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SIMULATION OF THE EFFECTS OF GASTROINTESTINAL TRANSIT RATE ON DRUG AVAILABILITY FROM ASPIRIN SUSPENSIONS USING A MODIFIED DIALYSIS METHOD

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SUMMARY

A dialysis method that allows the effect of viscosity on the gastrointestinal transit rate to be simulated in vitro is described. The method has been applied to a series of aspirin suspensions. Various suspending agents have been used to produce suspension media with a range of viscosities. The results correlated with previously obtained bioavailability parameters and support the suggestion that the effect of viscosity on gastrointestinal transit rate is an important factor in determining the bioavailability of aspirin from such formulations when administered to the rabbit.

INTRODUCTION

Our previous bioavailability studies on aspirin suspensions in rabbits showed that the amount of drug absorbed increased with increase in viscosity of the suspension medium whilst the rate of absorption did not alter significantly over the range of viscosities that was used (Barzegar-Jalali and Richards, 1979b). This enhancement in the amount of drug absorbed was attributed to the reduction in gastric emptying rate that is caused by an increase in viscosity of the stomach contents.

In vitro studies on the release of drugs from suspension formulations have included the use of either a flask-stirrer method (Bates et al., 1969, 1973) or dialysis methods (Muranyi, 1973; Marty and Hersey, 1975; Shah and Sheth, 1976). The latter type of method was shown to be the more sensitive in detecting changes in the rate of release of aspirin from the suspensions that were used in the above-mentioned bioavailability study and a rank order relationship between kinetic parameters that described the release rate of aspirin and the viscosities of the suspension media was established (Barzegar-Jalali and Richards, 1979a).

It is obvious that the results of the above in vivo and in vitro studies on aspirin suspensions cannot be correlated because an increase in viscosity enhances the amount of drug absorbed but reduces its rate of release in vitro. This lack of correlation is likely to occur

whenever traditional in vitro methods are used because, although they may mimic the effects of viscosity on dissolution rates and on the transport rates of solute molecules and undissolved particles in a given medium, they do not mimic its effect on gastric and intestinal residence times. The present investigation describes a modified dialysis method, which allows this latter effect to be taken into account and so provides results that can be correlated with bioavailability parameters derived from the previously obtained in vivo data.

MATERIALS AND METHODS

The materials and methods of preparation of suspensions, each of which contained 4% w/v of aspirin, were as described previously (Barzegar-Jalali and Richards, 1979a).

The apparatus that was used in the determination of the release of aspirin from the suspension formulations is shown diagrammatically in Fig. 1. Water was circulated from a thermostatted bath through the double walls of the glass chamber to maintain a working

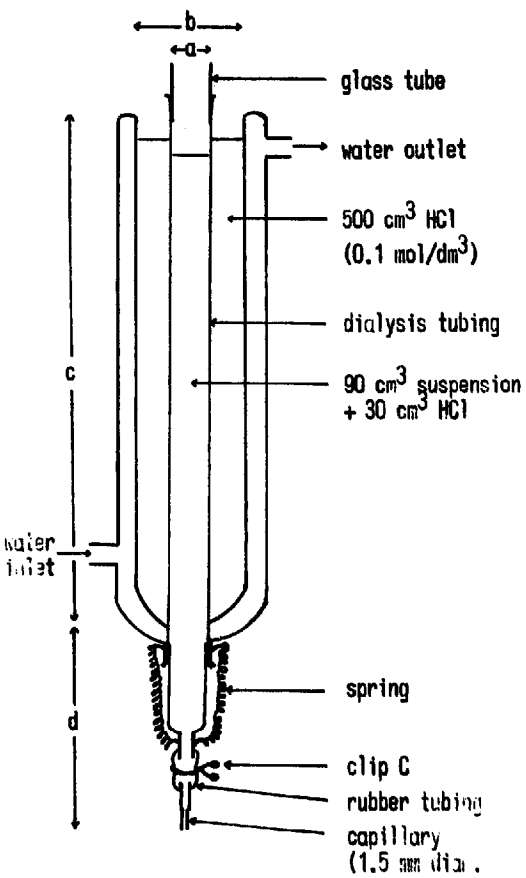

Fig. 1. Apparatus for determination of the release of drugs from suspensions as a function of their emptying rate in vitro; Residual dialysis method. (Dimensions: a = 2.14 cm, b = 5.6 cm, c = 29.5 cm and d = 9.0 cm.)

