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Bioavailability and In-vitro/in-vivo Correlation for Propranolol Hydrochloride Extended-release Bead Products Prepared Using Aqueous Polymeric Dispersions

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Abstract

The influence of formulation and extrinsic factors has been investigated for the in-vitro release of propranolol hydrochloride from controlled-release beads prepared using aqueous polymeric dispersions, Aquacoat and Surelease. A single-dose three-way crossover bioavailability study of two extended-release experimental formulations (80 mg), Inderal LA (80 mg) and an Inderal immediate-release dosage form (2 × 40 mg) was also conducted and a comparative analysis of pharmacokinetic parameters and the in-vitro release profiles was performed to assess in-vitro/in-vivo correlation.

Analysis showed that the in-vitro release data appeared to follow zero-order release kinetics. Intensity of agitation and dissolution method were found to have no significant effect on drug release from beads prepared using either of the coating dispersions studied or Inderal LA. Release of drug from beads coated with Aquacoat was faster in basic media than in acidic media; Surelease-coated beads, however, showed release characteristics that were less sensitive to changes in the pH of the dissolution fluid, and Inderal LA beads showed slower release profiles in acidic medium than in other dissolution media studied. Pharmacokinetic analysis of the data revealed sustained-release absorption characteristics without any evidence of dose-dumping from any of the extended-release dosage forms studied. Regression analysis of the fraction of drug absorbed against the percentage of the drug released in-vitro, at the corresponding times, yielded good in-vitro/in-vivo correlation (level A) for all the extended-release formulations studied.

The results showed that there was no dose-dumping from any of extended-release formulations and that the relative bioavailabilities of the experimental formulations were superior to that of the marketed formulation.

Several oral extended (controlled) drug delivery systems have been developed in recent years. The choice of method for achieving controlled release depends on several factors, including the physicochemical properties of the drug, its cost, concerns about environmental pollution and biodegradability requirements. Perhaps the most critical factor is, however, the drug release rate desired (Baker & Lonsdale 1974). Membrane drug delivery is one system that has received increasing attention as an effective means of controlling drug release because it enables the prolonged and precise release of drug with good reproducibility (Langer 1980).

Because of the numerous advantages of coated beads as extended-release dosage forms, incorporation of drugs on or in beads has been a prevalent practice in the pharmaceutical industry. Various methods of producing extended-release products from coated particles have been discussed by Rekhi et al (1989). Recently, aqueous colloidal dispersions of water-insoluble acrylic or cellulosic polymers have been developed; these eliminate problems associated with the use of solvent-based coatings.

In-vitro evaluation of solid oral dosage forms is a useful tool for controlling formulation and process variables. Although in-vitro testing might not always correlate with in-vivo performance of a product, it does provide significant guidelines for the development of extended-release formulations. Several approaches have been described and utilized for assessing in-vitro/in-vivo correlations for extended-release products (Skelly et al 1993; Hussein & Friedman 1990). The results derived from such analysis, particularly those describing the in-vivo release or the profile of absorption with time, are both informative and useful for correlating in-vitro and in-vivo data.

One of the major objectives of this study was to determine the bioavailability of experimental propranolol hydrochloride extended-release beads prepared using Aquacoat and Surelease, as aqueous coating dispersions, Inderal LA and a reference IR (Inderal) product. By use of the in-vitro release data and plasma concentration data, attempts were also made to assess in-vitro/in-vivo correlation for the extended-release formulations.

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Materials and Methods

In-vitro study

Materials. Propranolol hydrochloride, United States Pharmacopoeicy (USP), was manufactured by Lusochimica, Italy and supplied by Colorcon, West Point, PA, USA. Sugar spheres, National Formulary (NF) (Nu-Pareils, 18–20 mesh) were purchased from Ingredient Technology, Specialty Products Division, Pennsauken, NJ, USA; hydroxypropylmethylcellulose 2910, USP, was donated by The Dow Chemical Co, Midland, MI, USA; polyethylene glycol 3350, NF, was

donated by Union Carbide, Charleston, WV, USA; Aquacoat was donated by FMC Corporation, Philadelphia, PA, USA; Surelease was donated by Colorcon; dibutyl sebacate (Uniflex, DBS) was donated by Union Camp, Jacksonville, FL, USA.

Preparation of coated beads. Propranolol hydrochloride was applied to Nu-Pareils, 18–20 mesh, using the Wurster-Process (Uni-Glatt Lab. Unit; Glatt Air Techniques, Ramsey, NJ, USA). The drug (16% as dry weight on 500 mg of cores), with the aid of hydroxypropylmethylcellulose (4% on a dry-weight basis) and polyethylene glycol 3350 (0·4% on a dry-weight basis), as a plasticizer, was fixed on to the cores. Coating equipment and process conditions used in the preparation of coated beads were optimized as described by Rekhi et al (1989). Six different batches (1 kg each) were manufactured, screened through a 16 mesh sieve, mixed together to form one batch, and then subdivided into six sub-lots of 1 kg each for application of the coating material.

Effect of polymeric dispersions. In this study a comparison was made between the in-vitro performances of propranolol hydrochloride beads coated with Aquacoat and Surelease, two aqueous controlled-release film-coating materials.

