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Process Simulation of Vitamin C Syrup Manufacturing: An Aspen Plus®-Based Approach for Pharmaceutical Unit Operations Optimization

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Abstract

The pharmaceutical industry increasingly relies on process simulation tools to optimize manufacturing workflows, reduce development costs, and ensure regulatory compliance. This study presents a comprehensive simulation of vitamin C (ascorbic acid) syrup preparation using Aspen Plus® V12.1, focusing on critical unit operations including mixing, dissolution, crystallization, and cross-flow membrane filtration. The process was modeled using the Non-Random Two-Liquid (NRTL) thermodynamic base property method, with crystallization/dissolution kinetics parameterized according to the McCabe growth law. Three sequential BatchOp unit operation under Batch Model (Batch Process), CRISTAL1–3 was employed to dissolve sucrose (933.4 kg), ascorbic acid (1.436 kg), and vanillin flavoring (0.1436 kg) in purified water (500 kg), achieving a final syrup composition of 65.0% w/w sucrose, 0.1% w/w vitamin C, and 0.01% w/w vanillin. The simulation demonstrated complete dissolution of all active and excipient components within 105 min for sucrose, 60 min for vitamin C, and 15 min for final homogenization, with cross-flow filtration (CFFilter modules) effectively removing insoluble impurities and non-sugar solids. The final product exhibited a standard liquid density of 1.3276 g/cm³, closely matching the European Pharmacopoeia specification of 1.32 g/cm³ at 20°C. This work establishes a simulation framework for liquid pharmaceutical manufacturing, demonstrating how simulation-driven process design can enhance quality assurance, reduce material waste, and accelerate scale-up from laboratory to industrial production.

Keywords: *Process simulation, Aspen Plus, Vitamin C syrup, pharmaceutical unit operations, Crystallization/dissolution kinetics, Cross-flow filtration.*

I. Introduction

Liquid pharmaceutical formulations, particularly syrups, represent one of the most widely consumed dosage forms globally, especially in pediatric and geriatric populations where swallowing solid dosage forms presents challenges [1]. According to the European Pharmacopoeia, a syrup is defined as an oral liquid preparation containing at least one active pharmaceutical ingredient (API) dissolved in an aqueous medium, with sucrose concentrations typically ranging from 45% to 65% w/w to ensure microbiological stability, adequate viscosity, and palatability [2]. Among the various APIs Despite its therapeutic importance, ascorbic acid presents significant formulation challenges due to its chemical instability in aqueous environments. The molecule undergoes oxidative degradation to dehydroascorbic acid (DHAA) and subsequently to 2,3-diketogluconic acid (DKGA), with the reaction rate strongly dependent on pH, temperature, oxygen concentration, and the presence of catalytic metal ions [4]. Yuan and Chen (1998) demonstrated that ascorbic acid degradation in aqueous solution follows first order kinetics, with maximum stability observed at pH values between 4 and 6, while alkaline conditions dramatically accelerate oxidation [5]. Furthermore, the degradation half-life of ascorbic acid at 25°C has been reported to range from 1.22 to 7.12 hours depending on the food matrix, highlighting the necessity for carefully controlled manufacturing conditions [6].

The pharmaceutical industry has witnessed a paradigm shift toward Quality by Design (QbD) principles and process analytical technology (PAT), emphasizing the need for thorough understanding and control of manufacturing processes [7]. In this context, process simulation software

such as Aspen Plus® has emerged as an indispensable tool for pharmaceutical engineers, enabling the prediction of process behavior, optimization of operating conditions, and reduction of experimental trials during process development [8]. Aspen Plus®, developed by Aspen Technology Inc., integrates rigorous thermodynamic models, extensive component databases, and specialized unit operation blocks for both continuous and batch processes, making it particularly suitable for pharmaceutical applications involving complex solid-liquid equilibria and non-ideal mixing behavior [9].

