USE OF MICROREACTORS FOR DIABETES DRUG SYNTHESIS

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Natasha Greice Moreira Russo[1], Thalia Delgado Bezerra[2], Ivity Nicoleti Simonis[3], Leonardo Arruda da Silva[4], Luiz Felipe González Ortega Colella[5], Maria Fernanda de Moraes Leme Pedroso[6] and José Carlos Gonçalves Peres[7].

ABSTRACT

The fraction of the world population affected by type 2 diabetes mellitus and its trend of significant increase in the coming decades strongly stimulates improvements in the synthesis of drugs for glycemic control. The transposition of batch production to continuous processes in microreactors allows for reduced synthesis time and better throughput. In this paper, four microreactor designs were proposed—labyrinth, leaf, hive, and hive serpentine—to enable drug synthesis in a single microreactor with a volume greater than 1 mL. The mixing quality of the prototypes was evaluated by simulating their residence time distributions (DTR) using computational fluid dynamics (CFD). The RTDs were raised in response to the step of a methylene blue tracer and maintaining a spatial time of 20 min. In the leaf, honeycomb and serpentine designs with honeycomb, there was the formation of preferential paths for flow, evidenced by the structure of the velocity field and the average residence time of less than 20 min. Their fluid dynamic behaviors were hybrids between the ideal models of a battered flow reactor and a perfectly stirred mixing tank. The labyrinth design has a pressure drop seven times higher than the others because it allocates all the fluid in a single extensive channel, but it promoted mixing of the currents with the greatest homogeneity in the available volume and with a deviation of 0.36 % between the mean residence time and the spatial time, being the most promising design for the synthesis of drugs among those proposed.

Keywords: Glitazones. Microfluidics. Mixture. Simulation.

[1] Undergraduate student in Chemical Engineering - São Judas Tadeu University
Address: São Paulo/SP - Brazil
Email: natashagreice20@hotmail.com
[2] Undergraduate student in Chemical Engineering - São Judas Tadeu University
Address: São Paulo/SP - Brazil
E-mail: thaliadelgado.b00@gmail.com
[3] Undergraduate student in Chemical Engineering - São Judas Tadeu University
Address: São Paulo/SP - Brazil
Email: ivitynicoleti@outlook.com
[4] Undergraduate student in Chemical Engineering - São Judas Tadeu University
Address: São Paulo/SP - Brazil
E-mail: Leo.arruda0407@gmail.com
[5] Undergraduate student in Chemical Engineering - São Judas Tadeu University
Address: São Paulo/SP - Brazil
E-mail: luizfelipegoc@gmail.com
[6] Undergraduate student in Chemical Engineering - São Judas Tadeu University
Address: São Paulo/SP - Brazil
E-mail: maffee11@gmail.com
[7] Dr. in Chemical Engineering - Polytechnic School of USP
Address: São Paulo/SP - Brazil
E-mail: prof.joseperes@ulife.com.br

INTRODUCTION

Diabetes mellitus is a metabolic syndrome that affects about 10.5% of the world's population between the ages of 20 and 79 — 537 million people, 17 million of whom are Brazilians. In 2021, 6.7 million people died from diabetes (one death every 5 seconds) (IDF, 2021). It is estimated that more than 90% of diabetics have type 2 diabetes mellitus, which is caused by insulin resistance (MEIRING et al., 2022). The treatment of these cases consists of the use of drugs to control blood glucose levels, such as drugs of the sulfonylurea, biguanide and glitazone classes (KUMAR; NANJAN, 2010).

Considering the portion of the population affected by type 2 diabetes mellitus, it is relevant to seek ways to optimize the production of drugs for its treatment and reduce the final cost of new generation molecules with greater metabolic efficiency, democratizing access to the drug.

