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FULL PAPER

Continuous flow process for preparing budesonide

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Abstract

Budesonide, a glucocorticosteroid, is used as anti-asthmatic drug that became generic in 2019. Existing preparation methods of budesonide require utilization of corrosive acids and involve expensive purification process. Thus, a new cost-effective continuous flow process for the synthesis of budesonide which belongs to the class of 16,17 acetals of pregnane core, is discussed in the present research findings. Flow reactor parameters such as flow rate, temperature, residence time, solution volumes, anti-solvents and reactor frequency are subjected to investigation on the preparation of molar ratio of budesonide epimers. Further, the suitable parameters entail for obtaining the desired molar ratio of epimers. In another aspect, particle size optimization studies are also performed to get the desired budesonide solid product. A continuous flow process for preparation of budesonide is identified from the present research investigation which can be readily transferred to industrial scale up.

Keywords Budesonide · Glucocorticosteroid · Epimers · Isomeric ratio · Flow reactor

Introduction

FDA approved drug Budesonide is classified as a glucocorticosteroid and is currently being prescribed for treatment of severe asthma, allergic conditions caused by rhinitis and noncancerous nasal polyps [1]. Budesonide exerts its action in the lungs towards smooth breathing by reducing the respiratory swelling and irritations and thus it is available as inhaler in dosage form. Budesonide is also employed for treating inflammatory bowel disease, gastric irritations caused by ulcerative colitis etc. [2, 3]. According to the market research report 2021 to 2026, the global market value of budesonide is estimated around USD 204.33 million in 2020 and is expected to increase another 10% market in 2021. Usage of budesonide has inclined in the COVID-19 pandemics as it also acts on respiratory system. Budesonide's patent expired in the year 2019 [4], and thus generic pharma firms initiated the development of inhaler formulation. Chemically, budesonide is designated as (*RS*) 16a,17a-(Butylidenedioxy)-lip,21-dihydroxypregna-l,4-diene-3,20-dione, which belongs to the class of glucocorticoids and is known as Bofors (Swedish pharmaceutical company) [5]. Budesonide consists of an acetal at C-22 position (also positioned in dioxolane ring) and thus it exists as a mixture of *S* configured epimer-A and *R* configured epimer-B.

Previous methods for preparation of budesonide involved the reaction of 16α-hydroxy prednisolone (16-HPS) (**1**) with *n*-butyraldehyde in 1,4-dioxane (Solvent) and perchloric acid as catalyst which resulted in a mixture of two epimers (Scheme 1). Column chromatography and molecular-size exclusion chromatography are employed as purification procedures to obtain desired isomeric ratio of the budesonide

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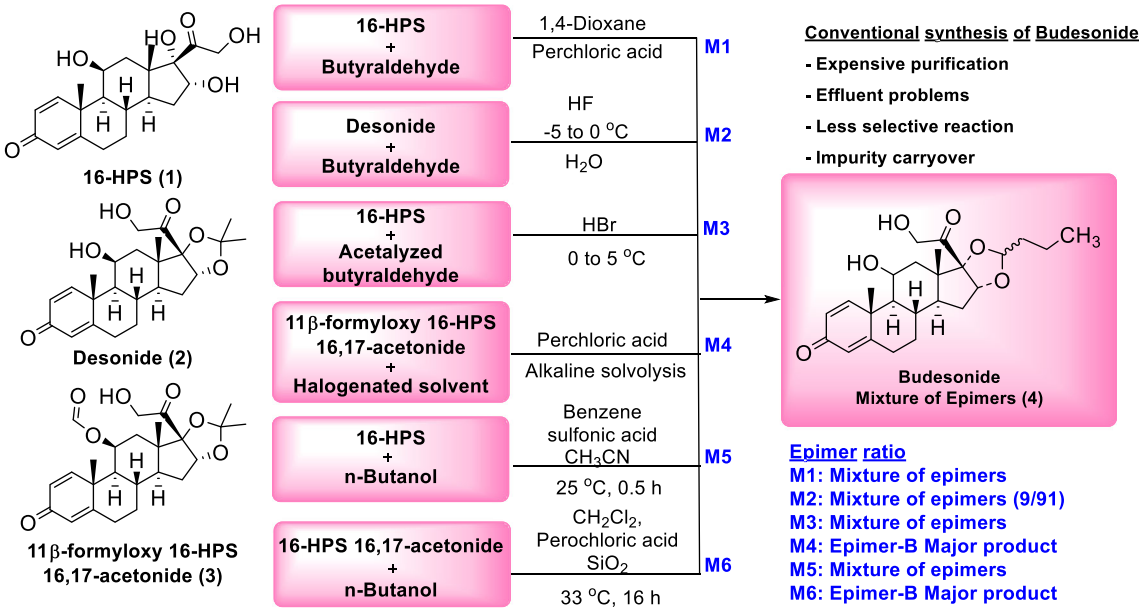


