EFFECT OF MIXED FILM COATING ON PHARMACOKINETICS OF PARACETAMOL TABLETS

K. Ofori-Kwakye[1], and J.T. Fell[2]
[1]*Department of Pharmaceutics,*
Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.
[2]*School of Pharmacy and Pharmaceutical Sciences,*
University of Manchester, Manchester M13 9PL, UK.

ABSTRACT

This study was carried out to evaluate the effect of mixed film coating on pharmacokinetics of paracetamol tablets. The tablet cores were prepared and film-coated with a mixture of pectin (0.98%w/w), chitosan (0.16%w/w), HPMC (0.06%w/w), glycerol (0.24%w/w) and 0.1M HCl (98.55%w/w). A single oral dose (1200 mg) of the coated tablets having a coat weight gain of 9%w/w was administered to 5 healthy male volunteers under fasting conditions. Saliva samples were collected at regular time intervals over a 16 h period and analysed for paracetamol by reverse phase HPLC. The main pharmacokinetic parameters were determined using non-compartmental analysis. The parameters for the uncoated tablets were similar to published values while wide variations were observed for the coated tablets. The mean lag time (T_{lag}) was higher in the coated tablets (2.14 ± 1.21 h) than the uncoated tablets (0.15 ± 0.05 h). The mean AUC_{0-a} (16.92 ± 9.84 $\mu g/ml^{-1}h^{-1}$) and mean C_{max} (3.15 ± 2.10 $\mu g/ml^{-1}$) of the coated tablets were 47% and 25%, respectively of the corresponding values of the uncoated tablets. There was a 9-fold increase in the mean T_{max} (8.40 ± 2.88 h) of the coated tablets as compared to the uncoated tablets. The rate and extent of drug absorption was low in the film-coated tablets compared to the uncoated tablets, demonstrating the ability of the mixed films to modulate drug release. The mixed pectin/chitosan/HPMC film coating has the potential for use in the design of controlled release dosage forms.

INTRODUCTION

Various drug delivery systems in the form of matrix tablets, compression coatings and beads have been used as carriers for the delivery of drugs and other bioactive materials to the body. The use of film coatings as vehicles for the delivery of drugs offers significant promise (Wakerly *et al.*, 1996; Basit, 2000; Semde *et al.*, 2000). The release of drugs from film-coated formulations will be dependent on the formulation properties of the dosage form as well as the permeability and mechanical properties of the films.

The use of mixed films in drug delivery involves the combination of the film-forming properties of two or more polymers to form a composite film coating system with enhanced physico-chemical properties. Mixed films can alter the

drug release profiles of tablet cores to achieve controlled drug release in the gastrointestinal tract (GIT). Such preparations are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Pectin and chitosan are naturally-occurring, hydrophilic polymers that have been used in numerous drug delivery applications (Ashford *et al.*, 1993; Kim *et al.*, 1999). These polymers are strong film-formers, biodegradable and have high safety profiles and are widely used in the food and pharmaceutical industries. A major drawback to the use of these polymers in drug delivery is their high solubility in aqueous media. To remedy this problem, gels of pectin, chitosan and hydroxypropylmethylcellulose (HPMC) have been mixed to form films having a reduced aqueous solubility and reduced permeability to a model drug than films prepared with gels of pectin or chitosan alone (Ofori-Kwakye and Fell, 2001). HPMC improves the mechanical properties of the mixed pectin/chitosan films.

This article investigates the effect of mixed film coating of pectin, chitosan and HPMC on the *in vivo* release kinetics of paracetamol tablets in 5 healthy human volunteers intended for controlled drug release in the GIT.

Materials and Methods
Materials
Pectin USP (Citrus Colloids, UK), High molecular weight chitosan (Chitosan HM) (Sigma-Aldrich,UK), HPMC (Colorcon, UK), Paracetamol powder and 4-acetaminophen (Sigma Chemical, USA), Lactose (DMV, The Netherlands), Microcystalline cellulose (Mendell Co. Ltd., UK), Magnesium stearate (GlaxoSmithKline, UK), Polyvinylpyrrolidone (PVP) (GAF Corp., USA), High performance liquid chromatography (HPLC) grade water and Methanol (Sigma-Aldrich, Germany), Distilled water (singly distilled and freshly prepared).

