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DISSOLUTION, BIOAVAILABILITY AND ULCEROGENIC STUDIES ON SOLID DISPERSIONS OF INDOMETHACIN IN WATER SOLUBLE CELLULOSE POLYMERS

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ABSTRACT

The dissolution rate, bioavailability and ulcerogenic activity of indomethacin dispersed in water soluble cellulose polymers was investigated. Solid dispersions of indomethacin in hydroxypropyl cellulose-SL (HPC-SL), hydroxypropyl-methyl cellulose (HPMC) and hydroxyethyl cellulose (HEC) were prepared by common solvent method with a view to improve its dissolution and absorption characteristics. The dispersions were evaluated by X-ray diffraction, TLC, IR, dissolution rate, bioavailability and ulcerogenic studies. TLC and IR studies indicated no interaction between indomethacin and carriers. Indomethacin in the dispersions was found to be in amorphous form. Marked increase in the dissolution rate and efficiency of indomethacin was observed in the case of solid dispersions. HPC-SL gave the highest dissolution improvement. A 30-fold increase in dissolution was observed with indomethacin-HPC-SL (9:1) dispersion.

In vivo studies in human subjects showed a significant increase in absorption rate (k_a) and serum levels of indomethacin with solid dispersions when compared to indomethacin alone. However, the extent of bioavailabilty was the same with both indomethacin and its solid dispersions. About 70-80 per cent reduction in ulcerogenic activity was observed with solid dispersions and the dispersions were found to have negligible ulcerogenic activity.

INTRODUCTION

The poor dissolution characteristics of relatively insoluble drugs has long been a problem to pharmaceutical industry. Among the various approaches to improve the dissolution of these drugs the preparation of solid dispersions has often proven to be successful[1]. We have been working on the application of water soluble cellulose polymers as carriers for solid dispersions. Indomethacin, a widely used non-steroidal anti-inflammatory, analgesic and anti-pyretic drug, is poorly soluble in water and aqueous fluids and its absorption is dissolution rate limited. USP XXII[2] has also prescribed a dissolution rate test specification for indomethacin capsules. Marked differences in the dissolution profiles and bioavailability of indomethacin formulations were also reported earlier[3,4]. In the present work solid dispersions of indomethacin in various water soluble cellulose polymers such as hydroxypropyl cellulose-SL (HPC-SL), hydroxypropylmethyl cellulose (HPMC) and hydroxyethyl cellulose (HEC) were prepared with a view to improve its dissolution and absorption characteristics and were evaluated by X-ray diffraction, TLC, IR, dissolution rate

and bioavailability studies. As the use of indomethacin is associated with g.i. side-effects majorly peptic ulceration with bleeding, the ulcerogenic activity of indomethacin dispersed in cellulose polymers was also evaluated. The results are reported here.

EXPERIMENTAL

Materials

Indomethacin I.P., hydroxypropyl cellulose-SL (Nisso; having a viscosity of 3.0-5.9 cp in a 2% by weight aqueous solution at 20°C); hydroxypropylmethyl cellulose (Pharmacoat 606; having a viscosity of 6 cp in a 2% by weight aqueous solution at 20°C); hydroxyethyl cellulose (Cellosize; WP type; viscosity grade 02; having a viscosity of 7-14 cp in a 5% by weight aqueous solution at 25°C).; methanol (ExcelaR-Glaxo) and methylene chloride (Qualigens) were used.

Preparation of Solid Dispersions

Solid dispersions of indomethacin were prepared by common solvent method. For HPC-SL and HEC methanol and for HPMC a mixture of methylene chloride and methanol (1:2) were used as solvents. The samples were prepared by dissolving both the drug and the carrier in the solvent to get a clear solution. The solvent was then removed by evaporation at 40°C under vacuum. The mass obtained was then crushed, pulverised and sifted through mesh number 120. In the case of HEC, as it is insoluble in most of the organic solvents a modified method in which the drug was dissolved in the solvent and the carrier was dispersed as fine particles and the solvent is then removed by

evaporation under vacuum, was used. In each case four concentrations of the carrier namely 5,10,25 and 50% were used in the preparation of solid dispersions.

Preparation of Physical Mixtures

Indomethacin and carriers were weighed accurately in 1:1 ratio, mixed thoroughly by trituration in a mortar, powdered and sifted through mesh number 120.