Effect of membrane thickness. Aquacoat (used undiluted) was mixed with dibutyl sebacate, 24% w/w based on Aquacoat solids. This plasticized coating dispersion was applied at levels of 5, 6 and 7% of the drug bead weight. Surelease, which comes ready-plasticized (with dibutyl sebacate), was studied at levels of 6, 7 and 8% of the drug bead weight. An overcoat of 1% Opadry YS-1-7006 (Colorcon) was applied. To ensure complete coalescence of the film Aquacoat-coated beads were fluidized for 1 h at 50–60°C; no such fluidizing was required for Surelease-coated beads, however.

Total assay. A composite sample (10 g) was collected from each batch and approximately 500 mg of the coated beads were ground into a fine powder. A sample of this powder (300 mg) was transferred to a 500-mL volumetric flask and after agitation for 1 h the samples were diluted to volume with water. This solution was diluted, passed through a 0·45-mm filter and assayed spectrophotometrically at 289 nm to determine the propranolol hydrochloride content. Three replicate determinations, each using a 500-mg sample of coated beads, were made for each coating experiment. Coating-process efficiency was determined by expressing mean actual drug content (of the drug-coated beads) as a percentage of target drug content.

Release study. Drug release was determined (n = 6) using beads containing the equivalent of 80 mg of propranolol hydrochloride; the USP 23 dissolution apparatus 1 (basket) with 900 mL distilled water (37 ± 0·5°C) and an agitation speed of 100 rev min^{-1} was used in all release studies. The samples (5 mL) were taken at specified time intervals, replaced with an equal volume of fresh media, filtered and assayed spectrophotometrically at 289 nm for drug content. At the conclusion of each dissolution study, beads were removed, ground and assayed to determine the residual drug content. Dissolution studies were also performed on Inderal LA and Inderal IR formulations, under identical conditions, before in-vivo study.

Effect of extrinsic factors. Although it is generally agreed that performing dissolution tests in formulation development is critical, there is disagreement about the suitability of an apparatus and method that should be used as a standard. Development of such a standard method is a difficult task because of the numerous factors influencing dissolution. Some of the factors are related to the physicochemical properties of the drug and variations in formulations whereas others, unrelated to the product, are the amount and type of dissolution fluid and geometry of the vessel.

The USP subcommittee and the Food and Drug Administration (FDA) have recently proposed a policy on modified-release dosage forms which includes establishment of in-vitro dissolution criteria using either the basket method at 100 rev min^{-1} or the paddle method at 50 rev min^{-1}. Several methods of dissolution testing for modified-release products are reported in the USP 23:

Effect of agitation speed. To study the effect of agitation speed on the release of drug, speeds of 50, 100, and 150 rev min^{-1} were used.

Effect of dissolution method. In addition to the USP basket method, dissolution studies were also performed using the USP paddle method at 50 rev min^{-1}.

Effect of dissolution fluid pH. The dissolution fluids (USP 23) used in the study were simulated gastrointestinal fluids (pH 1·2 and 7·5) and distilled water. To study the effect of change-over of dissolution media, dissolution was performed in simulated gastric fluid (pH 1·2) for 1 h and then changed to simulated intestinal fluid (pH 7·5) for the rest of the study, i.e. 11 h.

Release kinetics and statistical evaluation. To determine the goodness of fit and obtain the best estimate of slope and intercept for the straight lines, experimentally obtained values for the mass of drug released against time (n = 6), for different formulations and in various dissolution media, were fitted by multiple linear regression (Lotus 123, Lotus Development, Cambridge, MA, USA), after appropriate mathematical transformations.

The 95% confidence intervals of the slopes of the regressed lines were calculated to determine the significance levels amongst each factor under investigation. The overlapping of confidence intervals was used to test the hypothesis of parallelism between the two lines.

In-vivo study

Study design. Six healthy male volunteers (mean age 28 years) were enrolled in and completed the study. All subjects met the inclusion and exclusion criteria outlined by the FDA in-vivo bioequivalence study guidance for propranolol products (FDA 1984). The subjects were selected on the basis of negative history, normal physical examination and normal routine laboratory test results and were not permitted to take alcohol, tobacco or other drugs. Institutional Review Board approval was obtained and all subjects signed an informed consent form before initiation of the study.

Studies were conducted under medical supervision using a four-way Latin crossover design with a wash-out period of at least one week between each treatment period. Formulations

(Aquacoat, Surelease, Inderal (Ayerst Labs, NY, USA) LA Lot #8PHS1 expiry date 3/91, all 80 mg, and Inderal Lot #6NCD6 expiry date 7/91, 2 × 40 mg) were administered with water (180 mL) after overnight fasting which was continued for a minimum of 4 h after dosing. Blood samples (3 to 5 mL) were collected in sample tubes, centrifuged, and extracted serum was placed in glass tubes at −20°C until analysis.

Blood samples for extended-release products were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24 h after the administration of a single 80 mg dose. For immediate/conventional release formulation, Inderal 40 mg dose was administered at 0 and 6 hour intervals and blood samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 6.5, 7, 8, 10, 12 and 24 h after drug administration. Blood pressure (systolic and diastolic) and heart rate were measured before collection of each blood sample.

