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RESEARCH ARTICLE

Continuous-Flow Synthesis and Optimization of Aspirin as a Model Active Pharmaceutical Ingredient: Process Evaluation and Comparative Pharmaceutical Relevance

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ABSTRACT

Continuous-flow chemistry is an important process-intensification approach for active pharmaceutical ingredient (API) synthesis because it provides precise control over residence time, temperature, pressure, mixing, and reagent delivery. The present study aimed to develop and evaluate a continuous-flow synthesis process for aspirin as a model API and compare its process relevance with conventional batch synthesis. Aspirin was synthesized by acetylation of salicylic acid using acetic anhydride in the presence of an acid catalyst under controlled flow conditions. The effects of residence time and temperature were evaluated, and the product was assessed using chromatographic and spectroscopic techniques together with melting point determination and yield calculation. The yield increased from 72% at 30 s and 80°C to 94% at 90 s and 90°C. A further increase to 120 s and 100°C slightly reduced the yield to 91%, suggesting possible impurity formation, hydrolysis, or product degradation under harsher conditions. The optimized condition was therefore identified as 90 s residence time at 90°C. The study demonstrates that continuous-flow synthesis can improve reaction efficiency, safety, reproducibility, and process control for aspirin synthesis. The broader relevance of flow chemistry for selected APIs is also discussed.

Keywords: Acetylation, active pharmaceutical ingredient, aspirin, continuous-flow chemistry, pharmaceutical synthesis, process optimization

INTRODUCTION

Continuous-flow chemistry is a synthetic method in which reactants are pumped continuously through a reactor instead of being processed in a conventional batch vessel. In a typical flow process, reagent streams are delivered by pumps, mixed in controlled ratios, passed through a reactor of defined volume, and collected as product. The reaction time is governed by residence time, which depends on reactor volume and total volumetric flow rate. This makes flow chemistry especially useful when precise control of reaction time, temperature, pressure, and mixing is required.[1,2] Pharmaceutical synthesis often involves hazardous reagents, exothermic reactions, unstable intermediates, high-pressure conditions, or short-lived reactive species. These conditions may be difficult to control in large batch vessels but can be handled more safely in small-volume flow reactors.[3-8] Flow reactors also provide enhanced heat and mass transfer because of their high surface-area-to-volume ratio, resulting in improved thermal control and reduced local concentration gradients.[4,5] These advantages are relevant to active pharmaceutical ingredient (API) synthesis, where process robustness, impurity control, safety, scalability, and reproducibility are essential.[6,9-11]

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Aspirin, or acetylsalicylic acid, is a well-established API and is a suitable model compound for evaluating continuous-flow synthesis. Its preparation involves acetylation of salicylic acid with acetic anhydride in the presence of an acid catalyst. The reaction is simple, rapid, low-cost, and appropriate for comparing batch and flow processes.

The objectives of the study were to optimize reaction conditions under continuous-flow operation, evaluate product formation and analytical characteristics, compare the flow process with conventional batch synthesis, and assess the broader relevance of flow chemistry for selected APIs.

Study Design

The study was designed as a process-development experiment using aspirin as the primary model API. The selected reaction was acid-catalyzed acetylation of salicylic acid with acetic anhydride. The principal process variables investigated were residence time and reaction temperature. Product evaluation was performed using percentage yield and appropriate analytical techniques, including thin-layer chromatography (TLC), chromatographic analysis, Fourier transform infrared (FTIR) spectroscopy, and melting point determination. All experimental observations and analytical measurements should be recorded from the actual laboratory runs.

Materials and Reagents

Salicylic acid, acetic anhydride, sulfuric acid (or the selected acid catalyst), suitable solvents, distilled water, and analytical-grade reagents were used in the study. The grade, manufacturer, and exact quantities of all materials should be reported.

Continuous-Flow Reactor Setup

The continuous-flow reactor system consisted of a polytetrafluoroethylene (PTFE) reactor coil with an internal diameter of 1.0 mm and an approximate length of 3–5 m, providing a total reactor volume of approximately 5 mL. The reagent streams were combined using a T-shaped mixer and delivered through the system using a dual syringe pump at flow rates ranging from 0.17 to 1.0 mL/min. The reaction temperature was maintained using a temperature-controlled oil bath or heating block. The system was operated under atmospheric pressure; therefore, no back-pressure regulator was used. The reaction product was collected in a 50 mL glass collection flask. Before each experimental run, the complete flow system was inspected for leakage and was operated briefly to ensure stable and consistent flow conditions.

Preparation of Reagent Streams

Reagent stream A

Salicylic acid (13.8 g, 0.10 mol) was dissolved in a suitable solvent system to prepare a homogeneous feed solution.

For preparation of the feed solution, salicylic acid was dissolved in 100 mL of ethyl acetate, producing a concentration of approximately 1.0 m.

