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Bioavailability of sustained release indomethacin suppositories containing polycarbophil

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Abstract

The bioavailability of indomethacin from polyethylene glycol base, commercial suppositories Indocid*, MSD and from polyethylene glycol base containing 5, 6 and 8% of polycarbophil, with the purpose of obtaining a controlled release suppositories, was determined in dogs. The results show that polycarbophil as a bioadhesive increased absorption and improved the bioavailability of indomethacin where the areas under the curves for the commercial suppositories and those containing 0, 5, 6 and 8% polycarbophil were 19.5, 14.9, 31.2, 21.4 and 21.2 μg h ml^{-1}, respectively. The maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were 4.76, 2.98, 4.50, 2.36 and 1.29 μg/ml and 1, 1, 1, 1 and 12 h for the commercial suppositories and those containing 0, 5, 6 and 8% polycarbophil, respectively. The data indicate that as the polycarbophil concentration increased from 0 to 5% in the polyethylene glycol suppositories, the plasma levels and bioavailability improved significantly ($p < 0.1$, Student's t-test), whereas on increasing from 5 to 6 and 8% the plasma levels and bioavailability decreased significantly ($p < 0.05$). At 8% polycarbophil concentration, sustained release suppositories were produced but a decrease in plasma levels was observed.

Keywords: Indomethacin; Suppository; Sustained release; Polycarbophil; Bioavailability; Dog

1. Introduction

Polycarbophil (Markus, 1965), a water absorbable bioadhesive polymer, has been shown to have excellent bioadhesive properties (Ch'ng et al., 1985; Park and Robinson, 1985; Rao and Buri, 1989). It enhances drug absorption by increasing the intimacy and duration of contact of the delivery systems with absorbing tissues (Robinson and Li, 1984; Ch'ng et al., 1985; Longer et al., 1985; Hui and Robinson, 1986; Hosny, 1988; Gonda and Gipps, 1990; Hosny and Robinson, 1991).

It has been reported recently (Hosny, 1993) that polycarbophil can be a useful matrix for controlling the release of water soluble and water insoluble drugs from tablet formulations. It has also been demonstrated (Samaha et al., 1992; Hosny and Al-Angary, 1993) that the addition of polycarbophil at different concentrations to polyethylene glycol base reduces significantly the release of indomethacin from suppositories due

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to interaction (hydrogen bonding) between the carboxyl groups of polycarbophil and terminal hydroxyl groups of polyethylene glycol as has been shown by DSC thermograms. This interaction leads to strong cross-linking between the two polymers and more delayed release of the drug could result. The present study was undertaken to determine the effect of different concentrations of polycarbophil on bioavailability and sustaining plasma levels of indomethacin from polyethylene glycol suppositories relative to that of commercial Indocid* MSD.

2. Materials and methods

2.1. Materials

Indomethacin (Al-Hikma Pharmaceutical, Amman, Jordan), polycarbophil (lot no. x055013, Lee Laboratories Inc., Petersberg, VA, U.S.A.), and polyethylene glycol 4000 (BDH Chemicals Ltd, Poole, U.K.) were obtained from the indicated sources.

2.2. Preparation of indomethacin suppositories

All suppositories containing 100 mg indomethacin were prepared adopting the fusion method. The displacement values (Vidras et al., 1982) of indomethacin and polycarbophil were determined in polyethylene glycol 4000. The base was melted in a porcelain dish on a water bath. Indomethacin and polycarbophil were added in the required concentrations with subsequent trituration until a homogeneous mass was produced and the mixture then poured into a 1 g mold.

2.3. Rectal administration of indomethacin suppositories to dogs

Five healthy beagle dogs, three males and two females, were used in this study. Their mean weight ± standard deviation was 8.80 ± 1.64 kg. They were maintained on normal diet with free access to water. At least 1 week was permitted between successive dosings.

2.4. Determination of indomethacin in plasma

5 ml blood samples were withdrawn, before rectal administration of indomethacin suppositories, and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h post-administration, into heparinized vacutainer tubes. Plasma samples were taken after centrifugation and frozen until analysis. Indomethacin plasma concentrations were assayed using a specific and sensitive high-performance liquid chromatographic method (Al-Angary et al., 1990).

2.5. Pharmacokinetic analysis

The maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were read off from individual plasma concentration-time curves of indomethacin. The area under the plasma concentration-time curve (AUC) was calculated based on the linear trapezoidal rule. All data are expressed as mean ± S.D. ($X \pm$ S.D.)

