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In Vitro Evaluation of the Physicochemical Compatibility of Four Perfusion Mixtures: Case of an Ampoule of Paluject® in Glucose Serum with/or without Vogalene®

Alphonse Rodrigue Djiboune[1], Papa Mady Sy[1], Abdou Faye[1], Mamadou Soumboundou[2], Sidy Mouhamed Dieng[3], Mariama Dianké Diédhiou[1], Louis Augustin Diaga Diouf[1], Gora Mbaye[1], Mounibé Diarra[1]

[1]Physical Pharmaceutic Laboratory, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Dakar, Senegal
[2]Biophysics Laboratory, Healthy UFR of Thies, University of Thies, Thies, Senegal
[3]Galenic and Industrial Pharmacy Laboratory, Healthy UFR of Thies, University of Thies, Thies, Senegal
Email: alphonserodrigue.djiboune@ucad.edu.sn, mounibe.diarra@ucad.edu.sn

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Abstract

In this study, the physicochemical compatibility and stability of four drug mixtures were evaluated, and the common drug mixtures used in the treatment of severe malaria in children were simulated by gravity perfusion dynamic simulation experiment. The results showed that under experimental conditions, all drug mixtures exhibited clear transparency, stable density and refractive index, and pH values changed by no more than one unit, demonstrating compatibility and stability during the study period.

Keywords

Physicochemical Compatibility and Stability, Perfusion, Paluject®, Glucose Serum, Vogalene®

1. Introduction

Nowadays, intravenous perfusion occupies a large place in the therapeutic arsenal of patients in health establishments because it allows several drugs to be administered simultaneously on the same route in order to obtain a rapid response sought in the event of an emergency [1]. Unfortunately, injectable medications come in the form of either ready-to-use solutions, powders to dissolve, or concentrated solutions to dilute before use. In this case, their simultaneous administration via intravenous

infusion therefore involves the mastery and control of physicochemical parameters, such as the physicochemical compatibility of the active substances between themselves and of the substances with the different diluents (aqueous solvents) and the stability of the drugs mixed in the perfusion bag after dilution. As a result, mastering and controlling the physicochemical compatibility of drug mixtures makes it possible to avoid simultaneous administration of incompatible drugs. Otherwise, such administration could cause the appearance of a precipitate, gas emission, color change or inactivation of active substance(s) in solution or the formation of a (or) toxic compound(s) [2] [3]. Thus, the precipitate formed can obstruct the route and block the passage of drugs to the patient. But, if the precipitate enters the bloodstream without being resolubilized, it can block the blood vessels and cause consequences which can be potentially serious or even fatal in the short or long term. As for the inactivation of the active substance or substances, it may lead to a loss of effectiveness of the treatment in question. In addition, the toxic compound formed can also cause repairable or irreparable damage in humans [3]. Furthermore, the work of Taxis et *al.*, showed that the most common intravenous medication errors in hospitals concern physicochemical incompatibilities with a frequency of 25% [4]. In light of all this information, the intravenous perfusion of one or more drug(s) requires particular attention in all ages, especially in pediatrics and geriatrics because they have more limited routes. Moreover, the consequences resulting from physicochemical incompatibilities, notably cardiopulmonary and renal embolisms, are more frequent in newborns and infants [2]. Therefore, perfusion mixtures constitute a real public health problem, especially in pediatrics. Thus, in Senegal, the management of severe malaria with perfusion mixtures based on glucose serum is by far the most widely used practice [5]. The objective of the study was to evaluate the physicochemical compatibility and stability of four perfusion drug mixtures containing paluject® and vogalene® in order to provide assistance in preventing the risk of the physicochemical incompatibility and to facilitate the work of medical teams. In fact, paluject® is a drug used against malaria while vogalene® against vomiting.

2. Material and Methods

2.1. Material

Laboratory equipment and products including Quinine resorcinol (PALUJECT®), Metopimazine (VOGALENE®), 10% glucose serum and 5% glucose serum were used during the study.

2.2. Methods

We selected the medicinal mixtures after observing the practices carried out by nurses working in care units and administering quinine resorcinol (PALUJECT®) and Metopimazine (VOGALENE®). The concentrations of molecules studied were chosen on the basis of the concentrations recommended by the World Health Organization for the treatment of severe malaria for children [5]. Thus, the composition

of the four drug mixtures is mentioned in Table 1.

Table 1. Composition of the different drug mixtures studied.

