International Journal of Pharmaceutics, 55 (1989) 25–30
Elsevier

IJP 01845

An in vitro study of possible food–drug interactions of the controlled-release propranolol products

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(Received 18 July 1988)
(Modified version received 9 January 1989)
(Accepted 14 February 1989)

Key words: Propranolol controlled-release; Food–drug interaction; In vitro dissolution; Topographical characterization

Summary

The pH–dissolution profiles of 4 controlled release (C.R.) propranolol products were investigated. Three of the products were pretreated with peanut oil prior to the dissolution testing to simulate drug administration with a fatty meal. The results were displayed in 3-dimensional graphs utilizing the topographical plotting technique of Skelly et al. The influence of pH on the in vitro drug release from the C.R. formulations was found to be less significant than the effect of lipid. A substantial decrease in dissolution rate that occurs with lipid pretreatment across the entire pH range suggests that lipid may have a significant effect on these C.R. drug products which are subject to a high first-pass effect.

Introduction

The influence of food on the bioavailability of propranolol and other drugs subject to first-pass metabolism such as metoprolol and hydralazine have been studied in humans in recent years (Melander et al., 1977; Liedholm et al., 1983, 1986; Byrne et al., 1984). Food may affect the disintegration, dissolution, and absorption of solid oral formulations by delaying gastric emptying, prolonging gastrointestinal transit time and/or by inducing changes in gastrohepatic secretion of acid and enzymes. For high clearance first-pass drugs such as propranolol, food may also influence drug bioavailability by changing splanchnic blood flow and/or the first-pass metabolism in the liver.

Since it was first reported that the bioavailability of an immediately released (I.R.) dosage form of propranolol was significantly increased when dosed with a meal (Melander et al., 1977), studies have been conducted to determine the mechanisms responsible for the "food effect" (McLean et al., 1981; Svensson et al., 1983; Liedholm et al., 1986). Though some of the possible explanations such as first-pass metabolic inhibitions, inhibition of enzymes etc. have been fiercely debated, most investigators agree that a transient increase in splanchnic food flow after a meal contributes significantly to the increase of drug bioavailability.

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Contrary to the I.R. dosage form, the food–drug interaction involving controlled-release (C.R.) dosage forms of propranolol have not been well studied. One report on C.R. propranolol product showed that food had little or no effect on the plasma concentration–time profile of propranolol (compared to fasted drug administration) (Liedholm et al., 1983, Bryne et al., 1984). This is marked contrast to reports on the I.R. formulation of propranolol, which showed more than 50% increase in both the area under the concentration–time curve (AUC) and peak plasma concentration (C_{max}). Given the substantial use of C.R. propranolol, it is important that this "food effect" on different C.R. formulations be studied.

The purpose of the present study is to investigate the possible food–drug interaction of C.R. dosage forms of propranolol by an in vitro dissolution procedure developed in our laboratory. As demonstrated in our previous studies on quinidine (Skelly et al., 1987) and theophylline (Skelly et al., 1986; Maturu et al., 1986), it is projected that the dissolution behavior of propranolol C.R. formulations in the presence and absence of lipid, and varying pH provide some characteristics on in vivo food–drug interaction.

Experimental

Dosage forms

The controlled-release capsules of propranolol HCl, Inderal LA 80 mg (lot 6NWQ3, product A), Inderal LA 160 mg (lot 6NWS1, product B), Inderide LA 80/50 mg (lot 6NOR9, product C) and Inderide LA 160/50 mg (lot 1XW3, product D) were all manufactured by Ayerst Laboratories (U.S.A.). The latter two products contain both propranolol HCl and 50 mg hydrochlorothiazide.