Scheme 1 Previous synthetic route of budesonide

mixture [6]. Simultaneously, controlled formation/ketalization of epimers of budesonide in 1,4-dioxane and perchloric acid is not possible and thus equal quantities of both epimers are obtained as a crude product. In another method, using 16, 17-diols of 16-HPS (**2**) in the presence of hydrofluric acid (HF) epimer-B is obtained in significant quantities (Scheme 1) [7, 8]. The acetalyzed butyraldehyde is reacted with 48% HBr and epimer ratio is monitored by determining through mass and HPLC analysis (Scheme 1) [9]. In another case, the 16-HPS is reacted with butyraldehyde in presence of 1,4-dioxane co-solvated with water (or ethyl acetate with water) to provide crude budesonide which upon purification yielded the improved ratio of desired epimer (Scheme 1) [10]. The 11β-formyloxy 16-HPS 16,17-acetonide (**3**) is also indicated as starting material for obtaining budesonide using halogenated solvents, perchloric acid and alkaline solvolysis of formyl group (Scheme 1) to increase the content of preferential epimer [11–13].

Synthesis of budesonide is also carried out by the reaction of 16-HPS (**1**) with butanol in catalytic amounts of *p*-toluenesulfonic acid, benzenesulfonic acid at different temperature conditions (25 and 0 °C) for about 30 min to afford the crude crystallized product which consists of equal ratios of both epimers (Scheme 1) [14–16]. 16-HPS (**1**) is reacted with *n*-butanol in presence of acetonitrile and benzenesulfonic acid to afford crude budesonide (**4**) and is subjected to purification process (Scheme 1) [14–16]. The reaction conditions of 16-HPS with *n*-butanol in dichloromethane (halogenated hydrocarbon solvent) and granular SiO_2 in presence of higher amounts of acid catalysts are employed to obtain a maximum yield of desired *R* configured epimer-B in the product [17]. However, this process consists of excessive utilization of acid catalyst such as perchloric acid and makes it a more complicated reaction for workup and isolation of product (Scheme 1). These existing methods are associated with formation of isomeric ratios, which require expensive methods of purification and also comprises of traces of toxic 1,4-dioxane and perchloric acid as impurities in the dosage forms. Usage of excess HBr is harmful to environment as it is corrosive. Flow chemistry is of the new technical innovative methods introduced in organic chemistry which is prevailing as an alternative technique for continuous large-scale production of active pharmaceutical ingredients [18]. The biphasic (gas-liquid), high-temperature, photochemical, C-H functionalization and microwave alternative chemical reactions are optimized by flow reactors for scalability approaches [19, 20]. Flow-chemical reactions are not only depending on the reagents and reactions conditions, but also on dimension of the number, size, length, combination of flow reactors and scalability [21–23]. Budesonide from conventional preparation methods has disadvantages which include expensive purification process, effluent generation, less selectivity during product formation and impurities that are carried over. A precise method for preparation of budesonide in kilogram scale by eliminating toxicity parameters could reduce the production cost and utilization of expensive chemicals. Thus, continuous flow chemistry technique is adopted for the preparation of budesonide by controlling epimer ratio formation developed in the current work which will be transferred to kilogram production facility. Further, the particle size of budesonide product is also determined in the tested flow chemistry reaction conditions and optimized with desired size accordingly.

Results and discussion

A continuous flow chemistry-based synthesis of budesonide is optimized in the current research work. The starting materials include 11β, 16α, 17α, 21-tetrahydroxypregna-l, 4-diene-3, 20-dione (16α-Hydroxy Prednisolone or 16-HPS in 7 volumes of 47% HBr) and butyraldehyde which are passed through the flow reactors in the test reaction conditions to afford crude budesonide (**4**) (Fig. 1). The test reaction conditions are further modified by adjusting the key parameters such as temperature, residence time, mole ratio and reactor frequency. A series of parameters checked in continuous flow reaction process are depicted in Table 1. The epimer formation in crude/purified products with respect to the parameter is also observed carefully. In addition, the continuous flow chemistry reaction conditions are subjected to linking with crystallization of budesonide to afford dry powder.

The present continuous flow chemistry method helps in safe handling of reagents like HBr using pumps and tube without exposure hence avoiding any fumes in the environment, lower the reaction time, increase the process efficiency and retain consistent epimer ratio. Other benefits include, minimization of solvent load, shrinking effluents and waste generation in large scale productions. The present preparation method is also linked with prediction/estimation of desired particle size of budesonide (**4**) without micronization (Fig. 2). The obtained crude budesonide from example 1 is dissolved in 26 volumes of methanol, subjected to pump in the spinning disk reactor at 27 °C to afford solid product which upon washing procedures provided desired particles of budesonide (Fig. 2) [23]. From the formulation point of view, estimation of budesonide particle size expands its usage in multiple dosage forms especially aerosol or nebulizer [24–26]. Also, particle size distribution in the dosage forms (suspension or aerosol) is typically associated with absorption rate and bioavailability. Flow reaction parameters maintain the desired purity requirement of final product by lowering the formation of epimer A, which is highly desirable in diastereoisomeric mixture of budesonide. The present optimized continuous flow process technology can be extended for the preparation of corticosteroids such as Ciclesonide (**5**), Triamcinolone (**6**), Flunisolide (**7**) and Desonide (**2**) etc. For the present continuous synthesis, different type of flow reactors (Coflore Agitated Cell Reactor, Vapourtec and Synthetron™) [27–29] are used to study the repeatability or reproducibility. The present flow-chemistry approach has multiple advantages like improved heat transfer, mass transfer/mixing, reproducibility, ease of scalability and safety.