temperature of 37°C. The lower end of a length of Visking dialysis tubing (inflated diameter 2.14 cm), which had been soaked previously for 12 h in HCl (0.1 mol/dm^3) was clamped between the cone and socket of a Quickfit ground glass jount at the bottom of the apparatus. The tapering end of the tube attached to the cone was attached to a capillary tube (1.5 mm diameter) via a piece of rubber tubing equipped with a clip, C. The upper end of the dialysis tubing was attached to a glass tube, which was fixed to a stand in order that the dialysis chamber could be held erect in the apparatus.

Ninety cm^3 of a suspension, 12 cm^3 HCl (1.0 mol/dm^3) and 18 cm^3 HCl (0.1 mol/dm^3) were mixed gently, after prewarming each component to 37°C, and poured into the dialysis tubing with the clip C closed. The pH of the mixture was 1.2. Five hundred cm^3 of HCl (0.1 mol/dm^3) prewarmed to 37°C was poured into the glass chamber on the outside of the dialysis tubing. The timing of the experiment commenced at this point.

Clip C was opened for 10 s and the volume (V cm^3) of suspension, which was eluted in this period, was measured. This volume is obviously related to the viscosity of the suspension. Since small amounts of liquids appear to empty from the stomach at essentially constant (i.e. zero-order) rates (Wagner, 1971) and this might be the case when a suspension is administered to fasting subjects, an attempt to mimic this effect was made by opening clip C at 10 min intervals and allowing the same volume (V cm^3) of suspension to flow out during each period of opening. The later opening periods will extend beyond 10 s if a suspension is allowed to flow from the apparatus only under the influence of the diminishing hydrostatic pressure. In order to avoid errors arising from excessively long periods of opening the suspension flow was aided, if necessary, during these later periods by the use of a band pump attached to the glass tube, which supported the upper end of the dialysis tubing. The variation in duration of the opening periods was consequently slight in relation to the 10 min interval between consecutive openings. Thus, the average rate of flow (f) of suspension from the apparatus could be equated to V/10 cm^3/min. The maximum number of opening times for the most viscous suspension was 6.

The in vitro residence time (t_{res}), i.e. the time required for 100 cm^3 of each acidified suspension to flow from the apparatus under the conditions of this experiment, was calculated from Eqn. 1

$$t_{res} = \frac{100 - V}{f} \text{ min} \qquad (1)$$

A volume of 100 cm^3 was chosen when applying Eqn. 1 because the capacity of the apparatus below the effective length of the dialysis tube approximated to 20 cm^3, so that the maximum volume of acidified suspension in immediate contact with the dialysing membrane was 100 cm^3.

At the end of the calculated residence time the total amount of drug (A_{total}) that had dialyzed through the Visking tubing was calculated from the salicylate concentration of a sample that was removed from the solution outside the dialysis sac. This concentration was determined by the method of Weintraub and Gibaldi (1970).

The following exponential equations were obeyed under the experimental conditions described above and are presented as indicators of the performance of the apparatus.

$$f = 8.95\, \eta_{app}^{-0.32} \qquad (2)$$

$$t_{res} = 138.04\, f^{-1.73} \quad (3)$$

$$A_{total} = 398.11\, f^{-1.63} \quad (4)$$

where η_{app} is the apparent viscosity of the suspension medium at a shear rate of 100 s^{-1}, pH 1.2 and 37°C (see Barzegar-Jalali and Richards, 1979a). The correlation coefficients of these relationships were not less than 0.9524 at $P < 0.001$.

RESULTS AND DISCUSSION

We refer to the method of following the release of drug from a suspension, as described in this paper, as a residual dialysis method in order to distinguish it from the more traditional dialysis methods, in which material is not usually removed from the dialysis sac other than by the process of dialysis itself.

As can be readily appreciated, the surface area of undissolved particles inside the dialysis sac of this apparatus changes during the residence time, not only because dissolution is occurring but also because some particles are removed from the system at particular times. The following equations, which are similar to those derived by Wagner (1969), can be used to explain the effect of viscosity on the amount of drug released into the solution on the outside of the dialysis membrane in this system, i.e. on A_{total}.

