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Formulation and comparative evaluation of bioadhesive containing diclofenac sodium and commercial enteric coated tablets in-vitro and in dogs

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Abstract

Polycarbophil containing diclofenac sodium tablets were formulated using two different size of granules. The granules were obtained by evaporation under reduced pressure of polycarbophil particles loaded with alcoholic solution of the drug. The in-vitro release of these bioadhesive containing tablets was evaluated together with that of Ciba-Geigy commercially available enteric coated tablets 'Voltaren' in simulated gastric fluid for 2 h followed by another 2 h in simulated intestinal fluid. The Voltaren tablets released no drug in simulated gastric fluid but released all their drug contents within 1 h in simulated intestinal fluid. The tablets formulated using polycarbophil granules of smaller size (0.18–0.313 mm) released about 13% of their drug contents in simulated gastric fluid and released the remaining drug in simulated intestinal fluid within 0.5 h of dissolution, while tablets formulated with larger granules size (0.5–0.8 mm) released 10% of their drug contents in the first medium and released the remaining drug within 2 h in the second. The in-vivo evaluation in dogs of these two tablet formulations of polycarbophil and that of enteric coated Voltaren tablets each containing 50 mg drug revealed that the bioadhesive tablets formulated with smaller granules size were bioequivalent to Voltaren tablets producing a non-significantly different ($P > 0.05$) C_{max}, T_{max} and AUC. The results also indicated the effect of bioadhesive granules size on rate and extent of absorption where tablets formulated with smaller granules size showed higher C_{max}, shorter T_{max}, larger AUC and higher relative bioavailability compared with those tablets formulated with larger granules size.

Keywords: Formulation; In-vitro; In-vivo; Bioadhesive tablets; Diclofenac sodium; Enteric coated tablets; Dogs

1. Introduction

Diclofenac is a non-steroidal anti-inflammatory drug with analgesic and antipyretic activity (Sallman, 1986). It inhibits prostaglandin synthesis by inhibition of enzymatic transformation of arachidonic acid into prostaglandins (Menasse et al., 1978; Maier et al., 1979). About 12% of patients using diclofenac sodium experience side-effects of which gastrointestinal problems are the most frequent (Todd and Sorkin, 1988). To decrease the local gastric irritation diclofenac is marketed as enteric coated and as sustained release tablets. Polycarbophil (Markus, 1965) is one of the bioadhesive polymers that is capable of swelling to varying degrees in water, common organic sol-

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vents and strong mineral acids and bases. Polycarbophil has been shown to be a good bioadhesive that is effective in oral (Longer et al., 1985; Hosny and Al-Meshal, 1994a,b; Hosny et al. (1994)) rectal (Hosny, 1988; Hosny and Robinson, 1991; Hosny and Al-Angary, 1995; Hosny et al., 1995)), and ocular (Robinson and Li, 1984) drug delivery.

The objectives of this study were to (1) formulate polycarbophil containing diclofenac sodium tablets by loading the drug inside the polymer particles through swelling the latter in alcoholic solution of the drug followed by evaporation of the solvent; (2) determine the in-vitro dissolution and in-vivo availability of diclofenac sodium from tablets prepared from two granules sizes of this bioadhesive polymer in comparison with the commercially available enteric coated Voltaren tablets of Ciba-Geigy.

2. Materials and methods

2.1. Materials

Diclofenac sodium was kindly supplied by SPIMACO (Kassim, Saudi Arabia). Bulk polycarbophil was a kind gift from Lee Laboratories Inc. (Petersburg, VA, USA). Voltaren enteric coated tablets 50 mg were kindly provided by Ciba-Geigy scientific office (Riyadh, Saudi Arabia). Ethanol 96% extra pure from E. Merck (Darmstadt, Germany). All other chemicals and solvents were of analytical and HPLC grade.