The synthesis of budesonide is carried out by micro and/ or meso-structured continuous flow reactors (μFRs) towards continuous production within a strictly controlled environment. μFRs are employed in this process due to the ease of dispensing starting materials, guarded reaction settings, prompt mixing, uniform heat application, proven safety, and homogenous product formation. Another reason about selection of μFRs is to enhance chemical reactivity by process intensification approach and ease of technology transfer of budesonide. Further, automated flow reactors in the preparation of budesonide allows the assembling of essential components such as temperature controlling units, residence tubing coils, micro fluidic mixers, solvent/product separators and analytical instrumental equipments.

Optimization of flow chemistry methodology for preparation of budesonide

A pre-chilled solution of 0.4 M solution of 16α-Hydroxy prednisolone (16-HPS) (**1**) in aqueous HBr and 11.09 M butyraldehyde are separately passed into micro channel reactor using a suitable piston pump at a 11.0 mL/1.0 mL flow rate in the tubular reactor (diameter ranged between 1 to 10 mm) which is equipped with stirring facility. From the tested reaction conditions with various hydrohalic acids, hydrobromic acid (HBr) is identified as the preferential reagent that has impact on the budesonide

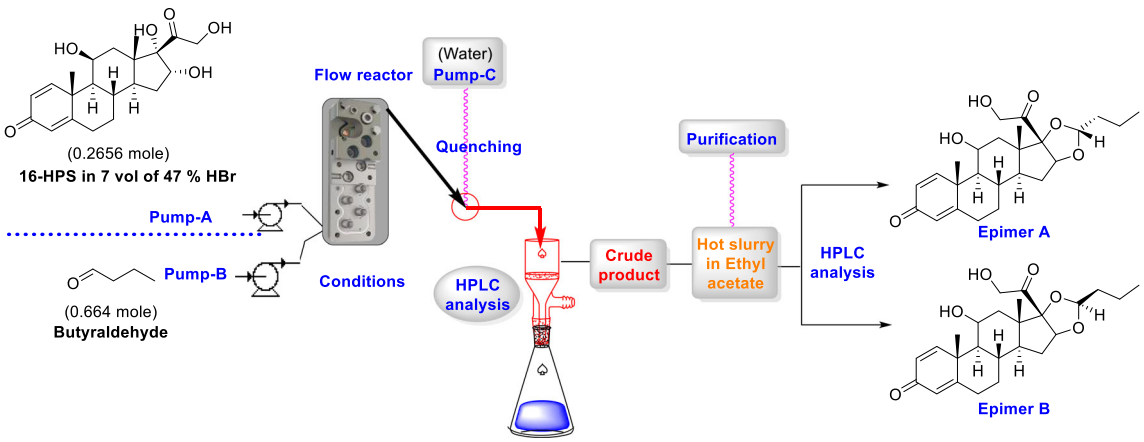


Fig. 1 The schematic view and continuous flow synthesis of budesonide

Table 1 Continuous flow chemistry tested parameters in preparation of budesonide

SNo	Temp (°C)	Residence time (min)	Mole ratio	Reactor frequency (Hz)	Flow rate (mL/min)			Extraction time (min)	Separation time (min)	Crude Epimer ratio		Purified Epimer ratio	
					16-HPS	Butyraldehyde	Water			A	B	A	B
1	10	5	1:2.5	7	11	1.0	15	10	5	51.9	39.6	47.4	52.0
2	5	5	1:2.5	7	11	1.0	17	10	5	53.0	40.2	48.4	51.0
3	0	5	1:2.5	7	11	1.0	19	10	5	54.0	40.6	48.9	51.4
4	0	7	1:2.5	7	7.86	0.71	20	15	7	52.1	41.9	47.9	50.8
5	5	7	1:2.5	7	7.86	0.71	22	15	7	51.8	42.7	48.5	51.5

0.4 M stock solution of 16-HPS: 60 g of 16-HPS is dissolved in 47% HBr to make 400 mL final stock solution; 11.09 M Burtyraldehyde: Butyraldehyde is used as neat reagent; and 55.56 M water: Water is used as neat solution. Reactor volume in this study is 60 mL with 25 mm diameter and 20 mm depth of cell (Coflore reactor with process channels (4 × 4 mm), 11 interconnected process channels and surface area unit volume of the overall reactor block (10 cells plus 11 channels) is 297.45 m^2/m^3). Around 100 inputs of reagents will give 95 g crude product which on purification affords 85 g with overall 75% efficiency

epimer formation. The reaction residence time is also adjusted to 5 min at 10 °C to achieve the steady state. Water is streamed through micro channel reactor which is equipped with peristatic piston pump (15 mL/min) to afford crude budesonide which is subjected to filtration process. Further, slurried crude budesonide in a suitable solvent can be prepared in a flow reactor or batch rector in solvents such as esters (ethyl or methyl or isopropyl acetate) and ethers (diisopropyl or ethyl methyl ether). Major benefits of present flow process methodology are reduction in reaction time from 3 h to 5 min, consistent epimer ratio, desired particle size of the budesonide without micronization and safe handling of caustic HBr.

