Bioavailability Studies of Paracetamol Bioadhesive Tablets

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Tablets of paracetamol control (plain), layered with bioadhesive polymer, HPMC K4M on one side and matrix tablets with the same polymer were prepared and tested for their bioavailability in normal, healthy male human volunteers in a randomised crossover study. Paracetamol in serum was estimated by a HPLC method with salicylamide as internal standard. The results indicate significant differences in mucoadhesive matrix type tablet with respect to pharmacokinetic parameters, Tmax, AUC and MRT. The study also indicated considerably higher bioavailability from these tablets with better therapeutic efficiency.

Recent interest has been expressed in the delivery of drugs to or via mucus membranes by the use of adhesive materials. Several mucosal adhesive formulations are now available or under development[1]. Oral bioadhesive drug delivery system offer a number of advantages like increasing the residence time in gastro intestinal tract (g.i.t.) giving a controlled release. Our earlier work[2-4] has proved the fact that oral bioadhesive tablets could be prepared successfully with adhesion to g.i.t. for greater then 8 h. It was also shown that by proper formulation, a controlled/prolonged release of these tablets could be achieved. The present investigation was undertaken to show whether the results obtained *in vitro* studies also produce corresponding result *in vivo*.

Paracetamol of Acto Pharmaceuticals, salicylamide of Hemco Pharmaceuticals, methanol for HPLC, diethyl ether (AR), potassium dihydrogen ortho phosphate, ortho phosphoric acid (AR), of SD fine chemicals, Mumbai were used in the present investigation.

A Shimadzu high performance liquid chromatography unit equipped with (i) SCL-6A module system controller, (ii) Solvent delivery module LC-6A, (iii) Column oven CTO-6A module, (iv) UV-visible spectrophotometric detector SPO-6AV module and (v) C-R4A Chromatopac data processor were used in the study. The injector port was with a 20 µl capacity loop. An octadecyl silane reverse phase column (shimpack CLC-ODS/H) which is a 15 cm long, 4.6 cm internal diameter stainless steel tube packed with totally porous silica spheres (5 µm diameter, 100A° pore diameter), whose surface was modified with octadecyl group and fitted with 2 µm inlet and outlet fitters was used.

Mobile phase-used was methanol: phosphate buffer of pH 3 (3:5) with a flow rate of 1 ml/min. Pump pressure was maintained at 260 kgf/cm^2 and the column temperature was RT (37°), UV detection was carried out at 240 nm with a detector sensitivity of 0.02 and attenuation of 0 the chart speed used was 2 mm/min.

Bioavailability studies were carried out in human volunteers of same age, sex and weight in a 3x3 randomised cross-over study with three products:conventional or control, HPMC K4M matrix tablets and HPMC K4M layered tablets of paracetamol.

The study was carried out in diurnally active, normal, healthy male volunteers with their weight ranging between 50-56 kg, height between 157-176 cm and age of 25 y. One gram tablets containing 700 mg of paracetamol were administered along with a glass of water after 10-12 h fasting to 12 volunteers. No food and drinks were allowed to be taken by the subjects for 3 h after drug administration. The study was performed in 3x3 randomised cross-over study, allowing a washout period of one week between each treatment. Blood samples (2 ml) were collected at intervals of 0, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 7.0, 9.0, 14.0 and 24 h following drug adminis-

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TABLE 1 - PHARMACOKINETIC DATA

Parameter	Product-A			Product-B			Product-C		
	Mean	S.D	SEM	Mean	S.D	SEM	Mean	S.D	SEM
Cmax (ug/ml)	11.99	0.426	0.26	10.65	0.48	3.58	10.63	0.89	1.95
Tmax (h)	2	0.816	0.47	5.33	0.47	0.27	1	0	0
Ka(h^{-1})	2.81	1.3	0.75	0.86	0.07	0.04	4.61	0	0.29
$T_{1/2}$ (h)	2	0.88	0.5	7.98	3.69	2.13	3.07	0.5	25.87
Cls/f (ml/h/kg)	199.99	44.44	25.66	98.82	29.39	16.97	202.82	44.82	83.58
Vss (1/kg)	864.45	47.8	27.59	1139.26	106.45	61.46	1050.16	144.76	7.6
AUC (0-24) (ug-h/ml)	65.9	7.47	4.3	119.7	17.13	9.89	69.62	13.19	7.6
AUC (0-∞) (ug-h/ml)	68.83	9.54	5.5	147.8	40.86	23.59	70.19	13.16	6.55
AUMC (0-24) (ug-h/ml)	294.05	578.08	45.08	1141.76	282.18	162.92	379.51	95.64	0.3
MRT (h)	4.89	1.09	0.63	14.01	4.63	2.67	5.48	0.51	1.26

