RESEARCH PAPER

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Formulation and Evaluation of Controlled Release Aspirin Tablets

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Aspirin is known to be effective in primary and secondary prevention of myocardial infarction. For this purpose aspirin release should be such that it prevents platelet thromboxane (TXA_2) generation without interfering with vascular prostacyclin (PGI_2) production. Hence controlled release tablets were prepared to meet the requirements. Both *in vitro* dissolution and *in vivo* urinary excretion studies were done to ensure the effectiveness of the formulations.The study proves the usefulness of Carbopol resins for formulating aspirin tablets for minimum risk and maximum therapeutic benefit to the patient.

Aspirin has always occupied a prominent place in health care as an analgesic and anti-pyretic in treatment regimens because of its high efficacy, low cost, its generally low toxicity and its availability to the patient as a non-prescription drug. It is now known to be effective in reducing myocardial infarction, stroke and mortality in high-risk patients because it prevents platelet aggregation[1].

The objective for undertaking this work was to prepare a controlled release formulation of low dose aspirin for prevention of myocardial infarction. A controlled release formulation results in selective inhibition of platelet thromboxane A_2 (TXA_2) generation in the portal circulation without interfering with vascular prostacyclin PGI_2. It also helps to prevent gastric irritation and/or bleeding[2,4]. Both *in vitro* and *in vivo* release evaluation were done to ensure the effectiveness of the formulation.

MATERIALS AND METHODS

The materials used in this study were aspirin from Alta Laboratories, Carbopol 971P from B.F.Goodrich[5], polyvinyl acetate phthalate (PVAP) from Colorcon India Ltd. and talc from S.D. Fine Chemicals.

Aspirin and Carbopol 971P were sieved through 80# mesh and talc through 120# mesh. They were properly mixed and tablets were prepared by direct compression using various drug–polymer ratios. Composition of various batches are mentioned in Table 1. Coating was done with an enteric polymer polyvinyl acetate phthalate (PVAP) to obtain the desirable release profile for 12 h.

TABLE 1: COMPOSITION OF VARIOUS BATCHES

Composition	C1	C2	C3
Aspirin	89 %	84%	84 %
Carbopol 971P	10 %	15%	15%
Talc	1 %	1 %	1 %
PVAP (% rise in wt of tablet)	—	—	2 %

In vitro release evaluation:

In vitro release testing of these tablets was performed employing USPXXIII dissolution test apparatus I using 900 ml of 0.1 N HCl (pH 1.2) for 2 h followed sequentially by 900 ml phosphate buffer (pH 6.8) for 8 h as the dissolution media. The aliquotes were withdrawn at half an hour intervals till 2 h and then hourly till next 8 h. The aliquotes were analyzed for aspirin content spectrophotometrically[6].

In vivo release evaluation:

In vivo release evaluation was done using one of the

* For correspondence

above formulation (C3) and compared with the marketed formulation (only enteric coated) by conducting urinary excretion studies. [The formulation C3 shows the desired release profile of 5-10% of aspirin in 0.1 N HCl and about 85% release in phosphate buffer after 10 h thus showing a 12 h release pattern]. Six healthy male and female subjects weighing between 50-60 kg with no history of gastrointestinal, liver or kidney disease were selected for this study. Each volunteer was instructed to abstain from all medication for one week before each administration and also during the day of experiment. After an overnight fast, each subject was instructed to void his/her bladder and 0 h urine sample was taken as control. The marketed formulation was administered orally with 100 ml of water. No food or liquids other than water were permitted for 4 h following ingestion of the dose. Drug excretion was monitored as a function of time. Urine samples were collected after ½ h, 1 h, and then hourly for next 3 h, every two hourly for the next 8 h and finally cumulative urine was collected for the next 12 h. Each subject was instructed to drink 100 ml of water after each urine collection for the first 3 h and a simple standard meal was served after the 4 h sampling. The same procedure was applied to the formulated controlled release tablet. The studies were conducted in a cross-over design fashion.