X-ray Diffraction Studies

X-ray diffractograms were obtained using Phillips diffractometer (PW 1140) and Cu-K_α radiation. Diffractograms were run at a scanning speed of 2°/min and a chart speed of 2°/2cm/2θ. The diffractograms are shown in Fig. 1.

Interaction Studies

A TLC method was used to study the chemical stability of indomethacin in solid dispersions. The solvent system consisting of methanol : strong ammonia solution (100:1.5) was employed. Indomethacin was detected by exposing to iodine vapours.

IR spectra of indomethacin and its solid dispersions were obtained using Perkin-Elmer 841 IR spectrophotometer. IR spectra of indomethacin and its solid dispersions in HPC-SL, HPMC and HEC were obtained by preparing a film of the preparation dispersed in Nujol.

Dissolution Rate Studies

The dissolution rate of indomethacin in pure form and from solid dispersions and physical mixtures was studied

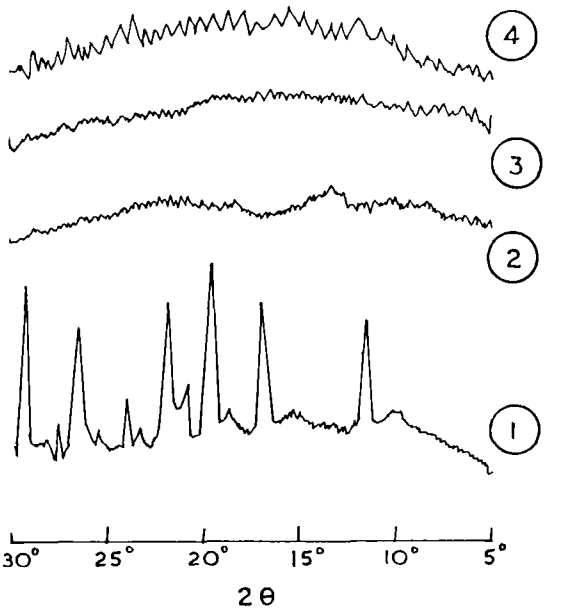

FIGURE 1

X-ray diffractograms of indomethacin in pure form (1) and in solid dispersions in HPC-SL (2), HPMC (3) and HEC (4) at 10% carrier concentration

using USP XXI Dissolution Rate Test Apparatus employing a paddle stirrer. In 900 ml of dissolution medium (a solvent blend consisting of 1 volume of phosphate buffer of pH 7.2 and 9 volumes of distilled water), a sample equivalent to 50 mg of indomethacin, a speed of 25 rpm and a temperature of 37°±1° were employed in each test. A 5 ml aliquot of dissolution medium was withdrawn at different time intervals, suitably diluted and assayed spectrophotometrically[2] at 318 nm using Shimadzu UV-150 spectrophotometer. The per cent of indomethacin dissolved at various time intervals was calculated and plotted against time (Fig. 2). From these

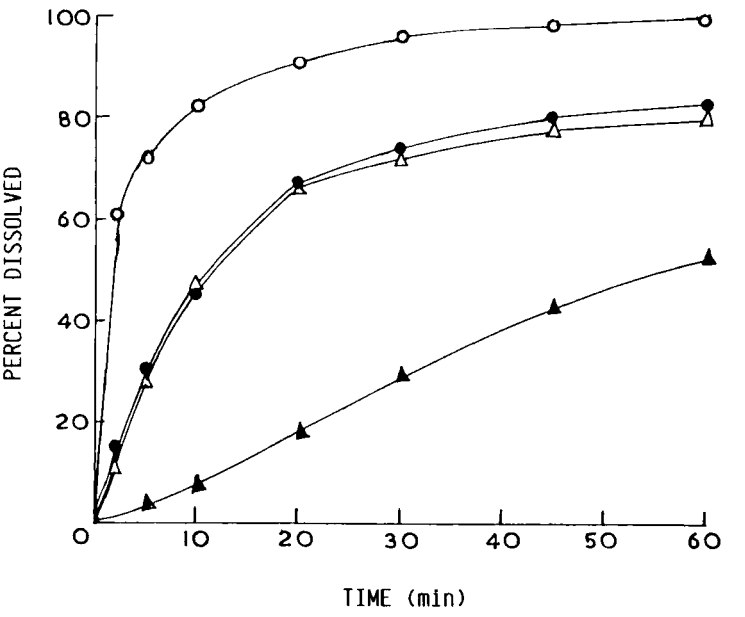

FIGURE 2

Dissolution profiles of indomethacin in pure form (▲) and from solid dispersions prepared with HPC-SL (0), HPMC (●) and HEC (△) at 10% carrier concentration