For the formation of these drugs and their intermediates, the pharmaceutical industry, in general, uses the batch process, in which drugs are produced in batches from the raw material, ensuring reaction control and the quantity of the resulting material. However, although it is widely used, batch production has some disadvantages: long reaction time and long interval between batches, which often results in variability in products, drugs with less than 100% of the active complex, in addition to having high production costs and reducing the plant's production capacity. (TAXWEILER; PERES, 2020)

In view of these negative points, there is a promising alternative for pharmaceutical industries: the implementation of microreactors, equipment composed of connected microchannels, typically smaller than 1 mm, within which the components of a chemical process interact in small volume, bringing together and maximizing the interaction between these components. (COLTRO et al., 2007; FACCHIN; PASQUINI, 1998; TAXWEILER; PERES, 2020; WATTS; WILES, 2012). It is worth mentioning that drugs with advanced molecular structure, such as Oseltamivir, Celecoxib, SC-560 and Dolutegravir, are already synthesized in microreactors by the pharmaceutical industry, demonstrating the feasibility of application. (SILVA et al., 2019).

In this sense, the use of microreactors can be a more economical and safer solution for the pharmaceutical industry, since these devices can operate in a laminar regime without affecting the quality of the mixture, due to their small dimensions and large contact area, allowing greater control over the reaction (PERES et al., 2019; BUGAY, C.A. et al., 2024). In addition, microreactors produce in less time and space, providing ease of handling, safety and a reduced environmental impact in case of explosions or toxic leaks (MACHADO et al., 2014).

However, the implementation of microreactors in the pharmaceutical industry faces obstacles, such as high costs for installation and adaptation, in addition to the need for technical specialization to operate the system, which is more complex (BUGAY, C.A. et al., 2024). It is worth noting that the design of the microreactor channels influences the performance of the reaction due to the formation of secondary flows that affect the mixing quality of the equipment (YI et al., 2014). The computational fluid dynamics (CFD) technique simulates flow inside a piece of equipment and allows optimizing its geometry to maximize mixing before the production of physical prototypes (JIANG et al. 2022).

Therefore, in order to propose innovations and optimization in the production process of drugs for diabetes, this paper aims to develop prototypes of microreactors using the simulation-based design approach. In particular, it is desired to:

a) Develop microreactor designs that promote adequate mixing in the reaction medium and thus favor the aforementioned synthesis;
b) Evaluate the influence of channel geometry on the velocity field via computational fluid dynamics (CFD) simulations;
c) Characterize the quality of the mixture in the prototypes proposed by the simulation of the residence time distribution (DTR);
d) Identify possible detractors of the microreactor efficiency, such as dead zones, and compare them with ideal flow models.

METHODOLOGY

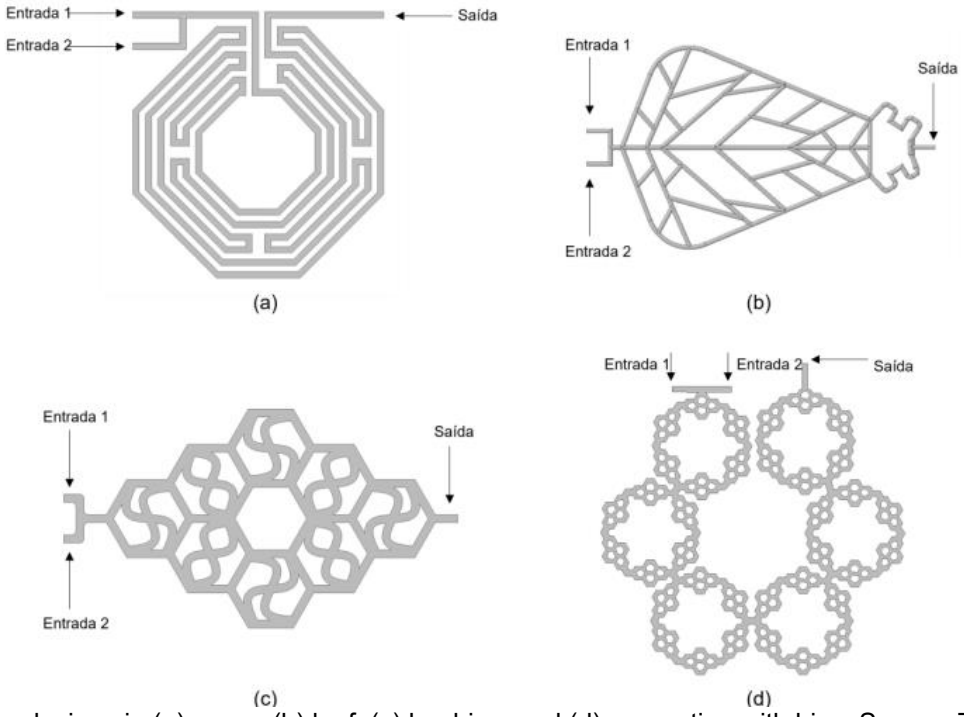
Silva et al. (2019) compared the synthesis of (Z)-5-benzylidene-2,4-thiazolidinadione, a drug derived from the glitazone class, in batch and continuous processes. In the first case, the authors obtained optimal reaction yield after 8 h of process. Transposing to a continuous process with two microreactors of 1.0 mL each associated in series, similar yields were obtained for a residence time of 20 min, a 96 % reduction in process time.

