Design of an Herbal Prebiotic Tablet: A Novel Dietary Supplement

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Objectives

- Create a novel prebiotic supplement from fermented turmeric, chicory root extract (inulin), and black pepper extract (piperine)
- Optimize the process design for product quality, equipment/plant size, and minimal production costs

Rationale, Market Size, and Ethical considerations

- Global dietary supplement market value: $133.1 billion[3]
- Prebiotic market worth $4.07 billion, expected 10.4% growth by 2023[4]
  - *Inulin* accounts for 40% of prebiotic market value[4] - powerful prebiotic that supports healthy bacteria in the microbiome
- *Turmeric* worth $44.2 million[3] - contains powerful antioxidant *curcumin* - considered among one of the most effective anti-inflammatory herbs
  - *Piperine* significantly increases bioavailability of curcumin
  - Fermenting turmeric further increases bioavailability of curcumin
- Herbal supplements may support healthy lifestyles and help prevent chronic diseases that could affect millions of people worldwide
  - Considered nontoxic to humans and environment
- Currently no supplements on the market combine these ingredients

Summary of Laboratory Experiments

- *Plackett-Burman Design of Experiments (DOE)*
  - Developed in 1960s to help optimize designs with many factors
  - Helps determine which factors have significant impact on an outcome

Variable Name	DOE	Minimum Value (-)	Maximum Value (+)	Units
Time in Extractor	A	4	30	Minutes
Percent Ethanol	B	20	100	%
Sterilization Time	C	2	5	Minutes
Sterilization Temp.	D	120	160	℃
Fermentation Time	E	7	10	Days
Culture Concentration	F	0.5	1.5	[g/L]
Fermentation Temp.	G	20	37	℃
Compaction Pressure	H	5	7	Tons
Tablet Diameter	I	10	20	mm
Tablet Thickness	J	3	6	mm
Tablet Weight (dummy)	K	1.48	1.52	g

Primary variables with one dummy variable, minimum and maximum experimental values, and corresponding variable code names included in the DOE.

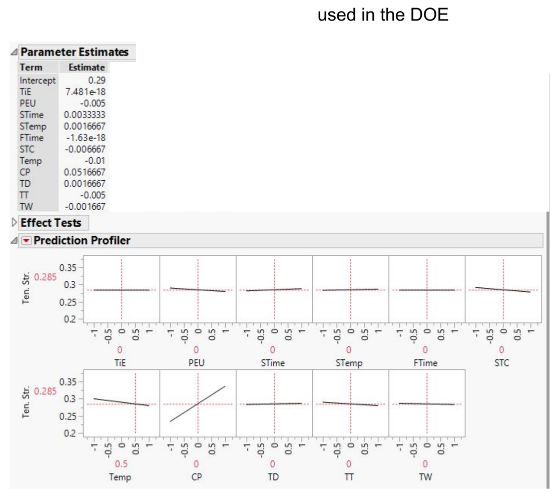
	Factors										
Run	A	B	C	D	E	F	G	H	I	J	K*
1	+	+	-	+	+	+	-	-	-	+	-
2	-	+	+	-	+	+	+	-	-	-	+
3	+	-	+	+	-	+	+	+	-	-	-
4	-	+	-	+	+	-	+	+	+	-	-
5	-	-	+	-	+	+	-	+	+	+	-
6	-	-	-	+	-	+	+	-	+	+	+
7	+	-	-	-	+	-	+	+	-	+	+
8	+	+	-	-	-	+	-	+	+	-	+
9	+	+	+	-	-	-	+	-	+	+	-
10	-	+	+	+	-	-	-	+	-	+	+
11	+	-	+	+	+	-	-	-	+	-	+
12	-	-	-	-	-	-	-	-	-	-	-

Experimental set up for an N=12 Plackett-Burman DOE. The plus signs (+) and negative signs (-) correspond to the maximum or minimum values, respectively, that were used in the run.