Mixtures	Glucose serum 5%	Glucose serum 10%	PALUJECT® (400 mg/4 ml)	VOGALENE® (10 mg/1 ml)
Mixture 1	500 ml		4 ml	
Mixture 2	500 ml		4 ml	1 ml
Mixture 3		500 ml	4 ml	
Mixture 4		500 ml	4 ml	1 ml

Concerning the study itself, we carried out a dynamic simulation of gravity perfusion via a device identical to that carried out in intensive care units during the treatment of severe malaria by perfusion. We mixed paluject® and vogalene® in the perfusion solutions then the liquid is collected in a 100 ml vial placed at the end of the perfusion line (Figure 1). The fluid flow rate was set at 42 drops per minute [5].

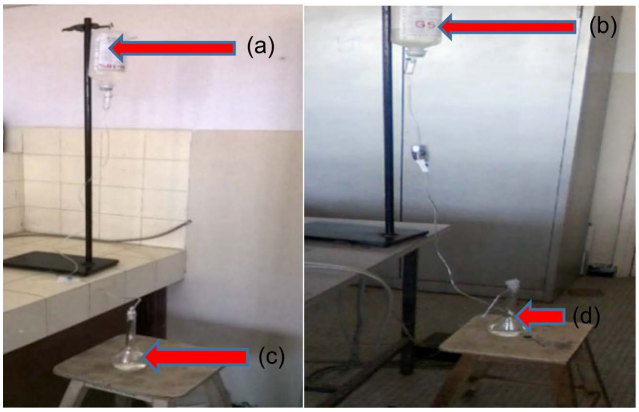

Figure 1. Perfusion mounting device. (a) Glucose serum 5%; (b) Glucose serum 10%; (c) and (d) Liquid is collected in a 100 ml vial.

Just after mixing the drugs in the perfusion bag, we increased the flow rate to collect sufficient liquid in the vial with which we performed tests such as visual inspection and determination of parameters including refractive index, density and pH. This time corresponds to time T_0. Then we set the flow rate to 42 drops/min. And after every hour until the fourth hour (T_4) we used the liquid collected in the vial to perform the same tests done at time T_0. The choice of theme and parameters studied was guided by a growing number of scientific publications on physicochemical incompatibility. Furthermore, these publications showed that visual inspection, color change and pH are the most studied parameters [6] [7]. The study was carried out at room temperature (27˚C). We worked with one mixture per day. The different parameters are measured three times for each mixture. The visual inspection was carried out in accordance with the requirements of the European Pharmacopoeia. To do this, three tubes were inspected macroscopically, first, against a white background to detect black, dark or opaque particles in suspension, then on a black background to detect crystals and other transparent foreign particles [8]. Concerning the measurement of the refractive index, we placed a few drops of the mixture on an ATAGO SPR T_2 type refractometer then we observed the refractive index with

the naked eye. For the density of the mixtures, we used a pycnometer with a capacity of 10 ml. In fact, we first determined the weight of the empty pycnometer (P_0), then that of the pycnometer containing the serum solution 5% or 10% (P_1) then the weight of the pycnometer containing the (P_2) mixtures and finally we applied the following relationship to calculate the density of each mixture:

$$d_l = \frac{P_2 - P_0}{P_1 - P_0}$$

d_l: density of the mixtures;

P_0: weight of empty pycnometer;

P_1: weight of the pycnometer containing 5% or 10% glucose serum;

P_2: weight of the pycnometer containing the mixtures.

As for the pH values, they were determined using a pH meter of the type CG820 SCH.

3. Results

On visual inspection, all perfusion drug mixtures were clear and slightly yellow during all four hours of observation (Table 2).

Table 2. Visual inspection of the drug mixtures studied.

Drug mixtures	Appearance of drug mixtures				
	T_0	T_1	T_2	T_3	T_4
Mixture 1	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slighty yellow color	Clear, slightly yellow color
Mixture 2	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color
Mixture 3	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color
Mixture 4	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color	Clear, slightly yellow color

The results of refractive index, density and pH of the perfusion drug mixtures are shown in Figures 2-4, respectively.