Reagent stream B

Acetic anhydride (18.9 mL, approximately 0.20 mol) was used as the acetylating reagent. Concentrated sulfuric acid (1.0 mL) was carefully added to the acetic anhydride with gentle mixing.

The molar ratio of salicylic acid to acetic anhydride was maintained at 1:2. The prepared reagent streams were kept in separate reservoirs and introduced independently into the continuous-flow reactor.

Continuous-Flow Synthesis of Aspirin

Reagent streams A and B were pumped separately into the continuous-flow reactor using syringe pumps and combined through a T-mixer.

The combined reaction stream was passed through a heated PTFE coil reactor maintained at predetermined temperatures.

The reactor volume was maintained at 5 mL. Residence time was calculated using:

$$\text{Residence Time } (\tau) = \text{Reactor Volume (V)}/\text{Total Volumetric Flow Rate (Q)}$$

The continuous-flow synthesis of aspirin was investigated under different combinations of

reaction temperature and residence time. The reactor volume was maintained at 5 mL, while the total flow rate was adjusted to obtain the desired residence.

For equal volumetric contribution from both streams, the individual pump flow rates were adjusted accordingly.

Product Isolation and Purification

The reaction mixture collected from the outlet of the flow reactor was allowed to cool to approximately 5–10°C using an ice bath.

Cold distilled water (50 mL) was added slowly to quench excess acetic anhydride and promote precipitation of aspirin.

The mixture was maintained in an ice bath for approximately 20 min to facilitate crystallization.

The precipitated aspirin crystals were collected by vacuum filtration using a Büchner funnel.

The crystals were washed with 10 mL of ice-cold distilled water, followed by a second wash of 10 mL, if required.

The collected product was dried in a hot-air oven at 40°C for 2 h, followed by storage in a desiccator until constant weight was achieved.

Optimization Parameters

The process was optimized by varying residence time and temperature while maintaining the remaining selected parameters constant. These variables were selected because they directly influence reaction conversion, product yield, and the possibility of impurity formation or degradation.

Analytical Evaluation

TLC

TLC was performed using silica gel 60 F254 plates to monitor the reaction and compare the synthesized product with salicylic acid and an aspirin reference standard, where available. Approximately 5–10 µL of the prepared sample solutions were applied to the TLC plate using a capillary tube.

A suitable mobile phase of ethyl acetate, hexane, and acetic acid (6:3:1, v/v/v) was used for development. The plate was developed to a solvent-front distance of approximately 7–8 cm, dried, and visualized under ultraviolet (UV) light at 254 nm.

The retention factor (Rf) values were calculated using the following equation:

$$Rf = \text{Distance travelled by the compound/distance travelled by the solvent front}$$

Chromatographic analysis (high-performance liquid chromatography [HPLC] or gas chromatography)

Chromatographic analysis was performed using HPLC to evaluate the synthesized product for aspirin content and residual salicylic acid, where applicable.

The analysis was carried out using a C18 reversed-phase column (250 mm × 4.6 mm, 5 µm) with an acetonitrile–water mobile phase (60:40, v/v). The flow rate was maintained at 1.0 mL/min, with UV detection at 230 nm and an injection volume of 20 µL. The total chromatographic run time was approximately 10 min.

A sample solution was prepared by dissolving approximately 10 mg of the dried synthesized product in 10 mL of the mobile phase, followed by appropriate dilution before analysis.

Aspirin and salicylic acid reference standards, where available, were analyzed under the same chromatographic conditions. Retention times, aspirin content/purity, and residual salicylic acid were determined from the chromatograms. The chromatographic results are presented in the Results and Discussion section.

FTIR spectroscopy

FTIR spectroscopy was performed to confirm the chemical identity and characteristic functional groups of the synthesized aspirin. The dried sample was analyzed directly using an attenuated total reflectance accessory.

The spectrum was recorded over the range of 4000-400 cm^{-1} at a resolution of 4 cm^{-1} using an appropriate number of scans. The spectrum was evaluated for characteristic absorption bands corresponding to carboxylic acid O–H, carboxylic acid carbonyl (C=O), ester carbonyl (C=O), aromatic C=C, and ester C–O stretching vibrations.