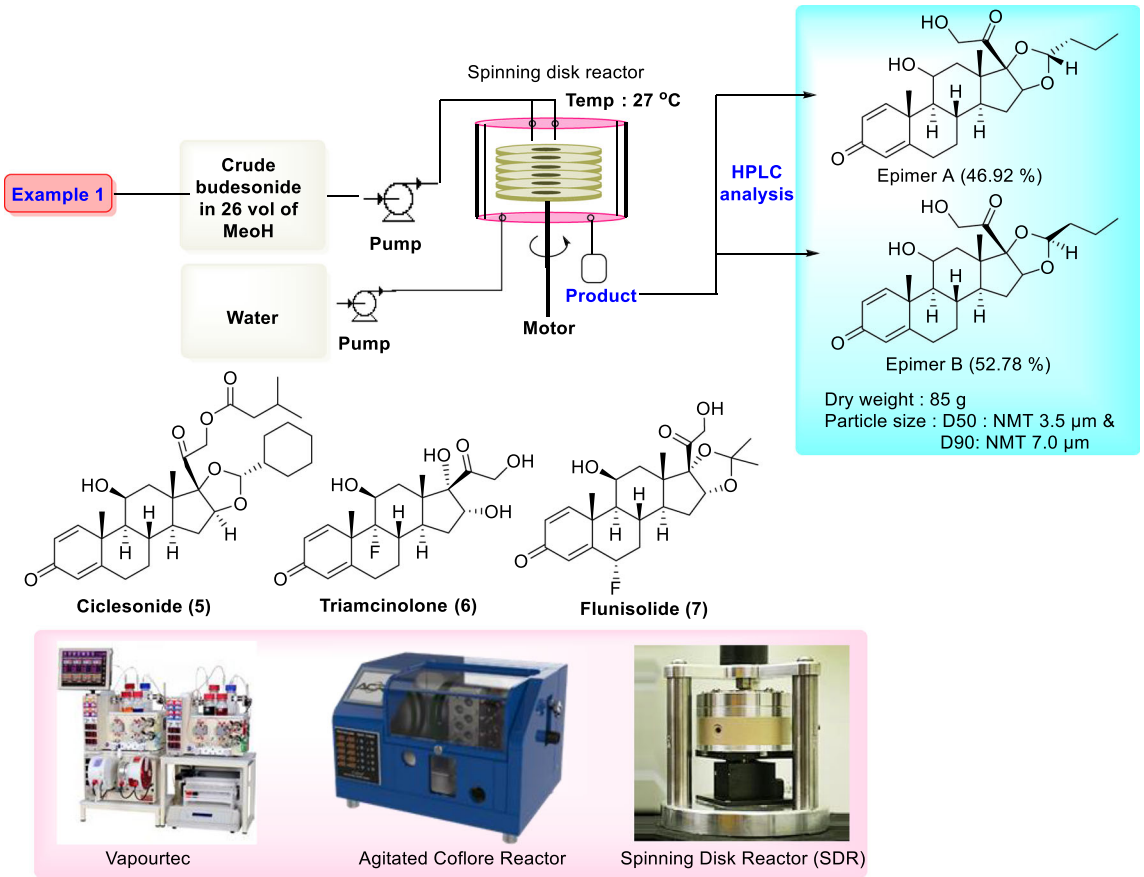


Fig. 2 An optimized reaction condition by continuous flow reactors used for crystallization

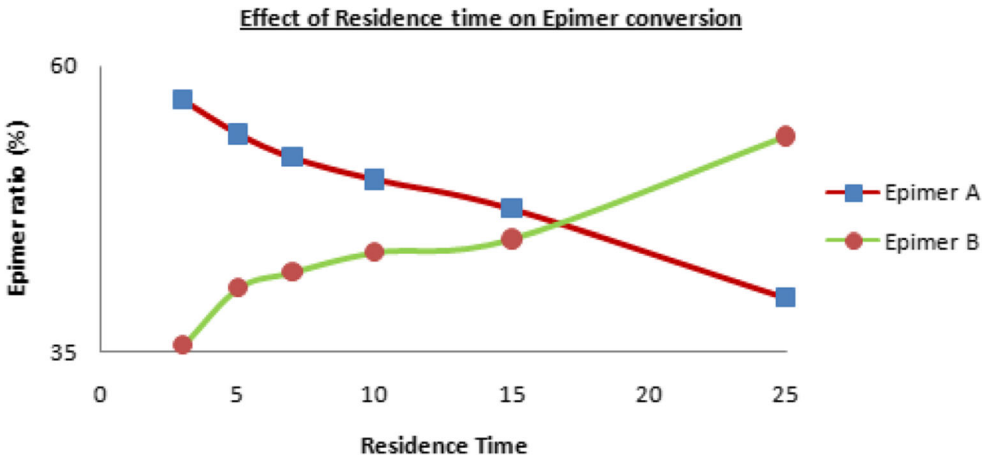


Fig. 3 Effect of residence time on epimer ratio

Study of flow chemistry parameters

The critical parameters of flow chemistry-based synthesis of budesonide are evaluated in the current study. The residence time required for conversion of epimers is one of the significant phenomenon identified in the present flow chemistry process optimization of budesonide. The chemical reaction is initially allowed at 0–5 °C with 2.5 equivalents of butyraldehyde (2.5 eq) until completion of reaction (Fig. 3). The flow process of budesonide at different residence time are investigated and its impact is identified on conversion of epimer A and epimer B. As residence time increases from 5 to 7 min, the conversion of epimer A to epimer B is also substantially amplified and thus allows current process to achieve budesonide with acceptable levels of epimer A.

