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# THE EFFECT OF SUSPENDING AGENTS ON THE RELEASE OF ASPIRIN FROM AQUEOUS SUSPENSIONS IN VITRO

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## SUMMARY

The effect of various suspending agents on the release of aspirin from aqueous suspensions in vitro was studied using a flask-stirrer method and a dialysis method. The latter proved to be more sensitive in detecting changes in the rate of release. The existence of a rank order relationship between kinetic parameters that described the release rate of aspirin and the viscosities of the suspension media was demonstrated.

## INTRODUCTION

The results of in vivo studies (Seager, 1968; Riegelman, 1969; Berlin et al., 1972) suggest that the bioavailability of drugs from suspension dosage forms may be affected by the nature and concentration of added suspending agents. In vitro studies on the release of drugs from suspension formulations have included methods involving the use of either a flask and stirrer dissolution rate apparatus (Bates et al., 1969, 1973) or dialysing membranes (Muranyi, 1973; Marty and Hersey, 1975; Shah and Sheth, 1976). This investigation was concerned with a comparison of the abilities of two such in vitro methods to discriminate between different suspension formulations of aspirin. The effects of various suspending agents on the kinetics of drug release in the more sensitive dialysis method were also studied.

## MATERIALS AND METHODS

Methylcellulose (low substitution) (B.D.H.), polyvinylpyrrolidone (M.W. 700,000) (B.D.H.), Tragacanth Powder B.P. (Butlers), sodium alginate (Manucol DM) (Alginate Industries), Compound Tragacanth Powder B.P. (Onward Pharmaceuticals), sodium carboxylethylcellulose (Edifas 50) (I.C.I.) and xanthan gum (I.C.I.) were used as supplied. Aspirin Powder B.P. (Thornton and Ross) was sieved and the 60/100 portion

was used to prepare the suspensions which contained 4% w/v of the drug.

In addition to distilled water (A) the following dispersions were used as the suspension media: 1.15% w/v sodium alginate (B); 1.5% w/v methylcellulose (C); 1.0% w/v sodium carboxymethylcellulose (D); 7.0% w/w polyvinylpyrrolidone (E); 1.0% w/v xanthan gum (F); 1.0% w/v Tragacanth Powder B.P. (G); and 4.0% w/v Compound Tragacanth B.P. (H). The methods recommended in the technical brochures (i.e. high-speed mixing) were used in the preparation of dispersions B and D. The method given in Martindale (1972) was used for C and those in the B.P.C. (1973) were used for G and H. Dispersions E and F were prepared in the manner described by Kassem and Mattha (1970).

The flow curve of each dispersion was determined at 37°C and at various pH values including the gastric pH (i.e. 1.2) over a shear rate range of 16–1300 $s^{-1}$ using a Haake Rotovisko viscometer fitted with a thermostatted concentric cylinder attachment.

Aspirin powder was dispersed in 24-h aged media and the resultant suspensions were stored overnight in a cool place (about 10°C). On the following morning the suspensions were allowed to reach room temperature and shaken vigorously before use.

*Release rate studies*

*(a) Flask-stirrer method*

This was based on the apparatus described by Poole (1969). A 2 $dm^3$ round-bottomed flask containing 1490 $cm^3$ of HCl (0.1 mol/$dm^3$) was placed in a water-bath maintained at 37 ± 0.1°C. A two-bladed glass stirrer, 8.1 cm in diameter, was positioned 4 cm from the bottom of the flask and connected to an electric motor (Citenco Ltd.), which rotated the stirrer in a counter-clockwise direction. Two different stirring speeds, i.e. 20 and 50 rpm, were used in separate experiments on each suspension. Five $cm^3$ of a suspension were pipetted into the flask and the pipette was washed out with 5 $cm^3$ of HCl (0.1 mol/$dm^3$). Use of these volumes allowed sink conditions to be maintained because the solubility of aspirin at pH 1.1 and 37°C is approximately 500 mg in 100 $cm^3$ (Mitchell and Broadhead, 1967). A 3 $cm^3$ sample was taken from the flask at different time intervals and each sample was replaced immediately by 3 $cm^3$ of HCl. The samples were filtered through a Millipore filter (0.45 $\mu$m pore diameter) and the salicylate content of each was determined by the method of Weintraub and Gibaldi (1970).