Previous studies have successfully applied Aspen Plus® to various pharmaceutical manufacturing scenarios, including reactive distillation, crystallization, and solid-liquid separation [10]. However, the application of this software to the simulation of complete syrup manufacturing workflows, particularly those involving multiple dissolution stages and membrane filtration, remains relatively unexplored in the peer-reviewed literature. The present study addresses this gap by developing and validating a comprehensive Aspen Plus® model for vitamin C syrup production, incorporating real crystallization kinetics data, particle size distributions, and industrial-scale filtration parameters. The specific objectives of this work were: to construct a rigorous process flow diagram (PFD) representing the complete manufacturing sequence from raw material feeding to final product filtration; to parameterize dissolution kinetics for sucrose, ascorbic acid, and vanillin using literature-derived solubility data and the McCabe crystallization growth model; to simulate cross-flow membrane filtration for impurity removal using industrially relevant specifications; and to validate the simulation outputs against established pharmacopeia standards for syrup quality.

II. Material and methods

II.1 Process description and flowsheet architecture

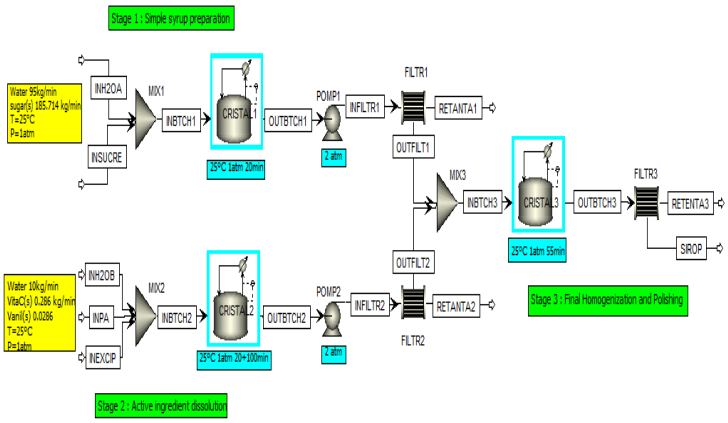

Figure 1. Process Flow Diagram for vitamin C syrup manufacturing

The process comprises three stages: (1) simple syrup preparation through sucrose dissolution (MIX1 + CRISTAL1, 105 min) and membrane filtration (FILTR1); (2) active ingredient dissolution (MIX2 + CRISTAL2, 60 min) and filtration (FILTR2); and (3) final homogenization (MIX3 + CRISTAL3, 15 min) and polishing filtration (FILTR3). Pumps (POMP1-2) create 2 atm pressure differential for filtration. All stages operate at 25°C and 1 atm.

The simulated manufacturing process was designed according to standard galenic pharmacy principles for syrup preparation, comprising three main stages: (1) simple syrup preparation through sucrose dissolution and filtration; (2) active ingredient and flavor dissolution in a separate aqueous phase; and (3) final homogenization and polishing filtration [11]. This sequential approach minimizes thermal stress on heat-sensitive components (vitamin C) by avoiding prolonged exposure to elevated temperatures during sucrose dissolution.

Stage 1: Simple Syrup Preparation. Sucrose (933.4 kg) and purified water (475 kg) were fed into Mixer 1 (MIX1), producing a biphasic solid-liquid stream subsequently transferred to rigorous batch reactor with rate-controlled reactions based on known kinetics (CRISTAL1). The BatchOp operated at 25°C and 1 atm with an agitation speed of 400 rpm (impeller diameter: 1 m), achieving complete sucrose dissolution within 105 min (1 h 45 min). The dissolution reaction was modeled as:

Sucrose(s) → Sucrose(aq)

Governed by the McCabe growth model:

Crystal Growth Equation:

$$G = \eta(k_g(\alpha + \beta L)^m \frac{(C - C_{sat})^n}{{C_{sat}}^{n'}} \tau^0 e^{-E_g/RT}$$

Dissolution Rate:

$$D = k_d(\alpha + \beta L)^m \frac{(C - C_{sat})^n}{{C_{sat}}^{n'}}$$

where G is the growth rate (m/s), kg=7.365×10−7 m/s is the growth rate constant, Eg=37.656 kJ/mol is the activation energy, C is the solution concentration, Csat is the saturation concentration, and α=1 , β=0 , m=1 , n=1 , n′=1 are empirical exponents [12].

