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SIMULATION OF PHYSIOLOGICAL pH - TIME PROFILE IN *IN VITRO* DISSOLUTION STUDY : RELATIONSHIP BETWEEN DISSOLUTION RATE AND BIOAVAILABILITY OF CONTROLLED RELEASE DOSAGE FORM

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ABSTRACT

An *in vitro* batch dissolution method, simulating the *in vivo* pH-time profile was developed, using the USP XX dissolution apparatus. Significant correlation between *in vitro* dissolution data and bioavailability of the drug from the controlled release dosage form was obtained.

INTRODUCTION

For a prolonged release dosage form, it is obligatory to demonstrate the prolonged release characteristics of the active ingredients through both *in vitro* and *in vivo* methods. Therefore, it is important to develop *in vitro* tests which could be utilized to predict the bioavailability of the active ingredients from the prolonged release dosage forms and which could also be relied upon to assure batch-to-batch performance. Considerable interest has been focussed on the development of a reliable *in vitro* dissolution test method which would be capable to exactly mimicking the *in vivo* dissolution rate controlled absorption of drugs from the solid dosage forms.

It is expected that the pH of gastrointestinal tract and the degree of ionization of the drug molecule would have a profound effect on the absorption of different drugs, although ionized molecules have shown significant absorption, albeit at a slower rate[1]. Commonly employed methods for *in vitro* dissolution study of the oral dosage forms involve the on-column or the batch exposure of the dosage forms to the simulated gastric and intestinal fluids[2], both of which methods lack to simulate the boundary *in vivo* pH profile, except a few using the continuous flow apparatus, simulating the continuously changing *in vivo* pH profile[3]. Long term dissolution testing of controlled release preparations especially require exact simulation of *in vivo* pH-time profile determined by pH and peristalsis of the gastrointestinal tract.

MATERIALS

The dosage form under test was polyvinyl chloride controlled release granules of sulfadiazine. The mean sieve size of the granules was 24 mesh. The chemicals : Sulfadiazine (May & Baker Limited, Bombay), Hydrochloric acid (E. Merck, Bombay), Sodium carbonate (Sarabhai Merck, Bombay), Sodium hydrogen carbonate (Sarabhai Merck, Bombay) were used without further treatment. All other chemicals were of analytical reagent grade.

METHODS

In vitro Dissolution Study :

The pH profile was achieved using the solutions of hydrochloric acid, sodium carbonate and sodium hydrogen carbonate in double distilled water. Table shows the composition of the solutions. Controlled release granules of sulfadiazine were placed in the USP XX dissolution basket, covered with # 100 mesh nylon screen to prevent granules coming out of the basket. Five hundred ml of the solution 'A' was taken in the dissolution beaker at 37 ± 1°C. The basket with the granules was rotated

TABLE

Composition of Dissolution Fluids

Solution	Composition per litre	pH
A	4.25 ml concentrated hydrochloric acid[a], water[b] to 1 litre	1.35 ± 0.05
B	40.0 gm anhydrous sodium carbonate[c], 50.0 gm anhydrous sodium bicarbonate[c], water[b] to 1 litre	9.30 ± 0.05
C	10.0 gm anhydrous sodium carbonate[c], 20.0 gm anhydrous sodium bicarbonate[c], water[b] to 1 litre	9.25 ± 0.05

a guaranteed reagent - E. Merck, India

b triple distilled water pH 5.5 - 6.0

c guaranteed reagent - Sarabhai Merck, India

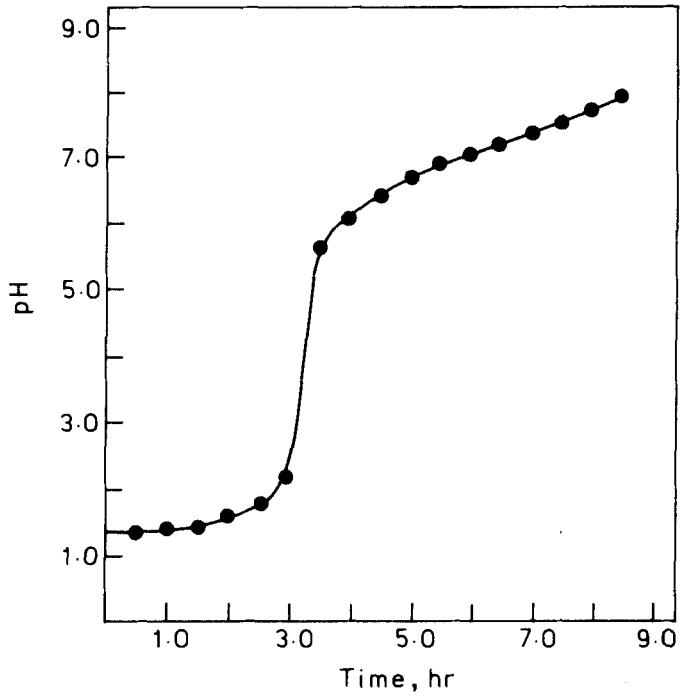

FIGURE 1

pH - time profile for *in vitro* dissolution study

at 100 r.p.m. Five ml of the sample aliquots were withdrawn each time and replenished the same volume with solution 'B' and this was continued till the pH 6.75 was achieved, which had been found to occur after ten withdrawals. Afterwards, the replenishings were performed with solution 'C' and this process was continued. The dissolved drug was assayed spectrophotometrically[4]. The sampling time was chosen to be 30 mins, in conformity with the *in vivo* transit time of the drug through different pH regions of the G.I.T. The pH - time profile thus obtained is shown in Fig.1.