Similarly, tuning of residence time to below 5 min led to increasing epimer A levels in the reaction process. Hence, the ideal residence time required for process technology of budesonide is identified be around 10 min or ranged between 5 to 7 min. From the optimized flow chemistry reaction conditions (Residence time: 5 min, Temp 0–5 °C), impact of equivalent amount of butyraldehyde (1.0 to 2.5 eq) needed for conversion of 11β, 16α, 17α, 21-tetrahydroxypregna-l, 4-diene-3, 20-dione (16-HPS) to budesonide is further explored. The reaction studies indicated 2.0 to 2.5 mol of butyraldehyde is enough to convert 16-HPS into desired product (Fig. 4). It explains the moles of Butyraldehyde required to convert 16-HPS. If less moles of butyraldehyde are used then the reaction does not go to completion in short period of time and if the reaction time is increased then the epimer ratio is not as desired. Hence 2.5 mol of Butyraldehyde is used for the complete conversion of 16-HPS.

The concentration of 2.5 mol of butyraldehyde with 5 min residence time is kept as a constant to optimize the ideal temperature conditions required to achieve epimer ratio. Epimer A ratio declined and epimer B inclined with tested temperature conditions (0, 5, 10 and 20 °C) (Fig. 5). Though, the degree of higher conversion of epimer A is observed at >10 °C, but the reaction proceeded with rapid translation which led to get unacceptable limits of the desired epimers. Hence to proceed with smooth reaction conditions, an ideal temperature range between 0 and 10 °C appeared as the preferable condition towards preparation of budesonide. Three major conditions include flow rate, residence time and temperature which converted 16-HPS to budesonide with epimer A within specified limit of between 53 and 50% and the content of 16α-hydroxy

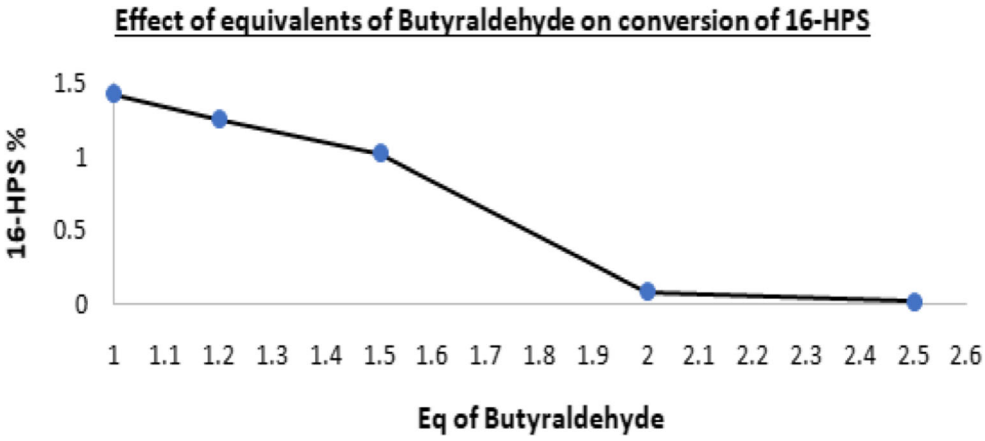


Fig. 4 Effect of butyraldehyde on 16-HPS conversion

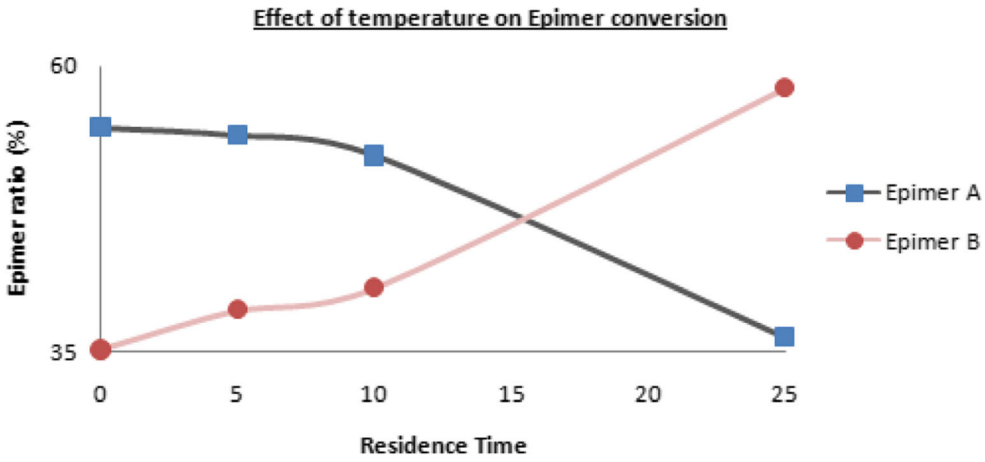


Fig. 5 Effect of temperature on epimer conversion

prednisolone (16-HPS) below 0.1% using flow chemistry techniques.