Dissolution studies

Dissolution tests were carried out in a 6-vessel dissolution apparatus (Distek 2000 and/or Vanderkamp 600 dissolution system, U.S.A.) employing rotating basket method (USP Method I). The rotating speed was set at 100 rpm with 900 ml medium at $37 \pm 0.5\,^{\circ}C$. Simulated gastric fluid without pepsin (SGF, pH 1.2), simulated intestinal fluid without pancreatin (SIF, pH 7.5), and buffers of 2.5, 4.5 and 6.8 pH were used as dissolution media. These buffers were prepared by titrating 0.2 M potassium biphthalate (for pHs 2.5 and 4.5) and 0.2 M monobasic potassium phosphate (for pHs 6.8 and 7.5) with 0.2 M HCl or NaOH according to USP XXI procedures. Each dissolution test was conducted for a maximum of 8 h with sampling at different time intervals.

Oil treatment of sample contents

To simulate an effect of a fatty meal, our modified in vitro method (Maturu et al., 1986) was employed. The content of each capsule instead of a whole capsule was placed into a 40-mesh stainless steel screen basket and immersed in a small beaker with 10 ml of peanut oil. The beaker was partially submerged in a water bath at $37\,^{\circ}C$ with gentle horizontal agitation for one hour. Thereafter, the basket was removed from the beaker and placed on the paper towel to remove excess oil before returning to the dissolution test. The intact capsule was not used because of the insolubility of the capsule cell in peanut oil during the pretreatment. For comparison, the dissolution rates for the untreated capsule contents instead of the whole capsule were determined.

Analysis of propranolol in the dissolution samples

The amount of propranolol dissolved in the dissolution medium was determined by a simple reversed phase high-performance liquid chromatographic system (WISP Model 710 Autosampling HPLC System, Waters Associates, Milford, MA, U.S.A.). To shorten the analysis time, a 10 cm reversed phase column (RP-8, Brownlee Labs, Santa Clara, CA, U.S.A.) with no precolumn was used. A mobile phase consisting of acetonitrile and 0.17% phosphoric acid (35 : 65) which was filtered and degassed was used to elute the propranolol from the column. The eluate was monitored at 290 nm with a variable wavelength UV detector (SF 773 Absorbance Detector, Kratos Analytical Instruments, Ramsey, NJ, U.S.A.) at 0.4 AUFS. Ten μl from each of the dissolution samples (collected through 20 μm external filter tip) were injected directly into the column. Since no sample preparation steps were involved and the

performance of the autosampler was very consistent and reproducible, no internal standard was needed for propranolol quantitation. The method was validated and the reproducibility of the assay showed less than 2% overall coefficient of variation for replicate injections. At 2 ml/min flow rate, propranolol was eluted at about 6 min under these chromatographic conditions. By comparing the peak areas of propranolol from sample solutions to the known standard concentrations, propranolol concentrations were determined.

Three-dimensional topographical plots

The dissolution results, obtained in the presence and absence of oil pretreatment, were plotted three-dimensionally using the computer program SASGRAPH as described previously (Skelly et al., 1986, 1987). Data were entered using the x-axis for time, the y-axis for pH and the z-axis for the mean percent of propranolol dissolved. Using this topographical characterization procedure, the overall pH and apparent lipid effects on the dissolution of propranolol C.R. products were easily observed.

Results and discussion

The mean dissolution profiles of tested propranolol C.R. products in different dissolution

TABLE 1

Dissolution profiles of controlled-release propranolol products (untreated) in different pH media