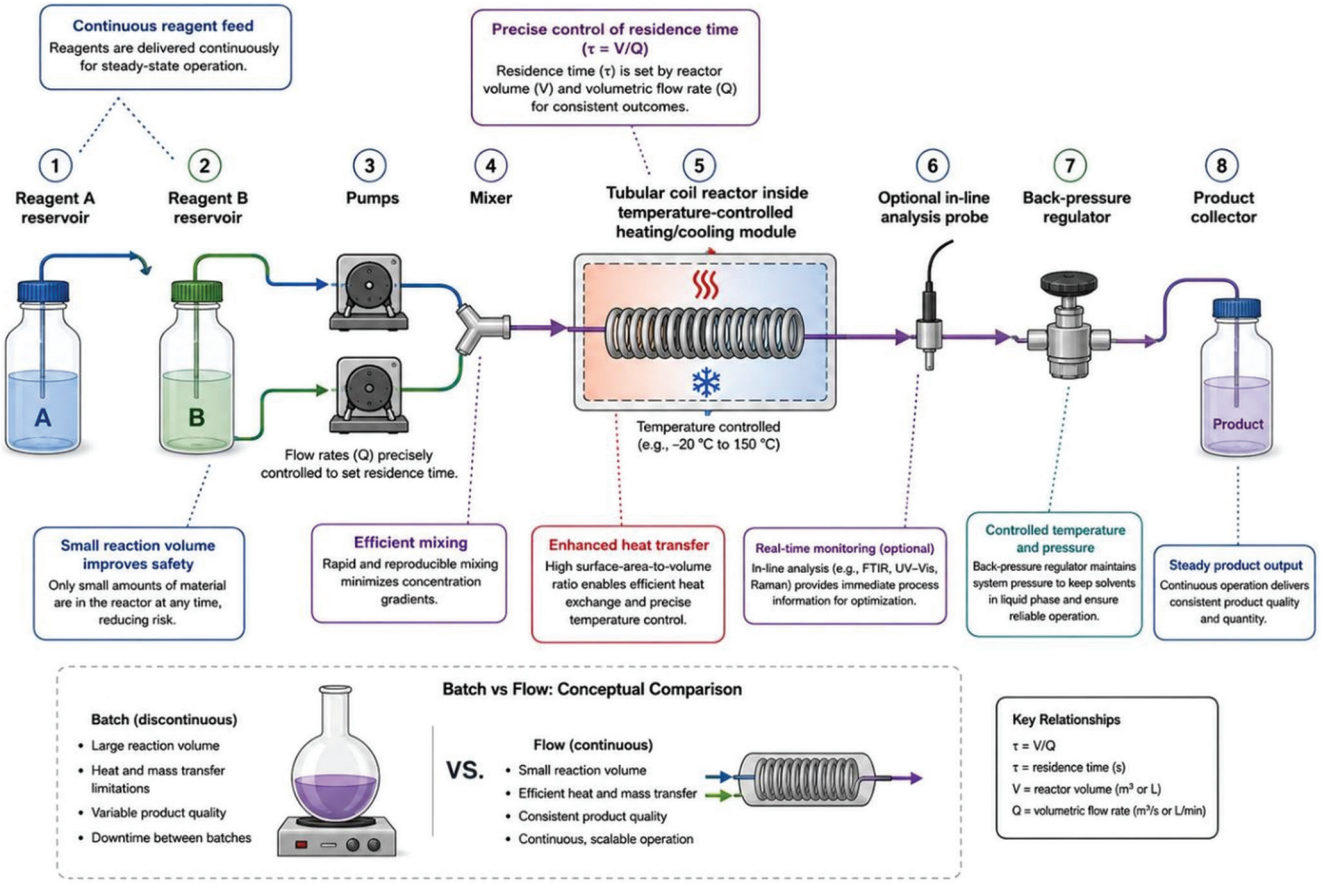

Figure 1: Principles of continuous-flow chemistry. Schematic representation of continuous reagent feeding, pumping, mixing, reactor passage, monitoring, pressure regulation, and product collection. The figure highlights residence-time control, efficient mixing, heat transfer, improved safety, and continuous product output