The obtained budesonide from optimized flow chemistry methodology, was further subjected for particle size estimation using different organic solvents. The solid product was dissolved in 26 volumes of methanol and pumped into the spinning disk reactor. Simultaneously, water is introduced into the reactor and the reactor is maintained at preset conditions like flow rate of solvents/solutions, rotation speed (RPM), agitation frequency and temperature under controlled system (Fig. 2). This spinning process precipitated budesonide respirable particles which are analyzed for estimation of particle size and other physico-chemical properties. The reaction is achieved in one single flow in a continuous reactors as depicted in Fig. 2.

The formation of precipitates/solid chemical products purely depends on factors such as agitation frequency/shear forces in reactor zones, concentration of solution, ratio of anti-solvent to solution, flow rates run at different ratios, temperatures of solution and anti-solvent. By focusing on above key facts, 0.102 M solution of budesonide is tested in organic solvents such as acetone and methanol by maintaining varying flow rate between 1.5 mL/min to 2.4 mL/min to pump into micro channel reactor. From the other pump, water at a flow rate between 43 mL/min to 52 mL/min is streamed into the flow reactor. Residence time for the amalgamated mixture in the reactor is set to 1 s to 10 s and is idealized to 2.5 s to 5 s as better condition from the tested point of temperature. The spinning reactor operation temperature is maintained between 20 to 40 °C, whereas reactor temperature range between 25 to

Table 2 Budesonide Particle size results

Budesonide Particle size results Methanol: Water (27 °C)		D50 (µm)	D90 (µm)
1:8 v/v	2000	4.95	9.73
1:13 v/v	2000	2.67	4.34
1:18 v/v	2000	2.69	4.17

Table 3 Fragments in mass spectra of Budesonide

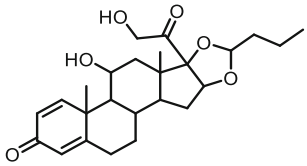
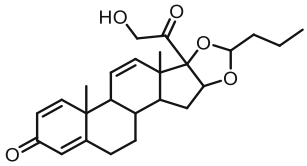
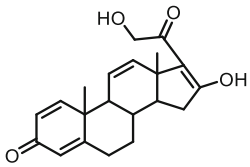
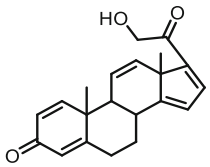
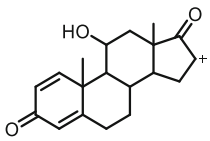
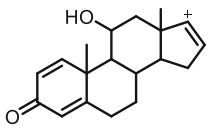
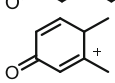
S. No.	Molecular Fragment Structure	m/e
1		431
2		413
3		341
4		323
5		281
6		265
7		121
8		55

Table 4 ^{1}HNMR analysis of budesonide

Chemical shift (ppm)	No. of Protons	Multiplicity	Assignment
0.79–0.84	6	Multiplet	23,25
0.89–2.5	18	Multiplet	7a,8a,9a,11,12,13,14,21, 22,28
4.0–5.2	7	Multiplet	10,2a,4,30,27,31
5.89	1	Singlet	20
6.13	1	Doublet	18
7.29	1	Doublet of Doublet	17

30 °C is identified as the preferential state for precipitation of budesonide which is isolated by normal work up. From the tested parameters, it was identified that, budesonide can be obtained in different particle size depending on the parameters (Table 2).

Physicochemical characterization

A concentration of 0.0025% w/v solution of budesonide in methanol shown absorption maxima A = 0.95 @ 243 nm using Shimadzu UV-1800 double beam spectrophotometer [27]. The FT-IR spectra of budesonide shows required frequencies like 3486 (O-H stretching), 2956, 2939, 2872 (aliphatic C-H stretching), 1723, 1666 (C=O stretching), 1405, 1393 (-CH_3 bending) and 1164, 1134, 1097 (C-O-C stretching) (cm^{-1}) which agree with the essential functional groups present in product. A typical budesonide mass spectra (LCMS/MS API 2000) has m/e ratios corresponding to small fragments along with required molecule ion peak (M + 1 = 431), as reported earlier (Table 3) [30, 31]. The NMR of budesonide in DMSO-d_6 and the chemical shift values identified in ^{1}H NMR and ^{13}C NMR are presented in Tables 4 and 5.

