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Comparative bioavailability of two new commercial tablet formulations and a reference formulation of haloperidol

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The bioavailability of two new tablet formulations (5 mg) of haloperidol was estimated relative to a reference product. Twenty-four healthy nonsmoker male subjects completed all three phases in that they received the reference (R) and the two test formulations (T_1 and T_2) in a balanced three-way crossover design. The protocol of this study and the forms for informed consents were reviewed and approved by the local institutional ethical board. Each subject received a 5 mg haloperidol tablet and serial blood samples were collected. Using a sensitive HPLC method (Midha et al 1988), plasma concentrations of haloperidol and reduced haloperidol were monitored over a period of 96 h following administration of each formulation. Haloperidol was measurable in the plasma of all the subjects, whereas reduced haloperidol was measurable in only 7 out of 24 subjects following each administration. Therefore, the assessment of bioequivalence in this study was based on haloperidol data only. The maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), and area under the curve up to the last measurable concentration (AUC^t) or infinity (AUC^{∞}) were compared by analysis of variance and found not to be significantly different across the formulations. Bioequivalence between any two formulations was assessed by two one-sided t tests. The pharmacokinetic parameters were calculated from both model independent and compartmental approaches with zero-order input rate using a kinetic model for fit of haloperidol concentrations. Plasma haloperidol concentration peaked, on average, at 1.39 h. The mean plasma concentration profiles from the three formulations were almost superimposable. The mean values for AUC^t and AUC^{∞} (ng.h/ml) were 34.22 and 41.19 for T_1, 34.53 and 41.85 for T_2 and 35.91 and 43.45 for R, respectively. The mean volume of distribution and the total clearance, uncorrected for bioavailability, for T_1, T_2 and R were 53.8, 54.2, 59 L/kg and 74, 75, 78 L/hr, respectively. The mean absorption and terminal elimination half-lives were 1.8 and 31.3 hours for T_1, 1.8 and 31.5 hours for T_2 and 2.2 and 35.2 hours for R, respectively. The relative bioavailability based on T_1:R or T_2:R ratios of AUC^t, AUC^{∞} and C_{max} was, in each case, in the range of 93–98% (within the acceptable range of 100 ± 20%). Also, the relative bioavailability of T_1 compared with T_2 was in the range of 98–102% in terms of the above bioavailability parameters. Considerable intersubject variation (CV %) was noted for all pharmacokinetics parameters for all three formulations.

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Effect of solid dispersions and physical mixtures of ibuprofen with Pluronic F127 and PEG 1000 on the in vitro drug release from ibuprofen-adhesive layers