Time (h)	Mean percent dissolved [a] (S.D.)				
	pH 1.2	pH 2.5	pH 4.5	pH 6.8	pH 7.5
Product A					
1	5.9 (1.7)	8.9 (0.8)	9.8 (1.8)	6.4 (1.0)	6.4 (1.1)
2	13.4 (3.1)	18.8 (1.5)	22.3 (2.6)	19.2 (1.0)	18.8 (2.6)
3	19.5 (3.7)	28.5 (1.6)	34.9 (3.0)	30.2 (1.4)	29.2 (2.8)
4	26.4 (4.8)	37.6 (1.5)	40.0 (5.6)	39.1 (1.6)	37.3 (3.2)
6	37.6 (5.4)	52.3 (1.9)	59.5 (2.6)	53.5 (2.4)	42.6 (1.0)
8	47.1 (6.5)	64.2 (4.3)	69.2 (2.9)	64.8 (2.5)	53.5 (3.5)
Product B					
1	6.4 (0.5)	11.6 (0.8)	10.0 (1.0)	8.3 (0.5)	7.3 (0.7)
2	14.0 (1.3)	26.0 (0.7)	23.3 (0.9)	22.7 (0.7)	19.9 (1.5)
3	21.4 (1.0)	39.0 (0.8)	35.0 (1.8)	35.3 (1.3)	31.1 (1.8)
4	29.4 (2.0)	49.1 (1.5)	45.0 (1.9)	45.4 (1.9)	39.5 (2.8)
6	41.1 (2.2)	64.8 (6.1)	59.1 (2.4)	59.1 (1.9)	54.5 (1.8)
8	52.8 (2.5)	66.5 (2.1)	69.3 (2.8)	69.1 (3.1)	64.4 (2.1)
Product C					
1	9.1 (1.4)	15.0 (1.9)	12.5 (1.7)	12.1 (1.8)	7.2 (1.2)
2	17.2 (2.0)	27.4 (2.1)	24.9 (2.3)	29.8 (2.1)	19.4 (1.3)
3	24.1 (0.6)	39.9 (2.7)	37.5 (2.8)	43.5 (3.8)	30.5 (0.6)
4	30.7 (1.8)	50.7 (2.5)	45.9 (3.5)	53.6 (5.6)	40.1 (1.9)
6	42.6 (1.0)	67.4 (4.6)	59.1 (2.4)	71.3 (4.9)	52.5 (1.8)
8	53.5 (3.5)	79.1 (3.8)	69.3 (2.2)	82.0 (4.8)	63.4 (2.7)
Product D					
1	11.9 (2.8)	17.8 (2.2)	18.2 (2.4)	16.2 (2.7)	12.3 (1.1)
2	20.7 (2.7)	29.5 (2.2)	30.1 (2.8)	32.1 (4.7)	27.1 (2.3)
3	28.6 (3.9)	39.4 (2.5)	39.0 (3.0)	44.3 (3.3)	37.0 (2.6)
4	34.6 (4.0)	47.7 (6.1)	45.9 (2.5)	54.1 (4.1)	44.9 (2.2)
6	44.0 (4.0)	61.0 (2.3)	55.8 (2.8)	67.0 (2.5)	55.5 (3.0)
8	51.8 (4.6)	68.1 (2.6)	63.4 (2.6)	76.2 (3.0)	61.9 (2.1)

[a] Mean values of 6 capsules.

media with pHs of 1.2, 2.5, 4.5, 6.8 and 7.5 are shown in Tables 1 and 2. The rate of the dissolution of untreated products A and B appears to be less dependent on pH especially above pH 2.5. On the other hand, untreated combination products C and D evidenced considerably higher dissolution rates at pHs 2.5 and 6.8. In comparison, however, the dissolution rates are drastically decreased in all pHs for all products which are pretreated with peanut oil (Table 2).

Since substantially smaller amounts of oil-pretreated propranolol dissolved during the 8 h of dissolution testing, one may speculate that some of the drug was extracted into the oil during the pretreatment procedure. In a separate experiment, samples subjected to oil treatment at 37 °C for up to 3 h were homogenized by pulverization in the dissolution media, the oil removed and virtually 100% of the drug was recovered. Therefore, the extraction of propranolol from the C.R. formulation into the oily substance does not occur.

