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Dropper Systems: A Short Review of Experimental and CFD Simulation Studies

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Abstract

Dropper-type dosing systems are responsible for most everyday applications, such as intermittent doses and eye drops, in addition to the preparation of solutions in scientific circles. However, careful evaluation of physical influences such as viscosity, surface tension, temperature, pressure and density related to a dosage it is not taken into account in the leaflets or tables of the drops/mL ratio. The present work presents a review of the available literature to identify and understand the factors present in this type of measurement, as well as the methods and analyzes normally used according to the Pharmacopoeia. Furthermore, in this work it is proposed the use of Computational Fluid Dynamics (CFD) to model and simulate this flow problem in order to predict the dripping phenomenon as a function of the physical conditions of the system. For that, researcher was made on the following topics: drip and dosage-related issues, CFD applied to dosing systems and data collection necessary for modeling and solving of the studied system. It was identified a deficiency in the standardization of dropper instruments. Data of physical characteristics of fluids that can be dosed in droppers were collected. The proposal to use CFD for the simulation and analysis of these cases is valid and used by several works related to laminar flows and the presence of drops.

Keywords: Dropping; Dosing Systems; CFD

Abbreviations: CFD: Computational Fluid Dynamics; FVM: Finite Volume Method; PDEs: Partial Differential Equations; IDDSI: International Dysphagia Diet Standardization Initiative; VOF: Volume of Fluid; WHO: World Health Organization; RVE: Representative Volume Element.

Introduction

Currently, liquid medication dosages are labeled according to a conversion table of drops to mL established by Sanitary Legislation. This table is widely used in hospitals, home treatment, and laboratories, and is also included in medication leaflets, including controlled substances. Although studies have been conducted on drug dosage, the factors that affect volume and viscosity - such as temperature, pressure, surface tension, and even the instrument used for medication dosing - are often overlooked. As a result, there can be variations in the desired quantity, leading to under or over-dosage, which in turn can have significant implications such as drug sensitization and increased treatment costs [1,2]. To examine the impact of these variables in a real-world scenario, a computational simulation can be conducted to study the behavior of the desired flow [3]. Computational Fluid Dynamics (CFD) is a branch of knowledge that deals with the numerical treatment of fluid flow, energy transfer, and related phenomena (such as chemical reactions, combustion, aeroacoustics, etc.) through computer simulations, which use the Finite Volume Method (FVM) to discretize the partial differential equations (PDEs) that describe fluid motion. The discretization of the PDEs transforms the governing equations of the fluid into appropriate algebraic expressions that can be solved by the selected CFD program. The development of the momentum equations that describe the three-dimensional motion of viscous Newtonian fluids is the result of the combined work of Claude Louis Marie Henri Navier and George Gabriel Stokes, who applied Newton's Law in vector form to a fluid element and also considered the conservation of mass equations [2].

Despite the global use and high importance of dosing systems, the difficulty in finding data due to the lack of standardization is one of the limitations of this work. An alternative is to perform various modeling studies using different rheological data, along with experimental validation. For instance, in the study by Hanson B, et al. [4], it is mentioned that the flow conditions inside syringes have not been published in any previous work, highlighting the need for an appropriate model to be constructed. There are currently pressing issues in dosing systems, such as the loss of doses related to COVID-19 vaccination, which is caused by variables such as syringes, needles, stock, distribution, and 25°C temperature variation. These factors have different degrees of importance in different locations, especially in large countries such as Brazil. Despite the widespread occurrence of these losses, they cannot be considered normal, especially in the face of increasing sustainability needs worldwide.

The effectiveness of a computational modeling relies on the combination of rheological models with the generated mesh which needs to converge. The most common flow tests include flow rate analysis, Reynolds number, Froude number, advection tests, shear tests, and others depending on the specific fluid case [3-5]. The adapted test used by the International Dysphagia Diet Standardization Initiative (IDDSI) to mea- sure the time it takes for a liquid to flow through a syringe is noteworthy. This test enables the determination of liquid consistency. The term consistency can be broad and analyzed as physical characteristics, such as density and viscosity, which are the focus of this study.

