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IN-VIVO EVALUATION OF A BIOADHESIVE CONTAINING INDOMETHACIN TABLETS

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ABSTRACT

The relative bioavailability of a bioadhesive containing, directly compressed, tablet formulation against the commercial indomethacin capsules "Indocid, MSD" has been investigated in dogs. The tablets showed a prolongation of the time to reach maximum concentration to 3 hours compared to 2 hours in capsules. They also showed 39% and 184% increase in maximum and minimum plasma concentration, respectively. The relative bioavailability of the tablets is 152% compared to capsules where the tablets showed a mean area under the plasma concentration-time curve of 26 ug.hr/ml compared to 17 ug.hr/ml for capsules.

INTRODUCTION

In recent years, significant interest has been shown in the development of novel bioadhesive polymers which could be carriers for drugs and serve as novel controlled release matrices[1-3].

An ideal bioadhesive should be nontoxic, non-absorbable from GIT, form strong non-covalent bond with mucin-epithelial cell surfaces, adhere quickly to moist tissues, allow easy incorporation of drug and offer no hindrance to its release, possess specific sites of attachment, and be economical[4-6].

Robinson and his group[3] showed that polycarbophil, a polyanionic polymer, approved by FDA for use in humans, has a good bioadhesive characteristics both in the stomach as well as in the small intestine. Although Rao and Buri[7] using same technique of

Robinson's group showed that polycarbophil had better adhesion in the stomach than in the intestine.

Polycarbophil[8] has been shown to be effective in reducing indomethacin gastric ulcers in rats, in addition to being good disintegrant and directly compressible vehicle[9]. It has also been shown to be useful in improving bioavailability of oral[10], ocular[11,12] and rectal delivery of drugs[13,14].

The purpose of this work is to determine the relative bioavailability of a prepared bioadhesive containing indomethacin tablets against that of a commercial indomethacin, MSD capsules (Indocid) in dogs.

MATERIALS AND METHODS

Materials

Indomethacin was obtained from Al-Hikma Pharmaceuticals (Aman, Jordan), Polycarbophil was a kind gift from Lee Laboratories, Inc. (Petersburg, USA). All other chemicals and reagents were of analytical grade.

Preparation of Tablets

Bioadhesive containing tablets were prepared by direct compression using a single punch tabletting machine (Korsch, Type EKO) fitted with a 6 mm flat faced punch. The average weight per tablet was 103±3 mg.

Administration of Indomethacin Tablets and Capsules to Dogs

Seven healthy male beagle dogs were recruited in this study in a two-way cross over design. Their mean weight ± standard deviation was 9.25±1.39 kg. They were fasted overnight and 2 hours post administration. At least one week was permitted between successive dosings. 4 ml blood samples were withdrawn at 0, 0.5, 1, 2, 3, 4 and 6 hours into heparinized vacutainer tubes. The tubes were centrifuged for 10 minutes and plasma was aspirated and kept frozen until analysis.

Assay Procedure

The plasma samples obtained were used for determining indomethacin concentration by a modification of high-performance liquid chromatography (HPLC) method[15] using a 4 um C-18 reversed phase column. The mobile phase consisted of ethanol:water:acetic acid (49:49:2 v/v) pumped isocractically at 1 ml/min. The effluent was monitored at 254 nm.

TABLE 1

Indomethacin Plasma Levels in Dogs From Commercial Capsules "Indocid,MSD".

Time (hrs)	0.5	1	2	3	4	6
Dog	Plasma Concentration (ug/ml)					
A	0.84	3.42	5.10	2.77	0.62	0.17
B	1.62	2.03	3.84	4.64	5.83	1.13
C	1.00	2.87	3.97	2.03	1.29	0.75
D	0.88	5.67	7.09	3.14	2.16	0.78
E	9.93	4.72	2.13	0.99	----	----
F	6.66	7.99	6.57	2.94	2.30	0.47
G	1.02	2.08	10.27	4.30	3.77	0.24
Mean	3.14	4.11	5.57	2.97	2.28	0.55
S.D.	3.66	2.17	2.68	1.25	1.99	0.40

RESULTS AND DISCUSSION

The individual indomethacin plasma concentration profile in dogs after administration of the commercial capsule "Indocid, MSD" and the bioadhesive containing tablets are shown in Tables 1 and 2, respectively. Table 1 shows that the time to reach maximum concentration (t_{max}) in plasma after capsules administration range from 0.5-3 hours with mean t_{max} of 2 hours and the maximum plasma indomethacin concentration (C_{max}) range from 3.97 to 10.27 ug/ml with mean concentration of 5.57 ug/ml. From Table 2, t_{max} after tablets administration is shown to range from 2-4 hours with mean t_{max} of 3 hours. While, C_{max} range from 7.18 to 11.31 ug/ml with mean concentration of 7.74 ug/ml. The results shown in Fig. 1 indicate that the bioadhesive containing tablets have longer t_{max} and higher C_{max} than the corresponding capsules. The longer t_{max} for the tablets can be attributed to the fact that the bioadhesive polycarbophil adheres the granules to the gastric mucosa resulting in a slower rate of emptying. This effect has been verified before by

TABLE 2

Indomethacin Plasma Levels in Dogs From A Bioadhesive Containing Tablets.