*(b) Dialysis method*

One end of a 25 cm length of Visking dialysis tubing having an inflated diameter of 2.14 cm was tied off after the tubing had been soaked in HCl (0.1 mol/$dm^3$) for at least 12 h. Fifty glass beads with an approximate diameter of 3 mm were placed into the tube. These beads regulated the oscillations of the dialysis sac during the experiment and markedly improved the reproducibility of the results. Five $cm^3$ of suspensions plus 5 $cm^3$ of HCl (0.1 mol/$dm^3$) were poured into the sac and that part of the sac above the level of its contents was flattened between the fingers. The sac was then suspended through the central neck of a 2 $dm^3$ two-necked round-bottomed flask, which contained 1490 $cm^3$ of HCl (0.1 mol/$dm^3$), and secured by a glass stopper in such a way that the surface of the contents of the sac was 1 cm below the surface of the dissolution medium. A thermometer and a glass tube connected to a flexible plastic tube were inserted through a rubber

stopper in the side neck of the flask and into the dissolution medium. The plastic tubing facilitated sampling whilst the flask was being shaken. The whole assembly was clamped in a shaking water-bath maintained at 37°C and adjusted to provide an oscillation frequency of 100 cycles/min. At this frequency not only was the dissolution medium well agitated but also the sac was oscillated in a constant manner, thus ensuring good mixing on either side of the membrane. Sampling and salicylate determinations were carried out as described in the previous method.

*Complexation studies*

A solution containing 40 mg aspirin in 24 $cm^3$ of HCl (0.1 $mol/dm^3$) was mixed with 1 $cm^3$ of the aqueous dispersion of suspending agent in a dialysis sac. The ratio of drug/suspending agent was the same as in the suspensions. The sac was suspended in a flask containing 800 $cm^3$ of HCl (0.1 $mol/dm^3$) at 37°C for 8 days with occasional shaking. The concentration of salicylate in the external solution was determined at the end of this time.

## RESULTS AND DISCUSSION

Although low speeds of agitation were used the flask-stirrer method was not sensitive enough to differentiate between the different suspensions of aspirin. For example, the dissolution curves obtained using a stirring rate of 50 rpm showed that 6.5 and 7.5 min respectively were required for 50% of the aspirin to pass into solution from formulation D, which had a low viscosity, and from formulation F, which had a high viscosity. At the lower stirring rate of 20 rpm the $t_{50\%}$ values still showed little difference (6.5 and 8.5 min, respectively).

The half-lives ($t_{1/2}$) calculated from the first order rate constant for the release of

TABLE 1

APPARENT RELEASE RATE PARAMETERS AND VISCOSITIES OF VARIOUS SUSPENSIONS OF ASPIRIN

| Formulation | $k_F$ [a] ($min^{-1}$) | $t_{1/2}$ (min) | $\eta_{app}$ [b] ($mN\ s\ m^{-2}$) |
|---|---|---|---|
| B | 0.0032 | 217 | [c] |
| F | 0.0039 | 178 | 142 |
| G | 0.0060 | 116 | 89 |
| E | 0.0068 | 102 | 60 |
| C | 0.0070 | 99 | 55 |
| D | 0.0079 | 88 | 9 |
| H | 0.0080 | 87 | 23 |
| A | 0.0141 | 49 | 1 |

[a] Apparent first order rate constant; each value is the mean from 3 experiments.
[b] Apparent viscosity of the suspension medium at pH = 1.2, temp. = 37°C and shear rate = 100 $s^{-1}$.
[c] $\eta_{app}$ was not calculated – see text for reason.

aspirin from the various suspensions in the dialysis apparatus are given in Table 1. They indicate that this method is much more sensitive as a means of following the in vitro release of drugs from suspension formulations.

Although dissolution of aspirin may be impeded in both methods by the presence of a suspending agent the difference in the discriminatory abilities of the two methods is not surprising. In the dialysis method dissolution must first occur in a small volume of liquid and the dissolved drug must then be transported through a membrane, whereas in the flask-stirrer method dispersal of the suspension occurs and subsequent dissolution of the aspirin can take place in a large volume of dissolution medium. Some of the advantages and disadvantages of dialysis methods in dissolution rate measurements have been discussed by Swarbrick (1970) and Shah and Sheth (1976) and these authors have pointed out that attention should be paid to the area of the dialysing membrane. In the present work the ratio of this area to the volume of liquid inside the sac is 2.69. In the methods used by Barzilay and Hersey (1968) and Shah and Sheth (1976) the ratios were 1.5 and 0.54, respectively. An additional advantage of the present dialysis method in the testing of suspensions arises from the fact that doses of such formulations are much less cohesive than tablets and capsules. Consequently, the addition of suspensions to a large volume of agitated medium leads to the fairly rapid dilution of the suspension ingredients. Thus, the effects of a suspending agent on the subsequent dissolution of a drug are likely to be much reduced when compared with its effects in the in vivo situation, particularly if the suspension is administered to fasting subjects. In the present method the volume of liquid inside the dialysis sac is only 10 $cm^3$ whereas in Shah and Sheth's apparatus it is 500 $cm^3$.

