ELSEVIER

International Journal of Pharmaceutics 136 (1996) 37–41

international journal of pharmaceutics

Effect of polycarbophil concentration on diclofenac sodium bioavailability from suppositories in beagle dogs

Ehab A. Hosny*, Esmail M. Niazy, Mohammed M. El-Dardari

Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box: 2457, Riyadh 11451, Saudi Arabia

Received 15 December 1995; accepted 7 February 1996

Abstract

The effect of polycarbophil in different concentrations (0, 5, 10 and 20% w/w) on the bioavailability of diclofenac sodium from polyethylene glycol suppositories was studied in six beagle dogs. The in-vivo data showed that the 5% concentration of polycarbophil is the best concentration to be used in formulating polyethylene glycol suppositories containing diclofenac sodium. At this concentration, the suppositories showed a relative bioavailability of 115.17% compared to that of suppositories containing 0% polycarbophil. The other two concentrations of polycarbophil (10 and 20%) gave relative bioavailability of 56.46 and 50.21%, respectively. The 5% polycarbophil concentration resulted in the highest C_{max} (6.35 ± 1.06 μg/ml) compared to 5.54 ± 1.21, 1.98 ± 0.70 and 1.93 ± 1.06 μg/ml for suppositories containing 0, 10 and 20% polycarbophil, respectively. It was also noted that as the polycarbophil concentration increased in the formulation the T_{max} decreased indicating faster absorption. Also, the K_{el} values decreased and the $t_{1/2}$ values increased indicating slower release of the drug from the formulation as the polycarbophil concentration increased. Polycarbophil as a bioadhesive is capable of inducing faster absorption and its effect on plasma concentration and bioavailability is dependent on its percentage used in the formulation.

Keywords: Diclofenac sodium; Suppositories; Polycarbophil concentration; Bioavailability; Beagle dogs

1. Introduction

Diclofenac sodium is a non-steroidal anti-inflammatory drug displaying potent anti-inflammatory, analgesic and antipyretic activities. It owes its principal effect to inhibition of enzyme cyclooxygenase which transforms arachidonic acid into prostaglandins, prostacyclin and thromboxanes (Menasse' et al., 1978; Ku et al., 1986). Diclofenac is almost completely absorbed from the intestinal tract (John, 1979; Riess et al., 1986) and it undergoes first-pass metabolism after oral administration and about 60% of the dose reaches the systemic circulation as unchanged compound (John, 1979).

The suppository form of a drug could avoid the first-pass liver metabolism depending on the height at which absorption occurs in the rectum. Where drugs carried by the inferior or middle

* Corresponding author.

PII S0378-5173(96)04485-7

hemorrhoidal veins go directly into the circulation, thus bypassing the liver, whereas drugs from the superior vein and orally administered drugs go directly to the liver before going to the general circulation. So, drugs that are extensively metabolised can avoid the so-called 'first-pass' metabolism if the rectal route is used and specifically if the suppository is retained in the bottom one-third of the rectal vault.

Polycarbophil (Markus, 1965) is one of the bioadhesive polymers (Gurney et al., 1984; Ch'ng et al., 1985; Longer et al., 1985; Nagai and Machida, 1985) that are capable of adhering to epithelial tissues or the mucus coat on the surface of a tissue. It has been used to improve the oral (Longer et al., 1985; Hosny and Al-Meshal, 1994; Hosny et al., 1994), ocular (Hui and Robinson, 1986) and rectal (Hosny, 1988; Hosny and Robinson, 1991; Hosny and Al-Angary, 1995; Hosny et al., 1995) drug delivery.

The objective of this work was to determine the effect of different concentrations of polycarbophil on the in-vivo availability of diclofenac sodium from suppositories in beagle dogs.

2. Materials and methods

2.1. Materials

Diclofenac sodium was obtained from SPIMACO (Qassim, Saudi Arabia). Bulk polycarbophil was a kind gift from Lee Laboratories Inc. (Petersburg, VA, USA). Polyethylene glycol 4000 was from E. Merck (Darmstadt, Germany). All other chemicals and solvents were of analytical and HPLC grade.

2.2. Methods

2.2.1. Preparation of suppositories

Suppository formulations containing 50 mg of diclofenac sodium were prepared by the fusion method by melting the base PEG 4000, on a water bath, adding the drug and the polycarbophil (if present) subsequently with trituration after each addition till a homogenous mass was produced. The molten mass was then poured into a 1-g mold and cooled in a refrigerator. The displacement values of polycarbophil and diclofenac sodium in PEG 4000 were determined (Vidras et al., 1982).

