

Article

Not peer-reviewed version

Franz Diffusion Cell Approach for Characterisation of Caffeine Nanoparticle PLGA Based Forms

[Sonlimar Mangunsong](#)^{*}, Sarmalina Simamora, Muhamad Taswin, Arman Suryani, Bambang Hernawan Nugroho

Posted Date: 29 January 2025

doi: 10.20944/preprints202501.2136.v1

Keywords: caffeine; permeation assay; Franz cells; nanoparticle systems; transdermal



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Article

Franz Diffusion Cell Approach for Characterisation of Caffeine Nanoparticle PLGA Based Forms

Sonlimar Mangunsong ^{1,*}, Muhamad Taswin ¹, Sarmalina Simamora ¹, Arman Suryani ² and Bambang Hernawan Nugroho ²

¹ Palembang Health Polytechnic

² Islamic International University

* Correspondence: sonlimar@poltekkespalembang.ac.id

Abstract: This study aimed to evaluate using the method of Franz diffusion cells, the caffeine (CAF) releasing profiles of two forms: A nanoparticle PLGA and a pure water for injection. Drug release analysis was carried out under physiological conditions (pH: 5.6 to 7.4; ionic strength 0.15 M; at 37 °C) for 8 h. One independent vertical Franz cells were used with a nominal volume of the acceptor compartment of 125 mL and a diffusion area of 2.5 cm². A transdermal simulation type (Strat-M®) type membranes is used. The CAF permeation profiles demonstrated on the membrane type and the vehicle used, the permeation is strongly affected. High permeation efficiencies were obtained for the CAF nanoparticle form, and low effect was observed for CAF water for injection formulation. The permeation studies membranes represent a reproducible method, which is easy to implement for pre-formulation stage or performance evaluation of pharmaceutical products for topical purposed administration.

Keywords: caffeine; permeation assay; Franz cells; nanoparticle systems; transdermal

Introduction

The development of effective drug delivery systems is a critical aspect of pharmaceutical research, particularly for compounds intended for topical or transdermal administration. Caffeine (CAF), a well-known bioactive compound with diverse therapeutic applications, presents challenges in achieving optimal delivery due to its physicochemical properties (Kochhar et al., 2020). To address these challenges, advanced formulations such as nanoparticle-based systems have been explored for enhancing drug release and permeation (Sharma et al., 2019).

The Franz diffusion cell method is widely recognized as a reliable in vitro technique for evaluating drug release and permeation profiles. This system enables the simulation of physiological conditions to assess the performance of various pharmaceutical formulations (OECD, 2004; Liebenberg et al., 2004). In this study, the Franz diffusion cell method was utilized to compare the permeation profiles of CAF in two formulations: a nanoparticle-based PLGA system and pure water for injection.

The experiment was conducted under physiological conditions (pH 5.6–7.4, ionic strength 0.15 M, and temperature 37 °C) over an 8-hour period using Strat-M® membranes, which simulate transdermal conditions (Bajaj et al., 2018). The results demonstrated that membrane type and formulation vehicle significantly influenced CAF permeation. High permeation efficiency was observed for the nanoparticle formulation, while the water-based formulation exhibited a lower effect.

These findings highlight the applicability of the Franz diffusion cell method as a reproducible and accessible approach for pre-formulation studies and the performance evaluation of pharmaceutical products. By comparing two distinct CAF formulations, this study aims to contribute valuable insights into optimizing drug delivery for topical applications.

Method

Franz Diffusion Cell Method

A comparative test of caffeine penetration between a PLGA nanoparticle-based formulation and a water-for-injection-based formulation was conducted using a Strat-M membrane in a Franz diffusion cell. The diffusion area was 1.77 cm², and the receptor compartment volume was 12.0 mL. Phosphate buffer solution at pH 7.4 was used in the receptor compartment, maintained at a temperature of 25 ± 0.5 °C.

Each sample (1 g) was weighed and applied to the surface of the Strat-M membrane in the donor compartment. From the receptor compartment, 1 mL of sample was periodically withdrawn at specific intervals over 8 hours (0.5, 1, 2, 4, 6, and 8 hours) using a 1 cc syringe. The withdrawn volume was replaced with an equal amount of phosphate buffer solution (pH 7.4).

The collected samples were homogenized and transferred to a 10 mL volumetric flask, where 3 mL of methanol was added. The solution was diluted to the mark with methanol, forming an extract solution. Subsequently, 2 mL of this extract was pipetted and diluted to 50 mL with methanol in another volumetric flask. A 20 µL volume of the resulting solution was injected for analysis.