Under sink and non-reactive conditions of dissolution the simplified form of the Noyes–Whitney equation, as expressed by Eqn. 5, may be applied

$$\frac{dW}{dt} = KSC_s \quad (5)$$

where dW/dt is the rate of appearance of solute in solution at time t, S is the surface area of undissolved solid available for dissolution, C_s is the solubility of the compound in the dissolution medium and K is a constant with the dimensions of length/time. It can be shown that K = D/h, where D is the diffusion coefficient of the solute in the dissolution medium and h is thickness of the diffusion layer. If it is assumed that the effective surface area S is proportional to the amount of undissolved drug (M) at time t, then $S = k'M$, where k' is a constant with the dimensions of length^2/mass. Substitution for S in Eqn. 5 yields

$$\frac{dW}{dt} = Kk'C_sM \quad (6)$$

Integration of Eqn. 6 between the limits of t = 0 and $t = t_{res}$ gives

$$W = Kk'C_s \int_0^{t_{res}} M(dt) \quad (7)$$

where W is the cumulative amount of drug dissolved during the residence time and the integral represents the cumulative mass that has been available for dissolution during the

TABLE 1

IN VITRO RELEASE RATE DATA AND BIOAVAILABILITY PARAMETERS FOR 4% w/v SUSPENSIONS OF ASPIRIN IN MEDIA WITH DIFFERENT VISCOSITIES

Formulations	η_{app} (mN s m^{-2})	f (cm^3/min)	t_{res} (min)	A_{total} (mg)	$\int_0^{tres} M(dt)$ (g · min)	k_{loss} (g/min)	k_F (min^{-1})	AUC_0^9 (mg · h/100 cm^3)	PC (mg/100 cm^3)
A	1	7.6	3.2	10.3	1.14	0.230	0.0141	110.74	15.94
D	9	5.0	10.0	38.9	7.52	0.150	0.0079	122.95	18.41
H	23	4.6	11.5	41.1	9.23	0.140	0.0080	141.09	21.53
C	55	2.5	30.0	90.0	33.76	0.075	0.0070	136.16	21.03
E	60	2.4	31.7	101.5	36.11	0.072	0.0068	136.32	21.75
G	89	2.0	40.1	130.0	48.14	0.060	0.0060	148.28	22.00
F	142	1.6	52.6	156.3	66.21	0.048	0.0039	149.42	23.00

The values obtained in the present investigation are the mean results from two experiments. η_{app} and k_F values are taken from Barzegar-Jalali and Richards (1979a); AUC_0^9 and PC values are taken from Barzegar-Jalali and Richards (1979b); formulations: in order to avoid confusion the key letters are the same as those used by Barzegar-Jalali and Richards (1979a); these refer to the following suspension media: A, distilled water; C, 1.5% methylcellulose; D, 1% sodium carboxymethylcellulose; E, 7% w/w PVP; F, 1% xanthan gum; G, 1% Tragacanth Powder B.P. and H, 4% Compound Tragacanth Powder B.P.

same period. In the present circumstances A_{total} can be substituted for W so that

$$A_{total} = Kk'C_s \int_0^{t_{res}} M(dt) \tag{8}$$

It is evident from Eqn. 8 that the viscosity of the dissolution medium will have opposing effects on the value of A_{total} obtained using the present method. Thus, an increase in viscosity will

(a) decrease the value of K and consequently reduce the amount of drug which dissolves in a given time, so that A_{total} decreases, and

(b) decrease the rate of flow of suspension from the apparatus, which reduces the rate at which undissolved solid is removed from the dissolution site, so that t_{res} is extended, $\int_0^{t_{res}} M(dt)$ is increased, and A_{total} rises.

The value of t_{res}, f, A_{total}, $\int_0^{t_{res}} M(dt)$ and the rate of loss of mass from the apparatus k_{loss} are given in Table 1. The last two parameters were derived from the areas under the linear plots of weight of drug remaining in the apparatus versus time and the slopes of these lines, respectively. Such derivations neglect the amount of drug that is in solution. Parameters, derived in previous studies (Barzegar-Jalali and Richards, 1979a, b) and relating to the viscosity of the suspension media, to the rate of release of drug from a traditional dialysis method and to the bioavailability of the drug are also given in Table 1.