The current work aims to clarify the influence of different physical properties on flow within drip instruments and to evaluate the physical description, i.e., the equations to be adopted in the computational modeling for the analysis. Secondary, the ease of data collection required for numerical simulation, the search for rheological data of possible fluid examples and studies that elucidate the construction or have geometries similar to the desired drip instrument.

Dosing Systems and Droppers

A dosing system is equipment that aims to manipulate different products with to obtain the most accurate amount of the manipulated substance. It is frequently used in wastewater treatment, agriculture, drug manipulation, among other fields. The dropper is typically composed of a tube that stores the liquid, usually made of plastic or glass, and a hollow rubber component that allows a certain amount of liquid to be retained or expelled through suction. It is a primary method for dosing in the pharmaceutical and chemical industries, as well as in laboratory settings for research purposes. The desired amount to be dosed is dispensed in the form of drops, which is a primary unit of measuring medication. An example of a drop-to-mL conversion table reproduced from Digital F [6], is shown in Table 1. Drops in the pharmaceutical field can be defined as a liquid preparation, in the form of a solution or suspension, intended for administration through oral, nasal, aural, or optical route [7]. In the absence of national standardization information regarding this instrument [8], the American Pharmacopoeia is used, which provides official dropper data [7]. It has an external diameter of 3mm, dispenses 20 drops of water per mL, at a temperature of 25°C, with the instrument in a perpendicular position to the container that will receive the drop.

Medicine	Active Principle	mg/mL	mg/ drop	drops/ mL	mL/ box	drops/ box
Medicine in drops						
Amplictil 4%	Chlorpromazine hydrochloride	40	1	40	20	800
Daforin	Fluoxetine hydrochloride.	20	1	20	20	400
Dogmatil	Sulpiride	20	1	20	30	600
Exodus	Escitalopram oxalate	20	1.23	20	15	300
Gardenal 4%	Phenobarbital	40	1	40	20	800
Haldol	Haloperidol	2	0.1	20	30	600
Neozine 4%	Levomepromazine	40	1	40	20	800
Neuleptil 1%	Periciazine	10	0.25	40	20	800
Neuleptil 4%	Periciazine	40	1	40	20	800
Reconter	Oxalate escitalopram	20	1.23	20	30	600
Tramal	Hydrochloride Tramadol	100	2.5	40	10	400
Lexotan	Bromazepam	2.5	0.1	25	20	500
Rivotril	Clonazepam	2.5	0.1	25	20	500
Solutions						
Depakene	Sodium Valproate	50	-	-	100	-
Melleril	Tioridazine Hydrochloride	30	-	-	50	-
Tegretol Susension.	Carbamazepine	20	-	-	100	-
Trileptal Suspension	Oxcarbazepine	60	-	-	100	-
Valpakine	Sodium valproate	200	-	-	40	-
Eye Drops						
Anestalcon 0.5%	Proxymetacaine hydrochloride	5	0.17	30	5	150
Anestesico	Tetracaine hydrochloride 1%	10	0.45	22	10	220
	Phenylephrine Hydrochloride 0.1%	1.1	0.05			
Ciclopédico	Cyclopentolate Hydrochloride	10	0.33	30	5	150
Maxitrol	Dexamethasone	1	-	22	5	110
	Neomycin sulfate	5				
	Polymyxin B sulfate	6000 UI/mL				
Tobrex	Tobramycin	3	0.09	33	5	165

Table 1: Table of drops to mL conversion, reproduced from Digital F [6].