Urine was assayed for the total salicylic acid content, after acid hydrolysis, using Levy's modified method[3]. In a sealed glass ampoule, 3 ml of urine sample and 3 ml of concentrated hydrochloric acid were incubated at 100° for 16 h to hydrolyze completely all metabolites to salicylic acid. After cooling, 2 ml of the above and 0.5 ml of 6 N HCl were extracted with 30 ml of carbon tetrachloride in a glass-stoppered bottle. Centrifugation was done for 5 min and the aqueous phase aspirated out. The organic solvent phase was removed and assayed colorimetrically after complexing with ferric nitrate in the acidic medium. The total salicylate assayed includes aspirin, salicylic acid and all other metabolites. To calculate the concentration of total salicylate in urine specimens, a calibration curve was constructed using a range of known concentrations of sodium salicylate in distilled water and with the same incubation and extraction procedures.

The pharmacokinetic parameters were determined and the *in vitro-in vivo* correlation was found out. The elimination rate constant was determined by the log ARE (amount remaining to be excreted) method. Statistical evaluation of data was done at 95 % confidence interval.

RESULTS AND DISCUSSION

Reproducible results were obtained throughout the study. From fig.1, it was seen that tablets with 15% Carbopol 971P and 2% enteric coating (C3) gave the desired 12-hour release pattern. It could be calculated that 1 unit of absorbance corresponds to 0.93 mg/ml of

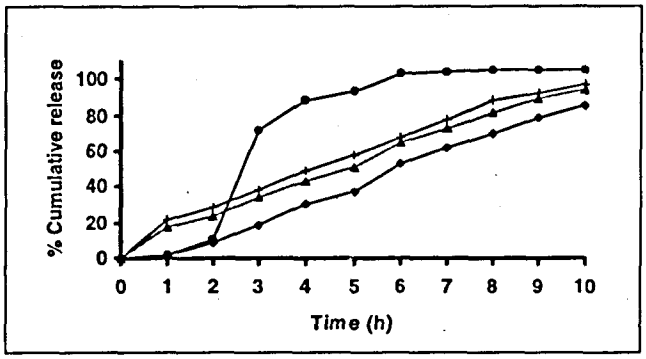

Fig. 1: *In vitro* release of aspirin from various formulations Aspirin release in per cent from the Marketed product (-●-), C1 (-+-), C3 (-◆-) and C2 (-▲-), respectively

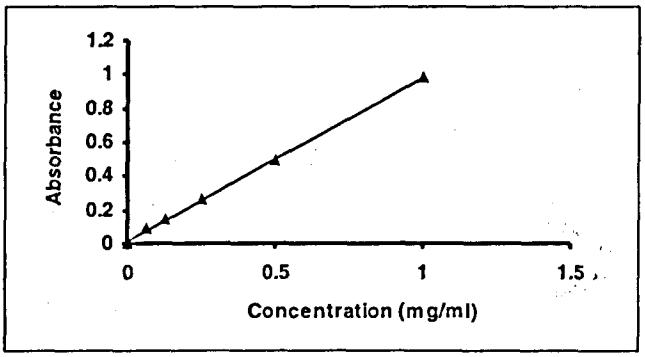

Fig. 2: Calibration curve
The linearity equation is Y=0.9894x + 0.0115 and the correlation coefficient is R^2 = 0.9993.

sodium salicylate and 1.04 mg/ml of aspirin. Results of the *in vivo* testing showed that these tablets had a uniform excretion rate compared to the marketed formulation (fig. 4). The *in vitro-in vivo* correlation was found to be good and hence *in vitro* release can be a measure for testing future batches. This study thus proves the usefulness of Carbopol resins for formulating aspirin tablets with minimum risk in addition to an effective therapy for the patient.

The two products for which excretion studies were done were found to be significantly different from each

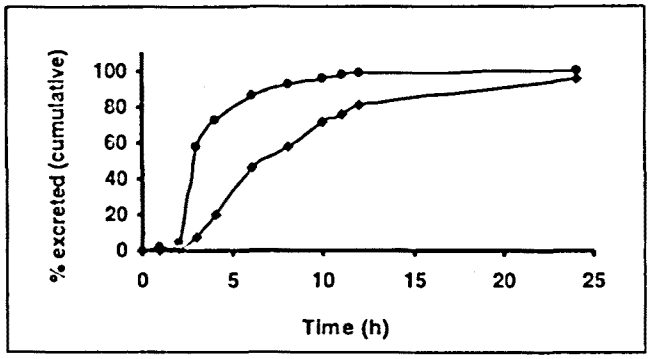

Fig. 3: Cumulative excretion of aspirin
Per cent cumulative excretion of aspirin from Marketed product (-o-) and C3 (-♦-) have been shown.