To facilitate the synthesis described above, four microreactor designs with a volume greater than 2.0 mL were proposed so that the reaction can be conducted in a single equipment. Figure 1 illustrates the virtual prototypes developed. The labyrinth design consists of a single channel arranged in a combination of traditional serpentine and spiral geometries, with the goal of increasing the surface area occupied by the channel compared to the total surface of the prototype's support plate. The leaf design mimics the sap-conducting vessels in plants by separating the runoff into several internal channels to mix the reactants. The hive design is an extension of the strategy of Jiang et al. (2014) to

maintain the uniformity of the reaction medium and thus increase mixing within the channels.

Finally, the hive serpentine design consists of six hives in series to match the residence time achieved by a serpentine structure with the blending quality expected for the hive arrangement. All prototypes have three-dimensional channels with a cross-section of 2 mm edge, except for the sheet design, whose cross-section is circular with a diameter of 2 mm. There are two fluid inlets to facilitate the feeding of distinct reagents and an outlet at the end of the channels.

Figure 1 - Proposals for microreactor designs for diabetes drug synthesis



Structure of the designs in (a) maze, (b) leaf, (c) beehive, and (d) serpentine with hive. Source: The authors (2024)

The flow in the developed prototypes was investigated at Autodesk® CFD 2023. First, the velocity field for water flow at 25 °C (density of 998 kg/m3, dynamic viscosity of 0.001 Pa·s) was solved in the proposed geometries. The feed flow rate of each prototype was adjusted according to its volume so that the space time[8] was 20 min for comparison with the serial microreactor system adopted by Silva et al. (2019). The Reynolds number in all cases was less than 3, corresponding to the laminar regime. The outlet of the channels was considered open to the atmosphere (zero relative pressure). Table 1 indicates the operating conditions on each prototype.

[8] Space time is the ratio of the prototype volume to the total feed throughput. It is equal to the average residence time for ideal reactor systems (FOGLER, 2022).

Table 1 - Boundary conditions in the simulation of prototype feeds

Prototype	Flow rate in each feed (uL/min)	Maximum Reynolds Number
Maze	118,2	1,97
Leaf	90,8	1,95
Beehive	71,7	1,2
Beehive streamer	139,5	2,32

Source: The authors (2024)

As a method of solving, the software solves the Navier-Stokes equation [Eq. (1)] through the finite volume method.

$$\frac{\partial(\rho u_i)}{\partial t} + \frac{\partial(\rho u_i u_j)}{\partial x_j} = -\frac{\partial P}{\partial x_i} + \mu \frac{\partial^2 u_i}{\partial x_j^2} \qquad (1)$$

To evaluate the mixture in the proposed microreactors, the residence time distribution (DTR) for each of them was simulated using a step-shaped injection. An inert tracer with the same water transport properties and diffusivity Di = 1.0 · 10^(-10) 〖m〗^2 /s was added, equivalent to that of methylene blue in water (GUPTA et al., 2004). In one of the prototype inlets, pure water was fed, while in the other, a pure tracer stream was fed with the same flow rate as the other inlet.

