Mixed Poloxamer-TPGS Micelles: An Innovative Strategy for Encapsulation of Liposoluble Drugs

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Abstract. The low water solubility of many drugs represents a major obstacle in the development of effective treatments. Nanotechnology emerges as a key tool to address this problem. Nanocarriers offer a versatile platform for encapsulating and transporting low-solubility drugs, improving their distribution in the body. This strategy not only increases the efficacy of treatments, but it also reduces the toxicity associated with conventional drugs. Mixed micelles of poloxamer and d-α-tocopherol polyethylene glycol succinate (TPGS) offer an innovative solution to improve drug solubility and biocompatibility. The combination of these polymeric surfactants allows modulating the properties of the micelle, increasing its ability to encapsulate hydrophobic compounds and improving its stability in aqueous media. This strategy not only optimizes the bioavailability of the drugs, but also presents the potential of reducing the dose needed to achieve the desired therapeutic effect, thus reducing the adverse effects associated with the treatment. In this work, mixed micelles of poloxamer and TPGS were used to improve the solubility of curcumin; different proportions of surfactants were used to prepare a series of formulations. The results showed that the hydrodynamic diameter of the micelles and the viscosity of the micellar solutions can be modulated by composition, allowing the properties of the system to be adjusted to the specific needs of each application. In addition, mixed micelles have a higher curcumin encapsulation capacity compared to systems formed by a single surfactant.

Keywords: Mixed micelles · curcumin · poloxamer · TPGS

1 Introduction

Recently, new active ingredient delivery systems based on nanotechnology have been developed. These systems have successfully addressed the drawbacks associated with the use of liposoluble drugs, allowing nanocarriers to enhance effective and specific

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biomolecular interactions to reduce treatment-induced side effects [1–4]. Poloxamers are triblock copolymers of polyethylene oxide (PEO) and polyethylene oxide (PPO), where the ratio between ethylene oxide and propylene oxide units determines the amphiphilic characteristic of the copolymers, which influences their thermosensitive properties and their ability to form gels at body temperature, making them ideal for drug delivery and biomedical applications [5–9]. On the other hand, D-A-tocopherol polyethylene glycol succinate (Vitamin E TPGS, or simply TPGS), an ethoxylated derivative of vitamin E, has great potential as a nanocarrier due to its high biocompatibility and its ability to improve the solubility of drugs, which increases the efficacy and reduces side effects caused by drugs with low solubility in aqueous media [7–9], as is the case of curcumin, which is a phytochemical with multiple benefits in people's health [10, 11]. In this work, the encapsulation capacity of mixed micellar systems was evaluated. The combination of two polymeric surfactants where both have a hydrophilic PEO chain with different hydrophobic chains (PPO vs Vitamin E) and different HLBs (Table 1), offers an alternative approach to expand the hydrophobic domain of the micelle while maintaining stability. The goal is to increase the curcumin-carrying capacity of the mixed micelles as compared to the individual systems [12, 13].

Table 1. Properties of surfactants

Surfactants	Hydrophilic units	Lipophilic units	HLB	MW (KDa)	CMC (M)	Cloud Point (°C)
Poloxamer 123	13 EO	22 PO	12	$2.2x10^{-3}$	1.85	42
Poloxamer 124	23 EO	20 PO	16	3.6×10^{-3}	2.2	65
TPGS	PEG 1000	1 Tocopherol	13	1.3×10^{-4}	1.5	78

2 Methodology

2.1 Formulation of Mixed Micellar Systems

Mixed micelles were prepared by using two types of poloxamers: P123 (Sigma Aldrich) and P124 enriched with 100 ppm vitamin E (BASF). TPGS was added to these poloxamers in different proportions (Table 2). Solubilization was carried out in deionized water by heating to 75 °C and constant agitation. Finally, curcumin was incorporated, and the mixture was kept under the same conditions for 4 h.

2.2 Encapsulation Efficiency (EE%) and Loading Capacity (LC%)

To determine the percentage of incorporation, 11 standard solutions were prepared with concentrations of curcumin or fenofibrate ranging from 3 ppm to 12 ppm; where a

Table 2. Formulations of micellar systems.