Product-A: Control tablet of Parace Product B : Paracetamol+HPMC K4M matrix and Product-C: Paracetamol+HPMC layered

TABLE 2 - DATA OF ANALYSIS OF VARIANCE (ANOVA) AND T-TEST

Analysis of variance (ANOVA)			t-test		
Parameter	Probability	F-value	Parameter	Products	Which are significant
Cmax	0.124	3.01	Tmax	A & B	significant at P£0.05
B & C					
Tmax	0.0005	3.75	AUC (0-24)	A & B	significant at P£0.05
B & C					
T 1/2	0.0086	3.78	AUC (0-∞)	B & A	significant at P£0.05
				B & C	
Cls	0.072	4.18	MRT	B & A	significant at P£0.05
				B & C	
Vss	0.1	3.41			
AUC (0-24)	0.001	10.29			
AUC (0-∞)	0.03	6.33			
MRT	0.002	6.8			

Product-A: Control tablet of paracetamol, Product-B: Paracetamol+HPMC K4M matrix and Product-C : Paracetamol+HPMC K4M layered

tration. The samples thus collected were centrifuged to obtain the serum. The samples were stored in frozen condition until assayed.

Paracetamol in the biological samples was estimated by a method of Uges et al.[5] To 0.2 ml of serum in a stoppered tube 0.1 ml of salicylamide (internal standard)

solution containing 0.5 µg of the substance was added and mixed. To this 4 ml of diethylether was added and tubes were vortexed about 10 min. The ether layer was separated (using a pasteur pipette) after centrifugation and evaporated to dryness under vacuum. The residue was dissolved in 100 µl of methanol and 15 µl was injected into the column.

In a pharmacokinetic study it is customary to fit the data into a compartment model and then obtain various pharmacokinetic parameters by independent pharmacokinetic approach (i.e., non compartmental approach). The various pharmacokinetic parameters like absorption rate constant (Ka), mean residence time (MRT) biological half life (T1/2), overall elimination rate constant (Ke), area under the concentration-time curve (AUC), area under the first moment curve (AUMC), apparent volume of distribution at steady state (Vss) and systemic clearance for fraction of dose absorbed (Cls/f) for paracetamol were obtained in each subject from serum concentration versus time data on the IBM compatible personnel computer. The data treated statistically by comparing the means of various pharmacokinetic parameters obtained in different subjects following the three treatments were compared by means of Analysis of variance (ANOVA) to reveal any variations in them and also grouped pharmacokinetic values were compared using the 't-test'. A difference was considered significant when the probability of chance explaining the results was reduced to 5%.

The study was performed with control (A), matrix tablets (B) and layered tablets (C) of paracetamol. The pharmacokinetic parameters maximum serum concentration (Cmax), time to attain maximum serum concentration (Tmax), absorption rate constant (Ka), clearance (Cls/f), steady state volume of distribution (Vss), area under the curve upto 24 hrs [AUC (0-24)], area under the curve upto infinite time [AUC (0-∞)], area under the first moment curve (AUMC) and mean residence time (MRT) were calculated by non-compartmental fitting of the data using model independent pharmacokinetic parameter method (RAMKIN). The values were shown in table-1. The mean values were taken for the statistical treatment. The bioavailability profiles for the products A, B and C based on the mean serum levels was shown in figure-1. From this figure it can be observed that the product-B is significantly different from product-A and C with respect to Cmax, AUC and other pharmacokinetic parameters.

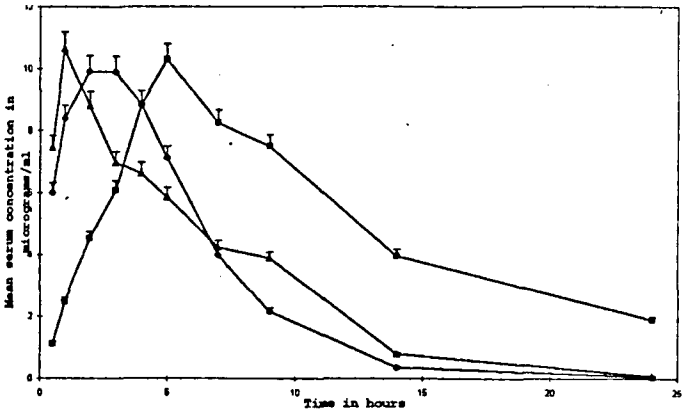

Fig. 1 : Mean serum levels of paracetamol
(-♦-) Product -A (-□-) Product - B - (-▲-) Product - C