2.2. Preparation of polycarbophil containing diclofenac sodium tablets

Diclofenac sodium (2 g) was dissolved in about 15 ml ethanol. Polycarbophil (16 g) of either particle size (0.18–0.313 mm or 0.5–0.8 mm) was then added to this alcoholic drug solution. After the polycarbophil was allowed to swell, alcohol was evaporated by heating in a water bath under reduced pressure. The resulting granules (after determination of their drug contents) were subjected to sieving and the sieved granules were directly compressed into tablets using a single punch tabletting machine (Korsch, Type EKO, Frankfurt, Germany).

2.3. Drug content determination

After grinding a known weight of polycarbophil containing diclofenac sodium granules, the drug was extracted several times with methanol. The methanolic solution was filtered through a 0.45 μm pore size filter and the volume was completed to 50 ml with methanol. An aliquot (10 ml) of the filtrate was centrifuged and 2 ml of the supernatant were diluted with methanol and assayed at 276 nm using a Pye Unicam SP8800 (Cambridge, UK) spectrophotometer.

2.4. In-vitro dissolution

The in-vitro release of the commercial enteric coated tablets (Voltaren), and the bioadhesive tablets containing diclofenac sodium of 0.18–0.313 mm or 0.5–0.8 mm granules was performed using USP dissolution apparatus I. The stirring rate was maintained at 100 rev./min and the temperature at 37 $\pm$ 0.5°C. The dissolution medium was 750 ml of 0.1 N HCl (pH 1.2) containing 0.1% w/w Tween 80. The test was carried out for 2 h at this pH and continued for another 2 h at pH 6.8 dissolution medium. The change in pH was achieved by adding 250 ml of 0.2 M tribasic sodium phosphate that has been equilibrated to 37 $\pm$ 0.5°C. The diclofenac concentration was continuously recorded at 276 nm, using a Phillips PU 8620 spectrophotometer (UK), connected to an IBM computer Model PS30, using TDS software from Phillips. Dissolution studies were performed in triplicate for each experiment to calculate an average dissolution rate (%).

2.5. Animals

Six male beagle dogs weighing 7–10 kg were used in this study. After an overnight fast during which water was allowed ad libitum, the dogs were placed in an upright position in restrainer stands. Their legs were shaven and a cephalic vein was cannulated for each dog using an 18-gauge cannula. The same dogs were used and remained in good health throughout the study.

2.6. Dosing and plasma sampling

The commercial enteric coated tablets (Voltaren 50 mg), the polycarbophil containing 50 mg diclofenac sodium tablets formulated of either 0.18–0.313 mm or 0.5–0.8 mm granules size were administered orally to fasted dogs on three different occasions. There was at least a 2-week interval between the treatments. Blood samples (4 ml) were withdrawn into heparinized vacutainer tubes before and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0 and 6.0 h post tablet administration. The blood samples were immediately centrifuged and aliquots of plasma aspirated were stored at − 20°C for subsequent assay.

2.7. Plasma assay of diclofenac sodium

The diclofenac sodium was determined in plasma according to a rapid and sensitive high-performance liquid chromatographic method (El-Sayed et al., 1988). The method involved the addition of 50-μl aliquots of the internal standard (flufenamic acid 500 ng) to plasma samples. After shaking on a vortex mixer for 1 min, precipitation of serum protein was accomplished by addition of 5 ml acetonitrile. After vortexing for 1 min and centrifuging for 5 min at 5000 rev./min, the supernatant was transferred to a 10-ml centrifuge tube and evaporated to dryness. The residue was reconstituted in 300 μl of HPLC eluent (acetonitrile/water, 50:50, v/v, adjusted to pH 3 with glacial acetic acid) and injected into the loop injector. The liquid chromatographic system consisted of a solvent delivery pump (Model 6000A), an injector (Model U6K) and a UV detector (Model 481) set at 276 nm. The samples were run on a U-Bondapak (3.9 × 150 mm) C_{18} reversed phase column. All were from Waters Associates (Milford, MA, USA).

