A Novel Continuous - Flow Synthesis of Olmesartan Medoxomil

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Abstract

Present invention relates a single solvent highly efficient continuous process for the preparation of Olmesartan medoxomil. Using a telescopic flow synthesis, crude Olmesartan medoxomil is prepared without a single isolation and the isolated crude is then further purified to get desired quality Olmesartan medoxomil.

In this Synthesis method, traditional batch pathway is isolated and reactions were conducted by using Flow reactors. Isolated final compound was analyzed by using spectral studies such that ^{1}H NMR, and ^{13}C NMR.

Keywords: Flow chemistry, API, Multistep synthesis, Flow synthesis

INTRODUCTION

Active pharmaceutical ingredients (APIs) are chemical-based molecules produced mostly in the United States, Europe, China, and India. In order to diagnose, treat, alleviate, and cure diseases. All medications consist of two primary ingredients: the active pharmaceutical ingredient (API), which is the main ingredient and must function both chemically and biologically in your body, and other ingredient is called excipients, such as lactose or mineral oil in the pill, which is chemically inert and give the medication things like volume, sweetness, or color. The body system receives assistance from these excipients in the distribution of APIs.However, their primary function is to treat the disease directly by acting on it (by pharmacological activity) in conjunction with a combination of inactive forms. The world's population consumes up to one lakh tones of pharmaceutical items (up to 24% of which are consumed in Europe alone).

Chemical reactions are the fundamental processes in which substances undergo transformations. Previously, reactions were carried out in flasks; however, nowadays, synthesis is accomplished using machines. Flow chemistry is a term that is accountable for accomplishing this. Use of flow chemistry in pharmaceutical and agriculture industry currently experiencing significant growth. Since the small dimensions of the reactors could produce multi Kg volume, it receives remarkable attention.

Flow chemistry is uniform combination of organic chemistry along with chemical engineering. It is the perfect blending of these two branches. Pumps moves fluid in the reactor known as flow reactor, they react over there and desired compound comes out through other end. Hence in different terminology it is also called as continuous manufacturing.

In the chemical society, flow chemistry applications have grown dramatically. Its modular design makes it easy to incorporate additional settings, tools, analytics, automation, and reagent for single- and multistep processes gives the approach of wide range of applicability. The fundamental and unique characteristics of this technique is, a high degree of precision in the delivery of reagents and solutions, along with great control over the conditions to which the solutions are exposed. Flow chemistry is useful to researchers in a variety of fields, from university teaching labs to production-scale process chemists. Precise control leads to great reproducibility and safety.

Multistep continuous-flow synthesis integrates individual synthesis and purification processes into an interconnected end to end

system that functions at a steady state and these activities can be easily automated to avoid manual interruptions. [1]
This approach offers high space-time yield and facilitates rapid scale-up which resulting in a significant reduction in both time and material cost associated with chemical development.[2-3]
Consequently, flow technology has emerged as a prominent area of research within the pharmaceutical and chemical sectors over the last ten years. [4-8] One of the beautification of flow chemistry is multistep reactions can be arranged in sequential manner without isolating intermediates if they are unstable, poisonous or moisture sensitive. Moreover this telescoping technique can be used for general set of reactions and final compound could be isolated without a single isolation. While the majority of flow systems have been designed for single step reactions, recent studies have demonstrated the applicability of flow technology to multistep reaction sequences.[9-12]

To fully utilise flow chemistry, a chemist must first be able to recognise the situations in which flow can be advantageous. It is crucial to understand the capabilities, drawbacks, and strengths and limitations [13] of the flow chemistry equipment, because over the past 20 years, this material has been thoroughly covered in general and highly detailed research and review publications, leading to the creation of an ever-expanding encyclopaedia of flow chemistry and the main focus of it is how to use it to perform chemical reactions more effectively.[14]

The simplest flow process is monophasic condition, in which no precipitation occurs which run very effectively. Mixed solution flows together in the reactor under certain conditions (heat, cold, etc.) and is exposed to these conditions for a certain period of time. According to the situation entire system can be pressurized by back pressure regulator (BPR). But the use of multiphasic reactions has significant benefits. Gases or immiscible solvents can be added to a flow solution by using a basic T or Y mixer. Compared to batch processes, biphasic reactions are generally accelerated using this technique due to the significant increase in surface areas between the layers and the increased mixing within each liquid slug. Gas - liquid reactions do not suffer from headspace issues and the solubility of the gas in the solution can be increased by pressurization.[15-16]