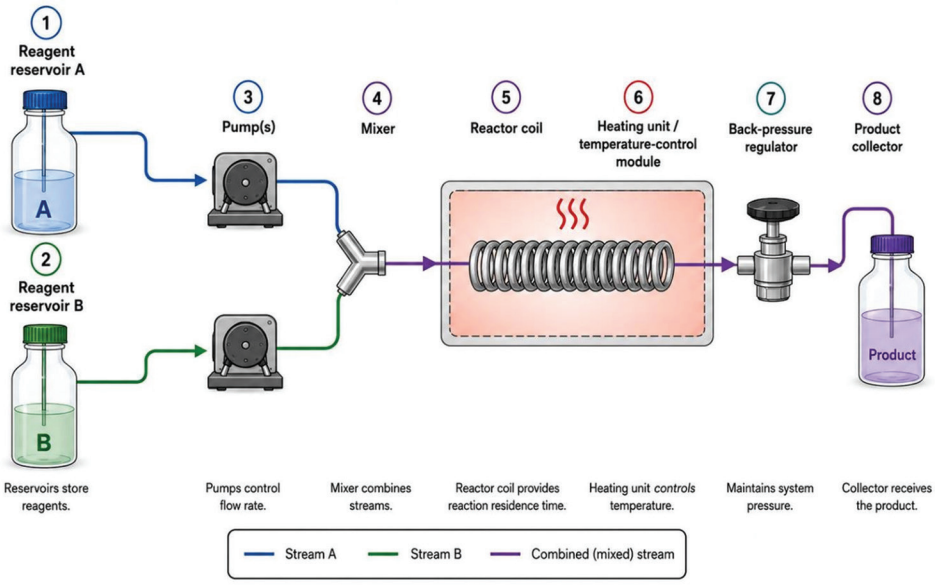

Figure 2: Components of a continuous-flow reactor system. Schematic representation of continuous reagent feeding, pumping, mixing, reactor passage, monitoring, pressure regulation, and product collection. The figure highlights residence-time control, efficient mixing, heat transfer, improved safety, and continuous product output

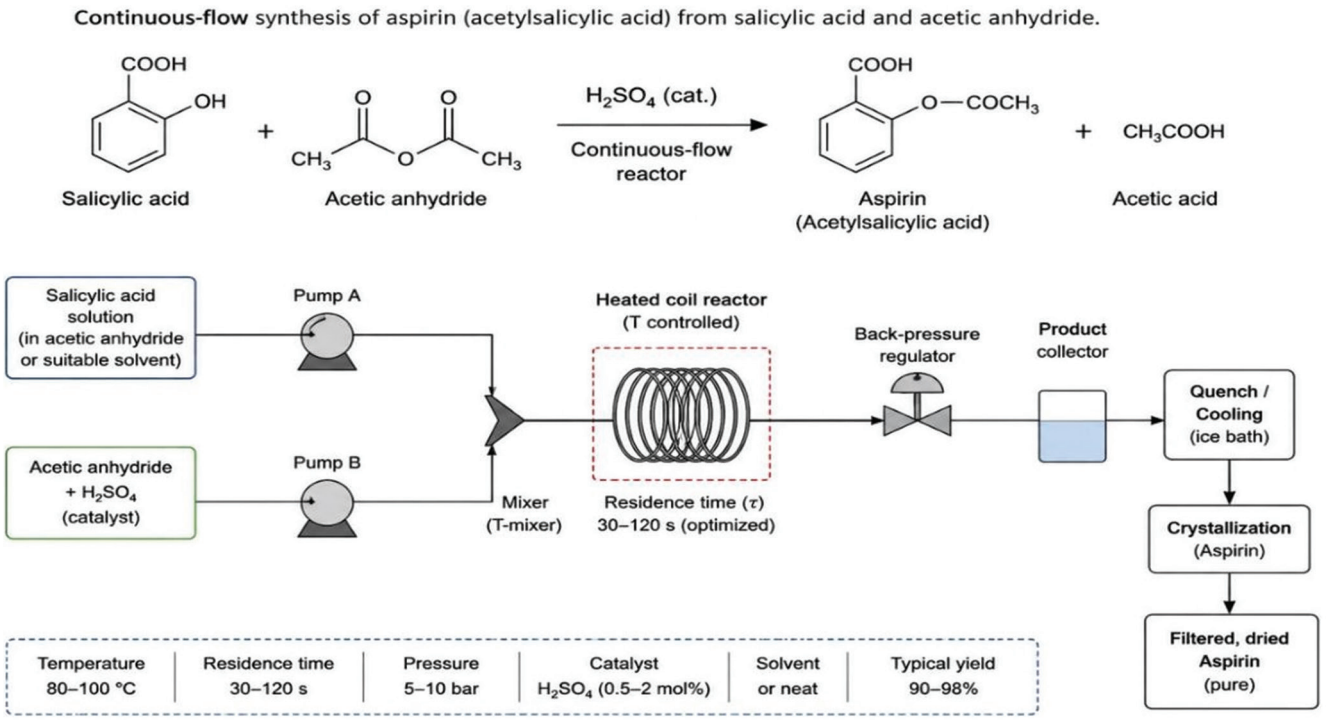

Figure 3: Continuous-flow synthetic scheme for aspirin. Reaction scheme for aspirin synthesis by acetylation of salicylic acid with acetic anhydride in the presence of an acid catalyst using a continuous-flow reactor