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The transdermal delivery of drugs can be enhanced by suppressing their melting point (Kasting et al 1987). In this work we examined this theory on the in vitro drug release from drug-in-adhesive layers. Ibuprofen (m.p. = 73.5–76.3°C) was used as model drug together with Pluronic F127 (m.p. = 54.4–60.5°C) and PEG 1000 (m.p. = 37–40.9°C). Solid dispersions were prepared with ibuprofen:polymer ratios ranging from 90:10 to 10:90 according to the fusion method and were allowed to solidify at 20°C in a lightproof desiccator for a week. The melting temperature range of the solid dispersions, ibuprofen, Pluronic F127 and PEG 1000 was then recorded (n = 3) using a hot stage microscope at a heating rate of 3°C/min and phase diagrams were constructed. The eutectic compositions were identified as 30:70 ibuprofen:Pluronic F127 and 15:85 ibuprofen:PEG 1000 at 43.45 ± 2.5°C and 29.6 ± 1.2°C, respectively. The following binary mixtures of ibuprofen:polymer were prepared as solid physical mixtures (PM) and solid dispersions (SD); 60:40, 40:60, 30:70 with Pluronic F127 and 60:40, 30:70, 25:75, 20:80 with PEG 1000. Each binary mixture was added into the required amount of liquid acrylic adhesive to produce dried circular adhesive layers with a target ibuprofen loading of 0.05 g and ibuprofen concentration of 10% w/w. Ibuprofen-adhesive layers without polymer were also prepared by mixing either solid or molten ibuprofen with the acrylic adhesive. All layers had a mean surface area of 4.5 ± 0.35 cm^2. The drug release of ibuprofen from each set of layers (n = 3) was tested over 5 h in a paddle dissolution apparatus using citrophosphate buffer (pH = 5.6) under sink conditions, at 32°C. The UV analysis was carried out at 272 nm. The cumulative ibuprofen release values ($mgcm^{-2}$) at 5 h were: 7.44 ± 0.5 (40:60) > 2.98 ± 0.5 (60:40) > 1.7 ± 0.15 (30:70) from the SD-adhesive layers with Pluronic F127; 5.81 ± 0.25 (30:70) > 5.4 ± 0.6 (25:75) > 4.5 ± 0.6 (20:80) > 2.4 ± 0.1 (60:40) from the SD-adhesive layers with PEG 1000; 4.44 ± 0.5 (40:60) > 2.65 ± 0.4 (60:40) > 1.3 ± 0.9 (30:70) from the PM-adhesive layers with Pluronic F127; 4.66 ± 0.7 (30:70) > 3.7 ± 0.5 (25:75) > 3.1 ± 0.3 (20:80) > 1.89 ± 0.1 (60:40) from the PM-adhesive layers with PEG 1000; 1.85 ± 0.04 and 1.55 ± 0.3 when molten and solid ibuprofen were used, respectively. Ibuprofen release did not improve using the eutectic composition with Pluronic F127, possibly due to increased ibuprofen solubilisation in the adhesive and subsequent decrease in the thermodynamic activity of the formulation. A significant increase in ibuprofen release (t-tests, $P < 0.05$) was shown for the compositions adjacent to the eutectic one, with Pluronic F127 (40:60) and PEG 1000 (20:80, 25:75, 30:70), from both SD- and PM-adhesive formulations, compared to the ibuprofen-adhesive formulations. Additional studies using different drugs will further examine the described findings.

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Studies on drug release from buccal adhesive tablets based on hydrophilic swellable matrices

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Buccal tablets have been a widely investigated oral dosage form in terms of reduction in dosage frequency, constant therapeutic effect, extended drug action period and localization of drug delivery. The objective of this study was to develop buccal-adhesive tablets that show prolonged release containing the poorly water-soluble drug (miconazaole nitrate) for oral administration. Methyl cellulose (MC) and hydroxyethyl cellulose (HEC) were employed as matrices due to their swelling and gel-forming characteristics. The matrix tablets were prepared by direct compression using α-lactose (L) or Carbopol 974 (C) as additional excipients. This investigation focuses on the influence of the proportion of the matrix material, and co-excipient (α-lactose or Carbopol) on the release rate of the drug from the tablets. In each case the tablet mass was 50 mg containing 10 mg miconazole. In vitro drug release studies were carried out using USP dissolution apparatus with baskets adapted for volumes of 200 mL. The dissolution medium was phosphate buffered saline (pH 7.4), maintained at 37 ± 0.1°C with a rotation speed of 50 rpm. Table 1 shows the composition of each tablet as well as the release rate (gradient of the % released over time for the first 2 h). HEC matrices showed greater drug release than the methyl cellulose for all comparable formulations, this is likely to be due to the increased hydrophilicity of HEC compared with MC (Rodriguez et al 2000). Drug is released from HEC according to erosion-controlled mechanisms due to its high water solubility yet MC is likely to control drug release via both erosion and swelling with diffusion through the swollen layer. Incorporation of Carbopol, a water swellable polymer greatly reduced drug release from both systems; this may be due to the total loss of erosion controlled release and a switch to diffusion controlled drug release. Incorporation of lactose into the formulations had little effect on the HEC formulations, this is likely to be due to the fact that both materials dissolve readily in water thus the mechanism of release of the drug was unchanged. Lactose in combination with MC greatly reduced drug release; the MC will both swell and erode at the surface thus drug is released via both diffusion and erosion. Lactose will dissolve thus there is a move towards erosion controlled drug release which was anticipated to show faster drug release. The slower release rate shown may be due to an interaction between the excipients preventing drug release or preventing the MC from swelling thus reducing drug release. Further investigations using microviscometry to measure polymer release rates will be performed to verify these suggestions (Esnaashari et al 2005).

