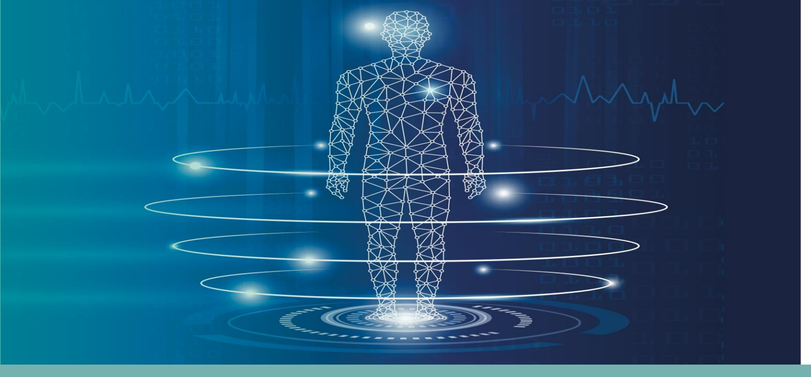

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Development of liposomes containing Nebivolol for topical treatment of Erectile Dysfunction

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Introduction:

Nebivolol hydrochloride (NEB), is a beta-blocker drug widely used to treat hypertension and chronic heart failure. It has vasodilatory properties due to its interaction with the L-arginine/nitric oxide pathway, which has prompted interest in its potential as a topical treatment for erectile dysfunction (ED). Lipid-based nanoparticles like liposomes (LP) are efficient drug delivery systems that can act as carriers and provide a localized skin depot, minimizing systemic effects [1-2]. The use of sulfobutylether-βCD (SBEβCD) and methyl-β CD (CAVASOL) has been included in the formulation given their demonstrated efficacy as permeation enhancers for topical formulations.

Aim of the work:

Development of a liposomal formulation containing nebivolol (NEB) for the topical treatment of erectile dysfunction (ED), in order to allow the release of nebivolol into the skin.

Materials:

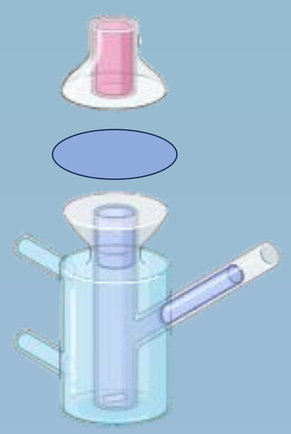
Nebivolol hydrochloride (NEB), kindly donated by A. Menarini,;
Sodium deoxycholate (SDC) and Cholesterol (CH), Merck group; Phospholipon (P), Lipoid; methyl-β CD (CAVASOL), Wacker; Solfobutylether- β CD (SBEβCD), Cyclolab.

Results and discussion:

The LP were prepared using the Thin Layer Evaporation (TLE). Two formulations from the literature were selected: **Formulation A**, with C, PC and SDC and **Formulation B**, with C, PC and without SDC [3-4]. Firstly, a screening Full Factorial Design (FFD 1) with 3 factors at 2 levels for a total of 11 experiments (8 + 3 center points) was applied. The software used was MODDE-GO version 12.01, Umetrics. Formulation N4 and N6 were selected from FFD1.
In order to improve drug permeation, two types of cyclodextrins were incorporated at different concentrations. An additional Experimental Design, FFD2, was used to select the most promising LP formulation. On the formulations selected from the FFD2, MTT tests were performed on keratinocytes, and permeation tests were conducted using the FRANZ diffusion cell system.

FFD 1	NEB Amount	Hydr Vol	SDC	Size (nm)	PDI	Z-pot (mV)	EE (%)
N1	5	10	Y	259,9	0,41	-40	100
N2	15	10	Y	481,1	0,53	-34,6	100
N3	5	20	Y	192,5	0,36	-42,4	100
N4	15	20	Y	235,7	0,18	-32,3	100
N5	5	10	N	92,2	0,27	+25,1	77
N6	15	10	N	85,7	0,27	+38,5	74
N7	5	20	N	84,9	0,31	+19	98
N8	15	20	N	88,2	0,31	+49	88
N9	10	15	Y	262,1	0,40	-44	100
N10	10	15	Y	280,7	0,39	-45,6	99
N11	10	15	Y	273,6	0,42	-43,6	98