Table 5 ^{13}CNMR analysis of budesonide

Chemical shift (ppm)	Type of Carbon	Assignment
13.78,13.81	CH_3	23
16.43,16.73	CH_2	22
16.83,17.14	CH_3	26
20.73,20.75	CH_3	28
29.95–30.57	CH	8
31.17	CH_2	13
32.37,32.92	CH_2	14
33.50,33.83	CH_2	12
34.45,36.49	CH_2	21
39.56,39.94	CH_2	11
43.63,43.65	C	6
45.14,46.25	C	16
49.38,51.96	CH	7
54.99,55.02	CH	9
65.58,65.99	CH_2	30
68.12,68.16	CH	10
80.81,81.88	CH	4
97.16,97.91	C	5
103.41,107.04	CH	2
121.61,121.66	CH	20
127.07,127.09	CH	18
170.06	C	15
156.38,156.41	CH	17
207.69	C=O	19
209.08	C=O	24

Budesonide contains a mixture of the two epimers C-22S (epimer A and C-22R epimer B) [the content of epimer A may be controlled during the synthesis: between 40.0 and 51.0% of the sum of the areas of the two epimers peaks of budesonide, according to current USP monograph]. The content of epimers in the production batches of budesonide are summarized (Table 6).

The flow chemistry based synthetic methodology of anti-inflammatory drug budesonide is optimized after a series of test conditions. The significance of described optimization strategy is discussed. Further, effect of reactor conditions on formation of epimer ratio is also provided. Based on the studies, ideal reactor conditions required for acceptable epimer ratio formation are achieved. The budesonide solid product was dissolved in an organic solvent to get a clear solution and was then precipitated by addition of an anti-solvent. Resulting product is filtered & dried. In order, to get uniformly distributed particles of budesonide, it was jet milled to investigate the desired particle size. Further, the percentage of epimer A was observed to be within a range from 40 to 51% in all of the experiments using flow chemistry.

Conclusion

In conclusion, we present a flow chemistry-based technique for the synthesis of anti-inflammatory drug budesonide. The optimization of reaction conditions also gave insight into selective preparation of epimer based on the time: temperature ratio. The conditions can be utilized for exclusive preparation of desired epimer, if required. The optimized conditions produce the approved ratio of epimers with ease of handling HBr.

Table 6 Optical isomerism of budesonide

Batch no. of Budesonide	Content of Epimer A NLT 40.0% and NMT 51.0%	Content of Epimer A + Epimer B (sum of bothepimers) NLT 98.0 and NMT 102.0%
B130234	50.6	99.5
B130235	50.5	100.5
B130236	50.6	99.8

The process can be commercialized using continuous flow chemistry to manufacture budesonide.

Experimental part

The UV and FT-IR analysis of budesonide is carried out by Shimadzu UV-1800 double beam spectrophotometer and Thermo Nicolet iS10 spectrophotometers. Mass spectra of sample is recorded by using LCMS/MS API 2000FT-IR spectra (scanned from 50 to 1050 amu). The ^{1}HNMR and ^{13}CNMR spectra are predicted in DMSO-d_6 solvent using 500 MHz Varian instrument. The particle size distribution of budesonide is analyzed by Mastersizer 2000 (Malvern Instrument). Elemental analysis of desired product is carried out by varioMICRO V1.4.5.

The preparation of budesonide is carried out by pumping 100 g (0.2656 mol) of 16α-hydroxy prednisolone (16-HPS) in 6 volumes of 47% HBr (665 mL) and 47.9 g (0.664 mol) of butyraldehyde solutions (constant ratio) through piston pump in flow reactor under different temperature conditions, flow rate and residence time. The agitation frequency of reactor is set at 7 Hz and reaction is quenched in-line by pumping water to precipitate crude product which finally filtered and analyzed. The experimental procedures followed for preparation of budesonide are provided with epimer ratio. The screening experiment and optimization was performed using Vapourtec and all experimental examples (Example 1 to 5) performed using Coflore.

Example 1 16α-Hydroxyprednisolone (16-HPS) (100 g, 0.2656 mol) (0.4 M Stock solution concentration) was dissolved in 6 vol of 47% HBr to make (665 mL) of stock solution. Butyraldehyde solution 11.09 M (47.9 g, 0.664 mol) and 16-HPS solution were pumped through piston pump in flow reactor (as shown in Fig. 1) at 10 °C (Reactor Volume: 60 mL). Flow rates of both pumps were set at (11.0:1.0) mL/min to have a residence time of 5 min and mol ratios of 1:2.5 (16-HPS: butyraldehyde). Reactor was agitated at frequency of 7 Hz. The reaction mass was then quenched in-line (4 × 4 mm and 18 mL of tube size and volume) with water (20 mL/min) which was pumped through another piston pump to precipitate out crude budesonide. The crude budesonide was isolated online by filtration. Isolated solids were analysed by HPLC for epimer content. This crude budesonide was then subjected to hot slurry in ethyl acetate to yield pure budesonide. Isolated solids were analysed by HPLC for epimer content. Yield: 95 g (83.33%), epimer A:47.4%, epimer B:52.03%.