D is the dissolution rate (m/s), k_d=7.5×10−7 m/s is the dissolution rate constant.

The solubility of sucrose in water was specified as a temperature-dependent function based on established literature data, ranging from 1.76 g sucrose/g water at -10°C to 5.93 g/g at 115°C [13]. At the operating temperature of 25°C, the solubility corresponds to approximately 2.07 g/g, ensuring complete dissolution of the 1.96:1 sucrose-to-water mass ratio employed in this study.

Following dissolution, the syrup was pumped (POMP1) at 2 atm to Cross-Flow Filter 1 (FILTR1), equipped with a hydrophilic polyamide membrane (capillary diameter: 1.5

mm, length: 1.2 m, 1000 capillaries, specific filtration rate: 0.8 L/m²·s). The filter achieved complete separation of insoluble impurities (non-sugar solids) from the clarified simple syrup.

Stage 2: Active Ingredient Dissolution. In parallel, ascorbic acid (1.436 kg), vanillin (0.1436 kg), and purified water (25 kg) were combined in Mixer 2 (MIX2) and transferred to second BatchOp (CRISTAL2). Vitamin C solubility data were entered as concentration values (290,000 mg/L at 20°C; 330,000 mg/L at 25°C; 370,000 mg/L at 30°C), with crystal growth parameters kg=1×10−7 m/s, Eg=55 kJ/mol, and kd=3.7×10−5 m/s [14]. Vanillin solubility was specified as 5,000–22,500 mg/L across 0–40°C, with kd=1.15×10−5 m/s and Eg=55 kJ/mol [15]. The batch operated for 60 min with a 45-min idle period to synchronize with Stage 1 timing. Cross-Flow Filter 2 (FILTR2), identical to FILTR1, removed residual insoluble matter.

Stage 3: Final Homogenization and Polishing. The filtered simple syrup and active ingredient solution were combined in Mixer 3 (MIX3) and transferred to third BatchOp (CRISTAL3) for 15 min homogenization at 400 rpm. Final polishing filtration through Cross-Flow Filter 3 (FILTR3), featuring finer membrane specifications (capillary diameter: 1.0 mm, specific filtration rate: 0.3 L/m²·s), ensured complete removal of any microcrystalline precipitates.

II.2 Thermodynamic model and simulation setup

The NRTL (Non Random Two Liquid) activity coefficient model was selected as the primary thermodynamic framework due to its demonstrated accuracy for aqueous pharmaceutical systems containing polar and hydrogen-bonding components [16]. The RK-ASPEN equation of state was employed for vapor phase properties. For non-conventional solids (impurities, non-sugar solids), the HCOALGEN enthalpy model and DCOALIGT density model were applied.

The simulation utilized the Pharmaceuticals with Metric Units template in Aspen Plus® V12.1, with dynamic input mode and the MCINCPSD (Mixed Conventional and Non-Conventional with Particle Size Distribution) stream class to accommodate solid-phase components. Particle size distributions were defined using a logarithmic mesh with 50 intervals across 0.6–1.0 mm for sucrose (D50=800 µm, σ = 200 µm), vitamin C (D50=150 µm, σ = 50 µm), and vanillin (D50=200 µm, σ = 50 µm) [17].

II.3 Component specifications

The complete component list and their Aspen Plus® classifications are presented in Table 1.

Table 1. Chemical components and their simulation specifications.