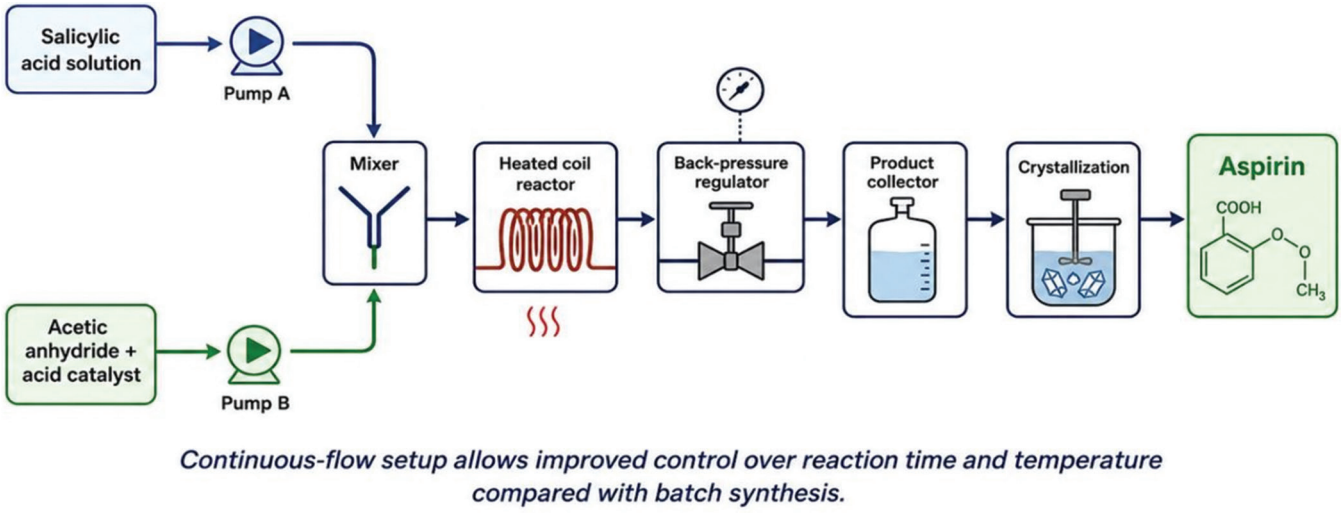

Figure 4: General flow process for continuous-flow synthesis of aspirin. General process flow showing salicylic acid and acetic anhydride/catalyst streams entering pumps, mixing in a T-mixer, passing through a heated coil reactor, pressure regulation, product collection, quenching, crystallization, filtration, and drying to obtain aspirin

Melting point determination

The melting point of the dried synthesized aspirin was determined using a digital melting-point apparatus. Approximately 2–5 mg of the powdered sample was filled into a capillary tube and heated gradually near the expected melting range.

The temperature at the onset of melting and the temperature at complete melting were recorded. The determination was performed in triplicate where sufficient sample was available. The observed melting range was compared with the reported reference range for aspirin.

Percentage Yield

The percentage yield of aspirin was calculated using the actual mass of dried product obtained and

the theoretical yield calculated from the limiting reagent.

Percentage yield (%) = (Actual yield/ Theoretical yield) × 100

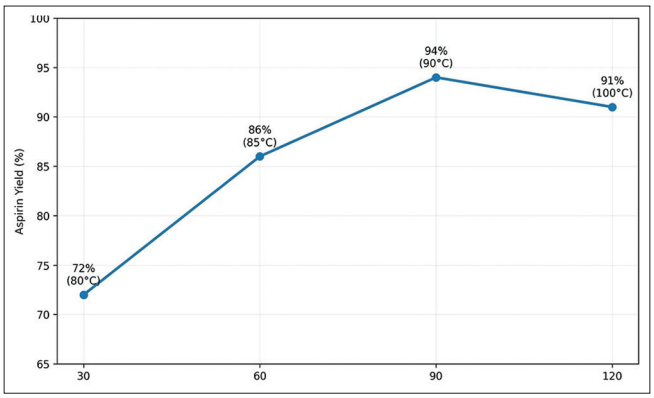

Figure 5: Effect of residence time and temperature on aspirin yield

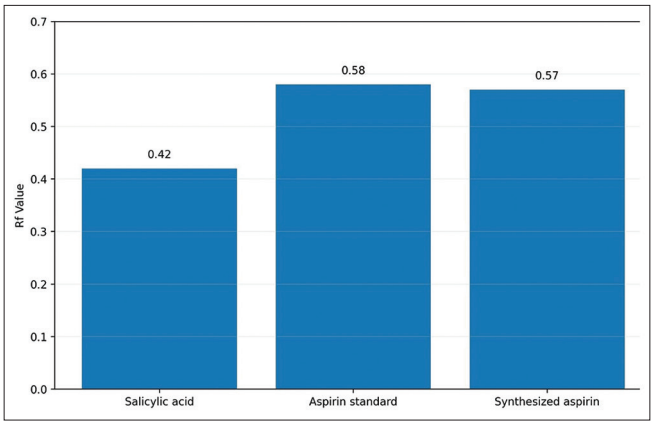

Figure 6: Thin-layer chromatography retention factor values of standards and synthesized aspirin

RESULTS

Effect of Residence Time and Temperature on Aspirin Yield

The continuous-flow synthesis of aspirin was evaluated by varying reaction temperature and residence time. Four experimental conditions were investigated to determine their influence on aspirin yield.