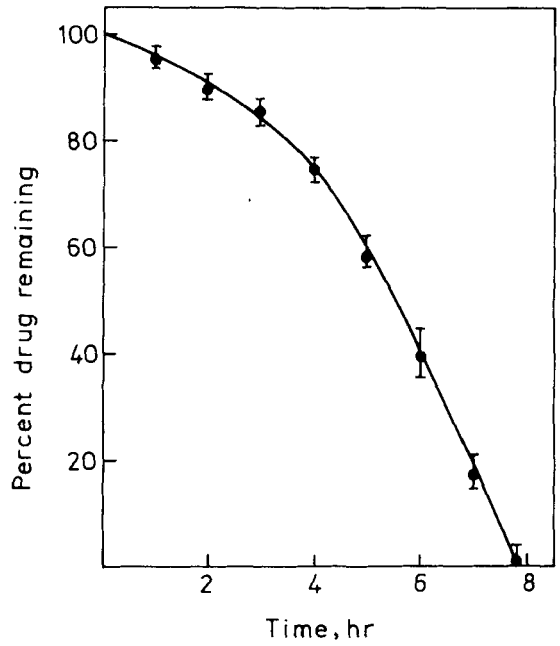

FIGURE 2

In vitro dissolution profile. Each point represents the average and range of triplicate experiments.

In vivo Studies in Rabbits :

Six male rabbits weighing 2.4 - 3.5 kg were fasted overnight for about 22 hours, while water was allowed *ad libitum*. On the following morning a 0 hr sample of blood was obtained from the marginal ear vein, and the sulfadiazine granules in hard gelatin capsule was placed in the rear pharynx of the rabbit with a plastic catheter-rubber balloon device through a hole in a wooden gag holding the mouth open. The capsule was then pushed by generating air pressure using the balloon. No water was given and the food was allowed at 3.5 hours. Blood samples were withdrawn from the marginal ear vein at preselected time intervals after the drug administration. The sera were seperated

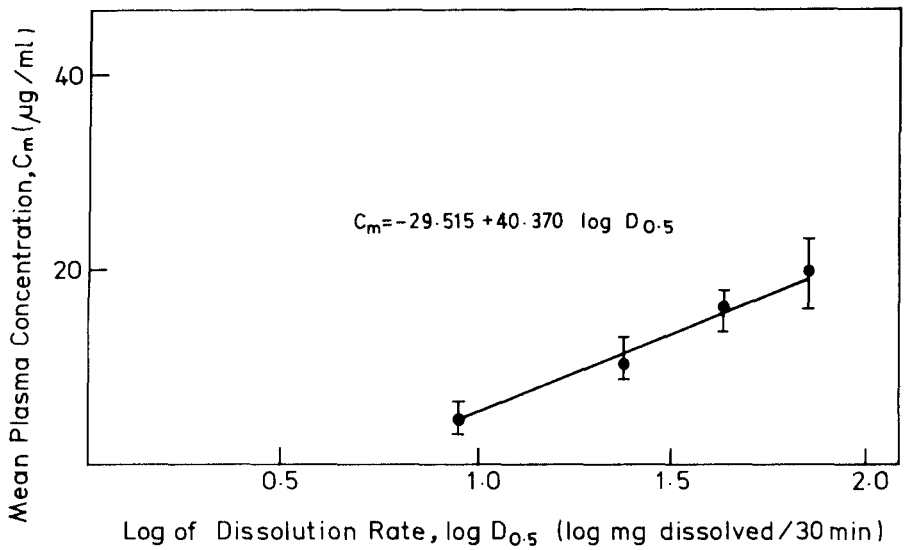

FIGURE 3

Correlation of dissolution rates and mean plasma drug concentrations in fasting rabbits. Each point represents the average ± S.E. in six animals. Correlation coefficient = 0.992 ($p<0.10$)

and the content of drug was assayed spectrophotometrically[4], after precipitation of the plasma proteins by trichloroacetic acid solution in water.

RESULTS AND DISCUSSIONS

The simulated pH - time profile correlated well with the *in vivo* physiological conditions reported earlier[5,6,7]. The dissolution media were prepared with such chemicals as are normal constituents, at the ionic level of the gastrointestinal content. The bioavailability studies on the fasting rabbits were carried out to determine the correlation of the *in vivo* results with the developed *in vitro* dissolution method. To

avoid overdose problem, the half of the minimum active ingredient content of the capsule equivalent to 200 mg/dose were administered to six rabbits. The *in vivo* studies were carried out in a strictly crossover fashion.

The *in vitro* dissolution profile is represented in the Fig.2. The relationship between the mean plasma level, C_m, and the logarithm of sulfadiazine dissolved in 0.5 hr, (log $D_{0.5}$) is shown in Fig.3. Significant correlation was obtained between C_m and log $D_{0.5}$ ($p<0.10$).

The described dissolution testing method not only conforms to the basic requirements of dissolution test but also simulates the *in vivo* pH - time profile which could be utilized in the routine assessment of controlled release dosage forms.

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