Example 2 16α-Hydroxyprednisolone (16-HPS) (100 g, 0.2656 mol) (0.4 M Stock solution concentration) was dissolved in 6 vol of 47% HBr to make (665 mL) of stock solution. Butyraldehyde 11.09 M (47.9 g, 0.664 mol) solution was used neat. Both the solutions were pumped through piston pump in flow reactor with flow rate (11:1.0) mL/min (as shown in Fig. 1) at 5 °C (reactor volume: 60 mL). Flow rates of both pumps were set to have a residence time of 5 min and mole ratios of 1:2.5 (16-HPS: butyraldehyde). Reactor was agitated at frequency of 7 Hz. The reaction mass was then quenched in-line (4 × 4 mm and 18 mL of tube size and volume) with water (20 mL/min) which was pumped through another piston pump to precipitate out crude budesonide. The crude budesonide was isolated online by filtration. Isolated solids were analysed by HPLC for epimer content. Epimer A: 53.0%, epimer B:40.2%. Crude budesonide was then subjected to hot slurry in ethyl acetate to yield pure budesonide. Isolated solids were analysed by HPLC for epimer content. Yield: 93 g (81.57%), epimer A: 48.44%, epimer B:51.03%.

Example 3 16α-Hydroxyprednisolone (16-HPS) (100 g, 0.2656 mol) (0.4 M Stock solution concentration) was dissolved in 6 vol of 47% HBr to make (665 mL) of stock solution.. Butyraldehyde solution 11.09 M (47.9 g, 0.664 mol) was used neat. Both the solutions were pumped through piston pump in flow reactor rate (11:1.0) mL/min (as shown in Fig. 1) at 0 °C (reactor volume: 88 mL). Flow rates of both pumps were set to have a residence time of 5 min and mole ratios of 1:2.5 (16-HPS: butyraldehyde). Reactor was agitated at frequency of 7 Hz. The reaction mass was then quenched in-line (4 × 4 mm and 18 mL of tube size and volume) with water (20 mL/min) which was pumped through another piston pump to precipitate out crude budesonide. The crude budesonide was isolated online by filtration. Isolated solids were analysed by HPLC for epimer content. Epimer A: 54.1%, epimer B: 40.6%.Crudebudesonide was then subjected to hot slurry in ethyl acetate to yield pure budesonide. Isolated solids were analysed by HPLC for epimer content. Yield: 95 g (83.33%), epimer A: 48.9%, epimer B: 51.4%.

Example 4 16α-Hydroxyprednisolone (16-HPS) (100 g, 0.2656 mol) (0.4 M Stock solution concentration) was dissolved in 6 vol of 47% HBr to make (665 mL) of stock solution. Butyraldehyde solution 11.09 M (47.9 g, 0.664 mol) was used neat. Both the solutions were pumped through piston pump in flow reactor (as shown in Fig. 1) at 0 °C (reactor volume: 60 mL). Flow rates (7.86:0.71) mL/min of both pumps were set to have a residence time of 7 min and mole ratios of 1:2.5 (16-HPS: butyraldehyde). Reactor was agitated at frequency of 7 Hz. The reaction mass was then quenched in-line line (4 × 4 mm and 18 mL of tube size and volume) with water (20 mL/min) which was pumped through another piston pump to precipitate out crude budesonide. Crude budesonide was isolated online by filtration. Isolated solids were analysed by HPLC for epimer content. Epimer A: 52.1%, Epimer B: 41.9%. This crude budesonide was then subjected to hot slurry in ethyl acetate to yield pure Budesonide. Isolated solids were analysed by HPLC for epimer content. Yield: 95 g (83.33%), epimer A: 47.9%, epimer B: 50.8%.

Example 5 16α-Hydroxyprednisolone (16-HPS) (100 g, 0.2656 mol) (0.4 M Stock solution concentration) dissolved in 6 vol of 47% HBr to make (665 mL) of stock solution. Butyraldehyde solution 11.09 M (47.9 g, 0.664 mol) was used neat. Both the solutions were pumped through piston pump in flow reactor (as shown in Fig. 1) at 5 °C (reactor volume: 60 mL). Flow rates of both pumps were set at (7.86:0.71) mL/min to have a residence time of 7 min and mole ratios of 1:2.5 (16-HPS: butyraldehyde). Reactor was agitated at frequency of 7 Hz. The reaction mass was then quenched in-line (4 × 4 mm and 18 mL of tube size and volume) with water (20 mL/min) which was pumped through another piston pump to precipitate out crude budesonide. The crude budesonide was isolated online by filtration. Isolated solids were analysed by HPLC for epimer content. Epimer A: 51.8%, epimer B: 42.7%. This crude budesonide was then subjected to hot slurry in ethyl acetate to yield pure budesonide. Isolated solids were analysed by HPLC for epimer content. Yield: 95 g (83.33%), epimer A: 48.5%, epimer B: 51.5%.

Particle size optimization

Example 6 Budesonide obtained by the process of the present invention satisfies the requirements of both the EU Pharmacopeia and the US Pharmacopeia by using flow chemistry as a tool.95 g budesonide obtained from example 1 was dissolved in 26 volumes of methanol (2.47 L). Budesonide solution (38.46 mg/mL) and water were pumped at flow rate of (10:80) ml/min in spinning disk reactor as shown in Fig. 2 at 27 °C. Solid obtained was then filtered online, washed with water & dried to yield of pure budesonide which gave desired particle size. Yield: 85 g.

Particle size: D50: NMT 3.5 μm & D90: NMT 7.0 μm, epimer A: 46.92, epimer B: 52.78.

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Declarations

Conflict of interests There are no conflicts to declare.

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