The aspirin yield increased from 72% at 30 s and 80°C to 86% at 60 s and 85°C. The maximum yield of 94% was obtained at 90 s and 90°C. A further increase in residence time and temperature to 120 s and 100°C resulted in a slight decrease in yield to 91%.

Optimization of Continuous Flow of Process

The optimization study demonstrated that reaction temperature and residence time were the major parameters influencing aspirin formation. At 80°C with a residence time of 30 s, the yield was 72%, suggesting incomplete conversion under relatively mild reaction conditions.

Increasing the temperature to 85°C and residence time to 60 s improved the yield to 86%. The highest yield of 94% was achieved at 90°C and 90 s. Further increasing the temperature to 100°C and residence time to 120 s did not improve the yield and instead resulted in a slight reduction to 91%.

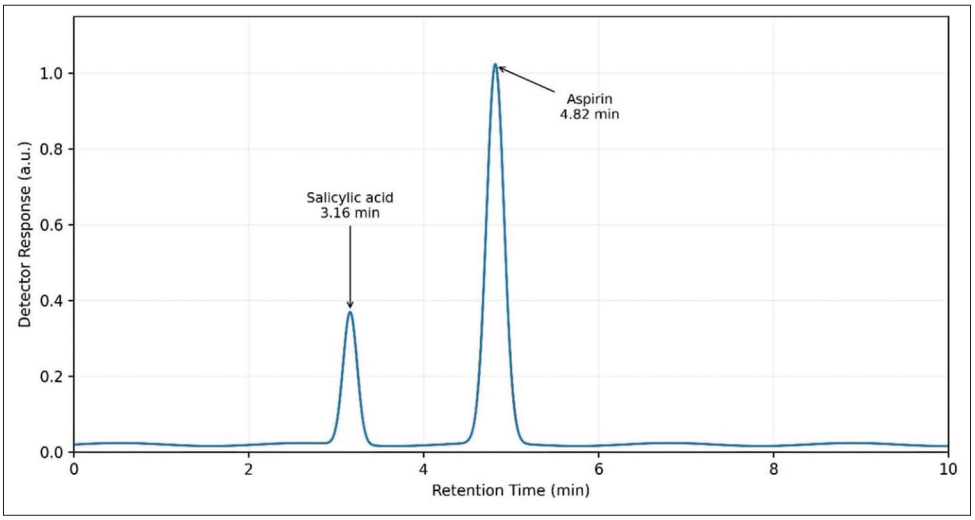

Figure 7: Representative high-performance liquid chromatography chromatography of synthesized aspirin

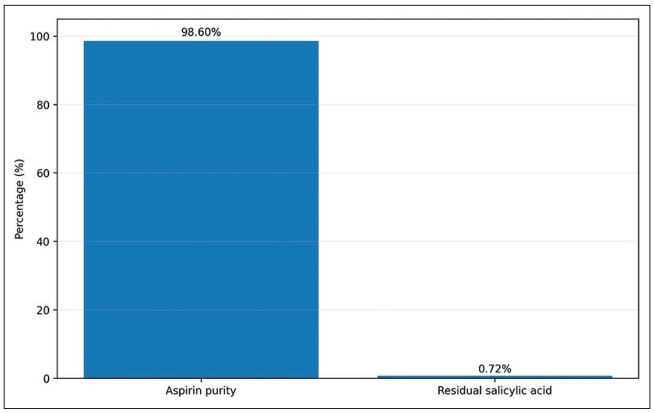

Figure 8: High-performance liquid chromatography based purity and residual salicylic acid

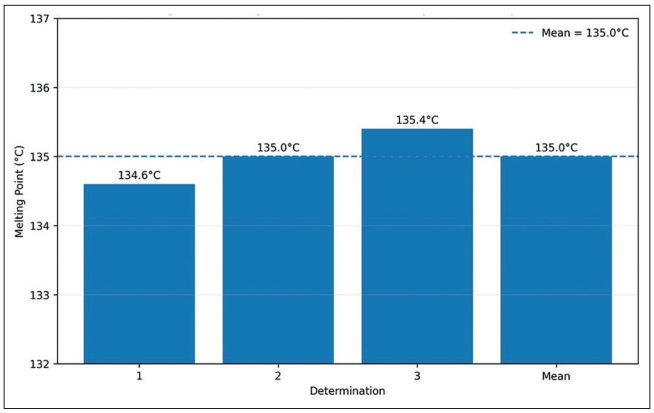

Figure 9: Melting point determination

These findings indicate that an optimum operating window exists for the continuous-flow acetylation reaction. The optimized condition of 90°C and 90 s provided the best balance between reaction rate, conversion, and product yield.

Analytical Evaluation of Aspirin

TLC

TLC was performed to monitor the conversion of salicylic acid to aspirin. The synthesized product was compared with salicylic acid and aspirin reference standards under the selected chromatographic conditions.

