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RESEARCH PAPER

Formulation and In Vitro and In Vivo Availability of Diclofenac Sodium Enteric-Coated Beads

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ABSTRACT

Diclofenac sodium enteric-coated beads were prepared using the conventional pan coating technique. Eudragit L_{100} was used as a pH-dependent release-controlling polymer. The beads were evaluated for their particle size distribution, drug loading efficiency, flowability, in vitro release in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8), and bioavailability in beagle dogs relative to the commercial enteric-coated tablets Voltaren®. The beads showed a narrow particle size distribution in which 83% of the beads were in the range of 1–2 mm. The actual yield of the beads was 90.5% and their drug loading was 92%. The beads released about 8% of the drug during 2 hr of dissolution in 0.1 N HCl, and the commercial tablets released no drug. In phosphate buffer (pH 6.8) both formulations released their drug content in 1 hr. Both formulations are, therefore, in compliance with the USP requirements for release from enteric-coated dosage forms.

The in vivo availability study in six beagle dogs revealed that the formulated enteric-coated beads filled in hard gelatin capsules had a 197.54% bioavailability relative to that of the commercial Voltaren tablets. The tablets showed a significantly lower ($p < 0.05$) area under curve for 0–8 hr ($AUC_{0-8\ hr}$) of 13.44 ± 15.02 μg hr/ml compared to 26.55 ± 5.19 μg hr/ml for the capsules. The capsules showed a nonsignificantly ($p > 0.05$) higher peak plasma concentration (C_{max}) of 6.77 ± 0.67 μg/ml compared to 5.88 ± 7.38 μg/ml for the tablets. The time to reach peak (T_{max}) values were 2 ± 1.48 and 2.25 ± 1.08 hr for the capsules and tablets, respectively. The capsules showed less interdog variability with respect to C_{max} (CV% 34.6) and AUC (CV% 19.55) compared to CV% 79.9 and 111.76, respectively, for the commercial tablets

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INTRODUCTION

Oral controlled-release multiple-unit dosage forms (e.g., pellets, granules, or microparticles) offer several advantages over single-unit dosage forms (e.g., capsules or tablets) (1,2). Local drug concentration and risk of toxicity because of locally restricted tablets can be avoided by the use of multiple-unit dosage forms which can spread uniformly throughout the gastrointestinal tract (GIT). This spreading could also improve the bioavailability, which potentially could result in a reduction in drug dose and side effects.

Several approaches to the development of beads for subsequent coating with release-controlling membrane were discussed in the literature (3–10). The traditional method of building up cores, which includes nonpareil seeds and granules for spheronization, is by the use of conventional pan coating. Previous work showed that beads possessing high quality and excellent reproducibility in addition to high drug content are easy to produce with the pan coating method (3–6).

Polymers used in film coating of solid dosage forms fall in two broad groups based on either cellulose or acrylic polymers (11,12). Films prepared from acrylic polymers (Eudragit®) are more flexible and therefore are suitable for coating of pellets (13,14).

Diclofenac sodium is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic activity (15). It causes gastrointestinal problems in about 12% of patients using it (16). In view of the advantages of enteric-coated beads, it was decided in this work to (*a*) formulate diclofenac sodium in the form of enteric-coated beads using Eudragit L_{100} as the coating polymer sensitive to pH changes in GIT, and (*b*) study the in vitro and in vivo availability of diclofenac sodium from the prepared beads filled in hard gelatin capsules compared to that of commercially available enteric-coated Voltaren® tablets (Ciba-Geigy, Switzerland).

EXPERIMENTAL

Materials

Diclofenac sodium was kindly supplied by SPIMACO (Kassim, Saudi Arabia). Eudragit L_{100} was from Rhom Pharma (GmbH, Darmstadt, Germany), sodium carboxymethylcellulose was from BDH Chemicals Ltd. (Poole, England), corn starch was from FMC Corp. (Philadelphia, PA), talc was from Charles B Chrystal Company Inc. (New York, NY), and castor oil was from Merk (Darmstadt, Germany). Sucrose and glucose were food grade. Isopropanol and acetone were of analytical grade.