2.2.2. Animal studies

Six healthy male beagle dogs weighing 12.58 ± 1.72 kg were used in this study. The dogs were maintained on a normal diet with free access to water. At least 1 week was permitted between successive dosing in the same animal. During the experimental period, each dog was placed in an upright position in a restrainer stand. The legs were shaven and a cephalic vein was cannulated using an 18 gauge cannula. Blood samples (5 ml) were taken into heparinized vaccutainer tubes at 0.0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 h after rectal administration. The tubes were then centrifuged for 10 min. and plasma was aspirated and stored at −20°C prior to analysis.

2.2.3. Diclofenac assay

Diclofenac in plasma was analysed by a rapid and sensitive high performance liquid chromatographic method (El-Sayed et al., 1988).

2.2.4. Pharmacokinetic calculations

The maximum plasma concentration (C_{max}) and the time to reach this maximum (T_{max}) were obtained from the plasma concentration-time curves. The area under the curve up to the last sampling time point (AUC_{0-6}) of diclofenac sodium in plasma was calculated by using the linear trapezoidal method. The elimination rate constant (K_{el}) was determined by the linear regression of the log linear terminal portion of the plasma concentration-time curve. The apparent elimination half-life ($t_{1/2}$) was calculated as $0.693/K_{el}$. The $AUC_{t \rightarrow \infty}$ was calculated using the relation $AUC_{t \rightarrow \infty} = C_t/K_{el}$ where C_t is the last measurable concentration. The $AUC_{0 \rightarrow \infty}$ values, as measurements of the extent of drug absorption, were determined by adding the two AUC's, $AUC_{0 \rightarrow \infty} = AUC_{0 \rightarrow t} + AUC_{t \rightarrow \infty}$.

2.2.5. Statistical analysis

The difference between formulations was evaluated using Analysis of Variance (ANOVA) on microcomputer statistical package (SAS, Statisti-

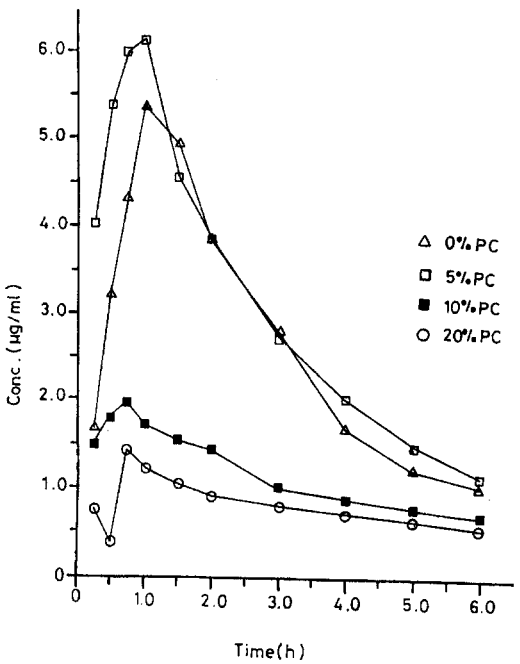

Fig. 1. Mean plasma concentration of diclofenac sodium after rectal administration of polyethylene glycol suppositories containing 0, 5, 10 and 20% (w/w) polycarbophil to six beagle dogs.

cal Analysis System). The difference was considered significant at P values of 0.05 or less. Furthermore, the data were analyzed by Fisher's Least Significant Difference (LSD) method to reveal any significant different between the formulations. All data were expressed as mean ± standard deviation (X ± S.D.).

3. Results and discussion

Fig. 1 and Table 1 provide the mean plasma concentration-time profiles of diclofenac sodium for the tested formulations as well as their mean pharmacokinetic parameters after their rectal insertion into beagle dogs. In order to study the effect of different polycarbophil concentrations (5, 10 and 20% w/w) on bioavailability of diclofenac sodium, it was necessary to test the polyethylene glycol suppositories containing no polycarbophil. This formulation resulted in C_{max} 5.54 ± 1.21 µg/ml and T_{max} of 1.15 ± 0.34 h. The $AUC_{0 \rightarrow 6}$ h was 15.86 ± 3.61 µg·h/ml and the $AUC_{0 \rightarrow \infty}$ was 18.72 ± 3.69 µg·h/ml. On addition of 5% concentration of polycarbophil to this formulation, the plasma concentrations increased significantly ($P < 0.05$) and C_{max} reached to 6.35 ± 2.14 µg/ml and the T_{max} is reduced to 0.95 ± 0.11 h indicating faster absorption. The $AUC_{0 \rightarrow 6}$ and $AUC_{0 \rightarrow \infty}$ increased to 17.59 ± 4.47 and 21.56 ± 4.62 µg·h/ml, respectively, producing relative bioavailability of 115.17% compared to the polyethylene glycol suppositories with no polycarbophil. This effect indicates that polycarbophil induced rapid absorption of diclofenac sodium from the suppositories by virtue of its effects on increasing the intimacy of contact to the absorbing mucosa, producing a steep concentra-