Run	Tensile Strength (MPa)
1	0.23
2	0.22
3	0.34
4	0.34
5	0.35
6	0.22
7	0.33
8	0.34
9	0.23
10	0.33
11	0.25
12	0.24

Tensile strength measurements from runs used in the DOE

- DOE aimed to optimize tablet tensile strength
- Tensile strength is critical for product quality
  - Design does not use excipients which normally would increase tablet strength
- JMP software used for statistical analysis
  - DOE results suggested that compaction pressure (CP) of the tablet press was the only significant factor on tensile strength



Results from JMP statistical analysis. Compaction pressure (CP) was determined to be the only significant factor on tensile strength.

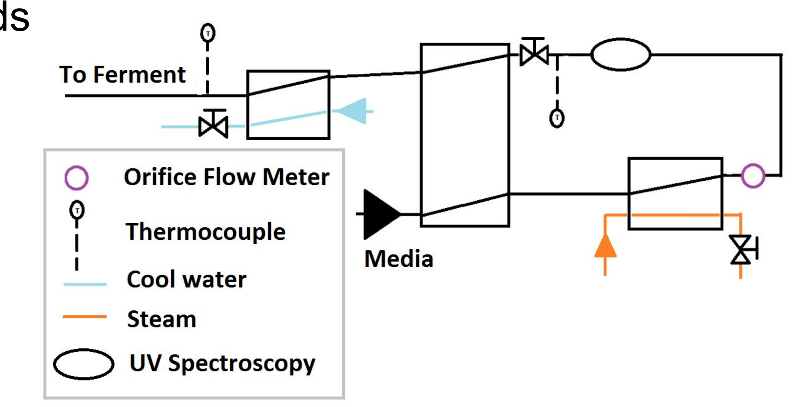
Process Description

Extraction

- Slice the roots into 2 mm thick slices
- Heat solution at 80°C for 20 minutes while being agitating at 47 RPM[1].
- Add ethanol, 49% by weight, centrifuge at 18,000 RPM[2].

Sterilization

- Sterilization before fermentation is essential to eliminate process line and product contamination
- Regenerative heating system to save on steam and water loads

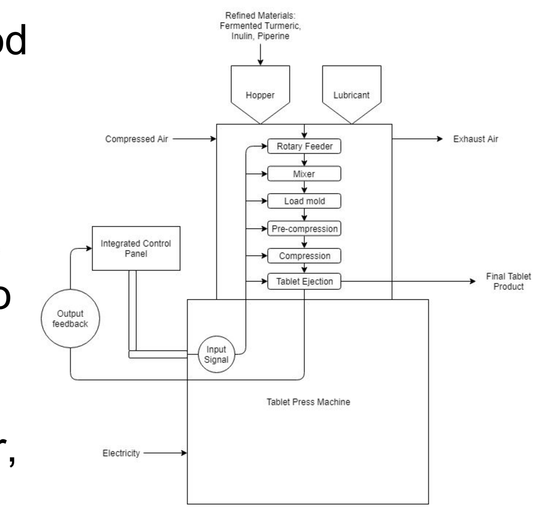


Fermentation

- Curcumin gets converted to tetrahydrocurcumin glucuronoside, which is more stable and has greater antioxidant properties than curcumin, no other known reaction accomplishes this
- Solid-state fermentation of turmeric using DI water, NaCl brine, and lactobacillus starter culture