3. Results and discussion

Tables 1–5 and Fig. 1 provide the dogs' plasma indomethacin concentration-time profiles for the commercial and the tested formulations, as well as the pharmacokinetic analysis. It is clear from the results shown in Table 1 that the commercial formula has no sustaining plasma levels of indomethacin even when considering dogs' plasma concentrations separately. The C_{max} of these commercial suppositories is 4.76 μg/ml, t_{max} 1 h and AUC 19.46 ± 5.89 μg h ml^{-1}. In order to determine a basis for studying the effect of polycarbophil on sustaining a release effect and plasma concentration it was necessary to start with suppositories containing no polycarbophil. From the data in Table 2 C_{max} is 3 μg/ml and t_{max} 1 h. The AUC is 14.95 ± 6.20 μg h ml^{-1} and the bioavailability relative to the commercial form was 76.82%.

In vitro release data of indomethacin suppositories using polycarbophil in our previous work (Hosny and Al-Angary, 1993) showed that at 5% polycarbophil concentration a sustained release suppository is produced releasing the drug con-

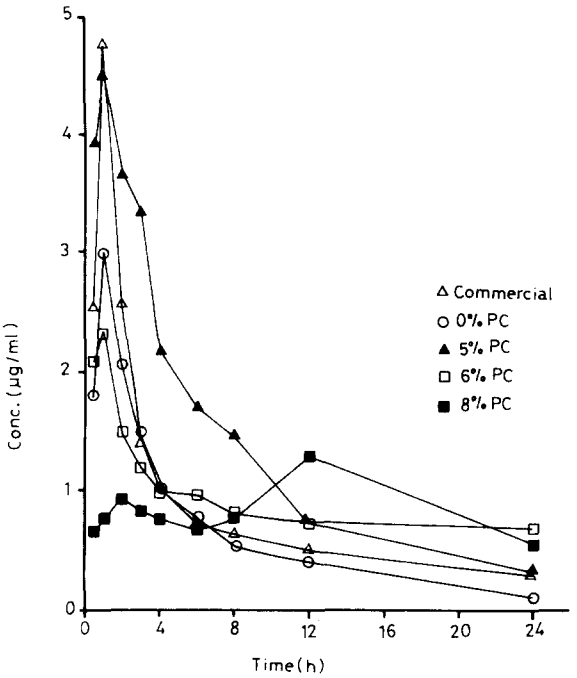

Fig. 1. Plasma indomethacin levels in dogs after administration of commercial suppositories and PEG suppositories containing 0, 5, 6 and 8% (w/w) polycarbophil.

tent in about 6 h while at 10 and 20% concentrations of the polymer only 36 and 17% of the drug is released respectively during the same time period. Therefore, the first formulation containing polycarbophil was designed to contain 5%. The results of these suppositories are listed in Table 3. It is clear that polycarbophil at this concentration results in a significant ($p < 0.1$, Student's t-test) improvement in indomethacin plasma levels, which can be attributed to its bioadhesive characteristics. The AUC increased from 14.95 to 31.17 $\mu g\ h\ ml^{-1}$ with a relative bioavailability of 208% compared to that of suppositories containing no polycarbophil and 160% relative to that of commercial suppositories. No improvement in the sustaining effect was observed for the individual dog's plasma levels indicating that the 5% concentration of polycarbophil is insufficient. Thus, it was necessary to use higher concentrations of polycarbophil to achieve the sustaining effect. The results from the same formula, but with the polycarbophil concentration increased to 6 and

Table 1Plasma indomethacin levels and pharmacokinetic parameters in dogs from commercial suppositories

Time (h)	Concentration (μg/ml)					X	S.D.
	B_1	B_2	B_3	B_4	B_5		
0.5	5.24	2.06	3.05	1.40	0.90	2.53	1.72
1	9.67	2.63	5.57	4.13	1.81	4.76	3.10
2	4.56	1.79	2.89	2.43	1.11	2.56	1.31
3	1.19	1.52	2.19	1.05	1.00	1.39	0.49
4	0.70	1.27	1.71	0.89	0.67	1.05	0.44
6	0.62	0.72	0.92	0.79	0.53	0.72	0.15
8	0.57	0.70	0.84	0.57	0.46	0.63	0.15
12	0.41	0.66	0.63	0.49	0.32	0.50	0.14
24	0.38	0.38	0.28	0.35	0.10	0.30	0.12
AUC	25.11	19.32	24.43	17.92	10.52	19.46	5.89

Table 2
Plasma indomethacin levels and pharmacokinetic parameters in dogs from polyethylene glycol suppositories

Time (h)	Concentration (μg/ml)					X	S.D.
	B_1	B_2	B_3	B_4	B_5		
0.5	0.72	1.40	1.53	4.35	0.95	1.79	1.47
1	2.28	3.10	2.92	4.98	1.60	2.98	1.27
2	1.71	2.30	1.15	3.80	1.20	2.03	1.09
3	1.14	1.73	0.81	2.65	0.95	1.46	0.75
4	0.90	1.20	0.67	1.68	0.60	1.01	0.44
6	0.70	0.95	0.54	0.90	0.45	0.71	0.22
8	0.57	0.86	0.45	0.65	0.30	0.53	0.16
12	0.40	0.65	0.30	0.45	0.15	0.39	0.18
24	0.10	0.20	0.09	0.10	–	0.10	0.07
AUC	13.18	19.74	11.29	22.83	7.73	14.95	6.20

