DEVELOPMENT OF A NORTRIPTYLINE HYDROCHLORIDE FILM AS SUPPORT THERAPY FOR SMOKING CESSATION

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PURPOSE

To investigate the percutaneous penetration of nortriptyline chlorhydrate (NTH) from film matrices of (hydroxypropyl)methyl cellulose (HPMC) for transdermal drug delivery.

EXPERIMENTAL METHODS

Film preparation:

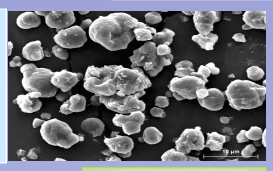
NTH was dissolved in a mixture of PG (15%), PEG 400 (1%) in distilled water at 0.2% (Film I), 1% (Film II), 2% (Film III), 4% (Film IV) and 6% (Film V). HPMC (2%) was then incorporated. Once gel consistency was obtained, the mixture was dried over night on a glass plate (BIO-RAD, Segrate (MI) Italy).

Film VI was obtained by addition of chitosan microparticles (NTH, 4% w/w to HPMC gel with NTH (6%).

Microparticle preparation:

Chitosan solutionsin acetic acid (1%, w/w) were homogenized (Teflon pestle, 1000 rpm) and left to stand for 24 h at room temperature. NTH (8%, w/w) in PG (15%, w/w) (50 g) was added to chitosan solution (50 g) and pH adjusted to 5.5. Spray-drying (Minispray Dryer, Büchi 190, Switzerland) was used). The size distribution was determined by the laser light scattering technique (Zetasizer Nano Series, Malvern Instruments, United Kingdom).

The morphology of the microparticles was observed with a scanning electron microscope (SEM, S-4100; Hitachi Co., Ltd, Tokyo, Japan). Spherical morphology was observed, with a size of 3.6 ±1.7 µm. The drug content was of 3.89 ± 0.23 % and the loading efficacy was of 97.5%.



Experiments in Franz diffusion cells: *In vitro* release from films and *In vitro* transdermal penetration

Membrane **Release experiments** → nitrocellulose membranes

Transdermal penetration → HSE from human volunteers

Donor compartment: tested preparations; **Receptor compartment:** phosphate buffer pH 5.5

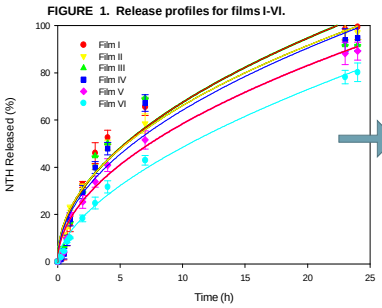
NTH analysis in the samples: HPLC method previously reported *(Melero A.et al. 2008)*

Data analysis

Cumulative amounts vs time were fitted by means of SigmaPlot 9.0 to the Power law equation (release experiments) or the Scheuplein equation (diffusion experiments).

RESULTS AND DISCUSSION

FIGURE 1. Release profiles for films I-VI.



Lines represent the theoretical values calculated by means of the best fit (n=4)

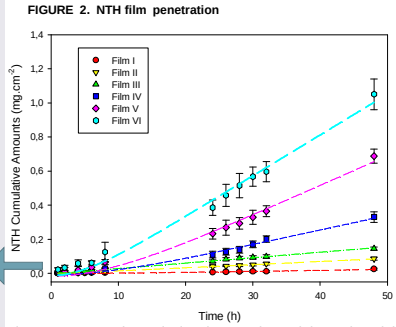
NTH released at 24 h was higher than 88 % of the dose for Films I to V; for Film VI was 79 %.

Kd values were similar for the patches from I to V and they show significant differences ($P<0.05$) with respect to Film VI, for which the diffusion constant was 12.47 mg/cm^2.h. This fact could be attributed to the **microparticles, which act as a reservoir**.

NTH released after 2 h was higher than NTH permeated through skin after 48 h. **Permeation enhancers should be used** to increase the NTH diffusion through the skin (Melero et al, 2008).

Lag time calculated for film VI is smaller than those obtained with the other films. It could be attributed to the effect of PG, what is present in the sheet and also in the microparticles.

FIGURE 2. NTH film penetration



Lines represent theoretical values estimated by Scheuplein equation (n=5).

CONCLUSION

Film VI (4.6 cm x 4.6 cm) should used for the initial dosage regimen in smoking cessation and 8 cm x 8 cm for the maintenance dose. Optmisation of the patch can be possible by incorporation of penetration enhancers (i.e. ethanol, oleic acid, polysorbate 80) in the films

REFERENCES Melero A., Garrigues T.M., Almudever P., Martın Villodre A., Lehr C.M., Schäfer U., (2008), Nortriptyline hydrochloride skin absorption: Development of a transdermal patch. European Journal of Pharmaceutics and Biopharmaceutics 69: 588–596

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