Preparation of Diclofenac Sodium-Loaded Beads

Beads were prepared from a powder mixture of 200 g sucrose, 200 g glucose, 5 g sodium carboxymethylcellulose (NaCMC), 50 g corn starch, and 100 g diclofenac sodium. This mixture was dry blended and placed in an 8-in. conventional coating pan rotated at 50 rpm. Aqueous solution of (0.5% w/v) NaCMC was sprayed onto this powder mixture to moisten it. The seeds formed were wetted again by spraying with NaCMC solution, then dusted by 50 g talc powder, and dried using a stream of hot air (40–50°C). The processes of wetting, dusting, and drying of the seeds was repeated until the beads were built to the desired size. The beads were then dried in an oven for 24 hr at 50°C and screened using a set of U.S. standard sieves. Beads having 1–2 mm size range were chosen for the preparation of enteric-coated diclofenac sodium beads.

Sieve Analysis

The size distribution of the prepared diclofenac beads was evaluated using a set of U.S. standard sieves. The sieve nest was shaken using an ATM (Chicago, IL) Sonic Sifter for 5 min. The net weights that were retained on each sieve were then determined and recorded. The average values were used for calculation of particle size distribution.

Measurement of Flowability

The initial and the tapped density of the beads of particle size range 1–2 mm, which were selected for the preparation of enteric-coated beads, were determined by the standard graduated cylinder method. The percent compressibility (17), used as a measure of flowability, was calculated using Eq. (1):

$$\% \text{ Compressibility} = [(P_t - P_0)/P_t] \times 100 \qquad (1)$$

where P_t is the tapped bulk density and P_0 is the initial bulk density.

Polymer Coating of Diclofenac Sodium Beads

The drug-loaded beads (100 g) were placed in the coating pan rotated at 50 rpm. The beads were coated by spraying Eudragit L_{100} solution in acetone–isopropanol

mixture (1:1) containing 10% castor oil as a plasticizer. The polymer-coated beads were then dried in a stream of hot air (40–50°C) for 24 hr to remove the residual solvents.

Determination of Drug Content

One hundred milligrams of the prepared beads was carefully ground in a mortar. The diclofenac sodium content was then extracted several times with phosphate buffer (pH 7.4). The filtered solutions, after completion to 100 ml with phosphate buffer, were assayed spectrophotometrically at 276 nm.

In Vitro Dissolution Studies

Beads equivalent to 50 mg diclofenac sodium were filled in hard gelatin capsules (size 0) and tested for their release characteristics using the USP dissolution apparatus I with 100 rpm basket rotational speed at 37 ± 0.5°C. The dissolution test was carried out in 750 ml of 0.1 N HCl (pH 1.2) containing 0.1% w/w Tween 80 for 2 hr and continued for another 1 hr at pH 6.8. The change in pH was achieved by adding 250 ml of 0.2 M tribasic sodium phosphate. The drug concentration and the percentage release were determined every 30 min at 276 nm using PU 8620 spectrophotometer (Philips, UK) connected to a model PS 30 IBM computer using TDS software from Philips. The in vitro release studies were performed in triplicate for the prepared beads and for the commercial enteric-coated Voltaren tablets.

Animal Studies

Six male beagle dogs 10.75 ± 1.30 kg were used in this study. Enteric-coated Voltaren tablets (50 mg) and the formulated capsules containing the equivalent of 50 mg of the drug in the form of enteric-coated pellets were administered to these dogs on two different occasions. One week was allowed between successive dosings. The dogs were starved for 18 hr prior to the experiments but water was allowed *ad libitum*. During the experiment period each dog was placed in an upright position in a restrainer stand. The legs were shaved and a cephalic vein was cannulated using an 18-gauge cannula. Five-milliliter blood samples were withdrawn in heparinized vaccutainer tubes before and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hr post administration. The tubes were centrifuged for 10 min and plasma was aspirated and kept frozen until analysis.