dissolution profiles T_{50} (time taken for 50% dissolution) and T_{90} (time taken for 90% dissolution) values were recorded. Dissolution efficiency (D.E) values were calculated from the dissolution profiles as suggested by Khan[5]. The results are given in Table 1.

Bioavailability Studies

In vivo bioavailability studies were conducted on (i) indomethacin (ii) indomethacin-HPC-SL (9:1) and (iii) indomethacin-HPMC (9:1) solid dispersions in healthy human

TABLE 1

Dissolution Parameters of Indomethacin from various Solid Dispersions

Solid Dispersion	Percent carrier concentration	T_{50} (min)	T_{90} (min)	D.E. (%)	First order dissolution rate constant (k_1) (min^{-1})
Indomethacin	--	54	>120	14.5	0.0051
Indomethacin HPC-SL	5	3.8	120	60.83	0.038
	10	1.8	21	73.13	0.068
	25	1.9	16	82.37	0.074
	50	2.0	13	82.96	0.081
Indomethacin-HPMC	5	48	>120	26.83	0.0053
	10	12	74	51.67	0.015
	25	8.5	48	58.50	0.020
	50	7.5	33	58.83	0.027
Indomethacin-HEC	5	14	>120	45.27	0.015
	10	11.5	>120	50.13	0.018
	25	2.0	13	84.51	0.087
	50	1.5	6	90.17	0.115

subjects as per a cross-over randomized block design (RBD). Each treatment (product) was replicted 5 times. Healthy human subjects of age range between 24-28 years (average weight was 58.5±4.5 kg) were participated in the study. All subjects were instructed to refrain from taking any medication during the study. Each subject was administered one product once a month. Indomethacin and its solid dispersions were administered at a dose of 25 mg of indomethacin. The products were taken orally in the morning following overnight fasting. No food or liquid other than water was permitted until 4 hours following administration of the product.

After collecting the zero-hour blood sample (blank), the product in the study was administered orally with a glassful of water. 2ml blood samples were collected at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 24.0 hours after administration. All the samples were stored under refrigerated conditions prior to assay. Serum concentrations of indomethacin were determined by a known spectrofluorometric method[6] as follows:

0.2 ml of serum was pipetted into a glass-stoppered centrifuge tube containing 2 ml of 1M citrate buffer (pH 5.0) and 10 ml of heptane containing 5% isoamyl alcohol. The contents of the tube were shaken for 15 min and then centrifuged. 8 ml of the heptane phase was pipetted into a centrifuge tube containing 5 ml of 0.1N sodium hydroxide and shaken for 5 min. After centrifuging, 3 ml of the lower aqueous phase was transferred into a test-tube containing 3 ml of distilled water. To this 0.5 ml of 2M hydrochloric acid, 2 ml of each of chloramine-T reagent and m-aminophenol reagent were added in sequence and shaken well.