Physical Influences and Model of the Flow

The study by Hanson B, et al. [4] also reports the use of a syringe for flow simulation analysis (Figure 1), with a specified model "Beckton-Dickson 302188" that complied with the ISO 7886-1 standard and followed IDDSI specifications for flow testing. The experimental analysis of the cited model served as a validation of the computer simulation carried out in this article, using the fluid dynamics and the volume of fluid (VOF) method. The interface between water and air inside the syringe over time was tracked using the Volume of Fluid (VOF) model. The tracking of the interfaces between the phases is accomplished by the solution of the continuity equation for the volume fraction of one of the phases (u = 0) [2], which is reduced in this case the two fluids (liquid and air) are incompressible and there is no mass transfer happening between them.

For the multiphase, immiscible and VOF characteristics, the following equations must be solved,

$$\frac{\partial \alpha}{\partial t} + \nabla \cdot (\alpha u) = 0 \quad (1)$$

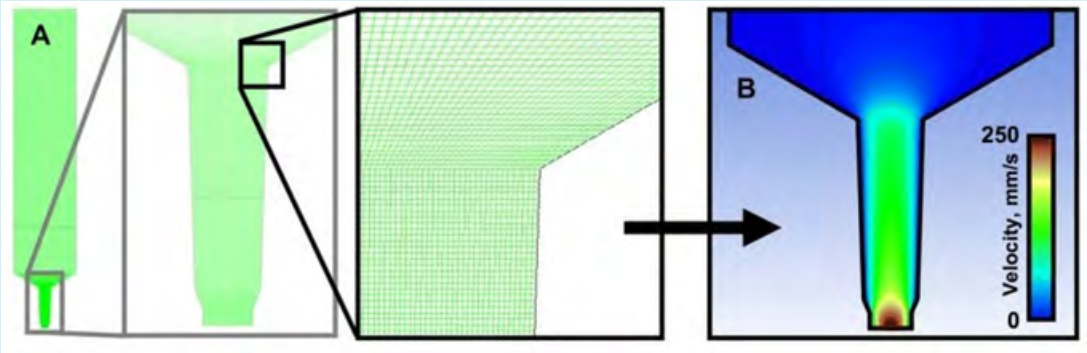

Figure 1: Discretization of the syringe geometry and velocity profile of a non-Newtonian fluid [4].

All information in this table is available in the leaflets of the respective brands, as well as the number of drops per mL and the amount of mg per mL.

$$\rho = \alpha\rho_{liq} + (1-\alpha)\rho_{gas} \quad (2)$$

where α is the scalar field of the fluid, where 1 means liquid and 0 gas.

The physicochemical properties of the drug, the way the patient instills the eye drops, as well as the diameter of the dropper tip orifice, are the main factors that determine the size of the eye drop [9]. The mass of the drop directly depends on the surface tension, the dropper orifice diameter, and temperature, and the angle at which the drop is released Malekzadeh and Zhang [10,11]. Equation 3 was proposed to expresses the relationship between the physical factors that influence droplet formation from droppers, capillary tubes, and drippers [7],

$$mg = D\pi\sigma, \quad (3)$$

where m is the mass of the drop, g is the gravitational acceleration constant, D is the diameter of the dropper nozzle, and σ is the surface tension. The drop detaches when the weight of the liquid, mg, exceeds the tension forces.

The influence of the viscosity of the liquid is analysed by Hanson B, et al. [4], highlighting the nozzle of the simulated structure. The regime of the flow in laminar or turbulent can be determined bey the Reynolds number,

$$Re = \frac{\rho u D}{\mu} \quad (4)$$

where ρ is the fluid density, u is the characteristic velocity of the fluid (for example, the average velocity), μ is the dynamic viscosity, and D is the characteristic length of the structure. In less viscous fluids, the liquid constantly drains from the nozzle, but in some thicker examples, bubble formation is observed in the nozzle and the flow is bubbles rather than continuous. In these cases, the surface tension and fluid viscosity generate pressure at the outlet as each bubble volume manages to break this tension, overcoming it. In the measurements done by Zhang X, et al. [12] tension, viscosity and curvature variation of the bubble formed were neglected in comparison to the capillary resistance generated by the tube. The pressure can be calculated considering the repetitive formation of a bubble in the diameter of the nozzle using the Young-Laplace equation,

$$P_{drop} - P_{atm} = \frac{2\sigma}{r} \quad (5)$$

where σ represents the liquid-air surface tension and r the radius of the exit nozzle.