The tracer concentration at the output of the prototypes was monitored over 3600 s and was obtained by solving their transient mass balance:

$$\frac{\partial(\rho x_A)}{\partial t} + \frac{\partial(\rho u_i x_A)}{\partial x_j} = -\frac{\partial}{\partial x_i}\left(\rho D_A \frac{\partial x_A}{\partial x_j}\right) \qquad (2)$$

The instantaneous concentration curves of the tracer at the exit, C(t), were simulated with a time step of 1 s and considering that the prototypes were initially filled only with water. Its raw data allowed the calculation of the cumulative distribution curves F(t) and the distribution of residence times E(t), defined by Fogler (2022) as:

$$F(t) = \frac{C\,(t)}{C_0} \qquad (3)$$

$$E(t) = \frac{C(t)}{\int_0^\infty C(t)\,dt} = \frac{d\,F(t)}{dt} \qquad (4)$$

As it is a distribution of probabilities, the DTR can be characterized by its momenta, among which the most relevant for the analysis of chemical reactors are the mean residence time (tm) and the variance of the mean residence time (σ2):

$$t_m = \int_0^\infty t\,E(t)\,dt \qquad (5)$$

$$\sigma^2 = \int_0^\infty (t - t_m)^2\,E(t)\,dt \qquad (6)$$

The RTD of a reactor depends on its volume. To analyze reactors with different volumes, the DTR can be dimensionalized using spatial time (τ) and a dimensionless time θ as proposed in Eq. (7):