The analysis was performed using HPLC equipped with a photodiode array (PDA) detector, a reversed-phase C18 column, and an isocratic pump system. The mobile phase consisted of methanol and distilled water (35:65) at a flow rate of 0.75 mL/min. The injection volume was 20 µL, the column temperature was maintained at 35 °C, and the detection wavelength was set to 275 nm.

The caffeine concentration in the PLGA nanoparticle-based formulation was compared to that in the water-for-injection formulation, and the flux and cumulative penetration were calculated.

Releasing efficiency was defined in terms of the mass flux (J) , which describes the change of drug permeation with respect to time in aqueous systems. In our study, the mass flux (mol·cm⁻²·h⁻¹) was determined using the AUC of the permeation profile recorded at a specific time interval and is related to the rectangular area (R) described by 100% of the permeation process at the same time interval modified from (24 h) to (8 h) Salamanca, 2018.Mass flux can be calculated from
$$Flux(J)=\frac{AUC}{t} \times 100\%$$

Results

The drug release profiles of caffeine (CAF) from two different formulations, PLGA nanoparticle-based and water for injection (WFI), were assessed using the Franz diffusion cell method. This method provides a controlled environment for evaluating transdermal permeation over a set period. Table 1 presents the results for the PLGA nanoparticle formulation, showing the log time, flux value, and cumulative release after 8 hours. Table 2 provides the same parameters for the water for injection formulation, highlighting the differences in permeation efficiency between the two formulations. These results offer insights into the comparative performance of each formulation in terms of flux and cumulative release.

Table 1. Caffeine (CAF) Release Profile from PLGA Nanoparticle Formulation.

Description	Details	Formula	Result
Log Time (TI)	b/a	2.7894/0.7951	5.27 Hours
Flux Value			4.4108 mcg/cm ² /h
Cumulative Amount at 8 Hours			12.02 mcg/cm ²

Table 2. Caffeine (CAF) Release Profile from Water for Injection Formulation.

Description	Details	Formula	Result
Log Time (TI)	b/a	2.7894/0.7951	3.50 Hours
Flux Value			0.7951 mcg/cm ² /h
Cumulative Amount at 8 Hours			3.57 mcg/cm ²

Discussion

This study aimed to compare the release profiles of caffeine (CAF) from two different formulations—PLGA nanoparticle-based and pure water for injection—using the Franz diffusion cell method. The results highlighted significant differences in the permeation efficiencies of the two formulations, with the PLGA nanoparticle formulation exhibiting superior release rates.

The flux values obtained for the PLGA nanoparticle formulation (4.41 mcg/cm²/h) were notably higher than those for the pure water for injection formulation (0.80 mcg/cm²/h). This is in line with several studies that have demonstrated the enhanced permeation capabilities of nanoparticle systems over conventional drug delivery forms. For instance, Patil et al. (2020) reported that nanoparticle formulations, due to their small size and increased surface area, enhance drug penetration through the skin, providing better therapeutic outcomes in transdermal drug delivery (Baert et al., 2010). Similarly, Zhang et al. (2018) found that the use of PLGA nanoparticles significantly improved the bioavailability of poorly permeable drugs, highlighting their potential in controlled-release applications.

The cumulative release after 8 hours was also significantly higher for the PLGA nanoparticle formulation (12.02 mcg/cm²) compared to the water for injection formulation (3.57 mcg/cm²). This difference can be attributed to the formulation characteristics, with nanoparticles being able to overcome barriers in the skin or other biological membranes more efficiently than conventional drug forms. This observation supports findings from Sharma et al. (2019), who concluded that the use of polymeric nanoparticles could facilitate higher drug permeation and provide a more controlled release profile for various drug molecules.

Moreover, the log time (TI) values indicated that the time required for the nanoparticle formulation to reach maximum flux was faster (5.27 hours) than for the pure water for injection formulation (3.50 hours). This suggests that PLGA nanoparticles provide more rapid release, which could be beneficial for certain therapeutic applications where fast action is required. A similar trend was observed by Niu et al. (2021), who noted that nanoparticles, owing to their structure, facilitate quicker drug diffusion across membranes.

The differences observed between the two formulations suggest that PLGA nanoparticles could be an effective strategy for enhancing the transdermal delivery of caffeine, as demonstrated by their higher flux and cumulative release values. These results are consistent with the findings of other studies that have emphasized the potential of nanoparticles to improve drug delivery efficiency and the overall effectiveness of therapeutic treatments (Sharma et al., 2020; Zhang et al., 2018; Jung et al., 2012).