Dropper-type infusion systems have already been the subject of several studies [13,14], which evaluated the same drug but with drippers from different manufacturing companies. They concluded that over- and under-dosing problems can occur, and suggest the standardization of drippers, as it is identified as one of the main cul- prits for the identified problems. The variation in the diameters of the external and internal openings of the dropper nozzle was analysed by Machado EV, et al. [15]. The computerized visual inspection system identified anomalies in the openings that resulted in variations in the diameter of the dropper nozzle, which suggests a variation in the size of the drops and the waste of medicines. The internal shape of the dropper nozzle has a direct influence on the size of the drop; the design and physical characteristics of the dropper are pre-determined in the construction project and may undergo dimensional variations due to material contraction, the temperature variation that the mold undergoes and the pressure exerted on the mold for production [16].

The influence of dosage control is discussed by Nagao-Dias AT, et al. [1], affirming that sensitization to a given drug occurs more easily with intermittent and repetitive administrations (eg penicillin or insulin) than with its uninterrupted administration. Thus, sensitized patients may

react with minimal doses, mainly through the parenteral route, considered more immunogenic. Furthermore, topical administration (cream, ointment, eye drops) may result in sensitization and subsequent allergic reaction. Also according to the Ministry of Health, together with ANVISA, in resolution- RDC No. 67 which provides for good practices in the handling of magistral preparations and workshops for human use in pharmacies, it can be mentioned that "the overdose of valproic acid can result in a deep coma", in addition to the occurrence of several effects related to the same problem in other drugs [17]. This is an example of a drug indicated for the treatment of seizures, epilepsy, absence seizures and bipolar disorder, in addition to being indicated for the prevention of migraine attacks.

In 2017, with the high risks of harm associated with drugs, the World Health Organization (WHO) initiated the 3rd global patient safety challenge.The goal is to reduce by 50% serious harm related to medication in the next five years, based on the development of safer and more efficient health systems in each part of the medication process, which are prescription, distribution, administration, monitoring and use, avoiding unsafe practices in the use of drugs [18].

Simulations of Dosing and Infusion Systems

In the CFD simulation stages, discretization of the geometric model is in the first stage, known as pre-processing, along with other important processes, such as discretization of differential equations, determination of constitutive equations and fluid properties and convergence criteria. The quality of the results obtained by simulation depends on models that accurately represent the physical problem together with the quality of the mesh in terms of control volumes, and on numerical methods that solve the equations with low error. Mesh convergence and numerical solution convergence are factors that go hand in hand, as the evaluation of one usually depends on the other. Convergence problems can usually be solved by changing the Courant number,

$$Co = \frac{|u|\Delta t}{\Delta x} \quad (6)$$

where u is the magnitude of the local velocity, Δt the time step and Δx the size of the mesh's local control volume. The Courant number is a local scalar quantity of the fluid domain that represents the advective flow in each representative volume element (RVE) [19]. These are examples of factors that must be taken care of as they are related to CFD modeling and simulation. However, examples of systems and containers with a similar structure that were modeled in the literature are also interesting, as they can also serve as a comparison and elucidation in the simulation of a dropper. For instance, a cylindrical vessel from Fukushima is simulated to analyze the water spray system that prevents toxic aerosols from precipitated and solidified fuels from escaping into the atmosphere when cutting and removing these fuels [20]. A two-phase gas-liquid flow in a vertical acrylic cylinder with different degrees of inclination is also simulated to study the movement and morphology of an air pocket inside a liquid-phase, in an experiment similar to the one called Taylor bubbles [21]. The numerical modeling and solution was carried out in the CFD CFX software provided by the company ANSYS. This work is similar to the experimental study of Azevedo MB, et al. [22].