Serum analytical method. Concentrations of propranolol in serum samples were determined by HPLC with fluorescence detection (Rekhi et al 1995a). The accuracy, linearity, precision, specificity, reproducibility, recovery and sensitivity of the method were validated before the commencement of the in-vivo study.

Pharmacokinetic analysis. Serum concentration- time data were fitted to a one-compartment open pharmacokinetic model using PCNONLIN V3 (Statistical Consultants, Lexington, KY, USA) according to equation 1:

$$C_s = FD/V \times K_a(K_a - K_e) \times (e^{-Ke(t-t0)} - e^{-Ka(t-t0)}) \quad (1)$$

where D is the dose (mg), F the fraction of dose bioavailable, V the apparent volume of distribution (mL), K_a the first-order absorption rate constant (h^{-1}), K_e the first-order elimination rate constant (h^{-1}), t_0 the absorption lag-time (h) and C_s the serum propranolol concentration ($ng\,mL^{-1}$) at time t (h).

The bioavailability parameters, peak plasma concentration (C_{max}), peak time (T_{max}) and extent of absorption (area under the plasma concentration-time curve, $AUC_{0-\infty}$) and pharmacokinetic parameters K_a, K_e, the half-life, t½, and t_0 were calculated and compared for each formulation. The mean bioavailability parameters for the four propranolol formulations were evaluated by analysis of variance for the effects of subject, treatment, period and treatment sequence, using the program Statgraphics V4.0 (Manugistics Inc., Rockville, MD, USA). The 90% confidence intervals for comparing the extended-release products were calculated by using the two one-sided *t*-test, as is currently advocated by the FDA guidance for bioequivalence testing (FDA 1992).

In-vitro/in-vivo correlation. In order to correlate the mean in-vitro release of drug in various dissolution media for the extended-release formulations with that obtained in-vivo, the fraction, F_t, of drug absorbed at a given time, t, was calculated using equation 2 (Wagner & Nelson 1964):

$$F_t = \{C_{(t)} + K_e(AUC_{(0-t)})\}/\{K_e(AUC_{(0-\infty)})\} \quad (2)$$

the fraction of drug absorbed was then plotted against the fraction released in-vitro at the corresponding times.

Table 1. Summary of total assay results.

Batch no	Drug loading (mg)	Coating total assay*,† (mg)	RSD (%)	Efficiency‡ (%)
I	80	34·33–34·65	0·47	79·26
II	80	37·39–37·61	0·30	90·47
III	80	37·47–37·84	0·49	90·44
IV	80	37·12–38·44	1·74	90·75
V	80	35·95–36·73	1·08	87·52
VI	80	36·72–37·94	1·64	89·74
Mixture I–VI	80	35·89–37·39	2·05	88·03

*Range of 3 determinations. †Amount present in 300 mg coated beads. ‡Calculated on the basis of amount used.

Results and Discussion

In-vitro study

Preparation of coated beads. To use a membrane as a means of controlling drug release, it is essential to develop an efficient coating system capable of yielding a uniform coat thickness. The successful operation of the coating process, utilizing the Wurster process, mainly lies in the proper adjustment of the air flow, temperature and the fluid application rate. These factors were extensively studied and optimized in an earlier study (Rekhi et al 1989).

The amount of propranolol hydrochloride present in 300 mg beads, after the application of fixing agent (and containing the drug) for six batches, are summarized in Table 1. The small individual variation from the mean values is indicative of the uniform distribution of the drug in the beads. The high coating-efficiency and good lot-to-lot reproducibility for the fixing experiments suggests the appropriateness of the Wurster process for the preparation of controlled-release beads. Also, as is evident from Fig. 1a, the surface morphology of the drug-coated beads appears to be smooth and continuous, suggesting these would make good core substrates for the coating process.

Effect of membrane thickness. Fig. 1 shows plots of amount of drug released vs time for beads coated with Aquacoat and Surelease. As expected, the release-rate decreased with increasing membrane thickness for both dispersions. Release from beads coated with higher levels of coating dispersion decreased as a result of higher ethylcellulose content, which, in turn, reduced the permeability of the film. Pronounced effects of small increments of coating thickness were, furthermore, shown for Aquacoat, a 30% w/w dispersion, compared with Surelease, a 25% w/w dispersion. In the manufacture of coated beads, optimizing the core substrate for formulation and process is as important as optimizing the coating formulation and coating process. Because the coating level of the polymeric dispersion used dictates the release rate, the smooth surface of the core substrate not only enables uniform coating thickness for each bead but also reduces intra-batch variability (Fig. 2a). This was shown by the low standard deviations ($< 1\%$) obtained for all the dissolution studies performed. Figs 2b and 2c show scanning electron micrographs (SEM) of beads coated with both polymeric dispersions. These pictures show a uniform and intact coating for both the polymeric dispersions and the cross-section shows a porous core structure with a coherent film boundary.

