Poster Session 3 – Biopharmaceutics

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Impact of molecular weight and drug solubility on in-vitro release of drug from HPMC controlled release matrix tablet

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It was proposed to investigate the effect of different molecular weight of HPMC and drug solubility on release rate and mechanism of propranolol HCl, salicylic acid and furosemide from matrix tablets. Tablets were prepared by direct compression using single punch tablet machine (Manesty-E2, UK) and 10 station tablet machine (Rimek Mini Press-I, India) (Table 1). In-vitro dissolution studies were performed in 900 mL of phosphate buffer (pH 6.8, $37 \pm 0.5°C$, 100 ± 2 rev min^{-1}) using a rotating basket dissolution apparatus (GMP model, Electrolab, TDT-08L, India). The Korsmeyer & Peppas equation (Peppas 1985) was used to compare the release kinetics and analyse drug release mechanism of controlled release system. The three viscosity grades of HPMC (K4M, K15M and K100M) showed similar release rates despite variations in the molecular size of HPMC. A significant difference was observed in release rate of formulation containing propranolol HCl (P4M, P15M and P100M; $F_{0.05} = 26.37$), salicylic acid (S4M, S15M and S100M; $F_{0.05} = 89.19$) and furosemide (F4M, F15M and F100M; $F_{0.05} = 24.72$) but no correlation between release rate and molecular weight of HPMC was observed. The results also support the previous explanation by Ford et al (1985) that the viscosity of the hydrated higher molecular weight matrixes may be identical despite of apparent difference in viscosity grades. However, solubility played an important role in the release rate and mechanism from the matrix tablets. After 9 h of study, 80–85%, 65–70% and 45–55% release was obtained from the formulations containing propranolol HCl, salicylic acid and furosemide, respectively. The variation in the release rates, K (Table 1), of the drugs may be attributed to differences in the solubility of the drug molecules. The drug release mechanism was interpreted using release exponent 'n' and found to be predominately diffusion controlled, anomalous and Case II transport for tablets containing propranolol HCl, salicylic acid and furosemide, respectively. The variation in the release mechanism can be attributed to a coupling of diffusion and erosion, with the relative contribution of each being determined, in part, by the solubility of drug molecule. In conclusion, no appreciable effect of molecular weight of HPMC on the drug release rate was observed. However solubility of drug molecule played important role in determining rate and mechanism of drug release.

Table 1 Formulation and release analysis of the matrix tablets

Code	Formulation*		Release analysis	
	Drug (25%)	HPMC (50%)	K value(h^{-n})	'n' value
P4M	Propranolol	K4M	0.265 ± 0.007	0.527 ± 0.012
P15M	HCl**	K15M	0.313 ± 0.014	0.449 ± 0.012
P100M		K100M	0.268 ± 0.016	0.500 ± 0.024
S4M	Salicylic	K4M	0.199 ± 0.007	0.576 ± 0.009
S15M	acid***	K15M	0.227 ± 0.007	0.493 ± 0.014
S100M		K100M	0.177 ± 0.004	0.603 ± 0.012
F4M	Furo-	K4M	0.078 ± 0.002	0.833 ± 0.010
F15M	semide***	K15M	0.070 ± 0.002	0.855 ± 0.033
F100M		K100M	0.063 ± 0.005	0.976 ± 0.030

*Other ingredients: lactose (23.5%); lubricant: magnesium stearate (1.5%); **tablets prepared in single punch tablet machine and ***tablets prepared in multiple punch tablet machine.

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Quantitative structure-pharmacokinetic relationships for phenothiazines and ACE inhibitors