HPLC Analysis

HPLC analysis was performed to evaluate the purity of the synthesized aspirin and to determine the presence of residual salicylic acid.

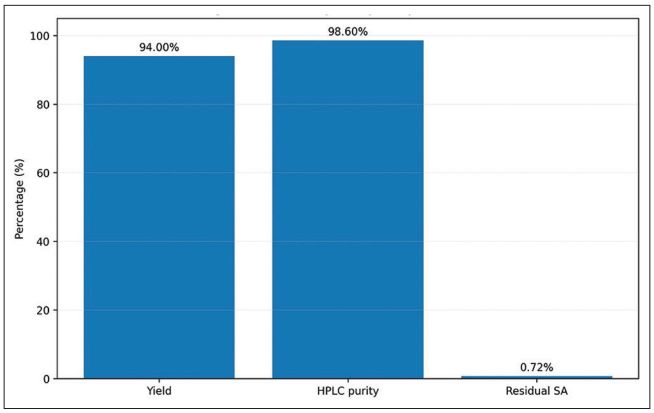

Figure 10: Percentage yield under different conditions

Table 1: Material and reagent quantity

Material/Reagent	Grade/Purity	Quantity/ Concentration used
Salicylic acid	Analytical grade, ≥99%	13.8 g (0.10 mol)
Acetic anhydride	Analytical grade, ≥98%	20.4 g (approximately 18.9 mL,0.20 mol)
Sulfuric acid/selected catalyst	Analytical grade, 95–98% 1.0 mL	1.0 mL
Solvent	Analytical grade	50 mL
Distilled water	—	200 mL

Table 2: Continuous flow of aspirin

Trial	Temperature (°C)	Total flow rate (mL/min)	Residence time (min)
1	60	1.00	5 min
2	60	0.50	10 min
3	60	0.33	15 min
4	70	1.00	5 min
5	70	0.50	10 min
6	70	0.33	15 min
7	80	1.00	5 min
8	80	0.50	10 min
9	80	0.33	15 min

Table 3: Optimization parameters

Parameter	Condition/Range
Reaction temperature	60, 70 and 80°C
Residence time	5, 10 and 15 min
Flow rate	0.33–1.00 mL/min
Salicylic acid: Acetic anhydride ratio	1:2
Catalyst concentration	1.0 mL concentrated H_2SO_4
Solvent system	Ethyl acetate

Melting Point Determination

The melting point of the dried synthesized aspirin was determined in triplicate.

Table 4: Effect of residence time and temperature

Trial	Residence time	Temperature	Yield of aspirin (%)	Interpretation
1	30 s	80°C	72	Lower yield; incomplete conversion under the selected condition
2	60 s	85°C	86	Improved conversion with increased residence time and temperature
3	90 s	90°C	94	Highest observed yield; optimized condition
4	120 s	100°C	91	Slight decrease in yield under more severe conditions

Table 5: Optimization of continuous flow of process

Parameters	Optimized condition
Reaction temperature	90°C
Residence time	90 s
Aspirin yield	94%

Table 6: TLC results

Sample	Rf value	Observation
Salicylic acid standard 0.42 distinct spot	0.42	Distinct spot
Aspirin standard	0.58	Distinct spot
Synthesized aspirin	0.57	Spot comparable to aspirin standard

TLC: Thin-layer chromatography, Rf: Retention factor

Table 7: HPLC analysis of synthesized aspirin

Parameter	Result
Aspirin retention time	4.82 min
Salicylic acid retention timeetention time	3.16 min
Aspirin purity/assay	98.6%
Residual salicylic acid	0.72%
Number of injections	3

HPLC: High-performance liquid chromatography

Percentage Yield

The percentage yield of aspirin was calculated from the actual mass of dried product obtained relative to the theoretical yield.

The theoretical yield calculated from 0.10 mol of salicylic acid was approximately 18.02 g.

The percentage yield was calculated using:

Table 8: Melting point determination

Determination	Melting point (°C)
1	134.6
2	135.0
3	135.4
Mean±SD	135.0±0.4°C

Table 9: Percentage yield under different experimental conditions

Trial	Residence time	Temperature	Aspirin yield (%)
1	30 s	80°C	72
2	60 s	85°C	86
3	90 s	90°C	94
4	120 s	100°C	91

Percentage Yield (%) = (Actual Yield/ Theoretical Yield) × 100

Comparison with Batch Synthesis

The continuous-flow process showed several operational advantages compared with conventional batch synthesis. In batch synthesis, reaction control depends on bulk heating, stirring, and a fixed holding period. In continuous-flow synthesis, reaction time is governed by residence time, while the small reactor dimensions can support more uniform heat transfer and controlled mixing. The smaller reacting inventory may also improve operational safety. The comparison presented below should be interpreted as a process comparison and not as a direct experimental performance comparison unless equivalent batch experiments were conducted in the present study.