Micellar system	V1	V2	V3	V4	V5
Poloxamer (P123 o P124)	0%	25%	50%	75%	100%
TPGS	100%	75%	50%	25%	0%

solution of water with ethanol as a target was used, from these standard solutions, the corresponding calibration curves were obtained. Finally, the following equations were used to calculate the percentage of incorporation and the carrying capacity of the active ingredients in the micelles:

$$\%EE = \frac{Amount\ of\ active\ ingredient\ loaded\ into\ the\ micelle(mg)}{Initial\ amount\ of\ active\ ingredient\ used\ (mg)} * 100 \quad (1)$$

$$\%LC = \frac{Amount\ of\ active\ ingredient\ loaded\ into\ the\ micelle(mg)}{Total\ amount\ of\ solids(mg)} * 100 \quad (2)$$

2.3 Characterizations

The hydrodynamic size of the micelles was characterized by dynamic light scattering (DLS) in a Zetasizer Nano ZS (Malvern Panalytical). Stability studies were performed by visually evaluating phase separation. In addition, viscosity was determined on an AR G2 rotational rheometer (TA Instruments) between 15 and 60 °C at 1000 m/min. The incorporation of active ingredients was quantified by UV-Vis spectroscopy in an Optizen POP (Mecasys).

3 Results

The results of DLS characterization of the P123/TPGS poloxamer-based systems (see Fig. 1) showed a gradual decrease in micelle size as the proportion of TPGS increased. The hydrodynamic diameters of the mixed micelles were in an intermediate range between those of the micelles formed by each surfactant separately, ranging from 6 to 12 nm. A direct correlation was observed between the composition of the micelles and their size: the micelles rich in P123 had larger diameters, while the smaller ones corresponded to systems with a higher TPGS content.

In P124/TPGS-based systems, the opposite effect was observed; this was due to the differences in PEO-PPO-PEO chainlengths of P124 compared to P123. The hydrodynamic diameter of the micelles decreased with increasing proportion of poloxamer 124, in the range of 4 to 7 nm. However, in mixed micelles with a higher proportion of P124 (V4 with 75% of P124), two size populations were detected, suggesting a coexistence of micelles rich in each of the surfactants. This behavior indicates that, at certain compositions, an ideal homogeneous mixture of surfactants was not achieved.

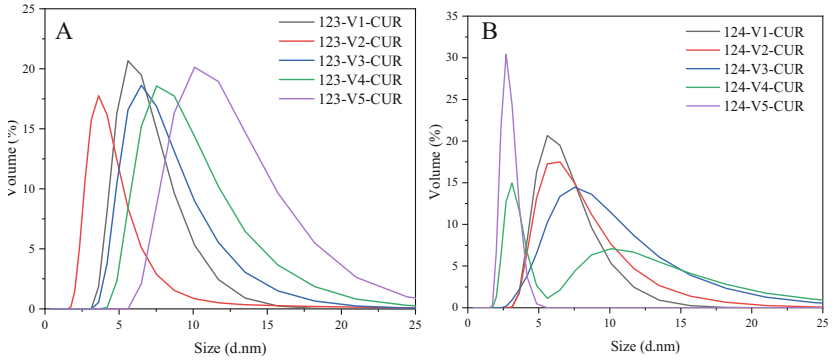


Fig. 1. Hydrodynamic diameter distribution by DLS of the mixed micellar systems loaded with curcumin: A) P123 and B) P124.

The viscosity results presented in Fig. 2A show that TPGS and P123/TPGS micelles in a 1:3 ratio (75% TPGS) undergo a progressive decrease in viscosity until they reach a minimum, followed by a drastic increase. This behavior suggests a possible instability of the micelles at certain concentrations, which could trigger aggregation. On the other hand, systems with a 1:1 and 3:1 ratio (50 and 25% TPGS) exhibit a behavior like that of pure P123 poloxamer. The decrease in viscosity with increasing temperature is attributed to an increase in the mobility of the micelles, which reduces the internal friction of the system. A similar trend is observed in systems with P124/TPGS (see 2B): viscosity decreases with increasing temperature. However, the presence of vitamin E in poloxamer 124 gives these micelles a behavior closer to that of pure TPGS micelles. Importantly, all mixed micellar systems with P123/TPGS and P124/TPGS at 37 °C (body temperature) have a viscosity lower than that of blood (3.5×10^{-3} Pa·s), which minimizes the risk of venous obstruction.