The variation that different syringes cause in specific determinations is examined by Dantas RO, et al. [23], comparing the model used by Hanson B, et al. [4] in their test with a model produced in Brazil by Saldanha Rodrigues LTDA. The study finds that differences occur even in the flow data that are considered official for liquid consistency by the method described by the International Dysphagia Diet Standardization Initiative (IDDSI), reinforcing that consistency determination should only be considered using the Becton and Dickinson syringe from the United States. The work of Longest W, et al. [24] also has a structure similar to the one studied and aims to develop quantitative correlations to predict the aerosolization behavior of an inhaler through CFD. The aerosolization and dose containment unit uses air inlet and outlet orifices inside a closed cylinder, which is designed to maximize the dispersion of dry powder sprays. It brings an implementation idea reinforcing the importance and usefulness of CFD in the development of drug delivery devices, but underutilized in the development of pharmaceutical inhalers.

The internal structure of a dropper nozzle commonly used by pharmaceutical pack- aging manufacturers is presented in more detail, reinforcing the idea of a lack of standardization and opening up the possibility of constructing meshes of this studied model to evaluate its effectiveness compared to other dropper nozzles [15]. Moreover, the influence of variations in the diameters of the openings of dropper nozzles, result-ing from the production process, on the size of eye drop droplets was determined, and the use of the computer vision system used to measure the openings of nozzles produced in the industry was suggested as a proposal for quality control.

Geometry of a syringe was constructed Hanson B, et al. [4], which was discretized in a structured way into quadrilateral elements with 7, and 000 cells after testing 3 equal meshes with different numbers of cells until convergence was reached. The case was simulated using the software FLUENT 17.2 and considers the filling of air at the same time as the emptying of the syringe, a phenomenon that should be considered in normal cases, as well as in the

proposal of this work.

The existence of residues on the walls of the dosing instrument is also mentioned Hanson B, et al. [4], stating that there is no practical, reliable, and computational approach to modeling a movable interface with these characteristics in a realistic way. This work proposes precisely this approach to analyzing the fluid-structure interaction, and cannot adopt the method of Zhang X, et al. [12] in neglecting data such as the viscosity of the solution. A standard model by IDDSI is used by Hanson B, et al. [4] and provides the identification of the syringe used experimentally. Although they are different dosage models, a dropper also has a similar structure and flow in an axial axis, reinforcing the possibility of comparison with this dosage method. On the other hand, an image of an official capillary dropper from the American Pharmacopoeia (Figure 2) with the available dimensions is proposed by Ferreira AO, et al. [7]. The work also contains the representation of other types of droppers, as well as dispensers attached to the bottles (Figure 3a, b), which are better demonstrated in Machado EV, et al. [25] (Figure 3c).

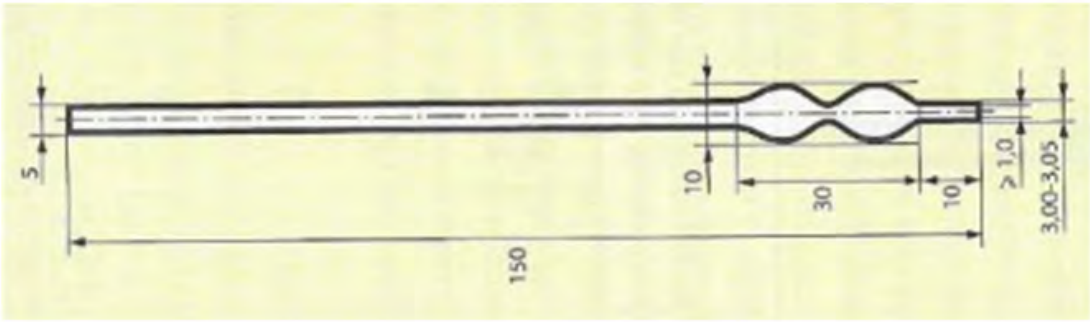

Figure 2: Official dropper dimensions Ferreira AO, et al. [7].