The topographical plots of the dissolution results at different pHs are shown in Fig. 1. The plots show that the topographical surfaces are relatively flat for products A and B (**I, II, III** and **IV**) over a broad range of pHs indicating the dissolution rates of these products are less susceptible to pH changes. However, the dissolution rate

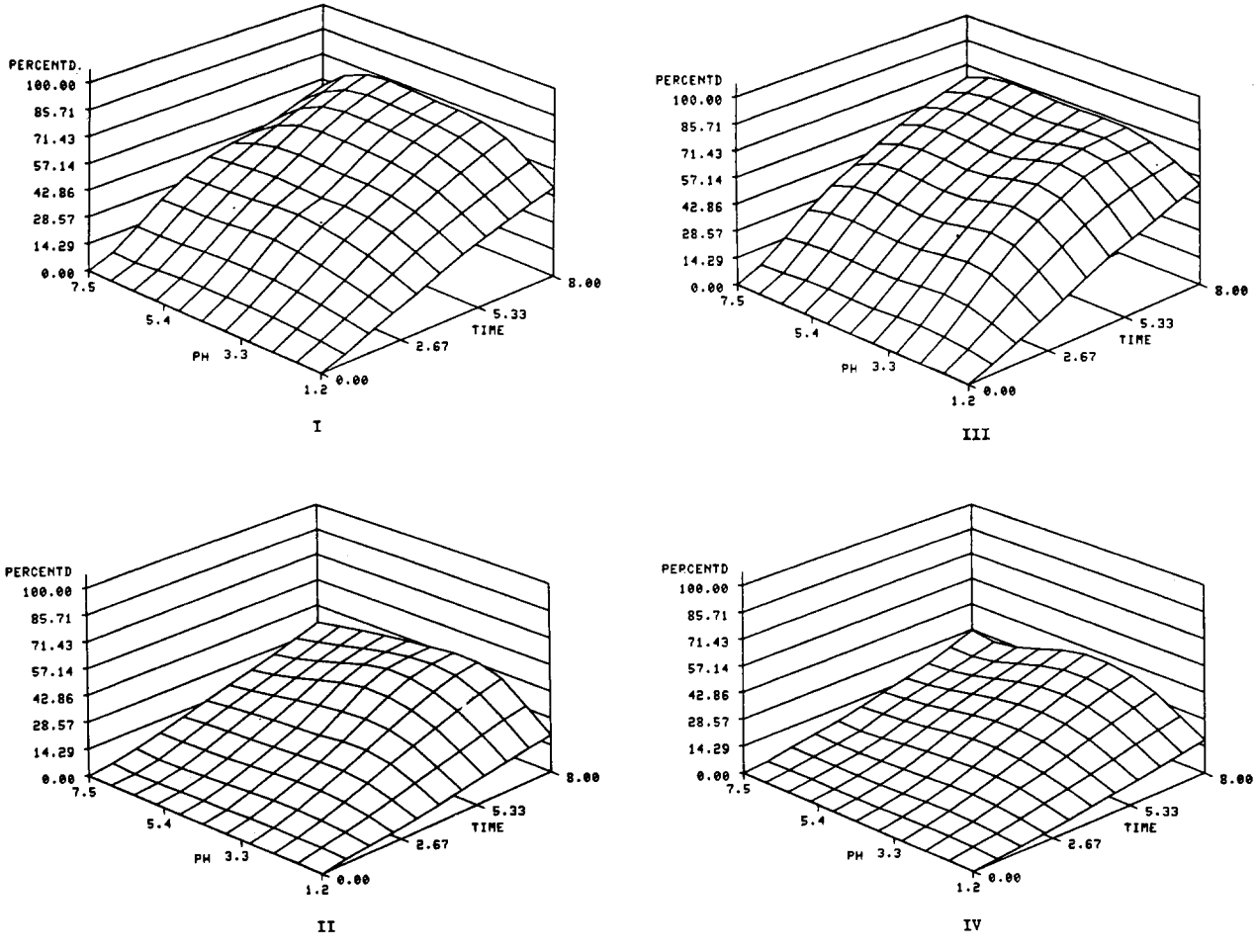
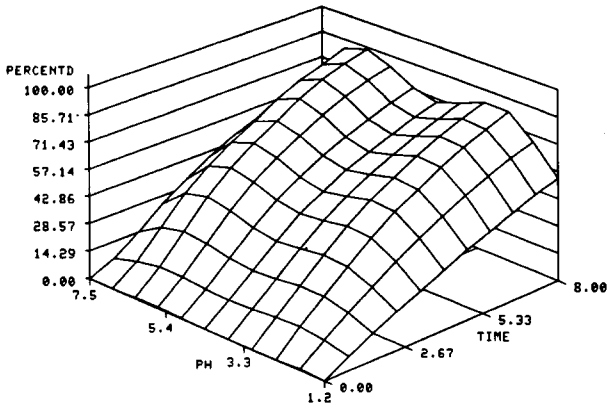
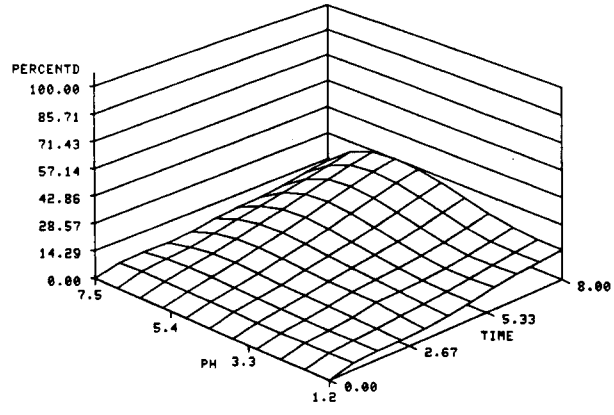