$$\theta = \frac{t}{\tau}\,;E(\theta) = \tau\,E(t) \qquad (7)$$

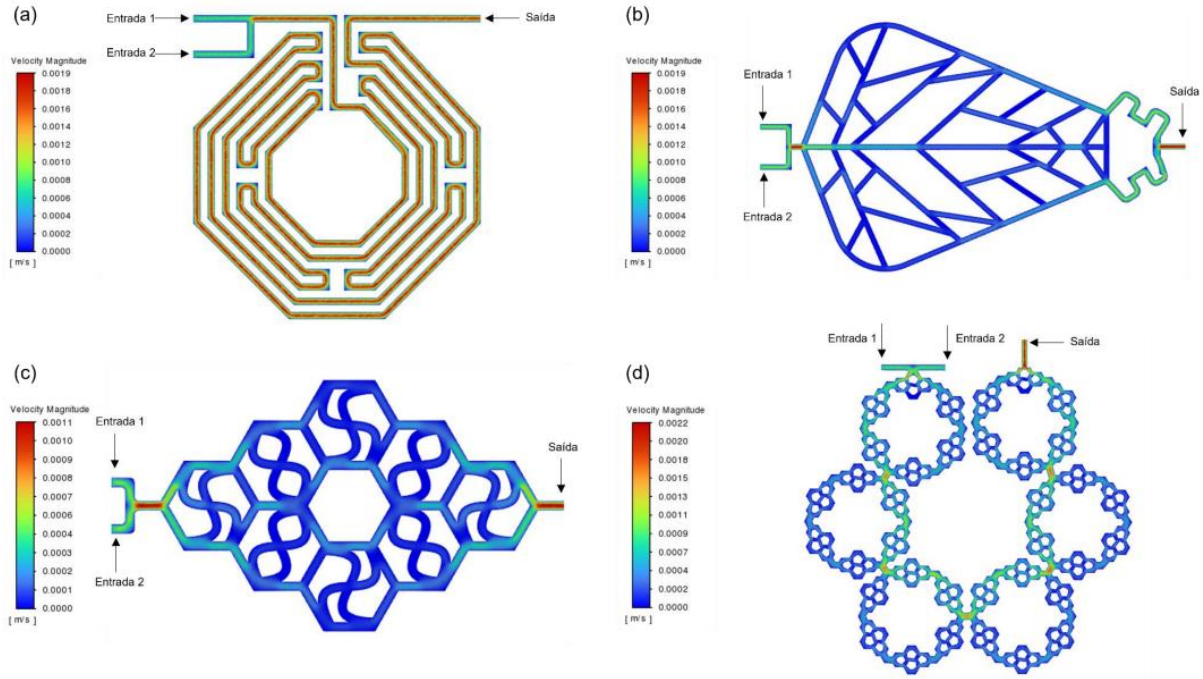
RESULTS AND DISCUSSIONS

The structure of the velocity field in a microreactor influences the quality of the mixture inside. Although there is a 94% variation between the minimum and maximum values of average speed in the prototypes – which occurred for the beehive and serpentine with hive designs, respectively – the Reynolds number has the same order of magnitude in all prototypes. Thus the similarity of the fluid phenomena is guaranteed

Figure 2 compares the distribution of velocities in the central plane of the developed prototypes. The labyrinth design showed higher speeds because it concentrated all the flow in a single channel, with an average value of 1.6 mm/s. In its curved sections, the formation of dead zones was noticed, regions of fluid stagnation, near the outer corners of the curves. This fact occurred due to the balance between the inertial force and the centrifugal force on the fluid when passing through the curves: most of it follows the curvilinear trajectory, but a small portion in the outer parts formed small recirculation zones that do not interact with the other regions. The extent of the dead zones, however, was small and did not affect the mixing capacity of the prototype, as indicated by its DTR (Figure 6).

In the other prototypes, the division of the feeds into subchannels led to the reduction of the average speed in the channels to the range of 0.3 mm/s to 0.9 mm/s. In the leaf and honeycomb designs, the flow exhibited a symmetrical distribution with respect to the central axis of the prototypes due to its geometric symmetry. The leaf design provided greater homogeneity of speeds compared to the honeycomb and serpentine designs with honeycomb. The average speed in the honeycomb design was the lowest compared to the others due to the fact that its volume was on average 36% lower than that of the other prototypes.

Figure 2 - Distribution of speeds in the developed prototypes



Designs in (a) labyrinth, (b) leaf, (c) beehive, and (d) streamer with beehive. Source: The authors (2024)

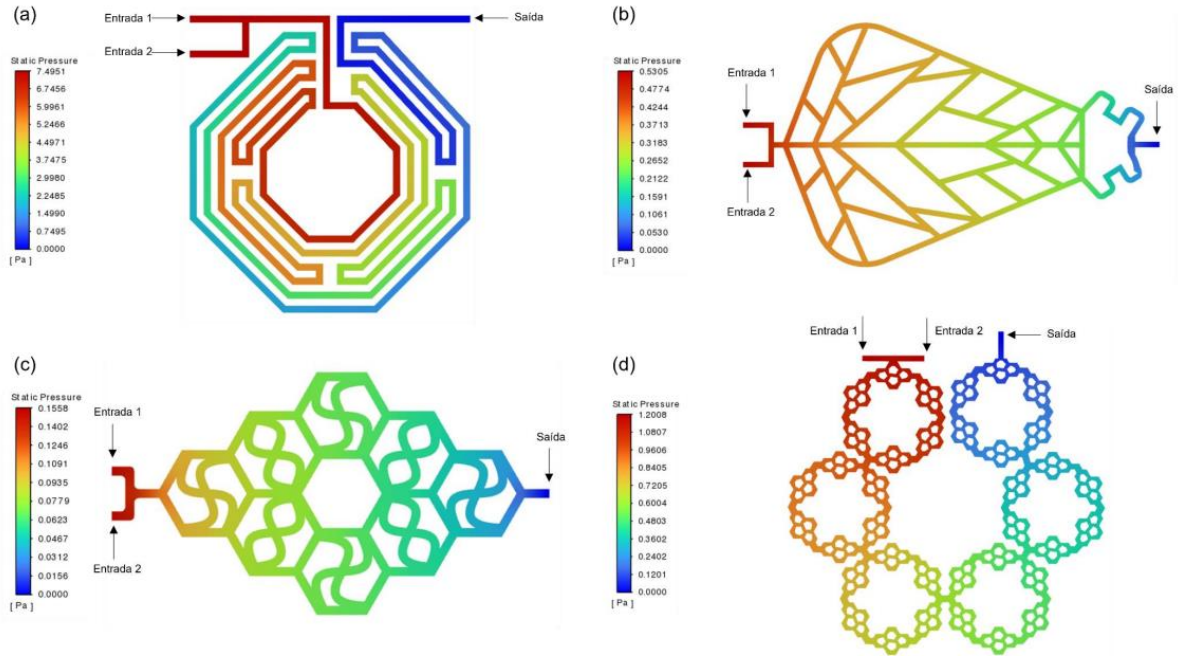
There was formation of preferential paths in the honeycomb and serpentine with honeycomb designs, with greater extension in the latter. In the beehive prototype, the fluid accumulated in the external channels and in the central hive, with an average speed twice as high as in the other sections. In the prototype of a coil with a honeycomb, there is a concentration of flow in the internal parts of the second to fourth coil of the series, with speeds between two and three times higher than in the external part. The preferred path in such a prototype may be due to the geometry of the feeding channels, which come together directly inside the first hive (in the others, the feeds mix before the main channels).