It can be concluded from the η_{app} values and the parameters describing the performances of the suspensions in the residual dialysis method, which are given in Table 1, that an increase in viscosity of the suspension medium leads to an increase in the value of A_{total}. Thus, the effect of viscosity described above in (b) appears to predominate over the effect outlined in (a).

The suitability of the residual dialysis method as an in vitro indicator of bioavailability

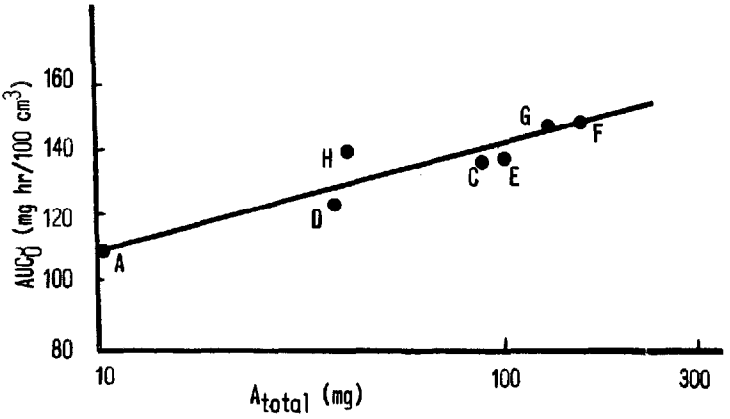

Fig. 2. Plot of mean area under the blood concentration–time curves (AUC_0^9) after administration of aspirin suspensions to rabbits versus the logarithm of the total amount of drug (A_{total}) released during residence times of the same suspensions in the residual dialysis apparatus. $AUC_0^9 = 30.26 \log A_{total} + 81.03$ ($r = 0.8974$, $P < 0.01$). See Table 1 for key to suspension formulations.

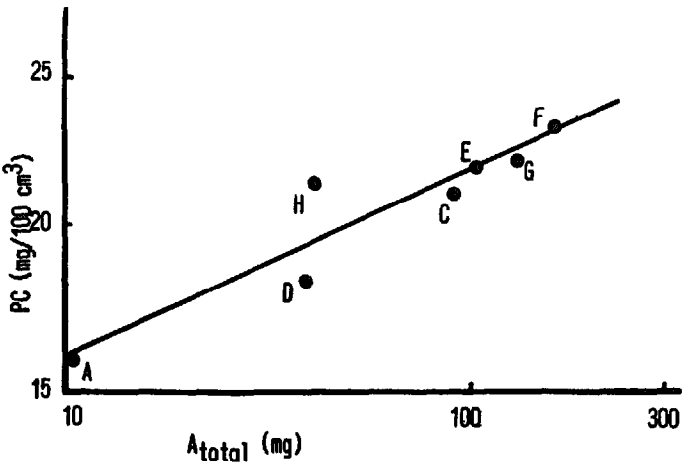

Fig. 3. Plot of mean peak concentration of drug in blood (PC) after administration of aspirin suspensions to rabbits versus the logarithm of the total amount of drug (A_{total}) released during residence times of the same suspensions in the residual dialysis apparatus. PC = 5.64 log A_{total} + 10.50 ($r = 0.9250$, $P < 0.001$). See Table 1 for key to suspension formulations.

for the suspensions used in this investigation is demonstrated by the correlations between the AUC_0^9 and PC values and the log A_{total} values as shown in Figs. 2 and 3. These correlations support the suggestion that gastric emptying rate is an important factor in determining the bioavailability of aspirin in suspension formulations.

The unsuitability of traditional dialysis methods as in vitro indicators of bioavailability when the effects of gastric and/or intestinal residence times are significant has already been mentioned. This point can be illustrated by examining the data in Table 1 for suspensions A and F which possess the lowest and highest viscosities, respectively. Thus, the first order rate constant (k_F) for the release of aspirin from suspension A is 3.61 times greater than the k_F value for suspension F. However, the A_{total} values obtained from the residual dialysis method for suspensions A and F are in the ratio of 1 : 15 : 24. Only the latter ratio is in the correct ranking order with respect to the bioavailability parameters AUC_0^9 and PC of suspensions A and F.

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