Tablet manufacture
Paracetamol tablet cores with a nominal weight of 750 mg; mean diameter of 13.04 ± 0.03 and mean thickness of 6.67 ± 0.06 (n = 10); breaking load of 9.6 ± 0.7 kp (n = 20) and friability of 0.16% were compressed with a rotary tablet machine (Manesty Ltd., Liverpool, UK) from granules of microcrystalline cellulose (Emcocel® LP200, 19.8% w/w; Emcocel® LM50, 19.8% w/w), lactose (19.8% w/w), paracetamol (39.7% w/w) and magnesium stearate (0.8% w/w).

Film coating
The tablet cores were film-coated with an Accelacota-10 tablet coater (Manesty Ltd., Liverpool, UK). The coating formulation, consisting of pectin USP (0.98% w/w), chitosan HM (0.16% w/w), HPMC E4M (0.06% w/w), glycerol (0.24% w/w) and 0.1M HCl (98.55% w/w), was sprayed onto the tablets with a Manesty spray gun in a perforated, 61 cm diameter 316L stainless steel coating drum. The coating formulation was stirred continuously with a mechanical stirrer to ensure homogeneity.

The process parameters used to coat the tablets were: inlet temperature (68-70°C), outlet temperature (50-52°C), tablet bed temperature (32-35°C), spray rate (13-15 g/ml), spray gun distance (18 cm), drum speed (8.7 rpm), inlet air flow (7.5-8.2 m³/h), atomising air pressure (1.5-2.0 bar), and fan pressure (0.7-1.0 bar).

Tablets with coat weight gain (CWG) of about 9% were produced and stored in plastic bags at room temperature until required.

Study design
Five healthy human volunteers with mean age of 34.4 ± 5.0 yr, weight of 76.4 ± 15.8 kg and height of 173.7 ± 5.0 cm were used for the study. The volunteers who gave their informed written consent, were all non-smokers, had no history of chronic disease and did not take any medication or alcohol during and at least three days before the study. After an overnight fast

(10-12 h), each volunteer swallowed a single dose of either the film-coated or the uncoated paracetamol tablets in a 2-way randomised study. The single dose of each formulation consisted of four (4) tablets containing approximately 1200 mg of paracetamol. The tablets were swallowed whole with 200 ml of water and a further 50 ml used to rinse the mouth to remove any adsorbed drug particles. A washout period of one week was allowed between the administrations of the two tablet formulations. No food was allowed for at least 2 h after tablet administration.

Saliva samples

Each volunteer collected saliva samples by spitting into 15 ml clear polystyrene screw-cap centrifuge tubes over a 1 min period. Samples were collected by chewing on Parafilm® (2.5 cm x 2.5 cm) to stimulate saliva production. The saliva samples were collected before tablet administration (blank sample) and at 10 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 12 h, 14 h, and 16 h after tablet administration. The collected samples were stored in a freezer until required. Before analysis, the samples were removed from the freezer and defrosted overnight. The samples were centrifuged at 3000 rpm for 20 min to remove both mucous and particulate matter.

Assay of paracetamol

The amount of paracetamol in the saliva samples was determined by means of a reversed-phase HPLC method previously described by Borin and Ayres (1989) with minor modifications. Solutions of paracetamol (10-1500 µg/ml) and 2-acetamidophenol (80µg/ml) were prepared in distilled water and used as stock and internal standard, respectively. Standard solutions were prepared by adding 25 µl of the stock solutions to 500 µl of the blank saliva. The test solutions were prepared by mixing 200 µl of the standard solutions or the salivary supernatant (unknown) with 200 µl of the internal standard in 3 ml screw cap vials.