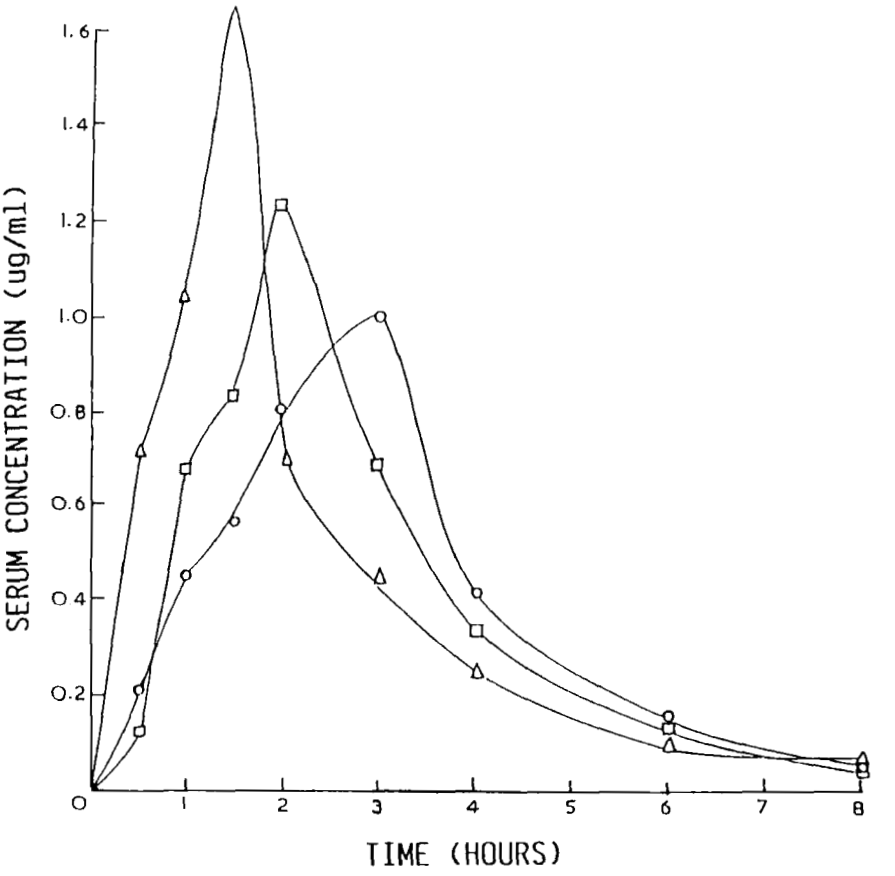

FIGURE 3

Mean serum concentration of indomethacin following oral administration of indomethacin (O), indomethacin-HPC-SL (9:1) (Δ) and indomethacin-HPMC (9:1) (□).

The fluorescence of the solution was measured at excitation and emission maxima of 465 and 490 nm respectively against the reagent blank prepared in the same manner.

From the time vs serum concentration curves (Fig. 3) peak serum concentration (C_{max}), time at which peak

TABLE 2

Pharmacokinetic and Bioavailability parameters estimated following Oral administration of Indomethacin and its Solid Dispersions

Solid dispersion	C_{max} (µg/ml)	t_p (hr)	k_{el} (hr^{-1})	$t_{\frac{1}{2}}$ (min)	[AUC] (µg-hr/ml)		Percentage absorbed in 1.5 hr	k_a (hr^{-1})
					0-3 hr	0-α		
Indomethacin	1.00	3.0	0.4744	87	1.72	3.36	43.2	0.5159
Indomethacin-HPC-SL (9:1)	1.63	1.5	0.4746	87	2.44	3.44	100.0	0.9016
Indomethacin-HPMC (9:1)	1.23	2.0	0.5003	83	2.02	3.30	62.7	0.6879

TABLE 3

Ulcerogenic activity of Indomethacin and its Dispersions

Preparation	Ulcer index Mean* ± S.E.	Remarks
Indomethacin	4.00 ± 0.26	Ulcerogenic
Indomethacin-HPC-SL	1.17 ± 0.31	70.75% reduction in ulcerogenic activity
Indomethacin-HPMC	0.83 ± 0.17	79.25% reduction in ulcerogenic activity
Indomethacin-HEC	1.05 ± 0.25	73.75% reduction in ulcerogenic activity

* Average of scoring in six animals

occurred (t_p) and area under the curve (AUC) were recorded. Elimination rate constant (k_{el}) and biological half-life ($t_{\frac{1}{2}}$) were calculated from the slope of the linear regression line in the elimination phase of the semi-logarithmic plot of time vs concentration. Absorption rate constant (k_a) was calculated by applying Wagner-Nelson's method to time vs concentration data. The results are given in Table 2.

Ulcerogenic Studies

Ulcerogenic studies were carried out by the method of Okabe[7]. Wistar rats of either sex weighing between 120-150

g were used. The animals were starved for 24 hours prior to experimentation. The pylorus was ligated under light ether anaesthesia. After the recovery of the animal, the preparation was administered orally at a dose equivalent to 5 mg of indomethacin per kg of body weight. The animals were sacrificed after 8 hours and the stomach mucosa was collected for the observation of ulceration. The mucosa of the fundus and the pyloric part of the stomach was observed with magnifying lens for ulcers and perforations. The rating of ulcer formation (ulcer index) was done according to scoring system described by Anderson and Soman[8]. The results are given in Table 3.