Assay Method of Diclofenac Sodium

The diclofenac sodium was assayed in plasma using a specific, rapid, and sensitive high-performance liquid chromatographic method (18).

Pharmacokinetic Analysis

The peak plasma concentration (C_{max}) and the time to reach that peak (T_{max}) were determined as mean ± standard deviation ($X \pm SD$) from the plasma concentration–time profile of each dog. The area under the plasma concentration–time curve up to the last sampling time ($AUC_{0-8\ hr}$) was determined using the linear trapezoidal rule.

Statistical Analysis

The significance of the difference between the pharmacokinetic parameters obtained after oral administration of the enteric-coated Voltaren tablets and the prepared enteric-coated pellets filled in capsules was evaluated using the unpaired Student's *t*-test on a microcomputer statistical package (SAS, Statistical Analysis System Institute Inc., Cary, NC). The differences were considered significant at p values of 0.05 or less.

RESULTS AND DISCUSSION

The physical evaluation of the diclofenac sodium beads revealed that they exhibited a narrow particle size range in which 83% of the beads were in the range of 1–2 mm. The actual yield of beads was 90.5%. The theoretical loading of the drug is 162 mg/g beads, but the actual loading was 149 mg/g, indicating that the efficiency of the manufacturing process is 91.98%, where the efficiency of the process = (actual assay/theoretical assay) × 100. The beads of particle size range 1–2 mm showed compressibility of 6–8%, which indicated excellent flowability of the beads.

Figure 1 shows the in vitro release profile of diclofenac sodium from the enteric-coated beads filled in capsules and the commercial enteric-coated Voltaren tablets. The commercial tablets released no drug in 0.1 N HCl (pH 1.2), and the formulated beads released 7.89 ± 0.55% of their drug content during 2 hr of dissolution. As the medium changed to pH 6.8, the beads released 37.73 ± 7.31 and 67.03 ± 6.44% of the drug after 0.25 and 0.5 hr, respectively, compared to 0.06 ± 0.11 and

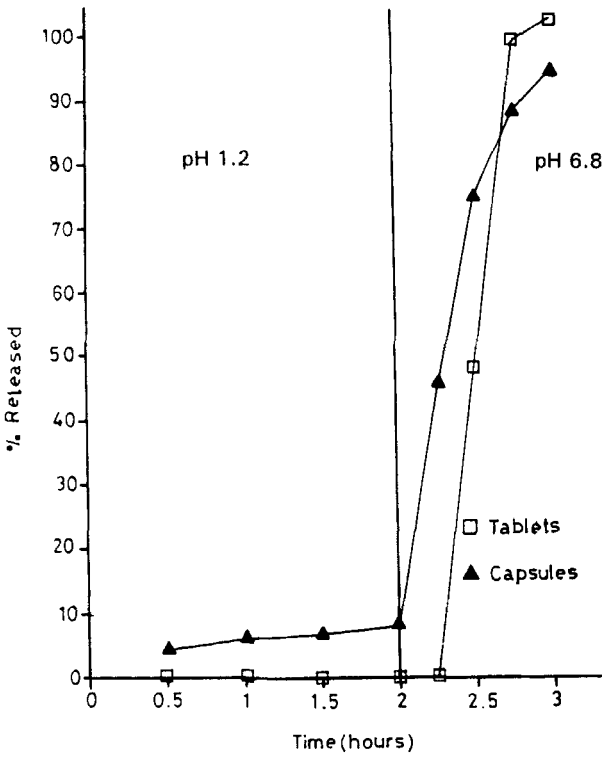

Figure 1. Diclofenac sodium percent released from commercial enteric-coated Voltaren tablets (□) and enteric-coated beads filled in hard gelatin capsules (▲) in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8).