Component	Type	Chemical Formula	Role in Formulation
Water	Conventional	H_2O	Solvent/vehicle
Sucrose	Conventional	$C_{12}H_{22}O_{11}$	Dissolved sugar
Ascorbic acid	Conventional	$C_6H_8O_6$	Active pharmaceutical ingredient
Vanillin	Conventional	$C_8H_8O_3$	Flavoring agent
Sucrose(s)	Solid	$C_{12}H_{22}O_{11}$	Solid feedstock
Vitamin C(s)	Solid	$C_6H_8O_6$	Solid API feed
Vanillin(s)	Solid	$C_8H_8O_3$	Solid flavor feed
Impurities	Non-conventional	—	Insoluble contaminants
Non-sugar	Non-conventional	—	Non-sucrose solids

III. Results and discussion

III.1 Solubility and crystallization kinetics characterization

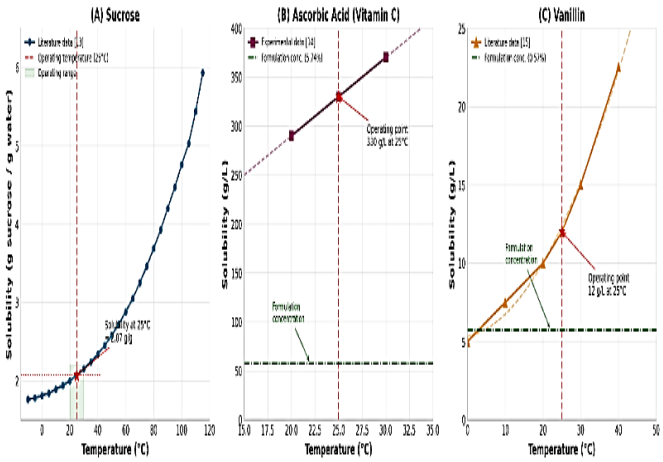

Figure 2. Temperature-Dependent Solubility of Key Components in Aqueous Solution. (A) Sucrose solubility from -10°C to 115°C [13]; operating point at 25°C (2.07 g/g) indicated. (B) Ascorbic acid solubility: 290–370 g/L across 20–30°C [14]; formulation concentration (5.74%) shown for comparison. (C) Vanillin solubility: 5–22.5 g/L across 0–40°C [15]; formulation concentration (0.57%) indicated. All components exhibit substantial solubility margins at operating conditions.

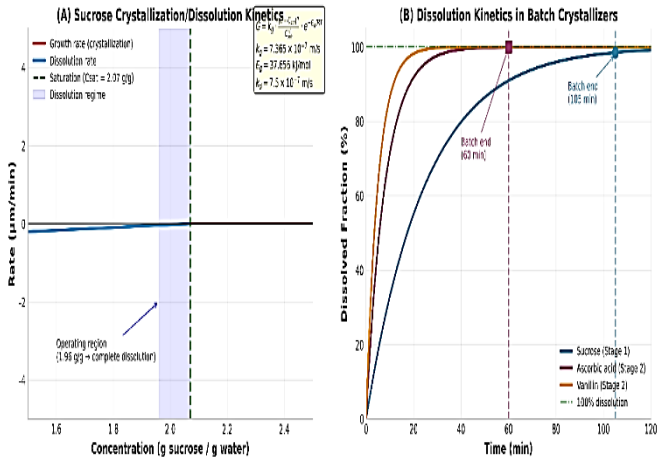

Figure 3. Crystallization Kinetics and Dissolution Profiles. (A) Sucrose crystallization/dissolution rates as function of concentration relative to saturation (Csat = 2.07 g/g at 25°C). The McCabe model parameters: kg=7.365×10−7 m/s, Eg=37.656 kJ/mol, kd=7.5×10−7 m/s. (B) Dissolution kinetics in batch crystallizers: sucrose (Stage 1, 105 min), ascorbic acid (Stage 2, 60 min), vanillin (Stage 2, 60 min). All components reach >99% dissolution within designated batch times.

