Macedonian pharmaceutical bulletin, 69 (Suppl 1) 19 - 20 (2023)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2023.69.03.009
Short communication

Novel self-nanoemulsifying drug delivery systems containing curcumin for topical drug delivery

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Introduction

Curcuma longa has been used both externally and internally for decades due to its beneficial effects on health and low toxicity. The polyphenolic compound called curcumin - which is the main active ingredient of the plant - can be isolated from the rhizome of the turmeric (Tomeh et al., 2019). Based on the literature, curcumin can be promising in the treatment of various clinical symptoms, as it is associated with significant anti-inflammatory and antioxidant activities (Goel et al., 2008). It also can exhibit beneficial effects in wound healing and prevention of chronic ultraviolet B damage. Despite these positive effects, a major criticism of curcumin is its poor bioavailability. According to the Biopharmaceutical Classification System (BCS), it belongs to group IV, which means that it shows very low water-solubility and permeability (McClements et al., 2015). Therefore, the in vivo effectiveness of curcumin is usually limited in aqueous solution. This study was aimed to design topical dosage forms containing curcumin in self-nanoemulsifying drug delivery system (SNEDDS) and to evaluate their in vitro and anti-inflammatory and antioxidant effects.

Materials and methods

First of all, solubility and emulsification efficiency studies were carried out to identify suitable SNEDDS components. By the construction of the pseudoternary phase diagrams, the quantities of the oil phase, surfactant, and co-surfactant in appropriate portions were determined. Self-nanoemulsifying drug delivery systems (SNEDDS) were developed by mixing the selected surfactant (Labrasol) and co-surfactant (Transcutol P) in 1:1 ratio and then isopropyl myristate (IPM) was added as the oil phase. The given concentration of curcumin was dissolved in the mixture. The composition of the formulated self-emulsifying systems was presented in Table 1.

Table 1. The composition of the formulated self-emulsifying systems

Comp.	Transcutol	Cremophor RH	Labrasol	IPM
A	37.5 g	37.5 g	-	15 g
B	30.0 g	30.0 g	-	30 g
C	37.5 g	-	37.5 g	15 g
D	30.0 g	-	30.0 g	30 g

A dynamic light scattering (DLS) device was used to determine the droplet size of the dispersed phase. The electrostatic potential (zeta potential) of the double layer surrounding the droplets was also measured with Zetasizer Nano S equipment. With the investigation of the zeta potential, the stability of the self-emulsifying systems was determined. The samples were freshly diluted with 100 mL distilled water and analyzed in triplicate in all measurements. The drug loading efficiency and the thermodynamic stability of the SNEDDS were also determined. The cytotoxic effects of the formulations were examined by the MTT assay on the human keratinocyte (HaCaT) cell line. The direct radical scavenging activity was investigated by 2,2-diphenyl-1-picrylhydrazyl (DPPH) method, while indirect antioxidant capacity was determined by the measurement of the superoxide dismutase enzyme level on HaCaT cell after the treatment. To investigate the anti-inflammatory effect of the curcumin

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containing SNEDDS, ELISA tests were performed on HaCaT cell line.

Curcumin containing creams and gels were formulated using two different emulsifiers (Tefose 63 and Sedefos 75) and two different gelling agents (Pemulen TR-1 and Carbopol 974P) as well. To determine the release rate of curcumin from the creams and gels permeation studies were performed by Franz vertical diffusion cells. Anti-inflammatory activity was measured using a carrageenan-induced rat paw edema assay. The level of inflammation induced by UV radiation after pretreatment was also determined in rats.

Results and discussion

The present study describes the development of novel curcumin-containing drug delivery systems and the investigation of their antioxidant and anti-inflammatory potential. It was found that the most dominant factor which influenced the area of the nano-emulsion existing zone was the amount of the oily phase. According to the results, the nano-emulsion existing zone was the largest in the case of the composition prepared with Labrasol - Transcutol P – IPM mixture in the same proportions. The DLS measurement verified that the higher oil content resulted in a larger particle size. Although the droplet size increased with the incorporation of the active ingredient, the polydispersity index (PDI) remained unchanged, indicating a homogeneous size distribution.

In self-emulsifying drug delivery systems, negative charge is common and it is accepted in the literature that a system is stable if its zeta potential is higher than ± 30 mV (Kuznetsova et al., 2015). Our formulations were characterized by slightly negative zeta potential, between -15.12 and -18.12 mV, which was due to the use of nonionic surfactants. However, during the thermodynamic stability testing, no precipitation, creaming, cracking, or phase-separation was observed, and these results overall suggest acceptable stability. The drug loading efficiency for formulations was found in the range of 93.11% to 99.12%. It was also observed that compositions with a higher concentration of oily phase possess a higher capacity to solubilize curcumin. In our study, the cytotoxicity of 1, 5, and 10 w/v% solutions of the formulated SNEDDS was determined. It was found that compositions formulated with Labrasol were better tolerated by both cell lines. The measured cell viabilities were higher than 70%, even when cells were treated with the 10 w/v% solution, which complies with ISO 10993-5 recommendations. SOD activity of HaCaT cells was monitored after the treatment with the different SNEDDS compositions. Treatment with Labrasol containing compositions caused a significantly higher SOD level. The results showed that curcumin had higher radical scavenging activity when it was incorporated into a SNEDDS.

This study demonstrated that treatments with gels containing curcumin incorporated in SNEDDS significantly reduced the level of TNF-α and IL-1β investigated on HaCaT cell line. The anti-inflammatory effect was also supported by in vivo experiments as it was presented in Figure 1.

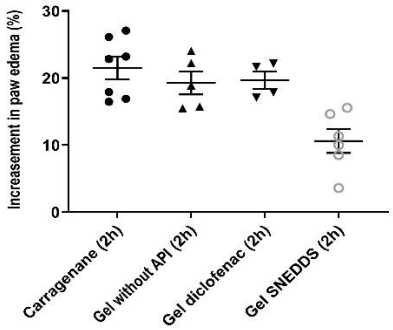

Fig. 1. Effect of the treatment of the selected gel composition on the carrageenan-induced rat paw edema.

Conclusion

According to the experiments, our formulations had high thermodynamic stability, and drug loading efficiency. All preparations greatly enhanced the anti-inflammatory effect of curcumin on HaCaT cells as well as its antioxidant capacity while maintaining acceptable cell viability. Thus, the formulation of curcumin into SNEDSS could be a promising approach for overcoming the solubility and bioavailability problems related to this highly lipophilic drug.

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