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When developing a drug, small changes to its structure are often made with the intent of optimising its activity and minimising side-effects. Such changes can also influence drug absorption, distribution and elimination, and these effects may be explored using quantitative structure–pharmacokinetic relationships (QSPR). We have investigated QSPR for certain phenothiazines and ACE inhibitors, using solubility parameter (δ) and molecular connectivity indices ($^1\chi$ and $^1\chi_v$) as predictors. Relationships between these and other molecular and physicochemical parameters were also investigated. Pharmacokinetic data were obtained from the literature for phenothiazines and ACE inhibitors. δ was calculated for these compounds according to the method of Fedors (1974). $^1\chi$ and $^1\chi_v$ were calculated by the method of Kier & Hall (1976) for the ACE inhibitors; as QSPR has already been investigated using these parameters for the phenothiazines, this was not repeated. Significant ($P < 0.05$) correlations obtained for the ACE inhibitors and phenothiazines are shown in Tables 1 and 2, respectively. All correlations were linear, except for δ and erythrocyte binding for the phenothiazines, which was quadratic. Interestingly, $^1\chi$ and $^1\chi_v$ correlated significantly with CL and % protein bound for the ACE inhibitors, but not the phenothiazines. This may be attributable to different binding characteristics and clearance mechanisms of the drugs. However, δ did correlate with CL for the phenothiazines, demonstrating that QSPR can be derived for this pharmacokinetic parameter. δ also correlated with % erythrocyte bound and V_{ss} for the phenothiazines, neither of which could be successfully modelled using $^1\chi$ and $^1\chi_v$. Correlations between δ and protein binding, CL_u, $V_{u,ss}$ or t½ for the phenothiazines, and between δ and protein binding, CL, CL_R, V or t½ for the ACE inhibitors were insignificant. $^1\chi$ and $^1\chi_v$ did not correlate with V or t½ for the ACE inhibitors, nor did $^1\chi_v$ correlate with CL for this group of drugs. δ did not correlate with $^1\chi$ or $^1\chi_v$ for either group of drugs, or with Van der Waals volume and surface area, pKa, Log P_u and Log P_i for the phenothiazines. In conclusion, both δ and the connectivity indices appear to have potential in QSPR, as several correlations were found with pharmacokinetic parameters for the phenothiazines and ACE inhibitors. Also, they do not appear to be conclusively related to any of the physicochemical or molecular parameters assessed here. However, the same correlations were not seen for both groups of drugs, suggesting that consideration of several physicochemical and molecular parameters is the best strategy for determining QSPR.

Table 1 Significant correlations between physicochemical, molecular and pharmacokinetic parameters for ACE inhibitors

Correlating parameters	r	n
δ and t_{max}	0.92	13
$^1\chi$ and % protein bound	0.65	15
$^1\chi$ and CL	−0.82	6
$^1\chi$ and CL_R	−0.87	9
$^1\chi_v$ and % protein bound	0.69	15
$^1\chi_v$ and CL_R	0.82	9
Log P and % protein bound	0.86	11
δ and Log P	0.57	20

Table 2 Significant correlations between physicochemical, molecular and pharmacokinetic parameters for phenothiazines

Correlating parameters	r	n
δ and % erythrocyte bound	0.55	23
δ and CL	−0.83	10
δ and V_{ss}	−0.94	10

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Effect of colonic microbial degradation of xanthan gum matrices on diclofenac sodium release in-vitro

