
Chance
0.12
0.1
0.08
0.06
0.04
0.02
0
-2.0E+08
-9.5E+07
-5.0E+07
-1.0E+07
4.0E+07
5.0E+07
8.0E+07
1.5E+08
2.5E+08
3.5E+08
4.5E+08
5.5E+08
6.5E+08
7.5E+08
Net Present Value

Questions?