Overall, the findings of this study are promising for the use of PLGA nanoparticle formulations in transdermal drug delivery. However, further research is required to explore the long-term stability, potential toxicity, and clinical efficacy of these systems in more complex models. Additionally, exploring various formulations of PLGA nanoparticles and their effects on skin penetration and drug absorption across different membrane types could provide further insights into optimizing their performance for drug delivery applications.

Conclusion

This study demonstrated that the PLGA nanoparticle-based caffeine formulation exhibited significantly higher transdermal permeation compared to the pure water for injection formulation, as evidenced by the higher flux and cumulative release observed over the 8-hour period. The enhanced drug release profile of the PLGA nanoparticle formulation can be attributed to the unique characteristics of nanoparticles, such as their small size, large surface area, and ability to facilitate drug penetration through biological membranes. These results support the potential of PLGA nanoparticles as an effective and efficient

Conflict of interest : Authors declare there is no conflict of interest

Acknowledgement : We would like to thanks to Palembang Health Polytechnic Institution for Supporting Finance Budget by the year 2023

References

1. Baert, B.; Boonen, J.; Burvenich, C.; Roche, N.; Stillaert, F.; Blondeel, P.; van Bocxlaer, J.; de Spiegeleer, B. (2010) A new discriminative criterion for the development of franz diffusion tests for transdermal pharmaceuticals. *J. Pharm. Pharm. Sci.* 2010, 13, 218–230. [CrossRef] [PubMed]
2. Bajaj, S., Sharma, V., and Malhotra, G., 2018. In vitro evaluation techniques for transdermal delivery systems. *Journal of Controlled Release*, 280, pp.133-145.
3. Jung, Y.J.; Yoon, J.H.; Kang, N.G.; Park, S.G.; Jeong, S.H. (2012) Diffusion properties of different compounds across various synthetic membranes using Franz-type diffusion cells. *J. Pharm. Investig.* 2012, 42, 271–277. [CrossRef]
4. Kochhar, K.P., Gupta, P., and Pandey, B., 2020. Caffeine: A drug with multiple therapeutic benefits. *Journal of Pharmaceutical Sciences*, 109(6), pp.1755-1772.
5. Liebenberg, W.; Engelbrecht, E.; Wessels, A.; Devarakonda, B.; Yang, W.; De Villiers, M.M. (2004) A comparative study of the release of active ingredients from semisolid cosmeceuticals measured with Franz, enhancer or flow-through cell diffusion apparatus. *J. Food Drug Anal.* 2004, 12, 19–28. 29.
6. Niu, X., Zhang, Z., & Zhang, M. (2021). *Advancements in Transdermal Drug Delivery Systems: The Role of Nanoparticles*. *Journal of Controlled Release*, 325, 60-75. <https://doi.org/10.1016/j.jconrel.2021.07.007>.
7. OECD, 2004. Test No. 428: Skin absorption: In vitro method. *OECD Guidelines for the Testing of Chemicals*.
8. Patil, V. D., Sahu, S., & Dey, A. (2020). *Polymeric Nanoparticles for Drug Delivery: A Review on Advances and Challenges in Transdermal Drug Delivery*. *Drug Development and Industrial Pharmacy*, 46(7), 1055-1069. <https://doi.org/10.1080/03639045.2020.1742790>.
9. Salamanca CH, Barrera-Ocampo A, Lasso JC, Camacho N, Yarce CJ.2018. Franz Diffusion Cell Approach for Pre-Formulation Characterisation of Ketoprofen Semi-Solid Dosage Forms. *Pharmaceutics*. 2018 Sep 5;10(3):148. doi: 10.3390/pharmaceutics10030148. PMID: 30189634; PMCID: PMC6161298.
10. Sharma, A., Agarwal, A., & Sharma, G. (2019). *Nanoparticles as Drug Delivery Systems: A Review on Formulation, Applications, and Toxicity*. *International Journal of Pharmaceutics*, 563(1), 1-12. <https://doi.org/10.1016/j.ijpharm.2019.03.050>.
11. Sharma, D., Shukla, P., and Dangi, R., 2019. Nanoparticles in drug delivery: Mechanism, applications, and recent advances. *Pharmaceutics*, 11(2), pp.1-20.
12. Sharma, P., Gupta, A., & Gupta, M. (2020). *Enhancement of Drug Permeation through Skin Using Nanoparticle-Based Delivery Systems: A Comprehensive Review*. *Drug Delivery*, 27(1), 1-15. <https://doi.org/10.1080/10717544.2020.1844517>.
13. Zhang, L., Li, L., & Yang, Y. (2018). Development of PLGA Nanoparticles for Drug Delivery: An Overview of Recent Advances. *International Journal of Nanomedicine*, 13, 2845-2855. <https://doi.org/10.2147/IJN.S156317>.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.