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A binary formulation of diclofenac sodium and xanthan gum polymer in ratio of 2:1, respectively, was granulated using isopropyl alcohol and then compressed into matrices at two levels of hardness, L1 and L2. The mean hardness (Newtons) for the L1 and L2 series of matrices was 59.38 ± 5.86 and 71.42 ± 6.95 ($n = 20$), respectively. The rates of diclofenac sodium release from the matrices were assessed in 350 mL phosphate buffer (pH 6.8), 1, 3 and 6% w/v rat faecal contents homogenised in 350 mL phosphate buffer (pH 6.8) using the USP basket apparatus. Rates of drug release were compared using the t_{15} or t_{35} (time for 15% or 35% of diclofenac sodium dissolved, respectively) values. Diclofenac sodium release from the matrices in phosphate buffer was almost linear and superimposable at the two levels of hardness (L1 and L2). No statistically significant difference was observed between the t_{15} or t_{35} values at L1 and L2 using Student's *t*-test ($P = 0.10$ and 0.25, respectively). In 1% rat faecal contents, there was an initial rise in the rate of diclofenac sodium release within 12 h and thereafter the rate of release gradually declined. This was true at L1 and L2 ($P = 0.21$ for t_{15} values). However, the rate of drug release was slower at L2 compared with L1 after 12 h, being significantly different for t_{35}, $P = 0.01$ (Table 1). Thus, although matrix hardness did not affect rate of drug release in phosphate buffer (pH 6.8), the harder matrices (L2) appeared to resist enzymatic degradation in the rat faecal content. In 3% and 6% rat faecal contents, the same observations were made as in the 1% rat faecal content (i.e. an initial rise within 12 h followed by a fall). However, comparing the rates of drug release in the different rat faecal contents, a gradual increase in diclofenac sodium release at the respective levels of hardness was observed as the rat faecal content of the dissolution medium was increased from 1% through 6% within the first 12 h ($P < 0.05$ for t_{15} values at L1 as well as L2 using analysis of variance for pair-wise comparisons). Conversely, the fall in rate of diclofenac sodium release after 12 h appeared to be more pronounced with increased rat faecal content (Table 1). The t_{35} values were significantly different ($P < 0.05$) at L1 as well as L2. This phenomenon is ascribable to a gradual fall in pH of the media due to enzymatic degradation of the xanthan gum polymer by the colonic bacteria (Wilson et al 2002) and a decreased solubility of diclofenac sodium with fall in pH. It is apparent therefore that higher faecal content resulted in an initial enhanced enzymatic effects on the polymer, which resulted an initial increase in the rate of diclofenac sodium release; concurrently, however, there was a gradual fall in pH. This study suggests that colon-targetable polymer matrices carrying acid-insoluble drugs like diclofenac sodium may fail to deliver the total drug load if the caecal transit is prolonged.

Table 1 T_{15} and T_{35} values in rat faecal contents

Faecal %	T_{15} (L1) (h)	T_{15} (L2) (h)	T_{35} (L1) (h)	T_{35} (L2) (h)	End pH
0	6.2 ± 0.1	5.9 ± 0.2	14.3 ± 0.4	14.1 ± 0.2	6.8
1	3.3 ± 0.3	3.5 ± 0.3	17.3 ± 0.3	18.4 ± 0.8	6.5
3	1.5 ± 0.1	2.3 ± 0.3	20.2 ± 2.5	21.3 ± 1.0	6.3
6	0.70 ± 0.04	1.7 ± 0.07	22.9 ± 0.6	22.1 ± 0.6	5.9

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The use of the TNO intestinal model (TIM-1) and GastroPLUS for the prediction of in-vivo performance of immediate release tablets

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The TNO Intestinal Model (TIM) is an in-vitro model that can mimic the dynamic conditions found within the stomach and small intestine. The model does this by simulating the secretion of enzymes, controlling the pH in each compartment of the model using a feedback system and controlling the movement through the gut model by peristalsis. The model can simulate fed conditions by introducing the actual meal into the system itself and setting enzymic secretion conditions via a protocol. This protocol can also control gastric emptying. To perform an experiment, a dosage form is introduced into the model and samples are taken throughout the run. The results can be expressed as concentration and amount of drug versus time. This determines an estimation of how much drug is available for absorption in each compartment at any one time (bioaccessibility). Additionally, sampling is performed such that an estimation of the total recovery of drug can be determined at the end of an experiment. Development work was carried out utilising the TIM and a paroxetine formulation. The aim of the experiment was to demonstrate reproducibility of the model and investigate in-vitro in-vivo correlation (IVIVC), using GastroPLUS predictions. An immediate release tablet formulation containing 20 mg paroxetine was tested, in duplicate, under fasted conditions. Samples were taken at regular intervals and the analysis was performed by HPLC. The two immediate release tablet experiments exhibited similar profiles and their overall drug recoveries were 77% and 73%, respectively, which demonstrates the excellent reproducibility of the model. A prediction of the plasma profile was carried out using GastroPLUS using this TIM data as input. The data was deconvoluted using WinNonLin in order to estimate this input/ dissolution profile as the 'fraction absorbed'. This deconvoluted TIM data predicted the measured plasma profile very well. The TIM system has provided an estimation of the amount of drug that is available for absorption. This data, once deconvoluted, can be used as input into the GastroPLUS model in order to predict the plasma profile. The use of the TIM model in conjunction with GastroPLUS, provides an excellent tool to aid in the selection of a formulation in pharmaceutical development.