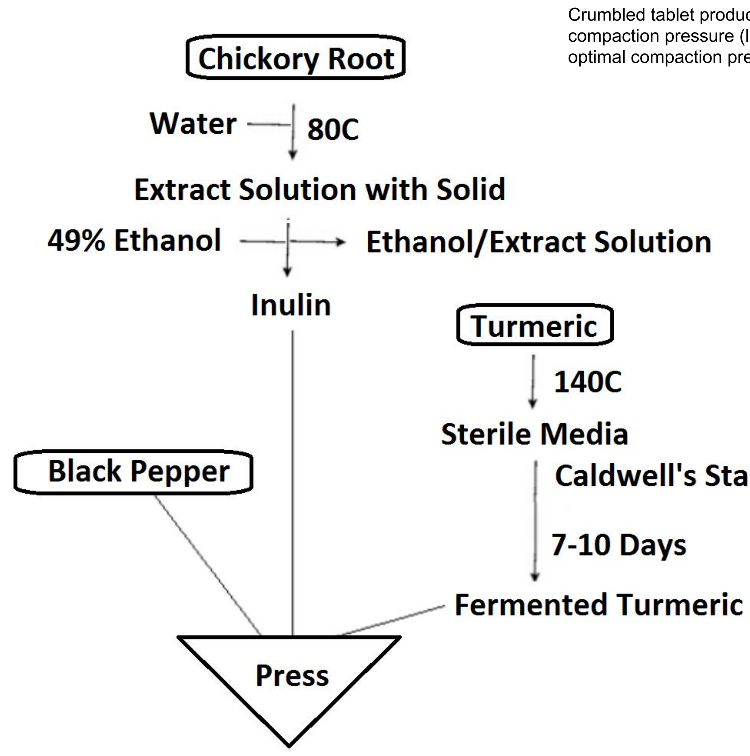
Tablet Pressing

- Direct compaction method chosen
  - Alternatives (dry/wet granulation) unnecessary for herbs
- Compiles ingredients into final tablet through integrated subprocesses
  - Hopper, Feeder, Mixer, Compaction
- Has most significant impact on physical properties of product



Crumbled tablet product without proper compaction pressure (left) vs. tablet with optimal compaction pressure (right)

Overall Process Summary



Economic Optimization of Unit Operations

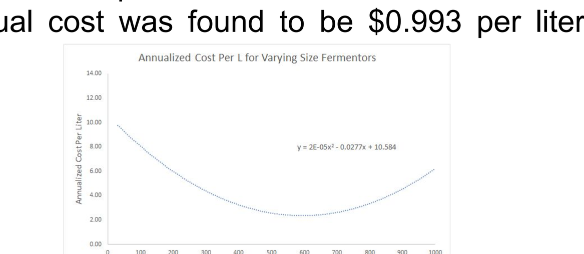
Extraction

- Main cost is ethanol - other costs include steam and power to heat vessel
- Best method to minimize annual costs is adjusting ethanol concentration vs. inulin precipitation
- Determined that using 49% ethanol during extraction minimized annual cost
- Constraints include need for safe and edible extraction chemicals. Alternative considered was enzyme liquefaction, too expensive for industrial scale.

Schemes of Ethanol Concentrations	I	II	III	IV	V	VI
Ethanol Concentration	20%	30%	40%	45%	50%	55%
Chicory Root Cost/yr	199,310.00	152,590.00	112,110.00	94,203.00	67,854.00	63,062.00
Ethanol Cost/yr	63,596.00	95,394.00	127,190.00	130,900.00	152,990.00	174,890.00
Heating Cost/yr	112,394.00	104,492.00	91,482.00	84,194.00	76,394.00	71,048.00
Water Cost/yr	44,058.45	40,960.86	35,860.94	33,004.05	29,946.45	27,850.82
Total Cost/yr	419,358.45	393,436.86	366,642.94	342,301.05	327,184.45	336,850.82

Fermentation

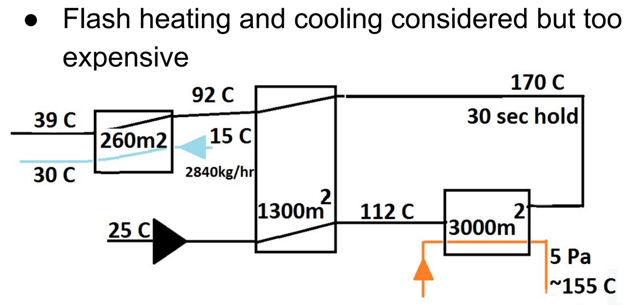
- Minimize annual cost for fermentation vessel and cost of electricity for agitation
- Constraints include preservation of the product, which was not able to be assessed on lab-scale experiments
- The lowest annual cost was found to be $0.993 per liter with a vessel volume of 693 L

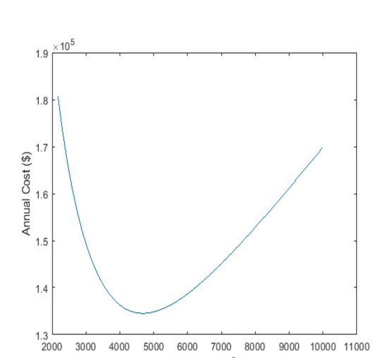


Annualized cost per unit volume of fermentation vessel with P4B single agitator.