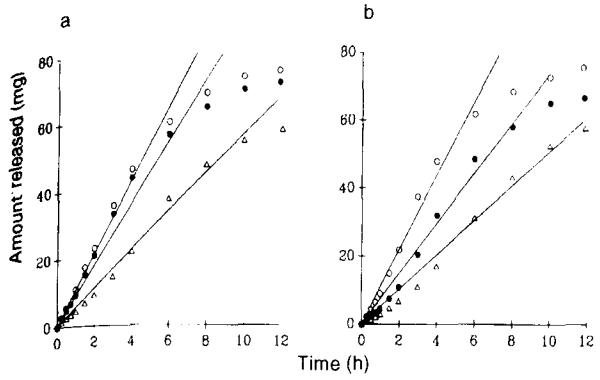

FIG. 1. Effect of membrane thickness on drug release from beads coated with Aquacoat (a, ○ 5, ● 5·5, △ 6%); Surelease (b, ○ 6, ● 7, △ 8%). USP basket method, 100 rev min^{-1}, distilled water (mean ± s.d., n = 6 for all dissolution profiles).

Drug release kinetics and mechanism. Plots of mass of drug released (mg) against time are shown in Fig. 1. Zero-order drug release was maintained up to about 70–80% of drug release, after which the release-rate declined, presumably because the decrease in the drug concentration in the cores below the saturation level resulted in a non-uniform concentration gradient. The release rate constants were calculated from a linear regression ($r^2 > 0.98$) fit of all points in the zero-order region. From the results of the release of propranolol hydrochloride from coated beads, studied at 37°C in dissolution media differing in osmotic pressures, it was, furthermore, concluded that the transfer of drug not only takes place by classical diffusion but was also modulated by osmotic pressure (Rekhi et al 1995b).

Effect of extrinsic factors

Effect of agitation speed. By altering the agitation speed during the release study, one can examine the effect, if any, on the drug release rate of the stagnant diffusion layer surrounding the beads. The computed release rate constants for both formulations at each agitation speed are reported in Table 2. The 95% confidence intervals (error bars) of the release rate constants in Fig. 3 overlap each other, indicating that agitation speed had no significant effect ($P < 0.05$) on drug release from both formulations prepared by using two polymeric dispersions. It is concluded from this study that drug transport from coated beads is determined solely by the membrane-controlled permeation process and the effect of the stagnant diffusion layer surrounding the beads is negligible.

Table 2. Effect of extrinsic factors on drug release rate.*

Method	Speed (rev min^{-1})	Release rate constant, K†,‡ (mg h^{-1})	r^2
Aquacoat 5·5%			
Paddle	50	9·861 ± 0·501	0·911
	50	9·825 ± 0·466	0·981
Basket	100	9·027 ± 0·298*	0·980
	150	9·128 ± 0·425	0·982
Surelease 7%			
Paddle	50	8·081 ± 0·311	0·990
	50	7·664 ± 0·262	0·992
Basket	100	7·554 ± 0·278*	0·991
	150	8·045 ± 0·271	0·992

†Best estimate computed by linear regression analysis, 95% confidence interval (n = 6). ‡Dissolution fluid, distilled water. *Release rate was non-significant ($P < 0.05$) for other dissolution conditions when compared with USP basket method (100 rev min^{-1}).

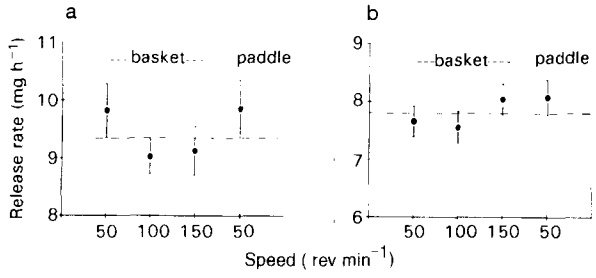

FIG. 3. Effect of extrinsic factors on drug release from beads coated with Aquacoat 5·5% (a), Surelease 7% (b). USP basket/paddle method, distilled water. Mean ± 95% confidence interval, n = 6 for all dissolution profiles.

Effect of dissolution method. The use of various dissolution methods had no significant effect ($P < 0.05$) on the release rate from beads coated with both polymeric dispersions (Table 2 and Fig. 3).

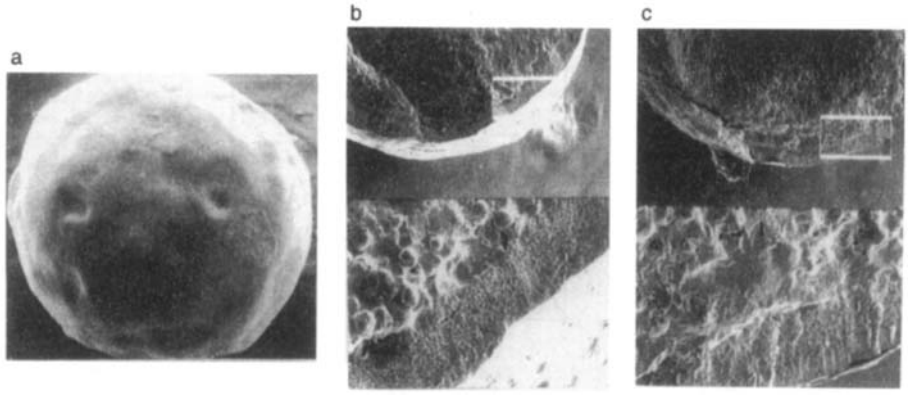

FIG. 2. Scanning electron micrographs of beads coated with drug, 80 mg, magnification × 40 (a), Aquacoat 5·5%, cross-section, magnification × 50 and × 250 (b), Surelease 7%, cross-section, magnification × 50 and × 250 (c).