2.8. Pharmacokinetic analysis

Peak plasma concentrations (C_{max}) and the corresponding times at which these are reached (T_{max}) were obtained by inspection of the plasma concentration-time profile of each dog. The area under the plasma concentration-time curve for an individual dog (AUC) was calculated by linear trapezoidal rule. All results were expressed as mean ± standard deviation (X ± S.D.).

2.9. Statistical analysis

The significance of the difference between the treatments was evaluated by using an unpaired Student's t-test on a microcomputer statistical package (SAS, Statistical Analysis Systems Institute Inc., Cary, NC). Probable value (P) of 0.05 or less was taken as significant.

3. Results and discussion

The evaluation of the prepared polycarbophil containing diclofenac sodium granules for their drug content revealed a 93% actual drug content as opposed to the theoretical drug loading. The tablet's weight was 485.0 ± 5.0 mg. Fig. 1 shows that the commercial enteric coated tablets (Voltaren) released no drug during the 2-h period of in-vitro release in simulated gastric fluid (pH 1.2). The tablets formulated using polycarbophil

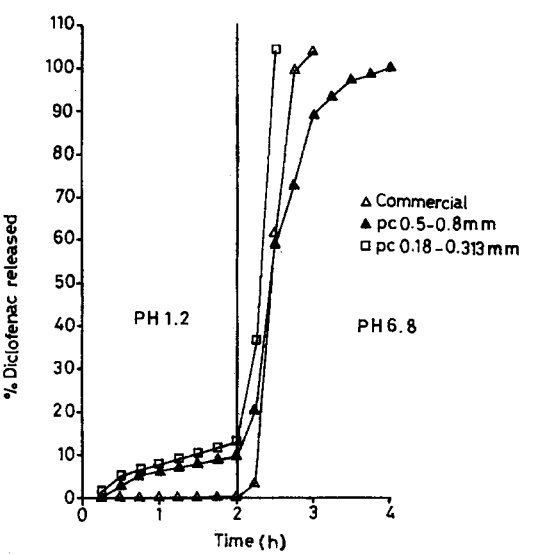

Fig. 1. Comparison of the percent release of diclofenac sodium from commercial enteric coated tablets (△) and polycarbophil containing tablets of 0.18–0.313 mm (□) and 0.5–0.8 mm (▲) particle size in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8).

containing diclofenac sodium granules of size 0.18–0.313 mm or 0.5–0.8 mm released 12.66 ± 0.27% and 9.78 ± 0.16% drug, respectively, during the same time period in the acidic pH. As the pH increased to 6.8, complete release from Voltaren tablets took place within first hour of dissolution. The formulated bioadhesive tablets released their contents in 0.5 and 2 h for granules size 0.18–0.313 mm and 0.5–0.8 mm, respectively. It is evident from Fig. 1 that as the size of the granules decreased, the release rate increased. It is also clear that most of the drug is released in the alkaline pH 6.8. The amount of the drug released in the acidic pH medium was small as the bioadhesive containing tablets absorbed the 0.1 N HCl causing the swelling of the polymer particles, disintegrating the tablets and precipitating the drug inside the granules. The drug diffuses slowly out of the swollen polymer particles releasing this amount (about 10%) in the simulated gastric fluid. At pH 6.8 the diclofenac inside the polymer particles becomes soluble and rapid diffusion of the drug solution through the swollen polymer takes place. As the Voltaren tablets are enteric coated, they showed no release in acid medium, but released all their drug contents as their polymer coating dissolved in the simulated intestinal fluid (pH 6.8).