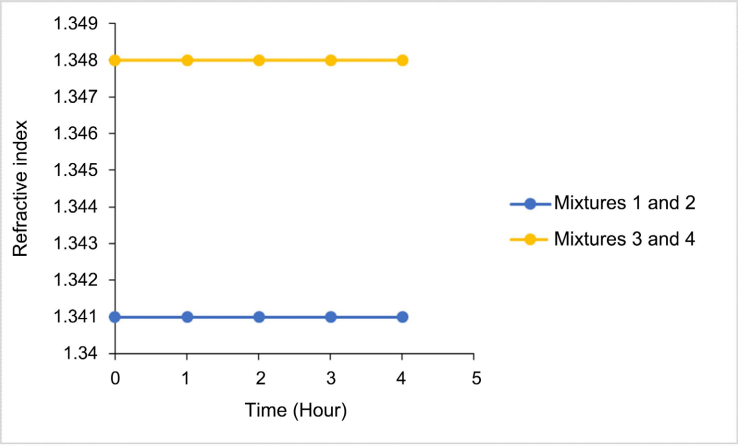

Figure 2. Variation of the mixture refractive index as a function of time.

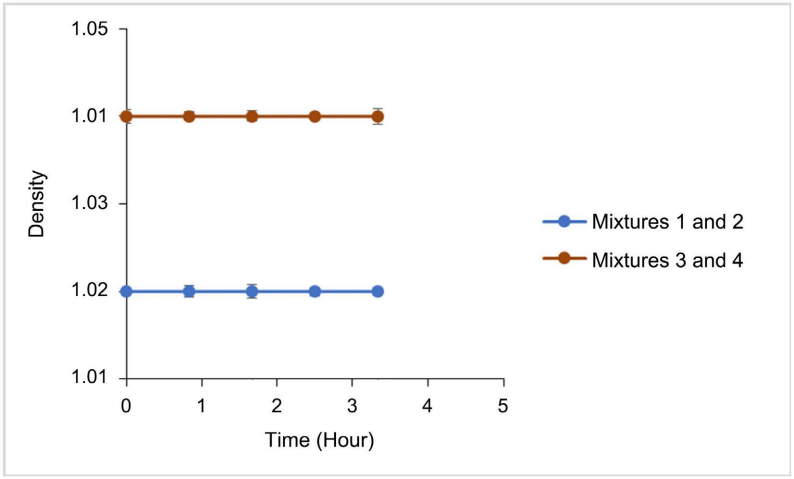

Figure 3. Variation of the mixture density as a function of time.

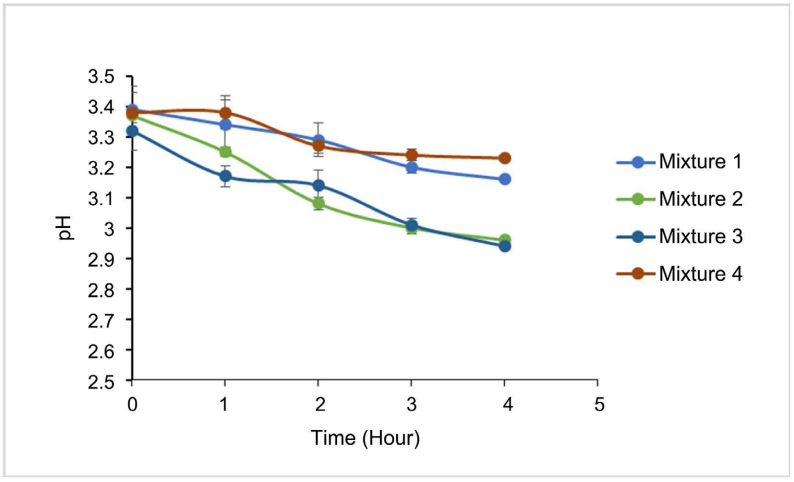

Figure 4. Variation of the mixture pH as a function of time.

4. Discussion

The study of the physicochemical compatibility of the different drug perfusion mixtures was carried out at 27˚C. The temperature remained constant throughout the simulation. Temperature is a very important factor to take into account because it can influence the physicochemical compatibility and stability of drugs in a mixture. In fact, an increase in temperature leads to an acceleration of the molecular degradation reactions. For example, when the temperature increases by 10% between the start and end of stimulation, the rate of degradation of molecules present in the aqueous mixture is often doubled. On the other hand, a sudden decrease in temperature can lead to crystallization or precipitation of the molecules present in the drug mixture. These two situations can cause therapeutic failures or toxicity [9]. The results of the visual inspection are mentioned in **Table 2**. They showed that the mixtures were clear and slightly yellow colored. These results reflect an absence of physical phenomena such as turbidity, color change, gas emission, and precipitates visible between the start and end of the simulation. The