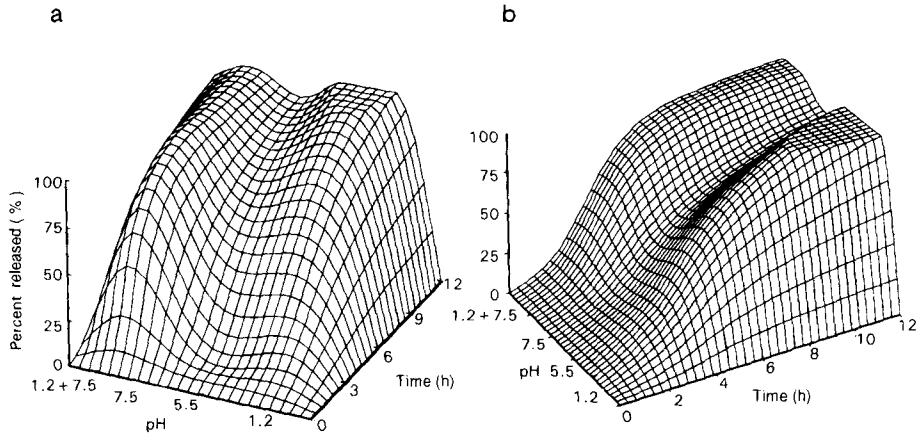

FIG. 4. Effect of pH of dissolution fluid on drug release from beads coated with Aquacoat 5·5% (a); Surelease 7% (b). USP basket method, 100 rev min^{-1}. n = 6 for all dissolution profiles.

Effect of dissolution fluid pH. The effect of dissolution fluid pH on the release of drug from beads coated with Aquacoat and Surelease is illustrated using a multi-dimensional topographical plotting technique. The topographical surface for Surelease-coated beads (Fig. 4b) is relatively flat compared with that for Aquacoat-coated beads (Fig. 4a), which is a U-shaped, showing that dissolution rate is more influenced by the change in dissolution-fluid pH. This technique is also useful in selecting the most discriminating dissolution medium.

Release of propranolol hydrochloride from beads coated with Aquacoat was noticeably different at pH 7.5 from that in the other dissolution media studied. This might be attributed to the pH-dependent solubility of the drug and/or the composition of the coating dispersion, i.e. the presence of the surfactant (sodium lauryl sulphate; Goodhart et al 1984; Bodmeier & Paeratakul 1991) as well as traces of carboxylic groups present in ethylcellulose (Lippold et al 1989) or to a combination of these. The pH-corrected solubility results are not consistent with the dissolution results obtained (i.e. faster release in basic than in acidic media). It could be postulated that the effect of pH might be attributed to the presence of sodium lauryl sulphate which could affect the partitioning of the drug into the simulated gastrointestinal fluids by virtue of the surfactant's state of ionization under acidic or basic conditions (Rekhi et al 1989). Similar pH-dependent release characteristics for Aquacoat have been reported in the literature (Derbin et al 1994).

Conversely, the drug-release characteristics of beads coated with Surelease were less affected by changes in the pH of the dissolution fluid. This could be attributed to the use of a different surfactant system, i.e. the presence of ammonium oleate in this dispersion. Similar findings have been reported in the literature (Iyer et al 1990; Chang et al 1987).

Comparative release study. Fig. 5 shows the effect of extrinsic factors on drug release for Inderal LA. From the plots it is evident that agitation speed and dissolution method had no effect on the amount of propranolol released. Drug release in simulated gastric fluid was, however, slower than in the other dissolution media.

Fig. 6 compares the release profiles of two formulations prepared by use of the two aqueous polymeric dispersions and Inderal LA (80 mg) in distilled water. These three formulations and the Inderal IR formulation were used for the in-vivo study.

In-vivo study

Pharmacokinetic parameters. The mean serum propranolol data for the six subjects are illustrated in Fig. 7. Serum

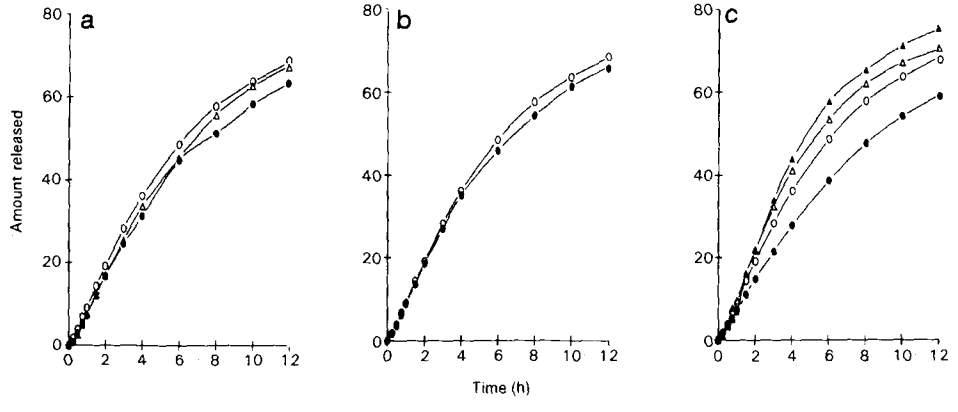

FIG. 5. Effect of agitation speed (a, △ 50, ○ 100, ● 150 rev min^{-1}), method of dissolution (b, ○ basket, ● paddle), and pH of dissolution fluid (c, ▲ pH 1.2 + 7·5, △ pH 7·5, ○ distilled water, ● pH 1·2) on drug release from Inderal LA capsules. USP basket method, 100 rev min^{-1}. Mean ± s.d., n = 6 for all dissolution profiles.