The structure of the velocity field affected the distribution of pressures in the prototypes, as shown in Figure 3. The direction of the flow in a single channel in the labyrinth design led to a pressure variation of seven to forty-nine times greater than in the others, an effect similar to that observed with the single-channel and segmented channel

microreactors proposed by An et al. (2012) for methane combustion. The leaf and honeycomb designs were the ones that require the least pumping power. In this aspect, the behavior of the honeycomb coil design proved to be a combination of the others: the pressure suffered small variations within each hive and is more significant from one hive to another, as in the labyrinth design (whose structure is a serpentine channel), but the pressure drop between the inlets and the outlet is closer to the segmented channel designs.

The mixing quality of the prototypes can be evaluated qualitatively by the steady-state tracer distribution, a condition reached after 3600 s in the DTR test. Because the flow rates of the tracer and water feeds were the same, the fluid can be considered perfectly mixed to tracer mass fraction of 50%.

Figure 3 — Map of pressures in developed prototypes



Designs in (a) labyrinth, (b) leaf, (c) beehive, and (d) streamer with beehive. Source: The authors (2024)

Figure 4 shows that the labyrinth design was the one that best promoted tracer mixing, because the distance traveled by the fluid for the mass fraction of this species to reach 50 % was the smallest among the proposed prototypes. The honeycomb coil design exhibited poor mixing quality, a trend expected by the preferential flow of fluid in the internal parts: more than half of the volume of this prototype did not effectively contribute to mixing the feed streams. A change in the arrangement of the feeding channels could improve the use of the external parts of the hives and improve the mixing of the prototype.

The leaf and honeycomb designs showed very similar mixing trends, which are evidenced by the overlap of their DTR curves seen in Figure 5. There was a low tendency to mix in these prototypes, but with better use of the internal volume compared to the coil

design with honeycomb. The figure also indicates that the labyrinth design behaved closer to the ideal Impistonate Flow Reactor (PFR) model.