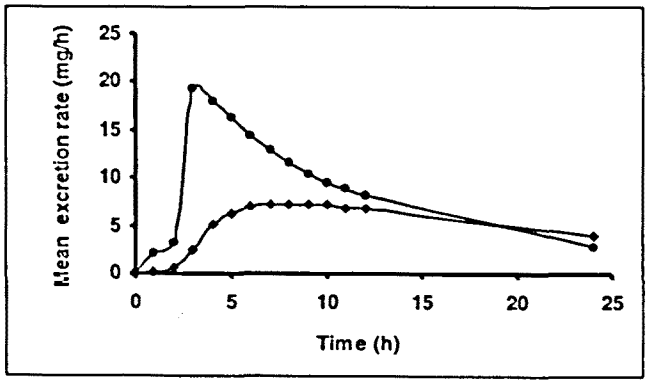

Fig. 4: Urinary excretion rate
Mean urinary excretion rate of Marketed product (-o-) and C3 (-♦-).

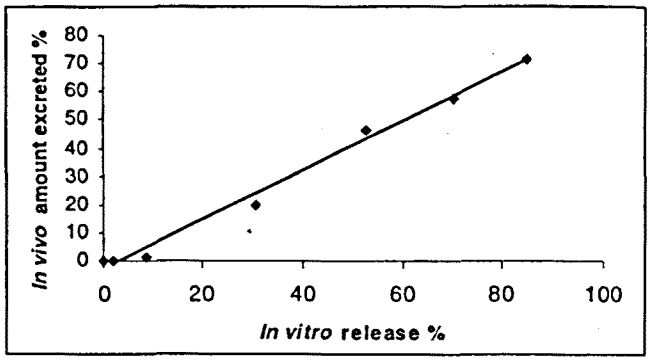

Fig. 5: *In vitro – In vivo* correlation
The equation of the line is Y=0.873x– 2.9048. The correlation coefficient $R^2 = 0.9919$. (-♦-) stands for the % cumulative *in vitro* and *in vivo* release of formulation C3.

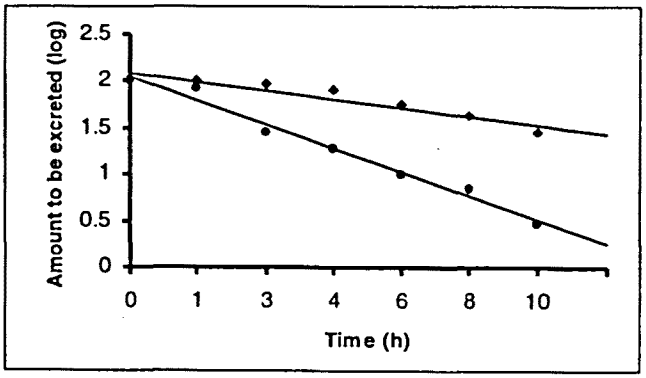

Fig. 6: Determination of elimination constant.
(-O-) and (-♦-) stands for the amount to be excreted (log) of Marketed product and C3 respectively

TABLE 2: RESULTS OF *IN VIVO* TESTING

Pharmacokinetic parameters	Marketed product	Controlled release tablet (C3)	T -value	S / N.S*
C max (mg/h)	19.3	7.17	16.075	S
Tmax (h)	3	8	4.87	S
Kel (elimination constant)	0.35	0.129	6.79	S
$T_{1/2}$ (elimination half life h)	1.98	5.36	5.5575	S

*S signifies that the t-value is significant and N.S signifies that the t-value is insignificant at the chosen interval.

other when analysis of variance was performed. The pharmacokinetic parameters of the two products were also found to be significantly different by the t-test. (Results as in Table 2). However there was no significant variation observed in the responses of the volunteers.

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I, Dr. Rao V.S.V. Vadlamudi hereby declare that the particulars gives above are true to the bast of my knowledge and belief.

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