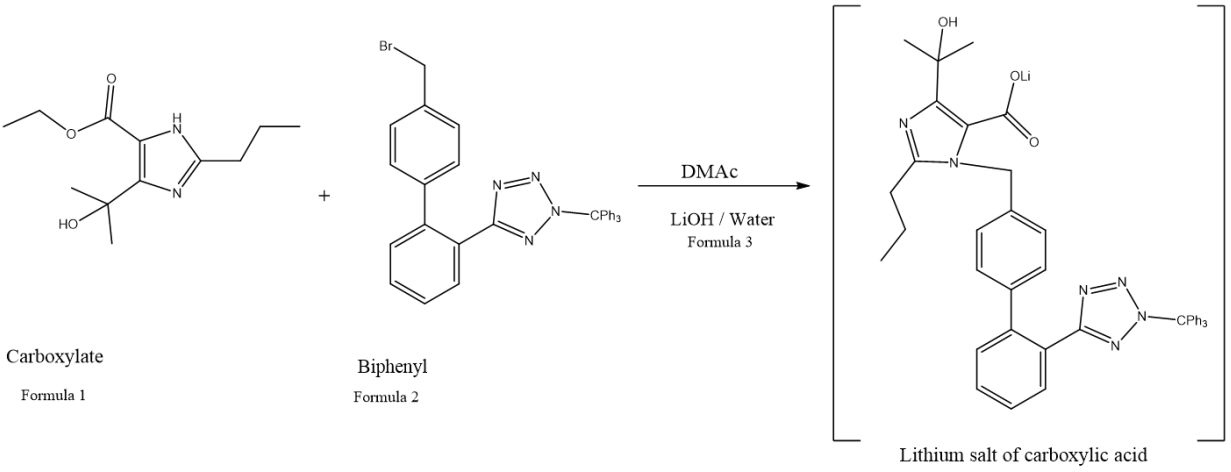
By using this technique only we have synthesized Olmesartan Medoxomil (Anti hypertensive drug).
High blood pressure or hypertension is a serious disease that negatively affects the life anticipation and overall health. [17] The major objects of treating hypertension are lowering blood pressure and avoiding consequences like stroke, cerebral vascular disease and renal failure.[18] Olmesartan medoxomil is regularly used drug which is approved by U.S Food and drug administration for the treatment of hypertension. Olmesartan Medoxomil is currently being used as an alternative therapeutic antihypertensive agent for patients intolerant to angiotensin converting enzyme inhibitors. This molecule was approved as drug by USFDA in the month of April 2002 for treatment of hypertension.

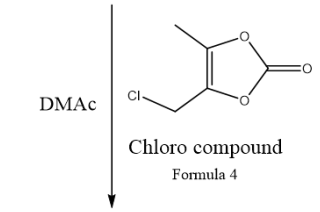
Here we have successfully synthesized Olmesartan Medoxomil in a single solvent with the help of telescoping flow chemistry.

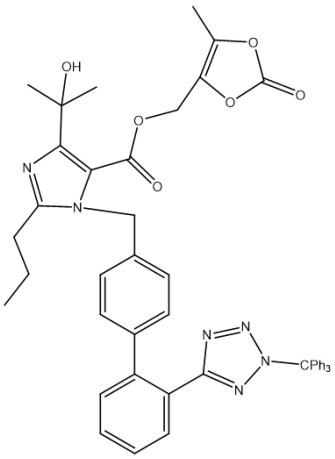
EXPERIMENTAL SECTION

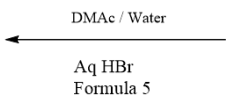
Chemicals of laboratory quality were procured from S.D. Fine Chemicals (Mumbai, India) for the synthesis. The melting point was determined using open capillary tubes in a Hicon, India apparatus, and the results were left uncorrected. Every reaction progress was regularly observed via thin-layer chromatography (TLC) with Merck silica gel 60 F254 coated aluminum plates and a variety of solvent systems with varying polarities like Ethyl acetate: Hexane, Methanol : Dichloromethane and Methanol : Ethyl acetate in various percentage combinations were used as mobile phases. By using a TMS internal reference standard (chemical shifts in δ), 1H NMR (400 MHz) and 13C NMR (100 MHz) were recorded on DMSO-d6 solution in a 5 mm tube on a Varian 400 MHz Unity Inova.