addition of VOGALENE® in mixtures 2 and 4 did not modify the appearance of the mixtures despite the difference in glucose concentration. These results comply with the requirements of four pharmacopoeias including the European, American, British and Japanese Pharmacopoeia which stipulate that injectable solutions, examined under appropriate visibility conditions, must be "clear and practically free of particles" [10]. Furthermore, these four pharmacopoeias stipulate that the physicochemical incompatibility of drugs in a mixture can result in the formation of visible precipitates, gases, opacity, crystals or a change in coloring, viscosity or immiscibility [11] [12]. None of these incompatibility parameters were observed during our study. So, we can say without doubt that the drugs studied were compatible and stable. However, physical compatibility does not tell us about the chemical degradation of the active ingredients present in these mixtures. Visual inspection remains very useful in problematic situations of intravenous administration, because it makes it possible to detect a possible precipitation of constituents leading to loss of the catheter, venous thrombosis, renal infarctus, vascular stenosis, etc. [13] [14]. Compared to the refractive index measurement, the results are mentioned in **Figure 2**. These results showed a constant refractive index from T_0 to T_4 for each mixture during the duration of the simulation. These results reflect a lack of interaction between the molecules present in the mixtures. In fact, measuring the refractive index provides information on the formation or not of new compounds derived from intermolecular interactions in solutions. Thus, at a fixed temperature, pressure and density, the refractive index increases with the molar concentration of the solute. Moreover, the values of the refractive index for mixtures 3 and 4 (glucose serum 10%) are higher than those noted for mixtures 1 and 2 (glucose serum 5%). Furthermore, intermolecular interactions increase with the molar concentration of the solute in the solutions. Therefore, the refractive index also increases with the intermolecular interactions present in the solutions.

The following relationship establishes the existing link between the refractive index and the molar concentration of the solute [15].

$$n = K \cdot C + n^{\circ}$$

n is the refractive index;

K (dm^3/mol) is a constant which depends on the physicochemical properties of the solute;

C (mol/dm^3) is the molar concentration of the solution;

n° is the refractive index at infinite dilution [15].

Following the conclusions of these results, we can say that there was no intermolecular interaction between the different molecules and/with the solvents present in the mixtures or they were weak. Regarding density, the results are shown in **Figure 3**. The density values did not vary over the duration of the simulation for mixtures with the same glucose concentrations. Therefore, the addition of VOGALENE® did not lead to a variation in these values. On the other hand, we noted that the density values increased with the glucose concentration because mixtures 3 and 4 were denser than mixtures 1 and 2. The density of the mixtures is an

important physical parameter because during a perfusion of a medicinal mixture, variation in the density value within the liquid can compromise physical and chemical compatibilities. The density depends on the molar concentrations of the solutes, their spatial distribution in the perfusion solution (mixture), their molecular weights and the temperature of the medium [16]. In fact, a poor distribution of molecules in a mixture can induce a variation in density which causes errors which would be the cause of a modification of the plasma's kinetic parameters in particular the maximum concentration (Cmax) and the maximum time (Tmax) of the medication. Thus, in the case of quinine salts, these modifications can be responsible either for therapeutic failure leading to resistance of the plasmodium to quinine, or for toxicity leading to arrhythmia or even cardiac arrest [17] [18]. As we did not notice any variation in the density value, we can say that the different mixtures were compatible and stable. Regarding the pH measurement, the results are presented in **Figure 4**. Here, we noted variations in the pH values within the mixtures between the start and the end of the simulation. But, these variations are less than half a unit. The addition of vogalene and the variation in the glucose concentration did not impact the pH values of the different mixtures. These results are in agreement with a study carried out in Spain on the physical compatibility of drugs administered in the intensive care unit of the "Son Espases" university hospital. This study carried out between 2009 and 2011 showed that a pH variation of less than half a unit is a criterion for physical compatibility [19].

5. Conclusion

In light of the results collected, we can undoubtedly say that the drug mixtures for perfusion studied have been compatible and physically stable for the duration of the simulation. For a subsequent study, we plan to perform dosages of quinine base and metopimazine in the same mixtures and extend our study to other mixtures frequently used in perfusion in the intensive care units of hospitals in Senegal. Furthermore, this study provides an experimental basis and we advise clinicians to evaluate the compatibility of drugs introduced into perfusion bags in order to improve medication management in children with serious illnesses.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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