48.57 ± 12.14% released from the enteric-coated Voltaren tablets. This indicates that the release of the drug from the beads was significantly ($p < 0.05$) faster than release from the tablets. Within 1 hr in pH 6.8, the beads and the tablets released all of their drug contents. From these in vitro data, it is clear that both formulations are in compliance with the USP requirements for the enteric-coated dosage forms.

Tables 1 and 2 show the diclofenac sodium concentrations in plasma after oral administration of the commercial Voltaren tablets and the enteric-coated beads filled in capsules to six beagle dogs, respectively. The AUC values after oral administration of the commercial tablets (Table 1) ranged from 0.72 to 40.26 μg·hr/ml with $X \pm SD$ of 13.44 ± 15.02 μg·hr/ml, and the AUCs resulted from administration of the encapsulated beads, Table 2, varied from 21.12 to 35.94 μg·hr/ml with $X \pm SD$ of 26.55 ± 5.19 μg·hr/ml. The calculations of these AUCs show a significant ($p < 0.05$) increase for administration of the encapsulated beads over that of commercial tablets. These data demonstrate the higher interdog variability in bioavailability from the commercial tablets compared to the beads (CV% 111.76 compared to 19.55, respectively). The mean plasma concentration of the six beagle dogs (Fig. 2) given the capsules containing the enteric-coated beads was significantly ($p < 0.01$) higher than that produced after oral administration of the commercial tablets.

Table 3 shows the mean pharmacokinetic parameters of diclofenac sodium after oral administration of the commercial enteric-coated tablets and the capsules containing the enteric-coated beads. The beads produced a mean plasma concentration of 6.77 ± 0.67 μg/ml, which is insignificantly ($p > 0.05$) higher than that produced after administration of the tablets (5.88 ± 7.38 μg/ml). These C_{max} values were produced at 2 ± 1.48 and 2.25 ± 1.08 hr for the encapsulated beads and tablets, respec-

Table 1

Diclofenac Sodium Plasma Concentration After Oral Administration of Voltaren Tablets to Six Beagle Dogs

	Plasma Concentration (μg/ml)							
Time (hr)	A	B	C	D	E	F	Mean	SD
0.5	0.06	0.03	0.03	0.07	0.24	–	0.07	0.09
1.0	–	0.10	7.44	0.36	0.25	–	1.63	3.25
1.5	3.37	0.12	2.89	2.06	0.72	–	1.53	1.45
2.0	5.11	0.20	3.46	0.26	0.17	0.01	1.54	2.19
3.0	2.36	–	3.03	19.84	0.29	0.67	4.37	7.68
4.0	2.27	0.16	4.32	10.90	0.25	1.94	3.31	4.02
5.0	1.14	0.14	2.03	3.44	0.11	0.97	1.31	1.27
6.0	0.96	0.07	1.05	2.00	0.19	0.72	0.83	0.70
8.0	0.71	0.05	0.80	1.65	0.12	0.28	0.60	0.60
AUC (μg·hr/ml)	13.45	0.72	19.52	40.26	1.72	4.95	13.44	15.02

Table 2

Diclofenac Sodium Plasma Concentration After Oral Administration of Enteric-Coated Beads Filled in Capsules to Six Beagle Dogs

	Plasma Concentration (μg/ml)							
Time (hr)	A	B	C	D	E	F	Mean	SD
0.5	2.00	5.94	2.67	5.16	3.44	1.02	3.37	1.88
1.0	6.83	4.29	5.52	6.42	5.05	1.45	4.93	1.93
1.5	6.84	5.03	7.06	4.54	5.85	7.84	6.19	1.27
2.0	4.47	4.06	5.51	4.84	5.32	4.21	4.74	0.59
3.0	2.82	4.14	4.08	2.06	4.15	2.73	3.33	0.91
4.0	3.28	5.46	2.46	3.88	3.82	4.21	3.85	1.00
5.0	2.15	6.63	1.61	3.79	3.09	5.67	3.82	1.98
6.0	1.62	5.10	0.92	3.10	2.01	2.69	2.57	1.46
8.0	1.13	2.87	0.50	2.40	1.76	1.72	1.73	0.85
AUC (μg·hr/ml)	22.50	35.94	21.12	27.18	26.14	26.42	26.55	5.19

