Effect of poly(ethylene glycol) and Hydroxipropyl-β-cyclodextrin on skin permeation of freeze-dried PLGA nanospheres containing Flurbiprofen

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INTRODUCTION

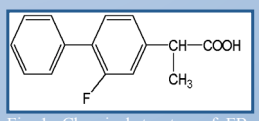

Fig. 1. Chemical structure of FB

Flurbiprofen (FB, *Fig.1*) is a non-steroidal anti-inflammatory drug (NSAID), which is used for the treatment of inflammatory skin diseases [1].

The use of colloidal drug delivery systems, such as poly(D,L-lactide-co-glycolide) (PLGA) nanospheres (NS), is considered nowadays a strategy to enhance the bioavailability of topically administered drugs [2]. The encapsulation of NSAID drugs in particulate drug delivery systems represents an innovative alternative to minimize side effects, while preserving their efficacy. This can be obtained by the capacity of these systems to provide controlled release or to improve the drug penetration into the skin.

Based on these considerations, PLGA NS alone and with different concentrations (5 - 15% *w/v*) of poly(ethylene glycol) (PEG) containing FB were developed. The influence of PEG on skin permeation of FB and its combined effect with Hydroxipropyl-β-cyclodextrin (HPβCD) was studied using Franz-type diffusion cells.

MATERIALS AND METHODS

PLGA 50:50 (Resomer® RG 503H) and copolymers of PLGA 50:50 and PEG (Resomer® RGP type d5055, d50105 and d50155) were obtained from Boehringer Ingelheim (Germany). Poloxamer 188 (Lutrol® F68) was given from BASF (Barcelona, Spain). FB and HPβCD were obtained from Sigma (St.Louis, MO). Double distilled water was used after filtration in a Millipore® system. All other chemicals and reagent used in the study were of analytical grade.

NS of PLGA and PLGA-PEG with and without HPβCD were produced by solvent displacement technique as described previously [2] and freeze-dried. Morphometrical properties and the zeta potential (ζ) of colloidal systems were determined by photon correlation spectroscopy (PCS) and electrophoretic mobility respectively, using a Zetasizer nano ZS (Malvern Inst., Malvern, UK).

In vitro permeation studies were performed using amber glass Franz-type diffusion cells and human skin as permeation membrane. Formulations were placed in the donor compartment. To know the amount of FB permeated, several samples from the receptor fluid were taken over a period of 24 hours. Analysis of FB was done by reversed-phase high-performance chromatography.

In vivo skin irritation was studied by the Draize test [3]. A single dose of each sample was applyed to a small area of the shaved, scarified and non-scarified skin of albino rabbits for up to 4h. The production of an irritant response (erythema and oedema formation) was determined by visual inspection of the skin and scoring of the responses at 1, 24, 48 and 72 h after patch removal. Dermal irritation was scored and recorded according to the grades described in the OECD Guideline 404 (2002).

RESULTS AND DISCUSSION

Morphometrical properties of the NS developed are listed in *Table 1*. As can be observed, particle size tends to decrease with increasing the PEG content. This could be due to combined effect of the reduction in molecular weight and increase in amphiphilic character of the copolymer [4]. The high entrapment efficiency (EE) obtained (75 – 90 %) for both PLGA and PLGA-PEG NS could be explained by the hydrophobic nature of FB. EE values were significantly influenced by the presence of PEG in PLGA chains. The presence of PEG increases the hydrophilicity of the copolymer resulting in lower EE values as the concentration of PEG increases.

Table 1. Morphometrical properties of the NS developed (n=3).

Formulations	Molecular weight (KDa)	Particle size (nm) ± SD	Polidispersity index ±SD	ξ-potential (mV)±SD	EE (%) ±SD
FB-PLGA	34	197.5 ± 1.4	0.062 ± 0.022	-33.5 ± 0.4	90.3 ± 3.2
FB-PLGA:PEG 5%	95 PLGA + 5 PEG	150.4 ± 1.6	0.052 ± 0.043	-22.2 ± 0.2	87.7 ± 3.7
FB-PLGA:PEG 10%	45 PLGA + 5 PEG	123.3 ± 1.6	0.094 ± 0.063	-17.0 ± 0.6	80.5 ± 5.0
FB-PLGA:PEG 15%	28 PLGA + 5 PEG	96.8 ± 0.8	0.085 ± 0.019	-12.3 ± 1.7	75.0 ± 2.4

No changes in morphometrical properties were obtained when adding 5% HPβCD to the NS developed (data not shown).

The effect of PLGA and PLGA-PEG NS and its combined effect with HPβCD on skin permeation of FB was evaluated (*Fig. 2 and Table 2*). It was found that when FB was encapsulated in PLGA NS, a slight increase in the FB flux was obtained compared with control solution. Moreover, the presence of PEG increased FB flux by 2-fold. No significant differences were observed among the formulations containing different concentration of PEG (*ANOVA test, P> 0.05*), reaching maximum enhancer effect with 5% w/v PEG.

When 5 % w/v HPβCD was added to the PLGA and PLGA-PEG NS, a significant decrease in FB flux was obtained for all formulations masking the effect of the promoter PEG. This might be explain because of the retardation of drug release due to the presence of the HPβCD, which provides a sustained release of the drug for a long period of time.

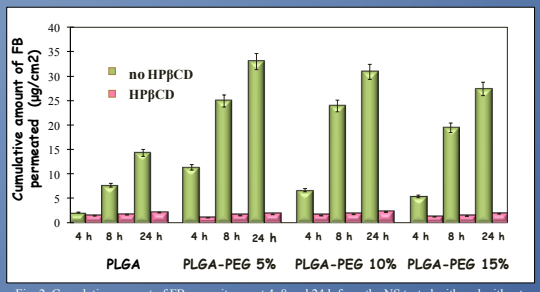

Fig. 2. Cumulative amount of FB per unit area at 4, 8 and 24 h from the NS tested with and without HPβCD. Each value is the mean ± SD of 3 determinations

Table 2. Permeability Coefficient and Flux for the NS developed.

Formulations	Composition	Permeability Coefficient ($x10^{-3}$) (cm h^{-1})	Flux (µg h^{-1} cm^{-2})
FB-solution	-	0.32 (0.30-0.47)	0.48 (0.46-0.70)
FB-PLGA	-	0.39 (0.32-0.91)	0.59 (0.48-1.36)
	5% HPβCD	0.021 (0.017-0.022)	0.030 (0.027-0.030)
FB-PLGA:PEG 5%	-	0.79 (0.35-1.46)	1.18 (0.52-2.19)
	5% HPβCD	0.021 (0.018-0.022)	0.031 (0.027-0.033)
FB-PLGA:PEG 10%	-	0.78 (0.23-2.18)	1.16 (0.35-3.28)
	5% HPβCD	0.021 (0.018-0.047)	0.031 (0.027-0.070)
FB-PLGA:PEG 15%	-	0.71 (0.65-1.58)	1.06 (0.97-2.37)
	5% HPβCD	0.020 (0.018-0.11)	0.029 (0.027-0.16)

Results are shown as median and range (min–max)

Topical application of formulations to rabbit skin showed no sign of toxicity or irritation after the evaluation by the Draize test.

CONCLUSIONS

From the results obtained, we can conclude that PEG/ HPβCD can modulate the skin absorption of FB to attain local or systemic effect of the drug when necessary.

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