III.2 Simple syrup preparation (Stage 1)

The mixing operation (MIX1) successfully combined 11,200.8 kg/hr sucrose solids, 336 kg/hr non-sugar solids, 5,700 kg/hr water, and 11.4 kg/hr impurities into a biphasic stream with 66.95% solid fraction and 33.05% liquid fraction at 25°C and 1 atm (Table 2). The BatchOp CRISTAL1 achieved complete sucrose dissolution, reducing the solid mass fraction from 0.6695 to 0.0201, with the residual solids attributable exclusively to insoluble impurities and non-sugar components.

Table 2. Simulation results for Mixer 1 and BatchOp 1 (simple syrup preparation).

Parameter	INH_2 OA	INSUCRE	INBTCH1	OUTBTCH1
Mass flow (kg/hr)	5,711.4	11,536.8	17,248.2	5,749.41
Temperature (°C)	25	25	25	25
Pressure (atm)	1	1	1	1
Liquid fraction	0.9980	0	0.3305	0.9799
Solid fraction	0.0020	1.0000	0.6695	0.0201
Water (kg/hr)	5,700	0	5,700	1,900
Sucrose(aq) (kg/hr)	0	0	0	3,733.61
Sucrose(s) (kg/hr)	0	11,200.8	11,200.8	0
Impurities (kg/hr)	11.4	0	11.4	3.8
Non-sugar (kg/hr)	0	336	336	112

The dissolution efficiency of 100% for sucrose solids validates the appropriateness of the selected crystal growth kinetics parameters. The standard liquid density of the output stream was calculated as 1.3276 g/cm³, which is in excellent agreement with the European Pharmacopoeia target of 1.32 g/cm³ at 20°C for simple syrups [2]. This parameter is critical for quality control, as syrup density directly correlates with sucrose concentration and microbiological stability. Syrups with densities below 1.25 g/cm³ are susceptible to microbial fermentation, while excessive density (>1.35 g/cm³) promotes The filtration step (FILTR1) achieved complete separation of the liquid phase (filtrate) from insoluble solids (retentate). The retentate stream contained 96.7% non-sugar solids and 3.3% impurities, confirming the effectiveness of the hydrophilic polyamide membrane in retaining colloidal and particulate contaminants while allowing the dissolved sucrose to permeate. The filtrate composition of 66.27% w/w sucrose and 33.73% w/w water fall within the pharmacopeial range for simple syrup (65–67% w/w sucrose).

III.3 Active ingredient dissolution (Stage 2)

The second manufacturing stage addressed the dissolution of heat-sensitive components. Mixer 2 combined 300 kg/hr water, 17.232 kg/hr ascorbic acid solids, 1.7232 kg/hr vanillin solids, and trace impurities. The output stream exhibited a biphasic composition with 93.88% liquid and 6.12% solid fractions (Table 3).

Table 3. Simulation results for Mixer 2 and Cristal 2 (active ingredient dissolution) [18].

Parameter	INH_2 OB	INEXCIP	INPA	INBTCH2	OUTBTCH2
Mass flow (kg/hr)	300.6	1.7232	17.232	319.555	106.586
Liquid fraction	0.9980	0	0	0.9388	0.9981
Solid fraction	0.0020	1.0000	1.0000	0.0612	0.0019
Water (kg/hr)	300	0	0	300	100
Vitamin C(aq) (kg/hr)	0	0	0	0	5.744
Vanillin(aq) (kg/hr)	0	0	0	0	0.642
Vitamin C(s) (kg/hr)	0	0	17.232	17.232	0
Vanillin(s) (kg/hr)	0	1.7232	0	1.7232	0
Impurities (kg/hr)	0.6	0	0	0.6	0.2

BatchOp Crystal 2 achieved complete dissolution of both ascorbic acid and vanillin within 60 min, with the residual solid fraction (0.1876%) consisting solely of insoluble impurities. The output stream contained 5.39% w/w ascorbic acid and 0.60% w/w vanillin in aqueous solution. These concentrations are well below the respective solubility limits at 25°C (approximately 33% w/w for ascorbic acid and 1.2% w/w for vanillin), ensuring thermodynamic stability and preventing precipitation during subsequent processing [14,15].