The mean plasma concentrations of diclofenac sodium at each time point following administration of Voltaren 50 mg tablets and the two formulations containing polycarbophil are shown in Fig. 2. The results demonstrate the effect of the particle size on the rate and extent of release from the bioadhesive containing tablets. For tablets containing polycarbophil of particle size 0.18–0.313 mm a rapid release and absorption of diclofenac sodium occur producing a C_{max} of 6.92 ± 4.85 μg/ml with a respective T_{max} of 2.42 ± 0.97 h, while the tablets containing polycarbophil particle size 0.5–0.8 mm showed lower C_{max} of 3.86 ± 4.20 μg/ml and a longer T_{max} of 3.00 ± 0.95 h. These in-vivo results of the bioadhesive containing tablets revealed a good relationship between their in-vitro dissolution behavior and their C_{max}, T_{max} and AUC. As the bioadhesive tablets of larger particle size (0.5–0.8 mm) showed slow in-vitro dissolution, lower C_{max},

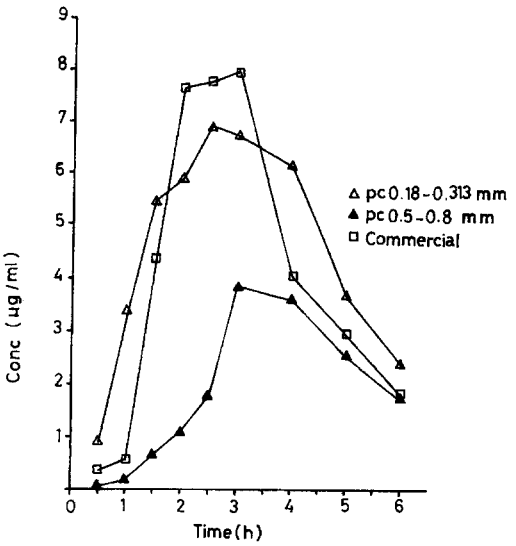

Fig. 2. Mean plasma concentration of diclofenac sodium following oral administration of commercial enteric coated tablets (□) and polycarbophil containing tablets of 0.18–0.313 mm (△) and 0.5–0.8 mm (▲) particle size to six dogs.

longer T_{max} and lower AUC (11.99 ± 7.71 μg · h per ml) compared with those tablets of smaller particle size of polycarbophil (0.18–0.313 mm) which showed faster in-vitro dissolution, higher C_{max}, shorter T_{max} and higher AUC (27.28 ± 13.42 μg · h per ml).

On comparing the commercial Voltaren tablets and bioadhesive containing tablets of smaller particle size (0.18–0.313 mm) as shown in Table 1, it was found that they are non-significantly different ($P > 0.05$) with respect to their C_{max} (7.97 ± 6.48 and 6.92 ± 4.85 μg · ml), T_{max} (2.90 ± 0.74 and 2.42 ± 0.97 h) and AUC (24.09 ± 21.46 and 27.28 ± 13.42 μg · h per ml) arranged for commercial and bioadhesive containing tablets, respectively.

As a conclusion, the bioadhesive tablets of particle size (0.18–0.313 mm) formulated in this study can be a good alternative to the enteric coated tablets commercially available as it produced similar bioavailability (113% relative to Voltaren tablets), it is easily manufactured and it is expected to be less irritant to gastric and intestinal mucosa as has been shown before with indomethacin tablets manufactured using the same bioadhesive (Hosny and Al-Meshal, 1994ab).

Table 1
Pharmacokinetic parameters (± S.D.) of diclofenac sodium following oral administration of commercial enteric coated and polycarbophil containing tablets of 0.18–0.313 mm or 0.5–0.8 mm particle size to six dogs

	Commercial tablets	Bioadhesive tablets	
		0.18–0.313 mm	0.5–0.8 mm
C_{max} (μg/ml)	7.97 ± 6.48	6.92 ± 4.85	3.86 ± 4.20
T_{max} (h)	3	2.5	3
AUC (μg · h/ml)	24.09 ± 21.46	27.28 ± 13.42	11.99 ± 7.71
Rel. bioavailability		113.24%	49.77%

This effect on reducing irritation is believed to be due to the bioadhesive characters of polycarbophil which allow it to adhere to the mucosal surface and create an effective cross-linked barrier that is water insoluble, thus protecting the underlying cell layers.

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