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The influence of viscosity on tablet disintegration in biorelevant media

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The advent of the Biopharmaceutical Classification System has led to the reassessment of compendial test media to provide good predictability of the in-vivo performance of a dosage form (Amidon et al 1995). Thus, in recent years, interest has focused on the development of physiologically relevant media, which attempt to mimic the in-vivo conditions of the gastrointestinal tract (Dressman et al 1998). Studies have concentrated on dissolution from solid dosage forms in these media with little attention being given to the preliminary step, disintegration. Alterations in media composition would influence factors such as surface tension and viscosity that would be expected to affect tablet disintegration. Previous studies using media designed to represent gastric conditions in both the fasted and fed states, and using tablets formulated to be rapidly and poorly disintegrating in aqueous media, showed that media composition significantly influenced tablet disintegration. In particular, disintegration in whole milk, used to simulate the fed stomach, was significantly longer than in most other media (Anwar et al 2002). Whole milk has a low surface tension and a relatively high viscosity compared with other physiologically relevant media (1.30 cP; 43.0 mN m^{-1}, respectively). The purpose of this study was to investigate whether viscosity was the controlling factor in the disintegration time of tablets, using media with similar surface tensions to milk, but differing viscosities. The surface tension and viscosity of a range of aqueous solutions of hydroxypropyl methylcellulose (HPMC E5) were determined by the Wilhelmy plate method and U tube viscometry, respectively. The standard BP 2000 test with discs was employed to assess the disintegration times of two sets of tablets, representing a rapidly disintegrating system (35% microcrystalline cellulose; 65% lactose; 3% magnesium stearate; 1% sodium starch glychollate; 0.4 min in water) and a poorly disintegrating system (95% microcrystalline cellulose; 5% magnesium stearate; 8 min in water). The tablets (0.5 g) were prepared manually in a 1.27 cm diameter flat faced punch and die at 3000 kg. The results are given in Table 1. Increasing viscosity retards the disintegration of tablets possibly by reducing the rate of penetration of liquids into the tablets. The

relatively high viscosity of whole milk may be a major factor in the slower disintegration of tablets in this media used to simulate the fed stomach contents.

Table 1 The influence of viscosity on tablet disintegration time

HPMC concn (%)	Surface tension ($mN\,m^{-1}$)	Viscosity (cP)	Disintegration time (rapid) (min)	Disintegration time (poor) (min)
0.5	45.7	1.08	1.9	18
0.75	45.6	1.32	2.1	20
1.0	45.4	1.59	2.3	27
1.5	44.9	2.21	3.5	35
2.0	45.1	3.08	4.3	38
Whole milk	43.0	1.30	2.2	33

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Autoradiographic imaging of aminolevulinic acid penetration through non-keratinised gynaecological tissue

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Vulval intraepithelial neoplasia (VIN) is a relatively rare condition, but may progress to invasive cancer if left untreated (Zawislak et al 2002). Lesions of VIN are readily amenable to photodynamic therapy (PDT) based on topical administration of aminolevulinic acid (ALA). However, lesions of VIN can extend as far as 2.5 mm from the surface, while ALA, being a small hydrophilic molecule, has been widely reported as being able to penetrate no further than 2 mm into skin. We have previously shown autoradiography to be a suitable technique for studying drug penetration into tissue of gynaecological origin (Woolfson et al 1995). The aim of this work was to use autoradiography as a qualitative measure of the penetration profile of ^{14}C-radiolabelled ALA through tissue. In addition, the effect of application time on the ALA distribution pattern through tissue was investigated. Due to the medical desire to preserve vulval structure and function, vulval tissue is removed only rarely, but as its histological picture is one of a keratinising epithelial tissue (Moore & Hacker 1998), then it is feasible to use a non-keratinised tissue, such as vaginal epithelium, as an excised model for drug penetration studies. Non-keratinised vaginal tissue, removed during routine repair operations and possessing no *stratum corneum* barrier, was obtained following appropriate ethical approval and fully informed patient consent. An ALA-loaded bioadhesive patch, spiked with a defined amount of ^{14}C-ALA was applied to the upper face of the vaginal tissue block, suitably mounted in a temperature-controlled (37°C) mount. After a determined period of time (1, 2 and 4 h) the tissue was recovered, flash frozen in a liquid nitrogen atmosphere and sectioned orthogonally to the plane of drug diffusion. Slices were exposed to autoradiographic film (Kodak Biomax MR) and developed to produce an image. This image was scanned using densitometric software (Bio-Rad Quantity One) and processed using three-dimensional contouring software (Delta-Graph) to give a contour representation of ALA distribution. ALA released from a bioadhesive patch penetrated vaginal epithelial tissue to at least 6 mm, as shown using autoradiography. The concentration of ALA, as evaluated using the intensity of an arbitrary grey scale, in tissue was dependent on application time. Indeed, penetration was shown to be rapid, with a permeation front evident after only one hour. Contrary to previous thinking on the subject, ALA does not seem to penetrate tissue solely through ducts or glands. Instead a uniform gradient, beginning at the tissue surface, was observed in each case, conceivably due to the absence of a *stratum corneum* barrier to drug penetration.