Sterilization

- Minimization of cost by balancing heat exchanger cost through size, steam, and water loads
- Constraints include possible temperature dependent degradation of curcumin
- Flash heating and cooling considered but too expensive

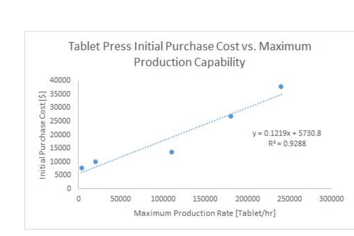




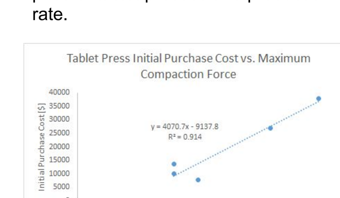
(Above) Equipment sizing through minimization of costs
(Left) Optimal Sterilization conditions

Tablet Pressing

- Low annual cost - optimized for possible plant growth and machine capabilities rather than costs
  - Operating costs (electricity) were considered negligible (<$10,00/year)
  - Initial purchase cost was considered to be the only significant annual cost
- Concluded that annualized initial purchase cost (~$2,500 - $4,000) was not worth opting for less expensive/capable machines
  - Purchasing less expensive machines generally decreased important capabilities such as maximum production rate and compaction force



Linear trend found between market price of tablet presses and production rate.



Linear trend found between market price of tablet presses and production rate.

Economic Analysis

- Investments calculated for a solid-liquid processing plant
- 10% investment rate
- 17,280kg/yr of production
- Equipment and Plant life: 10 years

Costs	Estimated by	Amount
Equipment	Equipment,spare parts, mods, etc	$143,000 (Principle)
FCI	Est. 4.28X Equipment Costs	$987,600 (Principle)
TCI	Est. 5.03X Equipment Costs	$1,160,600 (Principle)
Product Cost	Manufacturing and General Expenses	$6,491,447 (Annually) $45/bottle
Product Revenue	Sales of all product when plant is at max capacity	$8,640,000 (Annually) $60/bottle
ROI	Net profit, Working Capital, FCI	61%
IRR	Cash Flow	25%

Year	Sales	Expenses	Depreciation	Net Profit	Tax	Cash Flow
1	$2,160,000	$6,491,447	$23,074	-$2,800,443	$980,155	-$2,777,369
2	$4,320,000	$6,491,447	$23,074	-$1,396,443	$488,755	-$1,373,369
3	$8,640,000	$6,491,447	$23,074	$1,411,557	$494,045	$1,434,631
4	$8,640,000	$6,491,447	$23,074	$1,411,557	$494,045	$1,434,631
5	$8,640,000	$6,491,447	$23,074	$1,411,557	$494,045	$1,434,631
6	$8,640,000	$6,491,447	$23,074	$1,411,557	$494,045	$1,434,631
7	$8,640,000	$6,491,447	$23,074	$1,411,557	$494,045	$1,434,631
8	$8,640,000	$6,491,447	$23,074	$1,411,557	$494,045	$1,434,631
9	$8,640,000	$6,491,447	$23,074	$1,411,557	$494,045	$1,434,631
10	$8,640,000	$6,491,447	$23,074	$1,411,557	$494,045	$1,434,631

Conclusions & Areas of Exploration

- This design is promising in terms of having a high market demand, being feasible with current industrial processes, and yielding a high profit.
- Future work should consider specific factors not able to be quantified in this work such as the amount of curcumin that is converted to tetrahydrocurcumin glucuronide, the purity of extracted inulin, and the degradation of the tablet both physically and chemically over time. These factors could then be optimized to increase health benefits.
- In vivo consortial evolutionary studies of the human microbiota while taking this supplement would be another future step to further support our claims of this prebiotic supplement having health benefits. *Bifidobacterium* and *Lactobacillus* are the two main bacterial groups which we hypothesize our supplement supports and these should be among the first investigated for growth.

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