Table 1
Mean[a] pharmacokinetic parameters of diclofenac sodium after rectal administration of polyethylene glycol suppositories containing 0, 5, 10 and 20% (w/w) polycarbophil

Parameter	Polycarbophil Conc. (%)			
	0%	5%	10%	20%
C_{max} (µg/ml)	5.54 ± 1.21	6.35 ± 2.14	1.98 ± 0.70	1.93 ± 1.06
T_{max} (h)	1.15 ± 0.34	0.95 ± 0.11	0.75 ± 0.0	0.38 ± 0.21
K_{el} (h^{-1})	0.37 ± 0.06	0.28 ± 0.04	0.18 ± 0.07	0.13 ± 0.04
$t_{1/2}$ (h)	1.79 ± 0.50	2.45 ± 0.31	4.35 ± 1.75	5.83 ± 1.62
$AUC_{0 \rightarrow t}$ (µg·h/ml)	15.86 ± 3.61	17.59 ± 4.47	6.52 ± 2.24	4.96 ± 1.32
$AUC_{0 \rightarrow \infty}$ (µg·h/ml)	18.72 ± 3.69	21.56 ± 4.62	10.57 ± 1.20	9.40 ± 1.48
Rel. bioavailability	—	115.17%	56.46%	50.21%

[a]Data presented as mean ± S.D.

tion gradient to favor drug absorption. Polycarbophil also causes localization of the suppository in the lower region of the rectum and hence improves the bioavailability of diclofenac sodium since it will avoid first-pass liver metabolism. Also, polycarbophil has been proved lately to increase the permeability of the epithelial tissues (LueBen et al., 1994). As the polycarbophil concentration increased to 10 and 20% w/w, the plasma concentration reduced significantly ($P < 0.05$) giving C_{max} of 1.98 ± 0.70 and 1.93 ± 1.06 μg/ml, respectively. Also, the areas under the curve are reduced significantly to 10.57 ± 1.20 and 9.40 ± 1.48 μg·h/ml, giving relative bioavailability of 56.46% and 50.21%, respectively. Increasing the polycarbophil concentration in the suppository formulations from 0 to 5, 10 and 20% resulted in reduction of T_{max} from 1.15 ± 0.34 to 0.95 ± 0.11, 0.75 ± 0.0 and 0.38 ± 0.21 h, respectively. This could be due to several factors. Some of these factors are related to the bioadhesive power of the polymer. Others are related to the formulation itself. It has been shown (Chen and Cyr, 1970) that for maximum adhesion to occur, perfect matching of adhesive sites should be achieved in presence of an optimum amount of water near or at the interface. If water present is not sufficient to hydrate the polymer, the adhesive sites are not completely liberated and exposed for bioadhesion. This could be the case in the rectum as the amount of rectal fluid is very limited and as the polycarbophil concentration increased in the formulation to 10 and 20%, the rectal fluid becomes insufficient to hydrate the polymer.

In the rectum, the rectal fluid has no buffer capacity and it usually takes the pH of the formulation. In these formulations, increasing the polycarbophil concentration from 0 to 5, 10 and 20% w/w decrease the pH from 6.1 to 5.6, 5.1 and 4.1, respectively. This decrease in pH affect the diclofenac sodium solubility as it decreases as the pH decrease.

The viscosity of the formulation and consequently the viscosity of the rectal fluid as a medium for dissolution of the drug affect both the bioadhesion strength and also the release of the drug from the suppository formulations. The viscosity of the suppositories increased markedly as the polymer concentration increased to 10 and 20%, thus reducing the release of the drug. Also maximum bioadhesion requires an optimum viscosity of the medium (Dittgen et al., 1989).

As a conclusion, polycarbophil as a good bioadhesive polymer that is not absorbed and does not produce any undesirable systemic effects and approved by FDA for use in humans could be used as an additive in suppository formulations to increase the rate and extent of drug absorption provided that it is used in the proper concentration.

Acknowledgements

The authors gratefully acknowledge the financial support of the Research Centre at the College of Pharmacy, King Saud University.

References

Chen, J.L. and Cyr, G.N., Composition producing adhesion through hydration in "Adhesion in biological systems", In: Manly, R.S. (Ed.), Academic Press, New York, 1970, pp. 163–181.