Table 3
Plasma indomethacin levels and pharmacokinetic parameters in dogs from polyethylene glycol suppositories containing 5% polycarbophil

Time (h)	Concentration (μg/ml)					X	S.D.
	B_1	B_2	B_3	B_4	B_5		
0.5	1.31	8.89	1.72	6.65	0.75	3.86	3.67
1	1.58	11.90	1.79	5.56	1.66	4.50	4.47
2	0.83	8.34	2.74	5.01	1.35	3.65	3.08
3	0.65	4.78	6.75	3.67	0.85	3.34	2.61
4	0.54	4.04	2.61	2.97	0.72	2.18	1.51
6	0.50	3.13	1.45	2.82	0.64	1.71	1.22
8	0.47	2.85	1.21	2.22	0.55	1.46	1.05
12	0.31	0.81	0.43	1.61	0.47	0.73	0.53
24	0.29	0.34	0.10	0.47	0.47	0.33	0.15
AUC	10.76	55.88	26.18	48.63	14.41	31.17	20.24

Table 4
Plasma indomethacin levels and pharmacokinetic parameters in dogs from polyethylene glycol suppositories containing 6% polycarbophil

Time (h)	Concentration (μg/ml)					X	S.D.
	B_1	B_2	B_3	B_4	B_5		
0.5	1.47	2.55	1.61	0.71	4.16	2.10	1.32
1	1.53	3.30	1.49	0.81	4.67	2.36	1.59
2	1.06	1.80	1.35	0.59	2.64	1.49	0.78
3	0.74	1.73	1.12	0.70	1.65	1.19	0.49
4	0.53	1.69	1.01	0.64	1.05	0.98	0.45
6	0.58	1.50	0.95	0.83	0.97	0.97	0.34
8	0.65	1.44	0.70	0.61	0.67	0.81	0.35
12	0.58	1.36	0.58	0.55	0.65	0.74	0.35
24	0.55	1.02	0.61	0.60	0.65	0.69	0.19
AUC	15.53	34.13	18.21	14.70	24.50	21.41	8.08

8%, are shown in Tables 4 and 5, respectively. As can be seen, there is little improvement in sustaining effect at 6% concentration and plasma indomethacin levels were reduced significantly ($p < 0.05$) with C_{max} amounting to 2.36 μg/ml, t_{max} 1 h and the AUC was also decreased to a value of 21.41 μg h ml^{-1}. The 8% concentration of polycarbophil induced a plateau plasma level of the drug over a period of 12 h as judged by the shift in t_{max}. However, the indomethacin plasma levels were relatively low. This may be due to the fact that polycarbophil at this concentration causes the particles to remain together with less dispersion in the rectal vault, so that the surface area exposed to the rectal fluid is reduced. The AUC was 21.18 μg h ml^{-1} with relative bioavailability of 142 and 109% compared to that of the formulation containing no polycarbophil and that of the commercial form, respectively.

Table 5
Plasma indomethacin levels and pharmacokinetic parameters in dogs from polyethylene glycol suppositories containing 8% polycarbophil

Time (h)	Concentration (μg/ml)					X	S.D.
	B_1	B_2	B_3	B_4	B_5		
0.5	0.78	0.49	1.09	0.36	0.49	0.64	0.29
1	0.74	0.46	1.49	0.43	0.75	0.77	0.43
2	0.60	0.39	2.20	0.66	0.83	0.94	0.72
3	0.70	0.41	1.51	0.60	0.87	0.82	0.42
4	0.87	0.41	1.14	0.63	0.76	0.76	0.27
6	0.79	0.43	0.85	0.62	0.70	0.68	0.16
8	1.01	0.55	0.89	0.68	0.67	0.76	0.19
12	1.70	0.85	0.88	1.49	1.51	1.29	0.39
24	0.63	0.46	0.68	0.70	0.41	0.58	0.13
AUC	25.54	14.07	22.57	22.11	21.60	21.18	4.26

In conclusion, addition of polycarbophil to polyethylene glycol suppositories results in an improvement of bioavailability. Also, as the concentration increased from 5 to 8% a sustained blood level for at least 12 h was achieved. The key step in formulation of these suppositories is to use the optimum concentration of polycarbophil, which achieves an improvement in blood levels, sustaining action and bioavailability. Higher concentrations of polycarbophil improve sustaining action but decrease blood levels and bioavailability, whereas lower concentrations improve blood levels and bioavailability but do not significantly improve the sustaining effect.

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