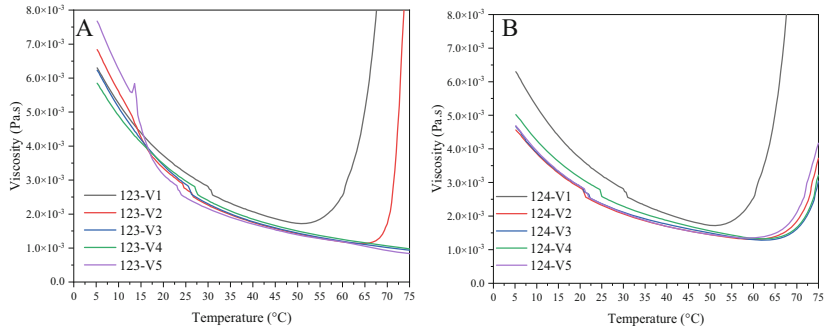


Fig. 2. Viscosity curve as a function of temperature of micellar systems: A) P123 and B) P124

The encapsulation efficiency (EE%) and loading capacity (%LC) results presented in Fig. 3 and Table 2 show that both P123 and P124 poloxamers, under various conditions, managed to encapsulate curcumin at levels above 1.20% by mass. Mixed systems

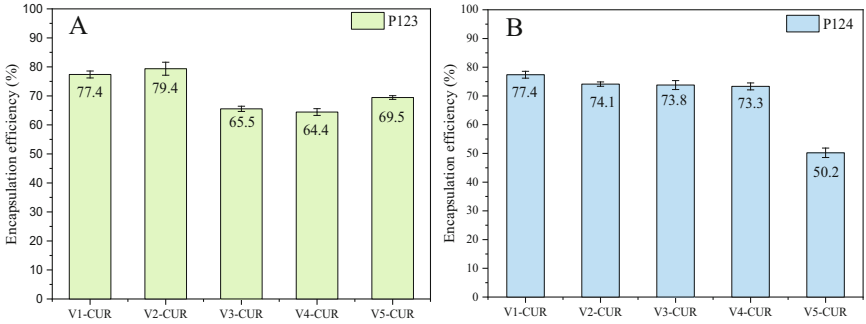


Fig. 3. Encapsulation of curcumin with different formulations: A) P123 and B) P124

with a 1:3 ratio of poloxamer and TPGS, respectively, exhibited the highest encapsulation efficiencies compared to other systems evaluated. Micelles formulated with P123 demonstrated, in general, a high encapsulation efficiency, exceeding 60% and reaching loading capacities greater than 1.40% in all the cases studied. On the other hand, the systems based on P124/TPGS presented a lower variability in the incorporation efficiency, remaining between 73% and 74%.

These differences in encapsulation efficiency can be attributed to the intrinsic properties of the P123 and P124 poloxamers. Despite sharing a basic structure composed of ethylene oxide and propylene oxide units, variations in the length of these chains confer each poloxamer different hydrophilic-lipophilic (HLB) characteristics, critical micellar concentration (CMC), and other unique properties that influence its ability to solubilize and encapsulate molecules such as curcumin. Importantly, in all cases evaluated, a significant improvement in the solubility of curcumin was observed compared to its free form, as shown in Table 3. This phenomenon is explained by the incorporation of the lipophilic drug inside the core of the micelles, which protects them from the aqueous medium and increases their apparent solubility.