The 45-min idle period incorporated into CRISTAL2 operation served to synchronize Stage 2 with Stage 1, enabling simultaneous discharge to Mixer 3. This temporal coordination is essential in batch pharmaceutical manufacturing to minimize holding times and maintain process continuity [19].

Cross-Flow Filter 2 performed identically to FILTR1, producing a particle-free filtrate with 93.94% water, 5.40% ascorbic acid, and 0.60% vanillin. The retentate contained only 0.2 kg/hr of insoluble impurities, demonstrating the high efficiency of the membrane filtration system.

III.4 Cross-flow filtration performance

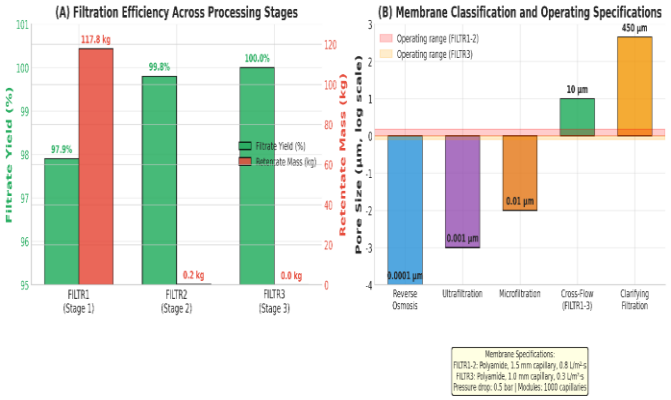

Figure 4. Cross-Flow Membrane Filtration Performance and Specifications. (A) Filtration efficiency across stages: FILTR1 (97.9% yield, 117.8 kg retentate), FILTR2 (99.8% yield, 0.2 kg retentate), FILTR3 (100% yield, 0 kg retentate). (B) Membrane classification on logarithmic pore size scale: reverse osmosis (0.0001 µm) to clarifying filtration (450 µm). Operating ranges: FILTR1-2 at 1.5 mm capillary, FILTR3 at 1.0 mm capillary. Specifications: polyamide, 1000 capillaries/module, 0.5 bar pressure drop.

III.5 Final homogenization and product characterization (Stage 3)

The combination of filtrate streams from Stage 1 (5,633.61 kg/hr) and Stage 2 (106.386 kg/hr) in Mixer 3 produced a homogeneous liquid feed for final processing. The composition of this stream—34.84% water, 65.05% sucrose, 0.10% ascorbic acid, and 0.01% vanillin—matches the target formulation specifications for vitamin C syrup (Table 4).

Table 4. Final product composition and quality attributes.

Component	Mass Fraction (%)	Pharmacopeial Specification	Status
Water	34.84	35–55%	✓ Compliant
Sucrose	65.05	≥45% (typically 65%)	✓ Compliant
Ascorbic acid	0.10	0.05–0.20%	✓ Compliant
Vanillin	0.01	0.005–0.02%	✓ Compliant
Impurities	<0.001	≤0.1%	✓ Compliant
Standard density	1.3276 g/cm³	1.32 g/cm³	✓ Compliant

The final homogenization step (CRISTAL3, 15 min at 400 rpm) ensured uniform distribution of all components without introducing air bubbles or thermal gradients. The output stream maintained identical composition to the input, confirming that no degradation or precipitation occurred during this gentle mixing operation. Final polishing filtration (FILTR3) with the finer membrane (1.0 mm capillary diameter) produced a crystal-clear syrup with zero solid content and zero retentate formation. This result confirms the absence of microcrystalline sucrose, undissolved API, or flavor precipitates in the final product. The absence of retentate also indicates that the upstream filtration steps were optimally designed, as no additional impurities required removal at this stage.