The test and standard solutions were analysed twice with an HPLC system consisting of two solvent delivery pumps and a system controller (Shimadzu Corp., Japan). A manual syringe loading sample injector (Rheodyne Inc., USA) was used to inject 10µl samples into the HPLC. The mobile phase consisted of 25% methanol in water with a flow rate of 1.5 ml/min. The detector sensitivity, response time and chart speed were 0.05 AUFS, 0.2 s and 1 cm/min, respectively. A 250 mm × 4.60 mm reverse phase Luna 5 C8 (2) analytical column (Phenomenex Ltd., UK) fitted with a guard column (Hichrom Ltd., UK) maintained at room temperature was used. Sample detection was achieved with a variable UV detector (Kontron Instruments, UK), set at 254 nm. Data were recorded on a Softron PC integrator (Kontron Instruments, UK).

A standard calibration curve, linear over the concentration range 0.48-71.43 µg/ml ($r^2 = 0.9998$) was prepared by using the peak area ratios of paracetamol:internal standard versus known paracetamol concentration fitted to a line via linear regression. The peak area ratios of paracetamol:internal standard for the saliva samples were determined and the paracetamol concentration in saliva determined with the use of the calibration curve. From the results, plots of saliva paracetamol concentration versus time for the volunteers were made.

Non-compartmental pharmacokinetic parameters

Pharmacokinetic parameters were determined for each volunteer using the standard non-compartmental analysis. The peak saliva drug concentration (C_{max}) and the time to reach the peak saliva drug concentration (T_{max}) were obtained directly from the saliva drug concentration-time profiles. The lag time (T_{lag}) was estimated from the experimental values as the midpoint between the last time at which no drug was detected and the initial time that the drug was detected in the saliva. The terminal elimination rate constant (K_{elim}) was determined by least

squares regression of the concentration-time data points lying in the terminal log-linear region of the curve and was also used to calculate the half-life ($T_{1/2}$ = -0.693/K_{elim}). The area under the saliva drug concentration-time curve (AUC_{0-t}) was determined by means of the linear trapezoidal rule. The $AUC_{0-\infty}$ was determined by dividing the last measured saliva drug concentration (C_t) by the K_{elim} and adding the resultant value to the AUC_{0-t}. Statistical analyses were carried out using one-way analysis of variance (ANOVA) from the MICROCAL ORIGIN version 3.54 program.

Results and Discussion
All the volunteers adhered to the study protocol and completed the study. The tablets were taken after an overnight fast and food was only allowed at least 2h after swallowing the tablets to promote rapid gastric emptying of the tablets. This is because the gastric emptying of tablets is affected by the size of the tablets and whether or not the tablets are administered to a fed or fasted stomach (Davis, 1987). The tablets used in the study were large, single unit tablets. Such tablets are treated by the stomach as indigestible material and are emptied along with the Phase III activity ('housekeeper' wave) of the Migrating Motor Complex.

Saliva was used as the body fluid for the analysis of paracetamol rather than blood plasma as a strong and highly significant correlation has been established between the saliva and plasma concentrations of paracetamol over a wide range of concentrations (Glynn and Bastain, 1973; Adithan and Thangam, 1982). Also saliva collection is non-invasive and therefore a simpler and painless method of acquiring body fluids.

The chromatographic conditions employed in the study resulted in the formation of two well-resolved chromatograms of paracetamol and 2-acetamidophenol (internal standard) with retention times of 3.46 min and 7.15 min, respectively.

Figures 1-5 show the saliva paracetamol concentration against time profiles for the volunteers. In all cases, the saliva concentration of paracetamol was lower in the film-coated tablets than in the uncoated tablets. Drug absorption from the uncoated tablets was fast and occurred over a relatively short period of time whilst absorption from the film-coated tablets was slow and occurred over an extended period of time. Drug absorption from the coated tablets was particularly well controlled in Volunteers 2, 3 and 5.

The mixed films in the coated tablets become hydrated in aqueous media forming a thick gelatinous layer that acts as a diffusion barrier around the tablet cores (Ofori-Kwakye, 2002). This increases the diffusion path length of the drug molecules and thus reduces the rate of drug release from the film-coated tablets. The hydration of the film coatings can also result in the leaching of pectin from the film matrices leading to an increase in the permeability of the film coatings (Ofori-Kwakye and Fell, 2003). Drug release from the film-coated tablets is thus through molecular diffusion through the gelatinous layer formed on exposure to aqueous media and/or erosion of the gel layers formed around the tablets. The leaching of pectin will also create aqueous channels or water-filled pores in the film coatings that may allow the diffusion of more drug molecules.