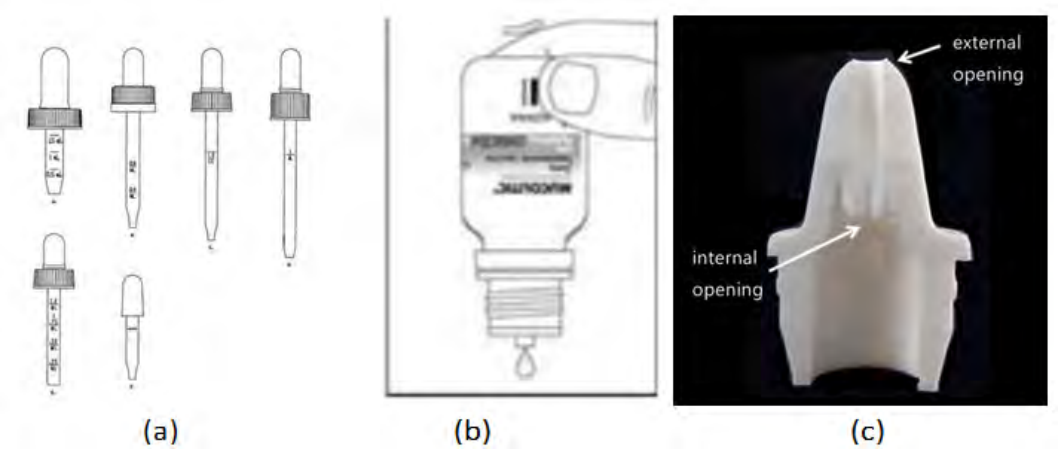

Figure 3: (a) Dropper examples and (b) dispensing device with attached dropper [7]. (c) Cross-sectional view of the built-in dropper [25].

A comparative study of syringe-based 3D food printers using screws is made, using CFD to understand and compare the flow field in the two extrusion-based 3D printing equipment selected [26]. The simulation was done using COMSOL Multiphysics, which is a commercial software based on the finite element method. The work can also be allocated in this area because the simulated region has similarity with dosing systems simulation works. Infusion systems such as infusion pumps that are commonly used in health care facilities have application for maintaining the level of some fluid in the body during or after surgeries, parenteral nutrition in pediatric patients and with the aid of drug administration quotealves2002bombas. It contains a slightly more complex structure than the desired one [27], basically consisting of an adapter, edge, dripping orifice, drip- ping chamber, equipment tube, tweezers, injectors and filter. Its prolonged extension can be the object of study of the physical characteristics that influence the dosages,

But with a very complicated modeling work. The work already mentions an application when infusion therapy is needed with an error of less than 5%, which can be a comparative object for possible analyses. In pipe flow cases and Volume of Fluid (VOF) simulations, it is essential to consider various data parameters for accurate analysis. The usage of data parameters such as air density, dynamic viscosity, and a table of prepared fluid data for the IDDSI test is suggested by Hanson B, et al. [4]. This table includes mixtures of glycerol with water, water mixed with starch, and water mixed with chewing gum, where the first mixture is an example of a Newtonian fluid while the other two are non-Newtonian fluids. Additionally, the author emphasizes that the hydrostatic pressure responsible for pushing the liquid out of the nozzle is proportional to both the weight and density of the liquid.