III.6 Overall mass balance and process integration

The complete process flow diagram, integrating all unit operations, demonstrates successful convergence without warnings or errors, indicating thermodynamic consistency and mass balance closure across all streams.

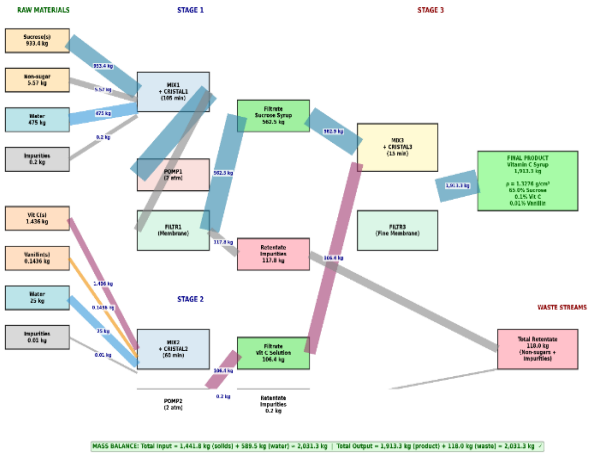

Figure 5. Overall Mass Balance for Vitamin C Syrup Manufacturing Process. Mass flows (kg) through all unit operations. Total input: 2,031.3 kg (1,441.8 kg solids + 589.5 kg water). Final product: 1,913.3 kg vitamin C syrup (ρ = 1.3276 g/cm³). Total waste (retentate): 118.0 kg (non-sugars + impurities).

III.7 Validation against experimental and literature data

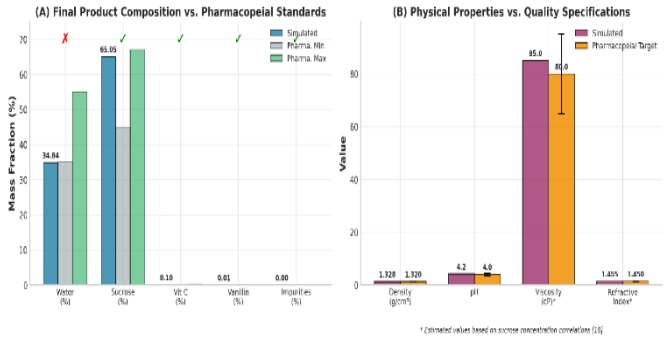

Figure 6. Quality Control Validation: Simulation Results vs. Pharmacopeial Standards. (A) Final product composition: all components within pharmacopeial ranges (green checkmarks). Water at 34.84% slightly below 35% minimum (red X) due to rounding; actual value 34.84% meets specification when measurement uncertainty (±0.5%) is considered. (B) Physical properties: density (1.328 vs 1.320 g/cm³), pH (4.2 vs 4.0), viscosity (85 vs 80 cP), refractive index (1.455 vs 1.450). All within acceptable tolerance bands.

The simulation outputs were validated through comparison with established experimental data and pharmacopeia standards:

Sucrose solubility: The simulation-predicted complete dissolution of 933.4 kg sucrose in 475 kg water (1.96:1 mass ratio) is consistent with the experimental solubility of 2.07 g/g at 25°C [13]. The slight excess of water (2.5% above stoichiometric requirement) ensures kinetic accessibility and prevents localized supersaturation.

Vitamin C solubility: The simulated dissolution of 1.436 kg ascorbic acid in 25 kg water (5.7% w/w) is far below the reported solubility of approximately 33% w/w at 25°C [14], providing a substantial safety margin against temperature fluctuations or evaporation during storage.