Tables 1 and 2 are the non-compartmental pharmacokinetic parameters for the uncoated and film-coated paracetamol tablets, respectively. The pharmacokinetic parameters for the uncoated tablets were similar to published values (Borin and Ayers, 1989; Hossain and Ayers, 1996) whilst variations in the parameters were observed for the coated tablets. A longer mean lag time (2.14 ± 1.21 h) was observed between the administration of the film-coated tablets and the onset of absorption in comparison to the uncoated tablets (0.15 ± 0.05 h) in the volunteers. The mixed film coating was thus able to substan-
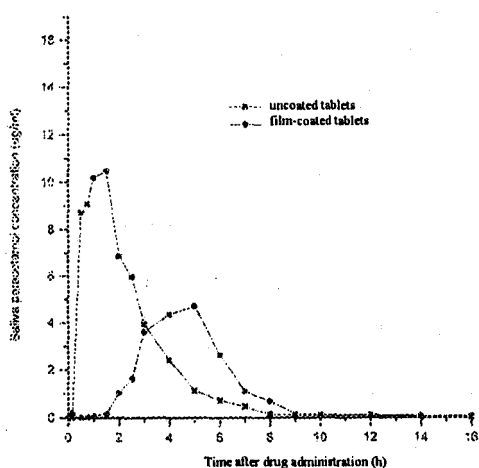
Fig. 1. *Saliva concentration of paracetamol after the administration of a single dose (1200 mg) of uncoated and film-coated (9% w/w) paracetamol tablets to Volunteer 1.*
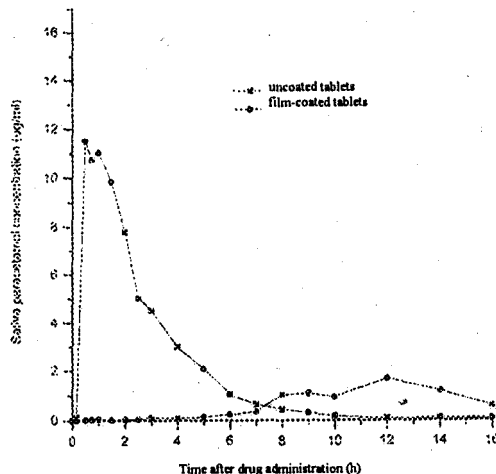

Fig. 3. *Saliva concentration of paracetamol after the administration of a single dose (1200 mg) of uncoated and film-coated (9% w/w) paracetamol tablets to Volunteer 3.*
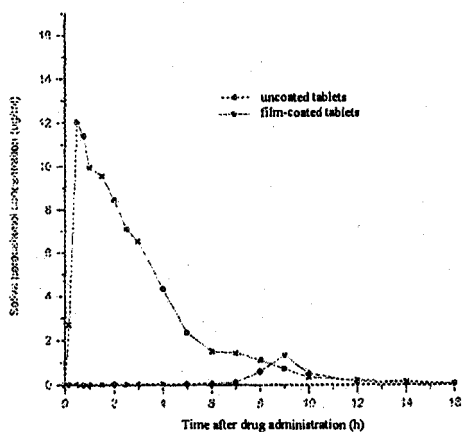

Fig. 2. *Saliva concentration of paracetamol after the administration of a single dose (1200 mg) of uncoated and film-coated (9% w/w) paracetamol tablets to Volunteer 2.*