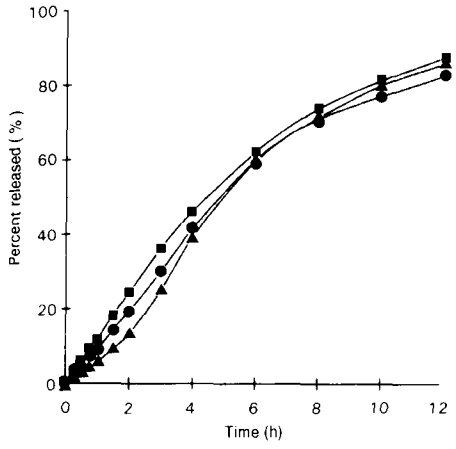

FIG. 6. Comparison of the dissolution profiles in distilled water. USP basket method, 100 rev min^{-1}. ● Aquacoat, ▲ Surelease, ■ Inderal LA. Mean ± s.d., n = 6 for all dissolution profiles.

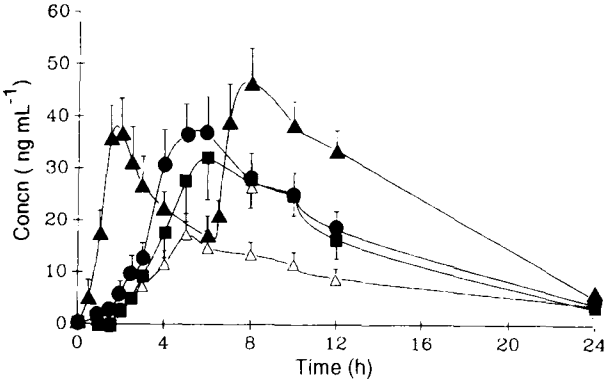

FIG. 7. Mean serum propranolol concentration–time profiles for six subjects after oral administration of the immediate-release (0 and 6 h) and three extended-release propranolol hydrochloride formulations. Aquacoat 5.5% (●), Surelease 7% (■), Inderal LA (△) and Inderal IR (▲) Mean ± s.e.m., n = 6.

concentration-time data were analysed by use of PCNONLIN. The suitability of the model to describe the data was judged by the correlation coefficient, the weighted residual of squares and visual inspection of residual plots. The initial estimates for input into the program were obtained from the literature (Bauman 1993).

Table 3 summarizes the pharmacokinetic parameters computed for the four formulations studied. As expected, the absorption of propranolol was slower from the extended-release formulations compared with the IR formulation. The rank order for the computed first-order absorption rate constants was: Inderal IR > Inderal LA > Aquacoat > Surelease. Computed lag-times showed the reverse rank order: Surelease > Aquacoat > Inderal LA. As commonly observed, there was no lag-time noted for Inderal IR formulation. The ratio of the apparent volume of distribution to the fraction absorbed (V/F) and the elimination half-life ($t_{1/2}$) for all formulations were in agreement with literature values (Bauman 1993). The longer elimination half-life (7·640 ± 3·291 h) for Inderal LA is perhaps not a true elimination half-life value as a result of the rather slow absorption of the drug causing a prolonged post-absorption phase (Garg et al 1987).

Bioavailability parameters. Two criteria must be met if a formulation is to be considered as being truly an extended-release or long-acting dosage form. Firstly, the C_{max} must be lower or close to the conventional IR formulation and, secondly, the rate of elimination of the drug must be reduced by prolonging the drug-absorption and distribution phases; this is reflected in an increase in T_{max}, the elimination half-life of the extended-release formulation.

C_{max} values obtained in this study for formulations coated with Aquacoat and Surelease were greater than those for Inderal LA; there was, however, no significant difference ($P < 0.05$) in C_{max} as a result of the use of Inderal IR and the three extended-release formulations studied (Fig. 8a). It was also apparent that 'dose dumping', an excessive release of drug resulting in high serum concentrations, did not occur after the

Table 3. Summary of pharmacokinetic parameters for propranolol formulations.