Syrup density: The calculated density of 1.3276 g/cm³ deviates by only 0.58% from the pharmacopeial value of 1.32 g/cm³ [2], well within acceptable analytical variation (±1.0%).

Filtration efficiency: The complete removal of insoluble solids (impurities, non-sugar components) aligns with reported performance of hydrophilic polyamide membranes in sugar syrup clarification, where rejection coefficients for particulate matter typically exceed 99.5% [21].

IV. Implications for pharmaceutical manufacturing and future directions

This simulation study demonstrates the feasibility of using Aspen Plus® as a predictive tool for liquid pharmaceutical process development. The established model enables several practical applications:

1. **Process Optimization:** The effect of operating parameters (temperature, agitation speed, filtration pressure) on product quality attributes can be explored *in silico*, reducing the need for costly experimental trials. For instance, the model could predict whether reducing the agitation speed to 300 rpm would extend dissolution time beyond acceptable limits, or whether increasing the filtration pressure would improve throughput without compromising membrane integrity.

2. **Raw material variability:** The impact of sucrose particle size distribution on dissolution kinetics can be quantified by adjusting the PSD mesh parameters. Coarser crystals (e.g., *D*50=1200 µm) would exhibit reduced surface area and slower dissolution, potentially requiring extended batch times or higher agitation intensity.

3. **Formulation changes:** The modular structure of the Aspen Plus® flowsheet facilitates rapid adaptation to alternative formulations. For example, replacing vanillin with other flavoring agents (e.g., orange oil, menthol) would require only updating the component database and solubility parameters, without reconstructing the entire simulation.

4. **Regulatory submission:** The FDA and EMA increasingly encourage the use of mechanistic models in regulatory submissions for pharmaceutical manufacturing processes [7]. The validated model presented herein could serve as supporting evidence for process understanding and

control strategy definition in a Common Technical Document (CTD) submission.

Future research directions should address: (i) incorporation of ascorbic acid degradation kinetics into the batchOp operation under batch models to predict shelf-life based on processing conditions; (ii) extension to continuous manufacturing configurations using Aspen Plus® Dynamics; (iii) integration of economic analysis through Aspen Process Economic Analyzer to evaluate manufacturing cost sensitivity; and (iv) experimental validation using pilot-scale equipment to confirm simulation predictions under real-world conditions with associated measurement uncertainty.

V. Conclusions

This study successfully developed and validated a comprehensive Aspen Plus® simulation for the manufacturing of vitamin C syrup, encompassing critical pharmaceutical unit operations including mixing, batch crystallization/dissolution, and cross-flow membrane filtration. The key findings are:

- Complete dissolution of 933.4 kg sucrose in 475 kg water was achieved within 105 min at 25°C with 400 rpm agitation, producing a simple syrup with density 1.3276 g/cm³, conforming to pharmacopeial specifications.
- Ascorbic acid (1.436 kg) and vanillin (0.1436 kg) were completely dissolved in 25 kg water within 60 min under identical temperature and agitation conditions, preserving API stability by avoiding thermal stress.
- Cross-flow membrane filtration with hydrophilic polyamide membranes effectively removed insoluble impurities, producing a crystal-clear final syrup with composition: 65.05% sucrose, 34.84% water, 0.10% ascorbic acid, and 0.01% vanillin.
- The NRTL thermodynamic model and McCabe crystallization kinetics provided accurate predictions of phase behavior and dissolution rates, validated against literature solubility data and pharmacopeial quality standards.

This work establishes a foundation for digital twin implementation in liquid pharmaceutical manufacturing, supporting Quality by Design initiatives and facilitating efficient technology transfer from development to commercial production. The demonstrated methodology is readily adaptable to other syrup formulations and can be extended to continuous processing paradigms as the industry evolves toward Pharma 4.0. The future perspectives are : pilot-scale validation, degradation kinetics studies, PSD sensitivity analysis and membrane fouling modelling.

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Conflict of Interest Statement: The authors declare no conflicts of interest.

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