To find out the statistical significance of the results Statpal computer programming was used. The statistical data based on ANOVA for the different products was shown in table-2. From this table it can be seen that pharmacokinetic parameters Tmax, AUC (0-24), AUC (0-∞) and MRT was significantly different at P≤0.05. To find out which of the products were significantly different from one another, grouped t-test (table-2) was performed using the same computer programme. The data revealed that product-B was significantly different form product-A and C with respect to Tmax, AUC(0-24), AUC(0-∞) and MRT. The results obtained from the bioavailability study show that the product-A and C were similar in their bioavailability profile and at the same time significantly different from product-B. Product-B was tablet with HPMC K4M matrix type with a drug and polymer ratio of 2:1. The polymer HPMC K4M was a swellable system and forms a coating over the drug particles thereby delaying the release of drug. The drug was release slowly into the gastro intestinal fluids through the process of diffusion and hence a considerable shift in Tmax was observed. Product-C was also containing HPMC K4M as a layer. The polymer layer was present only on one surface which is meant for bioadhesive attachment. The other surface of the tablet being free of polymer, releases the drug in a normal way and hence its bioavailability profile resembles that of control tablet-A. The terminal phase of the bioavailability profile of product-B from figure-1 indicates the controlled drug delivery from the product. The therapeutic concentration range in blood for the antipyretic and analgesic activity also enhanced with the product-B. The objective of achieving a controlled delivery with bioadhesive tablet system was partially achieved with the formulation of product-B. Paracetamol is a sparingly

water soluble drug. The drug is released from matrix network by diffusion slowly. Since the matrix tablet is bioadhesive in nature the drug is released from the tablet slowly and made available for absorption. As the drug is released in a gradually in controlled manner MRT has increased considerably.

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Physico-chemical Composition of Two Medicinal Plant Seed Oils

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The seeds of two medicinal plants, Awala and Bhendi Gulab were extracted with n-hexane to yield the oils in 15.8 and 17.4%. The seed oils were analysed for characteristics such as specific gravity, refractive index, colour, acid value, iodine value and saponification value. The fatty acid composition of these seed oils, as determined by GLC, showed the major fatty acids to be palmitic, oleic and linoleic acids.

Awala (Phyllanthus emblica, Fam. Euphorbiaceae) fruits are a rich source of Vitamin C[1]. It is useful in treatment of pulmonary tuberculosis. It is also used to a great extent in preparation of ayurvedic and household medicines. Dried fruits are also useful in diarrhoea. Bhendi Gulab (Thespesia populona Fam. Malvaceae) is also known as paras pipel[2]. The bark, leaves, flowers and fruits are useful in cutaneous affections such as scabies, ringworm and, eczema. This piece of work reports on, the physical and chemical characteristics of these seed oils alongwith the fatty acid composition by Gas liquid Chromatography (GLC).

The seeds were collected from local cultivators and were decorticated, powdered and extracted with n-hexane. The seeds were analysed for oil content and moisture content by ISI methods[3]. The seed oils, after filteration and desolventisation, were analysed for colour, specific gravity, refractive index acid value, iodine value and saponification value by standard ISI methods[4].

The oils were converted to their respective fatty acid methyl esters (FAME) by Kulkarni *et al* method[5]. The FAME were analysed by GLC unit having a flame ionizataion detector (FID) at 280°, on a 15% EGSS-X column packed on chromosorb-W (40-60 mesh). The chart speed was 60 cm/min. The temperatures were 300° and 200° at the injection port and column respectively. Nitrogen was used as a carrier gas having a flow rate of 30 ml/min. The air flow was maintained at 300 ml/min. The sample was applied in 1 uL quantity. The fatty acids were identified by comparing their RRT values with those of standards (Analabs, USA) by the method of Bhakare et al[6]. The quantification was done by triangulation method of Khotpal et al[7].

The physical and chemical characteristics of the seed oils (Table 1) show that Awala seeds has a slightly lower oil content than Bhendi Gulab seeds (15.8 and 17.4%). The seed oils had differing iodine values (132.8 and 89.4).

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