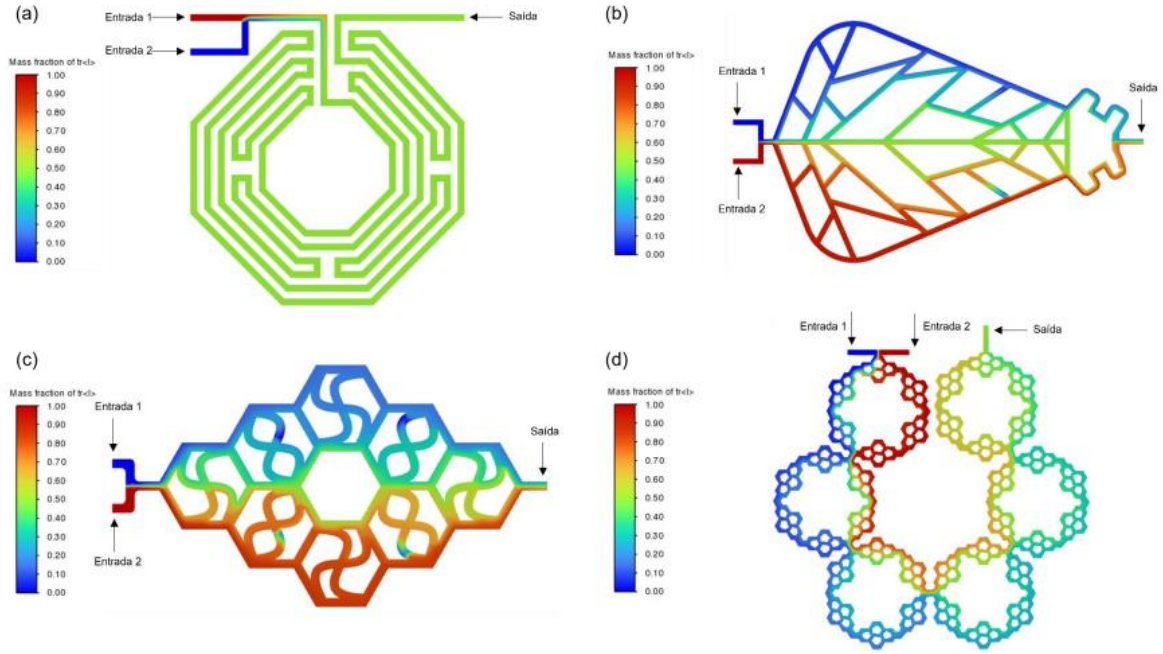
The comparison of prototypes to ideal flow models can be made quantitatively by the moments of their DTRs summarized in Table 2. It confirms the proximity between the flow in the labyrinth design and an ideal PFR: the mean residence time is 0.36 % higher than the spatial time and the standard deviation corresponds to 5.9 % of the mean residence time, indicating low dispersion.

Table 2 - Moments of the distribution of residence times of the developed prototypes

Parameter	Maze	Leaf	Beehive	Beehive streamer
Average residence time, t_m (min)	20,1	18,7	19,3	17,9
Standard deviation of mean time, σ (min)	1,2	5	5,9	5,4
Mean time variance, σ2 (min2)	1,4	25,2	34,8	29,3
Razão σ / t_m (%)	5,9	26,8	30,6	30,2
Deviation between t_m and τ (%)	0,36	6,9	3,7	12

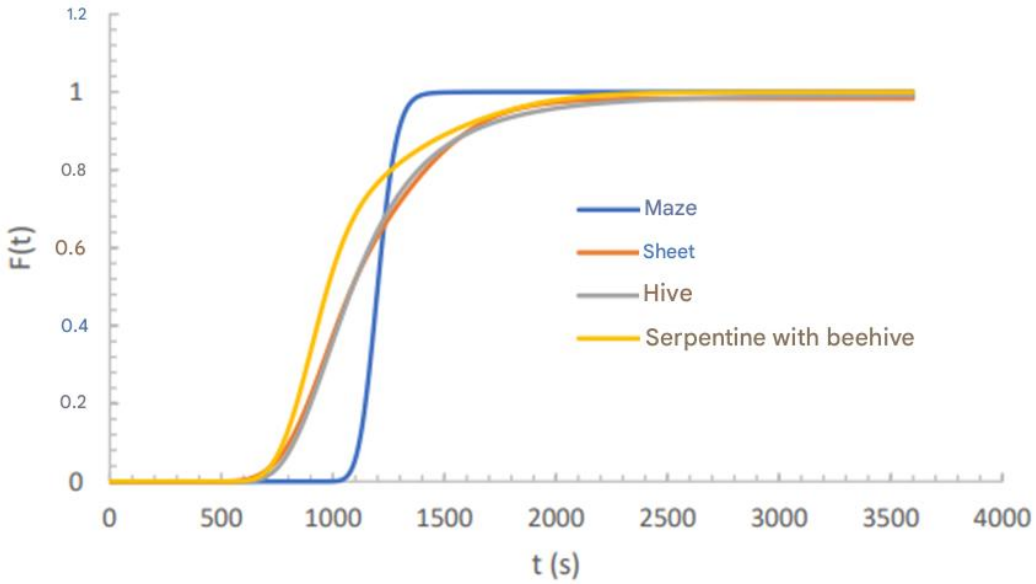
Source: The authors (2024)