Table 1 Release rate from the formulations tested

Polymer %	Excipient %	Release rate (%/h)
MC 80	L 0	35.7
MC 70	L 10	22.4
MC 60	L 20	17.7
MC 60	C 20	2.45
HEC 80	L 0	43.2
HEC 70	L 10	47.6
HEC 60	L 20	48.6
HEC 60	C 20	3.11

Esnaashari, et al (2005) *Int. J. Pharm*. **292**: 227–230

Rodriguez, et al (2000) In: Wise, D. L. (ed.) *Handbook of pharmaceutical controlled release technology*. New York: Marcel Dekker, pp 1–30

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In-vitro and in-vivo performance of a press coated tablet

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The aim of this study was to investigate the in-vitro and in-vivo performance of a press-coated tablet (PCT). The PCT consisted of a rapidly disintegrating theophylline core tablet, press-coated with barrier granules containing glyceryl behenate (GB) and low-substituted hydroxypropylcellulose (L-HPC). In-vitro studies of PCTs comprising varying concentration of GB and L-HPC were performed in 1L of distilled water using a USP II dissolution apparatus (50rpm). The in-vitro release of the PCTs was defined by the time to 50% of the drug release ($t_{50\%}$). The mean $t_{50\%}$ of drug release from the PCT increased as the ratio of GB to L-HPC increased (Table 1) similar to the trend reported in a previous study (Leaokittikul et al 2001). In-vivo γ-scintigraphic studies were carried out for the median formulation PCT-C in four beagle dogs. A hole (1 mm diameter × 2.4 mm deep) was drilled into the PCT into which 1.5 mg of radiolabelled lactose (1 MBq ^{99m}technetium-DTPA) was added before sealing with melted GB. The PCT was administered to the dogs on one occasion in the fasted state, and on subsequent occasion within 30 min of eating an FDA high fat breakfast. External markers of 0.1 MBq ^{99m}technetium-DTPA were used for positioning. A gamma camera equipped with a low energy collimator was used to obtain posterior images every 10 min until PCT disintegration was observed. All the procedures were performed according to a UK Home Office Animals (Scientific Procedure) Project Licence and animals were given free access to water before and during the study period. All of the tablets except one (in the fasted state) disintegrated in the stomach and in-vivo disintegration time was very similar to that predicted by in-vitro dissolution. The in-vivo lag time in both the fasted (88.5 ± 13 min) and fed (78.5 ± 11 min) states did not differ significantly ($P > 0.05$) from in-vitro $t_{50\%}$. Additionally no significant difference ($P > 0.05$) between in-vivo fasted and fed state disintegration time was observed, demonstrating that that the in-vivo performance of PCT-C was not influenced by the presence or absence of food in GI tract. In conclusion, composition of the barrier layer can be used as a parameter to modify the $t_{50\%}$ of drug release from PCTs, in-vivo performance of PCT-C is similar in the fed and fasted state, and a good correlation was found with in-vitro results. In-vivo performances of other formulations are currently the subject of ongoing studies.

Table 1 Formulation compositions and in-vitro performance of press coated tablets

Formulation	Barrier granules		$t_{50\%}$ (min) Mean ± s.d., n = 6
	GB (%)	LHPC (%)	
PCT-A	50	50	55 ± 5
PCT-B	60	40	69 ± 2
PCT-C	65	35	70 ± 4.6
PCT-D	70	30	84 ± 1.5
PCT-E	75	25	153 ± 4.7

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