Fig. 4. *Saliva concentration of paracetamol after the administration of a single dose (1200 mg) of uncoated and film-coated (9% w/w) paracetamol tablets to Volunteer 4.*
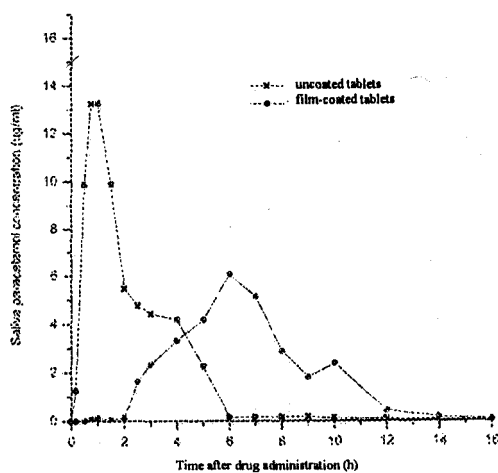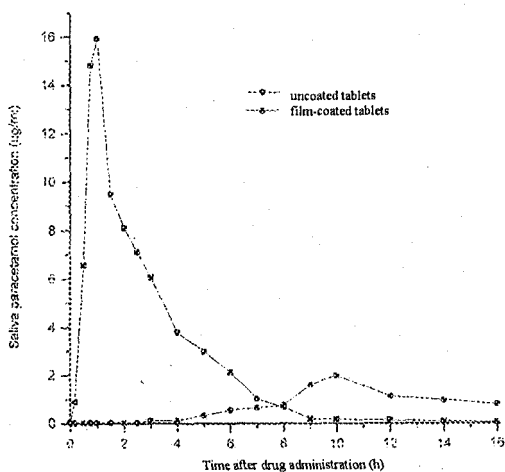
Fig. 5. Saliva concentration of paracetamol after the administration of a single dose (1200 mg) of uncoated and film-coated (9% w/w) paracetamol tablets to Volunteer 5.

Table 1: **Non-compartmental pharmacokinetic parameters for uncoated paracetamol tablets**

VOLUNTEER	C_{max}	T_{max}	T_{lag}	K_{elim}	$T_{1/2}$	AUC_{0-t}	$AUC_{0-\alpha}$
1	10.46	1.50	0.13	0.203	3.41	28.69	28.81
2	12.04	0.50	0.25	0.339	2.04	41.19	41.38
3	11.49	0.50	0.13	0.233	2.97	33.08	33.39
4	13.24	1.00	0.13	0.154	4.50	35.36	35.69
5	15.94	1.00	0.13	0.276	2.51	40.26	40.40
MEAN	12.63	0.90	0.15	0.241	3.09	35.72	35.93
SD[1]	2.10	0.42	0.05	0.071	0.94	5.17	5.17
CV[2] (%)	16.63	46.67	33.33	29.46	30.42	14.47	14.39

[1]SD = Standard deviation; [2]CV (%) = Coefficient of variation

Table 2:   Non-compartmental pharmacokinetic parameters for film-coated paracetamol tablets

VOLUNTEER	C_{max} (μgml^{-1})	T_{max} (h)	T_{lag} (h)	K_{elim} (h^{-1})	$T_{1/2}$ (h)	AUC_{0-t} $(\mu gml^{-1}h^{-1})$	$AUC_{0-\alpha}$ $(\mu gml^{-1}h^{-1})$
1	4.71	5.00	0.86	0.121	5.73	18.43	18.97
2	1.34	9.00	3.50	0.450	1.54	3.96	4.01
3	1.66	12.00	2.75	0.263	2.63	10.77	12.97
4	6.05	6.00	0.86	0.467	1.48	30.92	31.08
5	1.99	10.00	2.75	0.146	4.75	12.16	17.56
MEAN	3.15	8.40	2.14	0.289	3.23	15.25	16.92
SD[1]	2.10	2.88	1.21	0.163	1.93	10.16	9.84
CV^2 (%)	66.67	34.28	56.54	56.40	59.75	66.62	58.16

[1]SD = Standard deviation; [2]CV (%) = Coefficient of variation

tially delay the onset of drug release from the film-coated tablets. The mean C_{max} of paracetamol from the coated tablets (3.15 ± 2.10 µg/ml) was significantly (p <0.05) lower than that of the uncoated tablets (12.63 ± 2.10 µg/ml). The mean T_{max} for the film-coated tablets (8.40 ± 2.88 h) was significantly (p <0.05) higher than those of the uncoated tablets (0.9 ± 0.42 h). The mean C_{max} and T_{max} values indicate a slow rate of paracetamol absorption from the film-coated tablets. There were significant differences (p <0.05) in the mean AUC_{0-t} and $AUC_{0-\alpha}$ values between the coated and uncoated tablets. The relatively low value of the mean AUC_{0-t} and $AUC_{0-\alpha}$ for the film-coated tablets is suggestive of a low extent of drug absorption from the coated tablets.