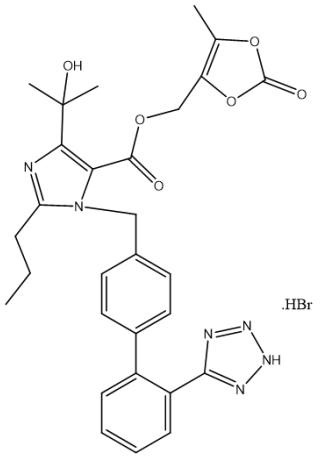
Reported reaction scheme for preparation of Olmesartan in patent EP2036904A1 (Example 1, 2 and 3)

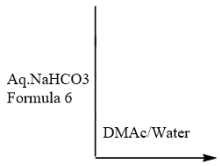

DMAc
LiOH / Water
Formula 3
Carboxylate
Formula 1
Biphenyl
Formula 2
Lithium salt of carboxylic acid

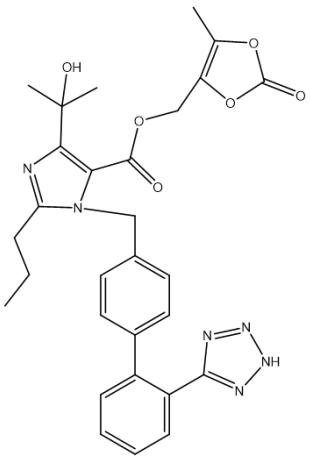

DMAc
Chloro compound
Formula 4


Trityl protected Olmesartan


DMAc / Water
Aq HBr
Formula 5


.HBr
HBR Salt


Aq.NaHCO3
Formula 6
DMAc/Water


Olmesartan Medoxomil API

SCHEME - 1

The synthesis of Olmesartan medoxomil as discussed in the patent EP2036409A1 (Example 1,2 and 3) has certain drawbacks,

i) As per this patent in each of the step (From ex 1, 2 and 3) reaction time for each step is too more, which in turn do not make the process viable for large scale manufacturing

iii) Reaction in presence of DMAc (Dimethyl acetamide) at elevated temperature for a period about 48 hours. The prolonged period of reaction maintenance leads to an increase in the manufacturing cycle time and decrease in the product yield and quality.

In the present work, we have incorporated DMAc as a single organic solvent and without isolation of trityl protected olmesartan (As that of EP2036409A1, Ex. 1, 2 and 3), we have again coupled this molecule further in-situ process to get desired olmesartan medoxomil.

Carboxylate (Formula 1) and biphenyl (Formula 2) quickly combined in 2ml reactor (1st reactor) at 50°C just for the mixing purpose. Again Aq.LiOH (Formula 3) was combined in 10ml reactor (2nd reactor) at 50°C with residence time **45 Seconds**, to give condensed compound with lithium salt of carboxylic acid, this intermediate further combines with Chloro compound diluted in DMAc (Formula 4) in 20ml static mixture (3rd reactor) with residence time **1Min** at 50°C to give trityl protected olmesartan (5) which further reacts with aqueous HBr (Formula 5) in 20ml static mixture (4th reactor) with residence time **47 Seconds** at 50°C to give HBr salt (6) which further reacts with aqueous NaHCO3 (Formula 6) in 30ml static mixture (5th reactor) with residence time **55 Seconds** to give a single layered yellowish reaction mass. This reaction moves through a back pressure regulator set to 1 – 2.5 bar (Zaiput, BPR-10). Reaction progress was analyzed by TLC. After entire collection, Toluene was added to extract the product, which on organic layer distillation and acetonitrile purification gives pure olmesartan medoxomil.

Solution preparation

(1) Carboxylate (Formula 1) was dissolved and diluted in DMAc to get 0.52M clear solution
(2) Biphenyl (Formula 2) was dissolved and diluted in DMAc to get 0.6M clear solution
(3) Lithium hydroxide (Formula 3) was dissolved and diluted in water to get 1.2M clear solution
(4) Chloro compound (Formula 4) was dissolved and diluted by DMAc to get 0.63M clear solution
(5) Aq. HBr (Formula 5) was dissolved and diluted in water to get 0.5M clear solution
(6) Sodium bicarbonate (Formula 6) was dissolved and diluted in water to get 1.2M clear solution