Time (hrs)	0.5	1	2	3	4	6
Dog	Plasma Concentration (ug/ml)					
A	0.19	6.71	11.31	8.00	1.62	0.60
B	0.26	2.16	4.74	9.08	4.10	0.75
C	1.41	7.79	9.81	3.52	2.20	1.53
D	0.85	4.10	11.02	9.78	3.65	2.50
E	0.02	0.22	0.68	7.59	9.75	1.52
F	0.21	0.45	8.59	9.02	4.66	2.83
G	0.21	3.09	6.60	7.18	5.68	1.20
Mean	0.45	3.50	7.54	7.74	4.52	1.56
S.D.	0.50	2.92	3.84	2.07	2.69	0.84

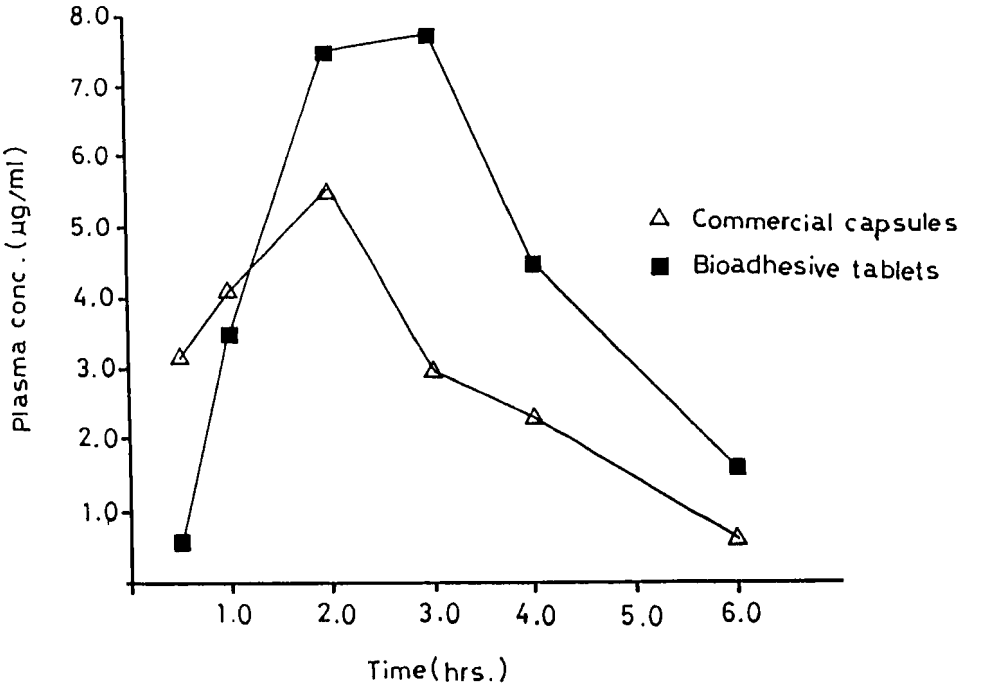

FIGURE 1

Mean plasma indomethacin concentrations following oral administration of (25 mg) of commercial capsules (△) and bioadhesive containing tablets (■).

TABLE 3

Pharmacokinetic Parameters of Commercial Capsules "Indocid" and A Bioadhesive Containing Tablets.

	Capsules	Tablets
C_{max} (ug/ml)	5.57	7.74
T_{max} (hrs)	2.0	3.0
AUC (ug.hr/ml)[a]	17.12±5.28	26.07±3.75
Rel. bioavailability[b]		152.28%

a) AUC determined by linear trapezoidal rule 0-6 hrs.
b) Relative bioavailability of tablets compared to capsules.

Longer et al[10]. Polycarbophil shows its maximum adhesiveness when it is neutral at pH <4.75[5,16]. This delaying time in stomach may improve dissolution of indomethacin. So increased fraction of the dose that reaches small intestine in ready absorbable form. This fact explains partially the higher plasma levels obtained from tablets. The other effect of the bioadhesive polycarbophil in achieving higher plasma levels from tablets is due to its adhesive effect where it improves therapy by increasing the initimacy of contact and duration of action at absorption site because of Van der Walls, hydrogen forces and similar forces[17,18].

Table 3 summarizes the pharmacokinetic parameters obtained from tablets and capsules. It shows that the area under the plasma concentration-time curve (AUC) for capsules is 17.12±5.28 ug.hr/ml compared to 26.07±3.75 ug.hr/ml for the bioadhesive containing tablets. So, these tablets are superior to the capsules showing a relative bioavailability of 152.3%.

In previous report Hosny and Al-Meshal[9] showed that these bioadhesive tablets containing polycarbophil disintegrate rapidly (<1 min.) and have mean hardness and standard deviation of 3.07±9.65 kg. The in-vitro release of the drug from these tablets was first order and non significantly slower ($P<0.05$) than from that of the capsules.

As a conclusion, the polycarbophil containing tablets are superior to the capsules regarding plasma concentration and bioavailability. They are also safe whereas the tablets disintegrate rapidly in stomach, polycarbophil protect the underlying cell layer by

forming a thick barrier, that separates cells from the environment, due to its crosslinking and the fact that it is water-insoluble as shown previously in the work of Hosny and Al-Meshal[10].

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