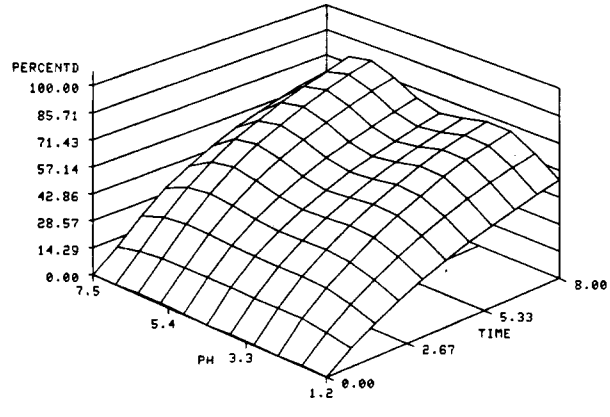
Fig. 1. Topographical dissolution characterization of products A, B, C and D as a function of time and pH. Data from untreated products were illustrated in **I, III, V** and **VII** for these 4 tested products and data from products pretreated with peanut oil were illustrated in **II, IV** and **VI** for products A, B and C, respectively.



V



VI



VII

Fig. 1 (continued).

TABLE 2

Dissolution profiles of controlled-release propranolol products pretreated with peanut oil in different pH media

Time (h)	Mean percent dissolved [a] (S.D.)				
	pH 1.2	pH 2.5	pH 4.5	pH 6.8	pH 7.5
Product A					
1	2.8 (1.2)	3.9 (1.6)	2.9 (1.2)	1.3 (0.3)	2.2 (1.2)
2	4.5 (0.1)	9.0 (3.0)	8.4 (2.4)	5.4 (1.5)	5.7 (1.7)
3	6.7 (1.2)	14.7 (3.3)	14.4 (2.8)	11.2 (2.4)	10.0 (3.2)
4	9.1 (0.4)	20.9 (3.9)	20.2 (3.7)	16.5 (2.7)	14.9 (3.1)
6	14.7 (2.0)	31.0 (5.3)	38.8 (4.3)	25.8 (4.0)	23.3 (5.6)
8	19.3 (2.9)	40.2 (5.6)	42.5 (5.8)	36.0 (4.6)	33.3 (7.3)
Product B					
1	1.5 (0.4)	3.5 (0.9)	2.2 (0.5)	2.0 (0.5)	1.3 (0.5)
2	3.5 (0.4)	6.6 (1.6)	5.8 (1.0)	4.4 (1.1)	4.5 (2.4)
3	5.7 (0.9)	11.7 (3.3)	10.8 (1.9)	6.1 (1.8)	6.7 (1.4)
4	8.2 (1.2)	15.7 (3.3)	17.6 (2.7)	11.3 (3.2)	10.1 (2.6)
6	12.6 (1.9)	24.8 (5.4)	28.1 (3.8)	18.7 (4.6)	17.3 (4.0)
8	17.3 (2.4)	32.7 (7.1)	38.6 (4.6)	26.4 (6.9)	28.2 (4.1)
Product C					
1	4.2 (0.4)	4.0 (1.2)	4.3 (1.5)	4.4 (1.2)	3.2 (1.2)
2	4.6 (0.8)	4.7 (2.0)	6.2 (2.3)	5.4 (0.9)	3.4 (1.6)
3	5.2 (1.5)	8.4 (1.3)	9.4 (1.8)	8.3 (1.2)	3.8 (2.3)
4	6.9 (2.0)	9.1 (2.9)	12.2 (1.4)	11.3 (2.5)	6.4 (2.0)
6	12.6 (1.6)	11.3 (3.5)	18.7 (4.4)	17.4 (4.0)	8.4 (3.3)
8	15.4 (3.4)	17.0 (3.1)	26.3 (4.9)	23.7 (6.4)	13.4 (7.1)

[a] Mean values of 6 capsules.

is drastically decreased by oil pretreatment throughout the 8 h testing interval (**II, IV**). Since dissolution rate is one of the most important rate-determining factors for drug absorption, the data would suggest that the in vivo absorption of these products would be significantly affected by concomitant administration with fatty food.