Ch'ng, H.S., Park, H., Kelly, P. and Robinson, J.R., Bioadhesive polymers as platforms for oral controlled drug delivery:II synthesis and evaluation of some swelling water insoluble bioadhesive polymers. *J. Pharm. Sci.*, 74 (1985) 399–405.

Dittgen, M., Oestereich, S. and Fittrich, F., Influence of the concentration of the mucous excipient on the bioadhesion ex vivo. *Pharmazie*, 44 (1989) 460–462.

El-Sayed, Y.M., Abdel-Hamid, M.E., Suleiman, M.S. and Najib, N.M., A rapid and sensitive high-performance liquid chromatographic method for determination of diclofenac sodium in serum and its use in pharmacokinetic studies. *J. Pharm. Pharmacol.*, 40 (1988) 727–729.

Gurney, R., Meyer, J.M. and Peppas, N.A., Bioadhesive intraoral release systems:design, testing and analysis. *Biomaterials*, 5 (1984) 334–340.

Hosny, E.A., Rectal drug delivery using a bioadhesive containing dosage form. Ph.D. Thesis, School of Pharmacy, University of Wisconsin, Madison, 1988.

Hosny, E.A. and Robinson, J.R., Rectal drug delivery of ketoprofen using a bioadhesive containing suppository, 2nd Anglo-Egyptian Conference of Pharmaceutical Scientists, Abstract Book, 18, Alexandria, Nov. 9–12, 1991.

Hosny, E.A. and Al-Meshal, M.A., In-vivo evaluation of a bioadhesive containing indomethacin tablets. *Drug Dev. Ind. Pharm.*, 20 (1994) 2715–2720.

Hosny, E.A., El-Sayed, Y.M., Al-Meshal, M.A. and Al-Angary, A.A., Effect of food on bioavailability of bioadhesive-containing indomethacin tablets in dogs. *Int. J. Pharm.*, 112 (1994) 87–91.

Hosny, E.A. and Al-Angary, A.A., Bioavailability of sustained release indomethacin suppositories containing polycarbophil. *Int. J. Pharm.*, 113 (1995) 209–213.

Hosny, E.A., Niazy, E.M. and El-Gorashi, A.S., Effect of polycarbophil concentration on in-vitro release and in-vivo availability in beagle dogs of dihydroergotamine mesylate suppositories. *Int. J. Pharm.*, 117 (1995) 147–150.

Hui, H.W. and Robinson, J.R., Effect of particle dissolution rate and drainage rate on ocular bioavailability. *J. Pharm. Sci.*, 75 (1986) 280–284.

John, V.A., The pharmacokinetics and metabolism of diclofenac sodium (Voltarol®) in animals and in man. In Haslock, I. et al. (Eds.), Diclofenac (Voltarol®) in the treatment of rheumatic diseases: a conspectus of international experience. *Rheumatol. Rehabil.*, 17 (Suppl. 2) (1979) 22–37.

Ku, E.C., Lee, W., Kothari, H.V. and Scholer, D.W., Effect of diclofenac sodium on the arachidonic acid cascade. *Am. J. Med.*, 80 (Suppl. 4B) (1986) 18–23.

Longer, M.A., Ch'ng, H.S. and Robinson, J.R., Bioadhesive polymers as platforms for oral controlled drug delivery: III. Oral delivery of chlorthiazide using a bioadhesive polymer. *J. Pharm. Sci.*, 74 (1985) 406–411.

LueBen, H.L., Lehr, C.M., Rentel, C.O., Naoch, A.B.J., de-Boer, A.G., Verhoef, J.C. and Junginger, H.E., Bioadhesive polymers for peroral delivery of peptide drugs. *J. Cont. Rel.*, 29 (1994) 329–338.

Markus, R.L., *US Patent*, 3, 202, 577, 1965.

Menasse', R., Hedwall, P.R. and Kraetz, J., Pharmacological properties of diclofenac sodium and its metabolites. *Scand. J. Rheum.*, Suppl. 22 (1978) 5–16.

Nagai, T. and Machida, Y., Mucosal adhesive dosage forms. *Pharm. Int.*, 6 (1985) 196–200.

Riess, W., Schmid, K., Botta, L. et al., Percutaneous absorption of diclofenac. *Arzneim. Forsch. Drug Res.*, 36 (1986) 1092–1096.

Vidras, N.J., Reid, V.E., Bohidar, N.R. and Plakogiannis, E.M., Medicament release from suppository bases: I. Physicochemical characteristics and bioavailability of indomethacin in rabbits. *J. Pharm. Sci.*, 71 (1982) 8–10.