tively. These T_{max} values were insignificantly ($p > 0.05$) different. The C_{max} values also indicate the greater interdog variability (CV% 79.9) after commercial tablet administration compared to that of 34.6%. This greater interdog variability in plasma concentrations and AUCs after tablet administration could be because the commercial tablets are a single-unit enteric-coated dosage form and differences in gastric emptying rate between dogs will result in variations in dissolution of the enteric-coated materials, and consequently differences in the rate and site of release of the drug in the intestine, because diclofenac sodium is absorbed mainly in the upper part of the intestine (duodenum). Failure or delay of the enteric coat to dissolve as the tablets leave the stomach results in a very low bioavailability, as may be observed in three dogs (B, E, and F, Table 1) out of six. For the capsules, the beads, because they are sufficiently small (<2 mm in diameter), seem to show a gradual emptying rate from the dog's stomach because they are able to pass the pylorus even when the sphincter is closed (19,20). This is demonstrated by the fact that all of the dogs showed comparable AUC, C_{max} and T_{max} values. The bioavailability of the capsules was 197.54% relative to the commercial tablets.

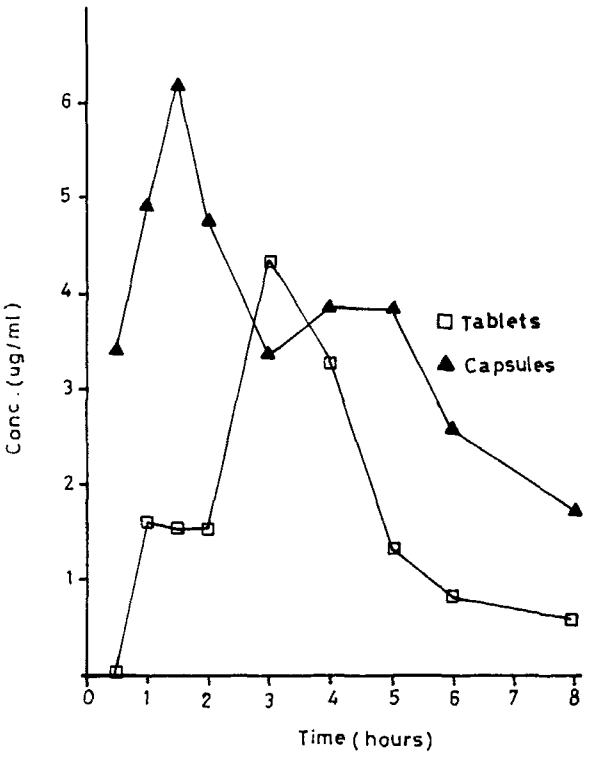

Figure 2. Mean plasma concentration of diclofenac sodium following oral administration of commercial enteric-coated Voltaren tablets (□) and enteric-coated beads filled in hard gelatin capsules (▲).

Table 3

Mean Pharmacokinetic Parameters of Diclofenac Sodium After Oral Administration of Voltaren Tablets and Formulated Enteric-Coated Beads Filled in Capsules to Six Beagle Dogs

Parameters	Voltaren Tablets	Formulated Capsules
C_{max} (μg/ml)	5.88 ± 7.38	6.77 ± 0.67
T_{max} (hr)	2.25 ± 1.08	2.00 ± 1.48
$AUC_{0\text{-}8\ hr}$ (μg·hr/ml)	13.45 ± 15.02	26.55 ± 5.19
Relative bioavailability		197.54%

CONCLUSION

The formulation of diclofenac sodium as enteric-coated beads which can be filled in capsules would be more advantageous than the present enteric-coated tablets because it achieves reproducible gastrointestinal transport, higher C_{max}, shorter T_{max}, greater AUC, and consequently higher relative bioavailability in addition to the great advantage of reducing gastric or duodenal irritation, which eventually leads to ulcer.

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