Parameter	Aquacoat		Surelease		Inderal LA		Inderal IR	
	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.
Ratio apparent volume of distribution to fraction absorbed (L)	834·29	361·90	902·27	4·81	798·70	101·90	837·10	32·27
First-order absorption rate constant (h^{-1})	0·45	0·45	0·36	0·14	0·49	0·19	0·70	0·27
First-order elimination rate constant (h^{-1})	0·26	0·15	0·19	0·08	0·11	0·05	0·18	0·04
Peak plasma concentration (ng mL^{-1})	35·67	16·48	31·13	14·44	14·78	7·05	28·60	7·30
Time of peak plasma concentration (h)	5·77	0·74	6·77	1·42	6·03	0·30	3·03	1·08
Area under the plasma concentration–time curve, 0–24 h (ng mL^{-1} h)	398·51	171·37	341·53	129·01	194·39	76·55	589·90	121·72
Total area under the plasma concentration–time curve, 0–∞ (ng mL^{-1} h)	419·42	186·57	361·26	132·71	226·08	71·49	621·74	136·88
Area under the moment curve, 0–24 h (ng mL^{-1} h)	3728·64	1493·32	3284·12	1305·98	2014·90	645·69	5590·33	1051·26
Total area under the moment curve, 0–∞ (ng mL^{-1} h)	4365·40	2139·81	3926·03	1842·19	3075·32	628·56	6562·11	1648·43
Mean residence time (h)	10·40	1·17	10·72	3·08	14·11	2·61	10·54	0·89
Absorption half-life (h)	2·57	1·53	2·27	1·08	1·52	0·44	1·40	0·94
Elimination half-life (h)	3·39	1·67	4·41	2·30	7·64	3·29	4·09	0·99
Lag-time (h)	2·14	0·54	2·59	0·64	1·89	0·09	–	–
Correlation coefficient, r	0·970	0·02	0·947	0·04	0·958	0·04	0·797	0·14

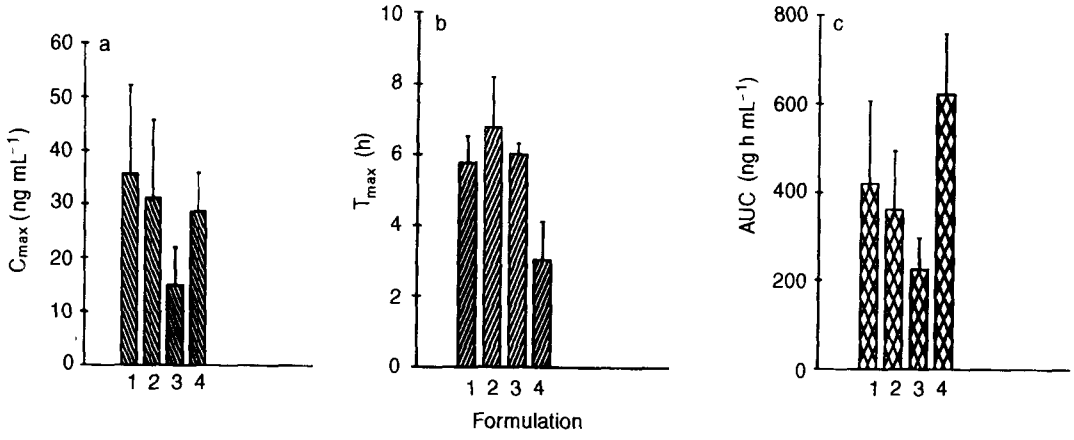

FIG. 8. Bioavailability parameters: maximum plasma concentration, C_{max} (a); time to maximum concentration, T_{max} (b); area under the plasma concentration-time curve, AUC (c) for Aquacoat (1), Surelease (2), Inderal LA (3) and Inderal IR (4). Mean ± s.d., n = 6.

administration of any of the extended-release formulations tested.

As expected, there was a significant difference between T_{max} for Inderal IR and T_{max} values for all the extended-release formulations (Fig. 8b). T_{max} after the administration of the extended-release dosage forms was about twice that for the conventional tablets. There was, however, no significant difference ($P < 0.05$) between the T_{max} values for the three extended-release formulations studied.

Analysis of variance results for AUC suggested that there was no significant difference ($P < 0.05$) between subjects or the sequence in which the formulations were administered. This suggests the absence of residual or carry over effects. The AUC values for Inderal IR and all the extended-release formulations were, however, significantly different; there were, furthermore, no significant differences ($P < 0.05$) between the AUC values for the Inderal LA and Surelease formulations. Relative bioavailabilities calculated for Inderal LA, Aquacoat and Surelease formulations were 35·5, 71·6 and 59·7%, respectively. The differences in AUC could, in part, be a result of underestimation of the AUC as a result of the slower rates of absorption (McAinsh & Gay 1985), because of greater conversion of propranolol to 4-hydroxypropranolol (Serlin et al 1983), because poor absorption of propranolol from the gastrointestinal tract contributes to the low bioavailability observed after administration of the extended-release formulations, or because of excretion of the capsule before complete release of all the drug (Takahashi et al 1990). The values for the bioavailability parameters for Inderal obtained in this study were in close agreement with those reported in the literature (Garg et al 1987; Nace & Wood 1987; Takahashi et al 1990).

The two experimental extended-release products were not found to be bioequivalent to the marketed formulation for C_{max} and AUC, on the basis of the 90% confidence interval for the mean ratios and the currently accepted criteria for equivalence. Experimental extended-release formulations showed superior relative bioavailability compared with the IR formulation.

In-vitro/in-vivo correlation

Historically, in-vitro/in-vivo correlations have usually been performed for conventional dosage forms by relating pharmacokinetic parameters such as C_{max} T_{max} or AUC to the in-vitro percent drug released under a given set of conditions. More recently, however, similar relationships and some additional correlative procedures have been used for extended-release products (Mojaverian et al 1992).