There was no significant difference (p< 0.05) in the mean $T_{1/2}$ and K_{elim} values for the coated and uncoated tablets. The mixed film coating modified the absorption profiles of the drug to an extent that the mean saliva concentration of paracetamol from the coated tablets was sub-therapeutic (3.15± 2.10 µg/ml) as an average saliva concentration of ≥ 5 µg/ml is reported by Hossain and Ayres (1996) to correlate with therapeutic efficacy. The mixed film coating thus have the effect of modulating the rate and extent of drug absorption from the film-coated tablets, making them suitable for controlled drug delivery.

CONCLUSIONS

Mixed films consisting of pectin, chitosan and HPMC was successfully used to coat paracetamol tablet cores. *In vivo* studies of the uncoated and film-coated tablets in 5 healthy volunteers have shown that the films are able to modulate the release of the drug, allowing the dosage form to exhibit controlled release properties. The films reduced the rate and extent of drug absorption from the coated tablets by reducing C_{max} and $AUC_{0-\alpha}$ and increasing the T_{max} of the volunteers as compared to the uncoated tablets.

A manipulation of the composition of the mixed film coatings will thus provide a suitable film coating system that will act as a carrier for the controlled delivery of drugs to the gastrointestinal tract.

REFERENCES

Adithan, C., Thangam, J. (1982). A comparative study of saliva and serum paracetamol levels using a simple spectroscopic method. British Journal of Clinical Pharmacology 14, 107-109.

Ashford, M., Fell, J.T., Atwood, D., Sharma, H., Woodhead, P. (1993). An evaluation of pectin as a carrier for drug targeting to the colon. Journal of Controlled Release 26, 213-220.

Basit, A.W. (2000). Oral colon-specific drug delivery using Amylose-based film coatings. Pharmaceutical Technology Europe 12, 30-36.

Borin, M. T., Ayres, J.W. (1989). Single dose bioavailability of acetaminophen following oral administration. International Journal of Pharmaceutics 54, 199-209.

Davis (1987). The design and evaluation of controlled-release dosage forms for oral drug delivery. STP Pharmaceutical Sciences 3, 412-417.

Glynn, J.P., Bastain, W. (1973). Salivary excretion of paracetamol in man. Journal of Pharmacy and Pharmacology 25, 420-421.

Hossain, M., Ayres, J.W. (1996). Relative bioavailability of a novel sustained-release acetaminophen moulded tablet. International Journal of Pharmaceutics 133, 223-235.

Kim, H.J., Lee, H.C., Oh, J.S., Shin, B.A., Oh, C.S., Park, R.D., Yang, K.S., Cho, C.S. (1999). Polyelectrolyte complex composed of chitosan and sodium alginate for wound dressing application. Journal of Biomaterials Science 10, 543-556.

Ofori-Kwakye, K., Fell, J.T. (2001). Biphasic drug release: the permeability of films containing pectin, chitosan and HPMC. International Journal of Pharmaceutics 226, 139-145.

Ofori-Kwakye, K., Fell, J.T. (2003). Leaching of pectin from mixed films containing pectin, chitosan and HPMC intended for biphasic drug delivery. International Journal of Pharmaceutics 250, 251-257.

Ofori-Kwakye, K. (2002). Studies on the use of mixed films for bimodal drug delivery. PhD Thesis. University of Manchester, United Kingdom.

Semde, R., Amighi, K., Devleeschouwer, M.J., Moes, A.J. (2000). Effect of pectinolytic enzymes on the theophylline release from pellets coated with water insoluble polymers containing pectin HM or calcium pectinate. International Journal of Pharmaceutics 197, 169-179.

Wakerly, Z., Fell, J.T., Atwood, D., Perkins, D. (1996). Pectin/ethylcellulose film coating formulations for colonic drug delivery. Pharmaceutical Research 13, 1210-1212.