Wave shape topographical surfaces were observed for untreated products C and D (**V, VII**). The dissolution rates for these two products which are more influenced by the pH of the dissolution fluid, show considerably higher dissolution rates at pHs 2.5 and 6.8. With oil pretreatment, again, a relative flat surface with significant drop in dissolution rates at all pHs was observed for product C (**VI**). Data for oil-treated product D was not available. However, a relatively flat topographical surface with low dissolution rates similar to product C was observed in our preliminary study. While the actual effect of gastro-hepatic secretion

of acids and enzymes on the absorption of the C.R. propanolol may be minimal, the possible prolongation of the drug absorption process, due to the slower drug release caused by the fatty food, cannot be ignored.

As we have previously shown with theophylline C.R. products (Maturu et al., 1986), the in vitro dissolution–rate profiles generated from this dissolution procedure (pretreatment with peanut oil) correlated well with the in vivo absorption of theophylline administered with a high fat meal. In that study testing the dissolution rate of a C.R. dosage form, following treatment with peanut oil, appeared to mimic the in vivo absorption under fatty meal conditions. Furthermore, since the release of drug from C.R. dosage form occurs throughout the entire gastrointestinal system which covers a wide range of pH (i.e. form pH 1 in the stomach to 7.8 in the intestine), the three-dimensional topographical illustration of dissolution results is undoubtedly the best procedure for identifying the in vitro pH effect that will influence the in vivo bioavailability of C.R. products (Skelly et al., 1987). Our results show that for C.R. propranolol products, no significant pH effect on dissolution rate was identified for predicting in vivo bioavailability. However, the drastic reduction of dissolution rate by lipid treatment of the product may implicate a potential influence of fatty meal on the in vivo bioavailability of the C.R. propranolol products which are subject to a high first-pass effect.

Acknowledgements

Dr. S.K. El-Arini was supported by a three-month grant from the Fulbright Commission for Educational and Cultural Exchange, National Research Center of Egypt. The authors wish to thank Dr. Martin Yau for his assistance in preparation of three-dimensional topographical plots. The assistance of Mr. J. Crawley in carrying out some of the dissolution experiments is also appreciated.

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