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Cyanocobalamin Ultraflexible Lipid Vesicles: Characterization and In-Vitro Evaluation of Drug-Skin Depth Profiles

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1. Introduction

Atopic dermatitis (AD) and psoriasis are the most common chronic inflammatory skin disorders, which importantly affect the quality of life of patients who suffer them. Among other causes, nitric oxide has been reported as part of the triggering factors in the pathogenesis of both conditions. Cyanocobalamin (vitamin B12) has shown efficacy as a nitric oxide scavenger and some clinical trials have given positive outcomes in its use for treating skin pathologies [1]. Passive skin diffusion is possible only for drugs with low molecular weights and intermediate lipophilicity. Unfortunately, the molecular weight and hydrophilicity of vitamin B12 do not predict its effective diffusion through the skin. The aim of this work was to design new lipid vesicles to encapsulate the vitamin B12 to enhance its skin penetration

2. Materials and methods

2.1. Preparation of lipid vesicles

Several formulations of liposomes (L), transferosomes (T), and ethosomes (E) were prepared by the classic film-hydration method [2]. Figure 1 redirects to the document where their quantitative composition, reconstitution conditions, and the methods used to purify them are shown.

Fig. 2. QR code for redirecting to the original work [1].

2.2. Characterization of lipid vesicles

The vesicles were characterized in terms of entrapment efficiency (EE), Size, PDI, Z-potential, flexibility, phospholipid content (PC), stability, and drug release. B12 was quantified by HPLC (360 nm; column C18, methanol:water 30:70; flow 1 mL min-1).

2.3. Drug penetration through the skin: Tape -stripping studies

One hundred microliters of each formulation containing lipid vesicles was applied to the delimited application area of skin. The system was then incubated at 32 ºC for 2, 4, and 6 h. After incubation, 20 strips of adhesive tape were applied sequentially to the skin, according to the standardized procedure, and then removed [1].

3. Results and Discussion

3.1. Characterization of lipid vesicles

3.1.1. Size, PDI and Z-potential and EE.

Size, PDI and Z-potential results are shown in Table 2. Transferosomes and ethosomes were the smaller in comparison to liposomes, and therefore the most optimal for transdermal de-

Components (% w/v)	Formulations				
	L1	L2	T1d	T2d	E1
Size	283 ± 6	278 ± 13	177 ± 4	171 ± 3	150 ± 5
PDI	0.269 ± 0.07	0.205 ± 0.002	0.223 ± 0.01	0.244 ± 0.03	0.200 ± 0.003
Z-pot (mV)	-11.2 ± 0.12	-10.1 ± 0.30	-5.51 ± 0.17	-5.17 ± 0.37	4.63 ± 0.75
EE (%)	20 ± 2	37 ± 4	24 ± 2	30 ± 1	11 ± 2
PC (%)	80 ± 4	84 ± 7	86 ± 6	82 ± 5	66 ± 2

Table 2. Characterization results of the B12 lipid vesicles in terms of Size, Z-potential, EE and PC.

livery purposes. PDI remained in all cases below 0.3, making all prototypes suitable for pharmaceutical purposes [2]. As expected, Z-potential values were negative due to the negative charge of phospholipids.

3.1.2. Vesicle flexibility

The vesicle size reduction rate and volume loss after cold extrusion as an indirect measurement of the vesicles deformability capacity [2]. Significant differences were obtained between liposomes and ultraflexible vesicles, as expected. Liposomes were retained in the 100 nm filters and forced to split into smaller particles to pass the pores.

3.1.3. Vesicle Stability

Short-term stability was assessed by Turbiscan analysis. TSI results (Figure 2) showed that transferosomes were the most stable formulation since no changes in light transmission and backscattering lines were reported over 24 h. On the contrary, liposomes experienced a notably sedimentation process and they were revealed as the most instable formulation.

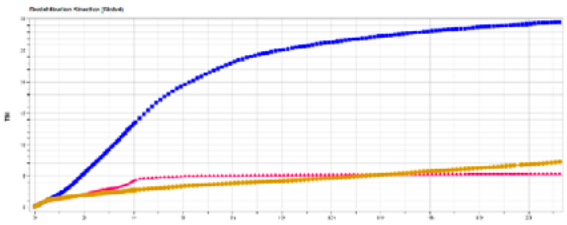

Fig. 2. Short-term stability data. L1 TSI (blue), T1 TSI (red) and E1 TSI (yellow)

3.1.4. Drug release

Figure 3 shows the B12 drug release pattern from all vesicles.

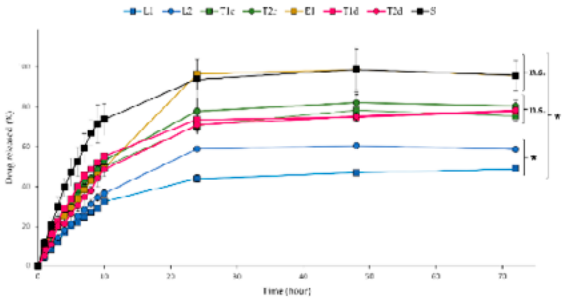

Fig. 3. Drug release pattern from all vesicles. Liposomes (blue), Transferosomes (red), Ethosomes (yellow) and drug solution (black)

A B12 solution 0.05 % w/v (S) was used as a control as it represents the drug diffusion profile without limitations. The rest of the lipid vesicle formulations showed a controlled release of drug, as shown in Figure 3. The long-term percentage of drug released is probably also affected by this vesicle properties. The lowest percentage of drug released corresponded to the liposomes and the highest to the ethosomes.

3.1. Drug penetration through the skin: Tape -stripping studies

The best penetration results were obtained using liposomes and transferosomes. L2 carries less B12 amounts than the other prototypes, consequently showing a considerably lower B12 amounts, only until approximately 15 m depth. Nevertheless, L1, T1d, and T2d vesicles allowed the B12 to reach the dermis (>25 m). L1 and T2d contained similar B12 doses, but after 12 h of incubation, the transferosomes showed higher permeation rates up to the deepest layers.

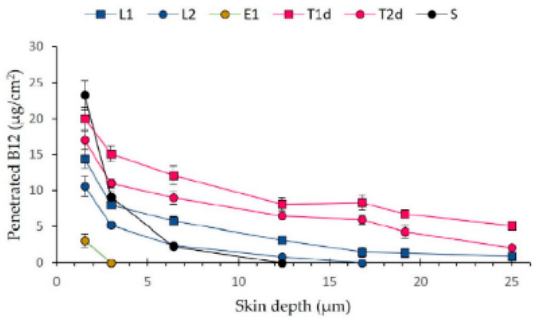

Fig. 4. Penetration profile of B12 delivered from lipid vesicles after 12 h. Liposomes (blue), Transferosomes (red), Ethosomes (yellow) and drug Solution (black)

4. Conclusions

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