FFD 2	CD conc	CD type	SDC	Size (nm)	PDI	Z-pot (mV)	EE (%)
N1	-1	CAVASOL	Y	346,7	0,53	27,2	100
N2	1	CAVASOL	Y	576,5	0,81	27,7	100
N3	-1	SBEBCD	Y	320,4	0,35	31,8	100
N4	1	SBEBCD	Y	622	0, 95	25,1	100
N5	-1	CAVASOL	N	105,7	0,29	47,3	77
N6	1	CAVASOL	N	121,6	0,22	49,8	74
N7	-1	SBEBCD	N	2936	0,19	6, 2	98
N8	1	SBEBCD	N	3606	0,43	8,3	88
N9	0	CAVASOL	Y	333,2	0,6	29,1	100
N10	0	CAVASOL	Y	308,2	0,38	27,2	99
N11	0	CAVASOL	Y	300	0,46	23,6	98

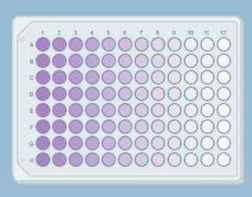


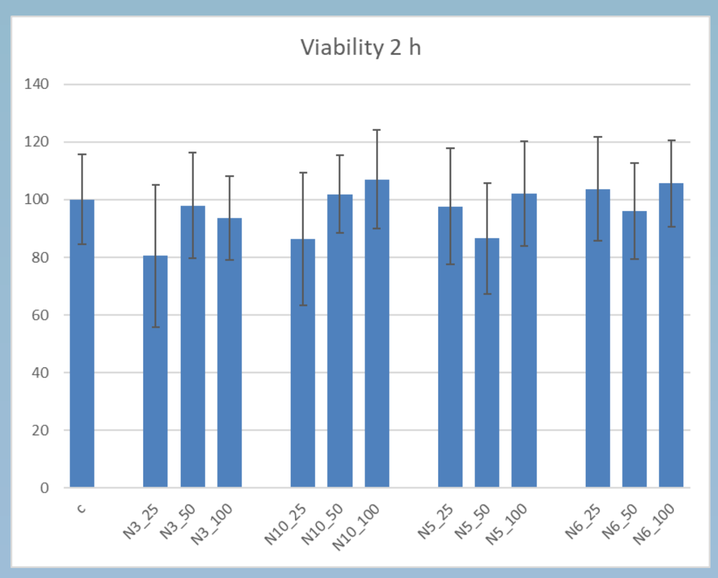
Franz Permeation Test:

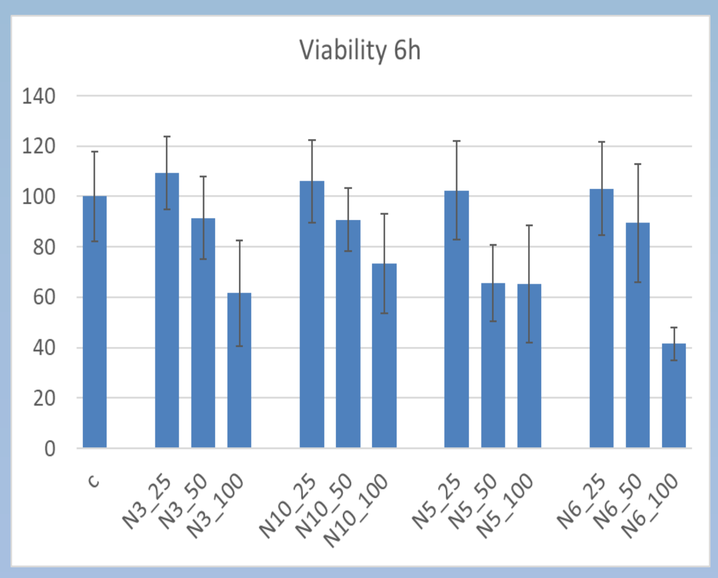
Formulation	% released in the membrane
N3	62,0
N5	5,9
N6	7,0
N10	67,3

- N3
- N5
- N6
- N10

MTT Test (2, 6h):







Conclusion and future prospectives:

Based on the results of the MTT test, it can be concluded that after 2 hours, none of the tested formulations showed toxicity. However, after 6 hours, all formulations tested at a concentration of 100 µg/ml and formulations 5 and 6 at 50 µg/ml showed significant toxicity.
The permeation test revealed a much greater release of NEB in the membrane simulating skin for formulations 3 and 10, containing both SDC and cyclodextrins, compared to formulations 5 and 6 which did not contain SDC.
Future studies will be performed on release test. Also permeation testing using porcine penile skin will be done. The most promising formulations will then be incorporated into a topical gel.

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