The properties of fluid mixtures play a crucial role in various scientific studies. For instance, a detailed analysis of surface tension and viscosity values of a 50% glycerol-water mixture is provided by Zhang X, et al. [12]. This study also suggests using a mixture of water with n-propanol for droplet formation analysis, among other glycerol-water percentage mixtures. Similarly, a comprehensive table (Table 2) that analyses various properties of different water-glycerin ratios at varying temperatures and volume percentages is presented by Azevedo MB, et al. [22]. This table provides valuable information about the density, viscosities, surface tensions, dimensionless numbers, and fluidity of the mixtures. The Reynolds number plays a crucial role in understanding fluid flow behavior. Average values of the Reynolds number are provided by Gomes MHR, et al. [27], indicating that for values below 2000, fluid particles have a well-defined trajectory and do not spread, while values above 4000 exhibit disordered and turbulent movement, that is not desirable for dropper flow observation. In the context of the worked syringe, values ranging from 100 to 1000 indicate that the flow nozzle of the syringe operates in a laminar flow regime, which is desirable for dropper flow observation [4].

Liquid	D (m)	T (^{0}C)	ρL	μL (Pa s)	σL (N/m)	M	E_0	Nf
100% W	0.019	29	995.8	0.0008	0.0702	1.17 ×10−11	50	10000
80% W + 20% G	0.019	30	1058.3	0.0015	0.0694	1.40 ×10−10	54	5703
50% W + 50% G	0.019	30	1141.6	0.0057	0.0668	3.04 ×10−8	60	1638
20% W + 80% G	0.019	30	1214.1	0.0499	0.0646	1.86 ×10−4	66	200
100% G	0.019	30	1257.4	0.5979	0.0626	4.06	71	17
100% W	0.024	24	997.1	0.0009	0.0708	1.82 ×10−11	79	12900
80% W + 20% G	0.024	26	1059.9	0.0017	0.0699	2.26 ×10−10	85	7321
50% W + 50% G	0.024	25	1144.2	0.0068	0.0672	6.04 ×10−8	96	1952
20% W + 80% G	0.024	26	1216.5	0.0629	0.0654	4.51 ×10−4	105	224
100% G	0.024	24	1261.3	0.9875	0.0628	29.86	113	15
100% W	0.034	26	996.6	0.0009	0.0711	1.80 ×10−11	159	22442
80% W + 20% G	0.034	29	1058.7	0.0016	0.0694	1.82 ×10−10	173	13320
50% W + 50% G	0.034	28	1142.7	0.0061	0.0668	3.99 ×10−8	194	3650
20% W + 80% G	0.034	28	1215.3	0.0559	0.0646	4.68 ×10−4	213	427
100% G	0.034	28.5	1258.7	0.7035	0.0626	7.8	228	35

Table 2: Water (W) glycerin (G) volume percentages, reproduced from Azevedo MB, et al. [22].

Overall, the analysis of fluid mixture properties and understanding the Reynolds number and its relationship with fluid flow behavior are vital for scientific research and can provide valuable insights for various applications.

Conclusion

The development of the present study allowed an analysis of the available literature in the area of CFD, dosage systems, droppers, physical influences on dosages and problematic around dosages. The work presented the problem about under- and over-dosages caused by deficiency of practical and computational proposition studies regarding physical variables that mainly influence the dropper dosing method. In addition, it reports new issues such as the need of standardization to a provision of official data regarding the dimensions of the instrument, mainly in Brazil.One of the problems surrounding physical

influence within the country is the large territorial extension and biodiversity that consequently covers the aspects of temperature, pressure, humidity, and a computational study is an applicable and plausible. The CFD area proposes to resolve the issue in a self-explanatory and logical way, as the main subject of the study is a fluid (such as medications and solutions). The hypothesis of using simulation is raised, being confirmed as necessary, possible and plausible by the cited bibliographical reference. Necessary data for the simulation of fluid examples were found in literature and can be easily determined in chemical and physical laboratories to other problems. Relevant information about the physics of the problem is also found in the literature, creating a path for choosing the required solution method. Furthermore, as experimental data from new examples of used fluids are collected and compared with computer simulations, a new dosing methodology related to drops or transfer of small volumes can be performed.

Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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