RESULTS AND DISCUSSION

Solid dispersions of indomethacin in HPC-SL, HPMC and HEC were found to be fine and free-flowing powders. Low s.d. values in per cent drug content ensured uniformity of drug content in each batch. In TLC studies indomethacin dispersed in various carriers showed the same R_f value as pure compound and no additional spots were detected. IR spectra of indomethacin in pure form and in solid dispersions were all identical. The principal IR absorption peaks of indomethacin at 1380 cm^{-1} (C-H stretching), 1460 cm^{-1} ($-O.CH_3$), 1610 cm^{-1} (aromatic), 1710, 1720 cm^{-1} (C=O), 3500 cm^{-1} (-OH) were all observed in the spectra of indomethacin as well as its dispersions. Thus TLC and IR spectra indicated no interaction between indomethacin and carriers. These observations also indicated that indomethacin was not decomposed during the preparation of solid dispersions.

The physical state of the drug in the solid dispersions was evaluated by X-ray diffraction studies. X-ray

diffractograms of indomethacin in pure form exhibited characteristic crystalline diffraction pattern (Fig. 1). Whereas in the case of solid dispersions the sharp diffraction peaks of indomethacin disappeared indicating its presence in an amorphous form in the dispersions.

Solid dispersions gave fast and rapid dissolution of indomethacin when compared to pure drug and physical mixtures. With each carrier as its proportion in the solid dispersion was increased the dissolution of indomethacin also increased. Among the cellulose polymers studied HPC-SL gave highest dissolution. A 30-fold increase in dissolution (basing on T_{50} values) was observed with HPC-SL at 10% carrier concentration. Comparative dissolution profiles of indomethacin from various solid dispersions prepared at 10% carrier concentration are shown in Fig. 2. Dissolution efficiency (D.E) was also more in the case of solid dispersions. The dissolution efficiency of indomethacin was increased from 14.5% for pure drug to 73.13%, 51.67% and 50.13% with HPC-SL, HPMC and HEC respectively at 10% carrier concentration.

The dissolution of indomethacin in pure form and from various solid dispersions followed first-order kinetics. The first-order dissolution rate constants were also higher for solid dispersions when compared to the pure drug (Table 1). The increased dissolution rate and efficiency observed in the case of solid dispersions is due to the molecular dispersion of indomethacin in an amorphous form in the matrix of the carrier.

The results of the **in vivo** bioavailability studies (Table 2) indicated fast absorption and higher serum levels

of indomethacin from solid dispersions when compared to indomethacin pure drug. The absorption rate constant (k_a) and $[AUC]_0^{3hr}$ were also more in the case of solid dispersions indicating higher rate of absorption of indomethacin from solid dispersions. However, $[AUC]_0^{\alpha}$ was found to be nearly the same with the pure drug and its dispersions indicating that the extent of bioavailability was the same with both indomethacin and its solid dispersions. As indomethacin is poorly soluble the observed increase in the rate of absorption in the case of solid dispersions is due to the rapid dissolution of indomethacin from these solid dispersions when compared to pure drug. The biological half-life was found to be nearly the same following the administration of indomethacin in pure form and in solid dispersion form indicating that the elimination characteristics of indomethacin remained unaltered when it was administered in solid dispersion form.

The results of the ulcerogenic studies (Table 3) indicated that the ulcer formation and the degree of severity were significantly reduced in the rats receiving the solid dispersions than those received indomethacin. About 70-80 per cent reduction in ulcerogenic activity was observed with solid dispersions and the dispersions were found to have negligible ulcerogenic activity.

CONCLUSIONS

Solid dispersion of indomethacin in HPC-SL, HPMC and HEC was found to be effective in increasing the dissolution rate and efficiency and absorption rate of indomethacin. These solid dispersions have negligible ulcerogenic activity. Hence solid dispersion of indomethacin in water soluble

cellulose polymers can be used to improve the dissolution and absorption rate of indomethacin and reduce its ulcerogenic activity.

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