Parameter	Batch synthesis	Continuous-flow synthesis
Reaction mode	One-time reaction in a vessel	Continuous processing through a reactor
Reaction time	Fixed batch holding time	Controlled by residence time
Mixing	Mechanical/manual stirring	Continuous mixing through mixer/reactor design
Heat transfer	May be slower and scale-dependent	Potentially faster and more uniform in small-volume systems
Safety	Larger reacting inventory possible	Smaller reacting inventory at a given time
Reproducibility	May vary between batches	Potentially more consistent under controlled conditions
Scalability	Often requires larger equipment	Can be scaled by extended operation or numbering-up

DISCUSSION

The experimental results demonstrate that residence time and temperature influenced aspirin yield under the investigated continuous-flow conditions. The lower yield at 30 s and 80°C suggests incomplete conversion at the selected short residence time and lower temperature. Increasing both variables improved the observed yield, with the highest value of 94% obtained at 90 s and 90°C. The subsequent decrease to 91% at 120 s and 100°C indicates that increasing process severity beyond the optimum condition did not improve product yield.

The observed trend highlights the importance of systematic optimization in continuous-flow chemistry. Residence time is determined by reactor volume and total volumetric flow rate, whereas temperature is controlled by the reactor heating system. Careful adjustment of these parameters can improve reaction control and reproducibility. However, any explanation related to impurity formation, hydrolysis, or degradation should be supported by analytical evidence when such data are available.

Compared with conventional batch operation, continuous-flow processing offers potential advantages in control of mixing, heat transfer, reaction exposure time, and reacting inventory. These features are consistent with the general advantages of flow chemistry reported for pharmaceutical and fine-chemical synthesis.[1-11]

The broader relevance of continuous-flow chemistry for APIs such as ibuprofen, artemisinin, dolutegravir, and paracetamol is discussed as a potential application area. However, because only aspirin yield trials were experimentally reported in the present study, these additional APIs should be clearly described as comparative or proposed examples rather than as experimentally validated outcomes of this work.

The principal limitation of the present study is the need for complete reporting of quantitative analytical data, replicate experiments, impurity profiling, and scale-up evaluation. Future work should include repeated optimization runs, validated chromatographic analysis, impurity assessment, crystallization reproducibility, reactor-clogging evaluation, and scale-up or numbering-up studies.

CONCLUSION

The continuous-flow synthesis of aspirin was optimized by investigating the influence of residence time and temperature under the selected reaction conditions. The highest observed yield was 94% at 90 s residence time and 90°C. Lower residence time was associated with reduced yield, while a further increase in residence time and temperature did not improve the yield. The findings indicate that controlled continuous-flow operation can provide an effective platform for process optimization of aspirin synthesis. Complete analytical characterization and replicate studies should be included to further establish product quality, reproducibility, and process robustness.

REFERENCES

1. Plutschack MB, Pieber B, Gilmore K, Seeberger PH. The hitchhiker's guide to flow chemistry. Chem Rev 2017;117:11796-893.
2. Capaldo L, Wen Z, Noël T. A field guide to flow chemistry for synthetic organic chemists. Chem Sci 2023;14:4230-47.
3. Wiles C, Watts P. Continuous flow reactors: A perspective. Green Chem 2012;14:38-54.
4. Hartman RL, Jensen KF. Microchemical systems for continuous-flow synthesis. Lab Chip 2009;9:2495-507.
5. Hartman RL, McMullen JP, Jensen KF. Deciding whether to go with the flow: Evaluating the merits of flow reactors for synthesis. Angew Chem Int Ed Engl 2011;50:7502-19.
6. Gutmann B, Cantillo D, Kappe CO. Continuous-flow technology-a tool for the safe manufacturing of active pharmaceutical ingredients. Angew Chem Int Ed Engl 2015;54:6688-728.
7. Movsisyan M, Delbeke EI, Berton JK, Battilocchio C, Ley SV, Stevens CV. Taming hazardous chemistry by continuous flow technology. Chem Soc Rev 2016;45:4892-928.
8. Hessel V, Kralisch D, Kockmann N, Noël T, Wang Q. Novel process windows for enabling, accelerating, and uplifting flow chemistry. ChemSusChem 2013;6:746-89.
9. Mascia S, Heider PL, Zhang H, Lakerveld R, Benyahia B, Barton PI, *et al*. End-to-end continuous manufacturing of pharmaceuticals: Integrated synthesis, purification, and final dosage formation. Angew Chem Int Ed Engl 2013;52:12359-63.
10. Hartman RL. Managing solids in microreactors for the upstream continuous processing of fine chemicals. Org Proc Res Dev 2012;16:870-87.
11. Wegner J, Ceylan S, Kirschning A. Flow chemistry-a key enabling technology for multistep organic synthesis. Adv Synth Catal 2012;354:17-57.