Flow reaction set-up -

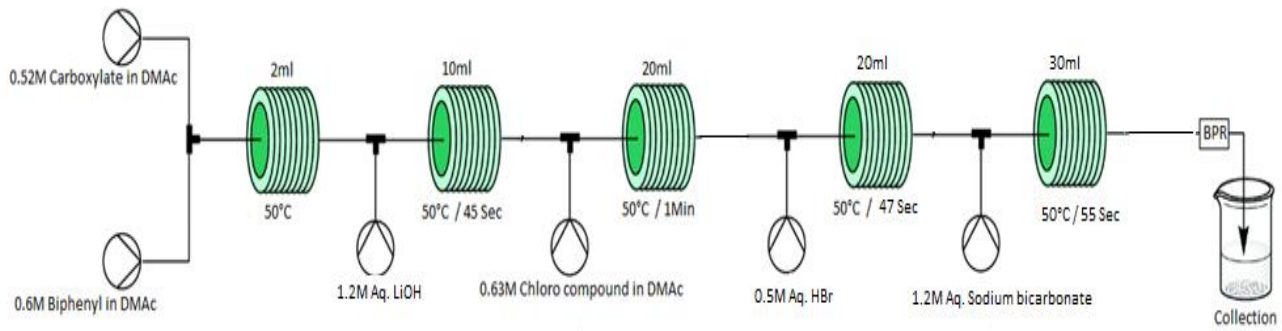


FIGURE – 1

Flow rates and equivalence calculations:

Sr No	Chemical	Mol Wt	Molarity	Flow rate	Equivalence
1	Carboxylate	240.30	0.52M	5.39 ml/min	1.00
2	Biphenyl	557.50	0.60M	5.13 ml/min	1.11
3	LiOH	23.95	1.2M	2.80 ml/min	1.22
4	Chloro compound	148.54	0.63M	6.68 ml/min	1.55
5	HBr	80.91	0.5M	5.5 ml/min	1.01
6	NaHCO3	84.01	1.2M	7.0 ml/min	3.11

FIGURE - 2

RESULTS AND DISCUSSION

Above experimented compound after isolation and drying, was analyzed by ^{1}H NMR an ^{13}C NMR. Data is attached with values.

^{1}H NMR: δ 0.88 (3H,t) J = 6.7Hz, δ 1.50 (6H,s) J = 7.7Hz, δ 1.72 (2H,tq) J= 6.7Hz, δ 1.92 (3H,s) J = 7.7Hz,
δ 2.55 (2H,t) J = 7.7Hz, δ 4.93 (2H,s) J = 7.9Hz, δ 5.25 (2H,s) J = 8.2Hz
δ 6.88 (ddd) J = 7.9,7.6,1.7Hz , δ 7.04 (ddd) J = 8.5,7.6,1.5Hz, δ 7.59 (2H,ddd) J = 8.6,1.4,0.5Hz
δ 7.83 (ddd) J = 8.5,7.6,1.5Hz, δ 7.84 (ddd) J=8.6,1.4,0.5Hz, δ 7.91 (ddd) J=7.9,1.5,0.5Hz

^{13}C NMR: δ 11.2 (1C,s), δ 14.0 (1C,s), δ 21.8 (1C,s), δ 25.9 (1C,s), δ 27.6 (2C,s), δ 53.5 (1C,s), δ 63.5 (1C,s), δ 79.7 (1C,s),
δ 120.4 (1C,s), δ 124.5 (2C,s), δ 127.2 (2C,s), δ 127.5 (1C,s), δ 128.4 (1C,s), δ 128.4 (1C,s),δ 128.8 (2C,s),
δ 133.7 (1C,s), δ 133.7 (1C,s), δ 134.1 (1C,s), δ 136.6 (1C,s)

CONCLUSION

The traditional batch process has several limitations and is sometimes in-appropriate for the development of rapid synthetic transformations. By switching from traditional batch process to Flow process, we managed to overcome several challenges such as dramatic reduction of reaction time, minimization of by-products, easy-to-use automation etc. The developed methodology was further tested on the synthesis of commercially viable APIs. An effective process for synthesis of Olmesartan medoxomil was developed and synthesized final product was analyzed by spectral analysis (^{1}H NMR, ^{13C} NMR,). It has been synthesized with Flow telescopic process without isolating intermediates. To the best of our knowledge, this work is the first example of flow chemistry using a low-cost reactor. In the future, these advances in the flow system will provide a cost-effective method for the preparation of drug molecules.

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