Figure 4 - Mixing trends in the developed prototypes



Steady-state tracer distribution in the designs in (a) maze, (b) leaf, (c) hive, and (d) serpentine with cholemia.
Source: The authors (2024)

Figure 5 - Response to the tracer step in one of the feeds in the simulated prototypes



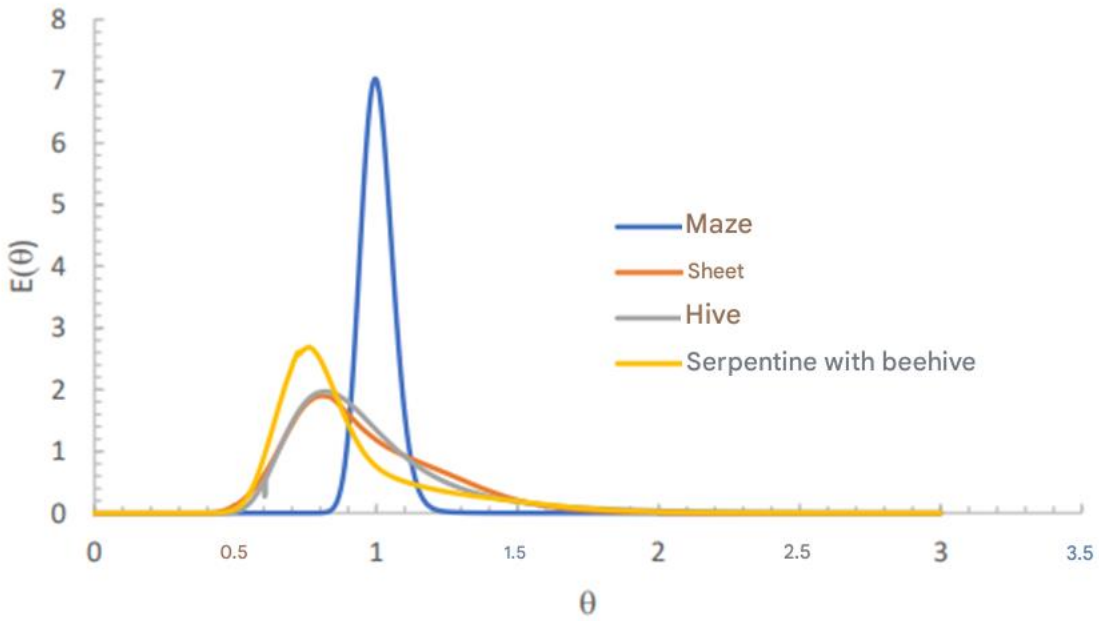
Source: The authors (2024)

The other prototypes had hybrid behavior between an ideal PFR and a perfect mixing tank (CSTR), since their DTRs exhibited elongated tails and shifted peaks from the tracer injection instant (Figure 5). The fact that their mean residence times are lower than the spatial time (ratio between the volume of the prototype and the total feed flow) evidences the existence of preferential flow paths that were predicted by the simulation of the steady-state velocity field.

CONCLUSION

Four prototypes of microreactors were proposed to enable the synthesis of diabetes drugs in a single equipment with a space time of 20 min. The labyrinth design proved to be the most promising. It optimized the plate volume occupied by the channels compared to a traditional coil design and provided the best mixing quality. The pumping power required in this prototype, however, was about seven times greater than that of the others due to the transport of the fluid in a single extensive channel. In the other proposed designs, there was the formation of preferential paths due to the dispersion of the flow in subchannels and evidenced by the average residence time shorter than the spatial time.

Figure 6 - Dimensionless residence time distribution for the proposed prototypes



Source: The authors (2024)

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