Table 3. Encapsulation efficiency of curcumin with different formulations

Micellar system	EE (%)	LC (%)	Solubility of Curcumin in the System (μg/mL)	Increased solubility*
P123-V1-CUR	78.4	1.8	2352.3	3920.5
P123-V2-CUR	76.4	1.8	2308.6	3847.7
P123-V3-CUR	64.6	1.5	1938.5	3230.8
P123-V4-CUR	63.7	1.4	1910.7	3184.5
P123-V5-CUR	69.1	1.6	2069.5	3449.3

(*continued*)

Table 3. (*continued*)

Micellar system	EE (%)	LC (%)	Solubility of Curcumin in the System (μg/mL)	Increased solubility*
P124-V1-CUR	78.4	1.8	2352.3	3920.5
P124-V2-CUR	75.2	1.7	2255.4	3759.1
P124-V3-CUR	72.8	1.7	2184.7	3641.2
P124-V4-CUR	72.2	1.6	2166.4	3610.8
P124-V5-CUR	51.2	1.2	1536.6	2561.1

* (calculated as: solubility of curcumin in micellar system / solubility of curcumin in water).

4 Conclusion

The study demonstrates that mixed micelles of poloxamer and TPGS offer a versatile system for the encapsulation of drugs such as curcumin. The composition of micelles significantly influences their size, stability, and encapsulation efficiency. The results obtained suggest that these formulations could have promising applications in the development of controlled drug delivery systems.

References

1. Wei, Q.Y., Xu, Y.M., Lau, A.T.Y.: Recent progress of nanocarrier-based therapy for solid malignancies. MDPI AG (2020). https://doi.org/10.3390/cancers12102783
2. Mishra, N., et al.: Targeted drug delivery: a review. REVIEW ARTICLE Am. J. PharmTech Res. **6**(1) (2016). www.ajptr.com
3. Rojas-aguirre, Y.: Q uímica, 286–291 (2016)
4. Kamboj, V.K., Kumar Verma, P.: Poloxamers based nanocarriers for drug delivery system. Scholars Research Library Der Pharmacia Lettre **7**(2), 264–269 (2015). www.scholarsresearchlibrary.com
5. De Mello, J.C., et al.: Enhancement of chlorpromazine antitumor activity by Pluronics F127/L81 nanostructured system against human multidrug resistant leukemia. Pharmacol. Res. **111**, 102–112 (2016). https://doi.org/10.1016/j.phrs.2016.05.032
6. Almeida, M., Magalhães, M., Veiga, F., Figueiras, A.: Poloxamers, poloxamines and polymeric micelles: Definition, structure and therapeutic applications in cancer. Journal of Polymer Research **25**(1) (2018). https://doi.org/10.1007/s10965-017-1426-x
7. Tavares Luiz, M., et al.: The use of TPGS in drug delivery systems to overcome biological barriers. Elsevier Ltd. (2021). https://doi.org/10.1016/j.eurpolymj.2020.110129
8. Guo, Y., Luo, J., Tan, S., Otieno, B.O., Zhang, Z.: The applications of Vitamin e TPGS in drug delivery (2013). https://doi.org/10.1016/j.ejps.2013.02.006
9. Zhang, Z., Tan, S., Feng, S.S.: Vitamin E TPGS as a molecular biomaterial for drug delivery (2012). https://doi.org/10.1016/j.biomaterials.2012.03.046
10. Li, X., Chen, T., Xu, L., Zhang, Z., Li, L., Chen, H.: Preparation of curcumin micelles and the in vitro and in vivo evaluation for cancer therapy. J. Biomed. Nanotechnol. **10**(8), 1458–1468 (2014). https://doi.org/10.1166/jbn.2014.1840

11. González-Albadalejo, J., et jal.: Curcumin and curcuminoids: chemistry, structural studies and biological properties. Anales de la Real Academia Nacional de Farmacia **81**(4), 278–310 (2015). http://www.analesranf.com/index.php/aranf/article/view/1665/1706
12. Islam, N., et al.: Poloxamer-188 and d-α-tocopheryl polyethylene glycol succinate (tpgs-1000) mixed micelles integrated orodispersible sublingual films to improve oral bioavailability of ebastine in vitro and in vivo characterization. Pharmaceutics **13**(1), 1–21 (2021). https://doi.org/10.3390/pharmaceutics13010054
13. Lee, C.F., Tseng, H.W., Bahadur, P., Chen, L.J.: Synergistic effect of binary mixed-pluronic systems on temperature dependent self-assembly process and drug solubility. Polymers (Basel) **10**(1) (2018). https://doi.org/10.3390/POLYM10010105