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The effect of milk on the dissolution behaviour of ibuprofen and ibuprofen tablets

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As part of a wider study of the effect of alternative, realistic dissolution media on the release of drugs from oral dosage forms, dissolution media based on milk and various individual milk constituents were investigated. The acidic BCS Class II drug ibuprofen was used and compendial dissolution testing was performed on commercial 400 mg tablets while intrinsic dissolution rate (IDR) testing was performed on compressed discs of drug substance. Tablet dissolution tests were performed using the USP 25 Apparatus 2 under test conditions of 37°C, 50 rev min^{-1} and 500 mL volume. IDR studies were performed using the USP25 Rotating Disk Method fitted with 8 mm dies. The conventional dissolution media used were simulated gastric fluid (SGF) having a pH of 1.1, SGF with 0.25% w/v of the surfactant sodium dodecyl sulphate (SDS) and simulated intestinal fluid (SIF) pH 6.8. The alternative media comprised equal-parts mixtures of SGF with whole, with semi-skimmed and with skimmed milk, SGF adjusted to pH 2.5 and 4.8% w/v lactose in SGF pH 2.5. Two further media were prepared comprising a 1.475% w/v dispersion of casein in SGF and a filtered version of the same. An SGF pH 2.5 medium was used to account for the increase in pH seen upon addition of milk to SGF pH 1.1. The dissolution samples were analysed by HPLC and the amount of ibuprofen dissolved was expressed as a percentage of the total available. Adding surfactant to the medium or increasing the pH beyond the pK_a of ibuprofen (4.4) by using SIF as the medium significantly increased the rate of dissolution. Addition of milk had a minor, but discernible effect ($P < 0.05$) that was not simply due to the increase in pH resulting from the addition of the milk (pH 2.5). In addition, there was no obvious correlation between the increased dissolution and the fat content of the milk ($P > 0.05$) or the presence of lactose in the medium. However, the presence of casein did increase dissolution and this seems to relate to the soluble fraction of the casein as the effect was enhanced by filtering the medium before use. The improved dissolution in certain media was not seen in the IDR studies so the effect may result from an interaction between the medium and the tablet formulation. Overall, the degree of dissolution of ibuprofen after 60 min in the IDR studies appears negligible. The addition of milk to the dissolution medium clearly improved the rate of dissolution of ibuprofen from the tablets and casein appears to play a role in this. This work has exemplified the need for more realistic fed state dissolution media to improve in-vitro in-vivo correlations during drug development.

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Table 1 Amount of ibuprofen dissolved from tablets after 60 min (n = 6)

Medium	% Dissolved	
	Mean	s.d.
SGF pH 1.1	4.8	0.37
SGF pH 2.5	3.3	0.17
SGF-SDS	42.8	2.04
SIF pH 6.8	95.2	1.83
SGF-whole milk	9.4	1.49
SGF-semi-skimmed milk	12.8	3.88
SGF-skimmed milk	12.0	3.92
SGF-Lactose	3.6	0.24
SGF-Casein	9.0	0.84
SGF-Casein (filtered)[a]	15.0	1.38

[a]n = 3.