While reviewing various approaches used to assess in-vitro/in-vivo correlation, the USP Subcommittee on dissolution (USP 23 1994) concluded that not all methods are of the same quality and, hence, categorized the correlation procedures into levels A, B, C, and D, in descending order of quality.

In-vitro/in-vivo correlation, particularly as they apply to extended-release dosage forms, have been assessed by use of several approaches, including plots of the mean percentage released against the mean percentage absorbed, and statistical moment analysis based on the correlation between the mean residence time and the mean dissolution time (Hussein & Friedman 1990).

To correlate the mean in-vitro release of a drug with an in-vivo parameter for the extended-release formulations, a plot was constructed of the fraction of drug absorbed against the fraction released, in-vitro, at the corresponding times. This approach was tested by plotting fraction absorbed against fraction released in various dissolution media. The fraction released in the change-over dissolution method (1 h in simulated gastric fluid then 11 h in simulated intestinal fluid) showed, furthermore, a good linear relationship ($r^2 > 0.98$, slope ~ 1) with the fraction absorbed, indicating good correlation for these formulations (Fig. 9). The corresponding regression parameters are summarized in Table 4. The slopes reported for each formulation suggest that the in-vivo

Table 4. Linear regression parameters (Y = mX + C)* for the extended-release formulations.

Formulation	Slope† (m)	Intercept (C)	r^2
Aquacoat	1·034	− 0·064	0·993
Surelease	1·036	− 0·171	0·978
Inderal LA	1·213	− 0·175	0·986

*Y = fraction absorbed obtained from Wagner-Nelson analysis (mean ± s.e.m.); X = fraction released after 1 h in simulated gastric fluid + 11 h in simulated intestinal fluid dissolution media; basket 100 rev min^{-1}. †non-significant ($P < 0.05$).

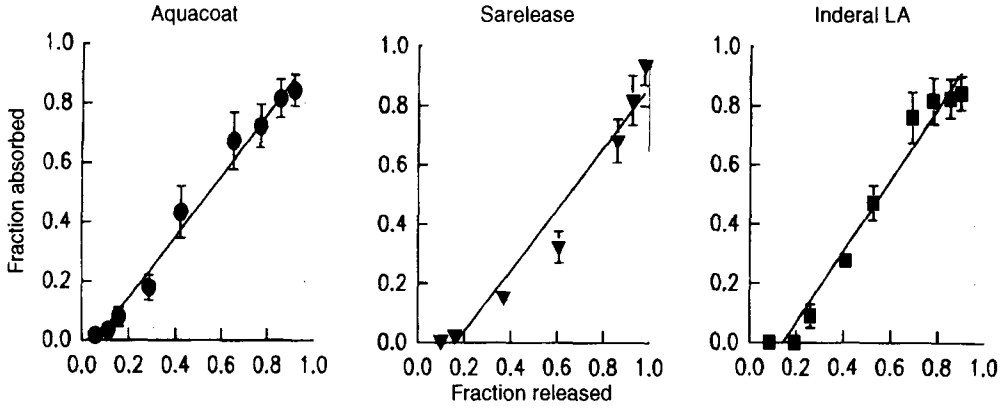

FIG. 9. Plots of mean fraction of drug absorbed (mean ± s.e.m., $n = 6$, calculated using the method of Wagner & Nelson (1964)) against the fraction of drug released (1-h simulated gastric fluid and 11-h simulated intestinal fluid) for the three extended-release formulations (Level A correlation).

absorption release rate was slower than that observed in-vitro. The observed negative intercepts are a result of the absorption lag-time noted after oral administration of extended-release dosage forms (Mojaverian et al 1992).

In-vitro evaluation of extended-release dosage forms is a useful tool for evaluating formulation and process variables. Although in-vitro testing might not always correlate with in-vivo performance of a product, attempts should be made to develop in-vitro tests that can be sensitive to critical manufacturing and process variables. This iterative process might require several cycles of in-vitro and in-vivo testing. This discriminating in-vitro dissolution test, furthermore, once developed, certainly has a number of regulatory advantages in a new drug approval process,viz: it serves as a quality control procedure for batch-to-batch release; it applies to scale-up and post approval changes, change of site of manufacture, and minor formulation and processing changes; it can be used as a product development tool for design and selection of appropriate formulations; and, most importantly, can help reduce cost by minimizing in-vivo study requirements (University of Maryland at Baltimore/FDA 1995).

In conclusion, controlled-release beads containing propranolol hydrochloride were prepared using Aquacoat and Surelease aqueous polymeric dispersions that conformed to USP 23 compendial requirements. There was no evidence of dose-dumping from any of the extended-release dosage forms. The relative bioavailabilities of the experimental formulations were superior to that of the marketed formulation. Inclusion of the IR dosage form enabled comparison of the absorption and in-vivo performance of the experimental formulations. This study suggests both that sustained absorption does not necessarily reduce systemic absorption and that formulation differences might contribute to the difference in bioavailability among the three extended-release formulations studied. Finally, a method consistent with the Level A correlation described by Skelly et al (1993) in the FDA/AAPS Workshop II, was developed to provide the manufacturer with a valuable in-vitro test that can be used as a surrogate to obtain useful information on the in-vivo absorption behaviour of such formulations.

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