The rate constant (k) for the dialysis of solutions containing no interacting species can be calculated from Eqn. 1,

$$\log[V_0A_T - (V_0 + V_i)A_0] = -\left[\frac{V_0 + V_i}{2.303V_0V_i}\right]kt + \log(V_0A_T) \qquad (1)$$

where $V_i$ and $V_0$ are the volumes of liquid inside and outside the dialysis sac, respectively, $A_0$ is the amount of drug that has dialyzed into the outside medium in time t and $A_T$ is the total amount of drug in the system. This equation was derived by Davis et al. (1971) and plots of $\log[V_0A_T-(V_0 + V_i)A_0]$ versus t for the data that they obtained from their studies on the dialysis of solutions of ephedrine and phenobarbitone were linear thus indicating the appropriateness of their model.

In the case of drug suspensions the amount of drug in solution at zero time is not known. However, Shah and Sheth (1976) used the total amount of dissolved and undissolved drug in the system to represent $A_T$ and their data obtained from the dialysis of nitrofurantoin suspensions gave linear graphs when plotted in the above manner. These workers pointed out that in such circumstances k will represent an apparent dialytic rate constant. They calculated the values of k from the slopes of such plots using Eqn. 2.

$$k = \frac{-(\text{slope})2.303V_0V_i}{V_0 + V_i} \qquad (2)$$

However, Shah and Sheth accorded the dimensions of a first order rate constant (i.e. time$^{-1}$) to their reported values of k but analysis of Eqn. 1 or Eqn. 2 shows that the dimensions are, in fact, volume/time. Equation 1 may be rewritten as Eqn. 3 provided that $V_0$ and $V_i$ remain constant

$$\log[V_0A_T - (V_0 + V_i)A_0] = \frac{-k_Ft}{2.303} + \log(V_0A_T) \tag{3}$$

where $k_F$ is a first order rate constant for the release of drug into the liquid on the outside of the dialysis sac. This constant can be calculated from the slope of the plots mentioned previously in connection with Eqn. 1 and is related to k by Eqn. 4

$$k_F = \left[\frac{V_0 + V_i}{V_0V_i}\right]k \tag{4}$$

The data obtained for all the systems involved in this study gave linear graphs when plotted in accordance with Eqn. 1 (or Eqn. 3). Representative graphs for formulations A and F, which possessed the lowest and highest viscosities, respectively, are shown in Fig. 1. The values of the apparent first order rate constants ($k_F$) are given in Table 1 together with the corresponding half-lives ($t_{1/2}$), which were calculated from Eqn. 5

$$t_{1/2} = \frac{0.693}{k_F} \tag{5}$$

Duncan's multiple range test (Duncan, 1955) was used to determine the statistical significance of the differences betweeen the mean values of $k_F$ that are given in Table 1. The results can be summarized as follows

B F G E C D H A

where any two formulations not underlined by the same line are significantly different

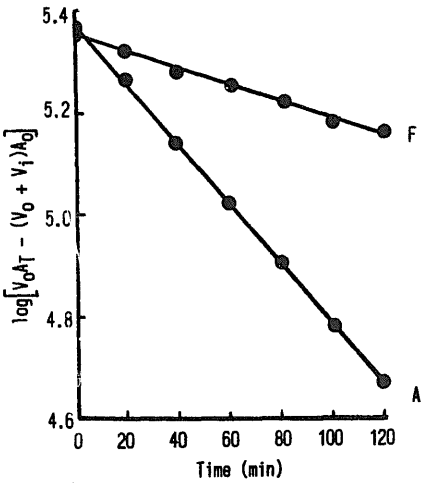


Fig. 1. Plots of the dialysis data at 37°C for 4% w/v suspensions of aspirin in distilled water (A) and 1% w/v xanthan gum (F).

($P < 0.01$) and any two formulations underlined by the same line are not significantly different.

The flow curves obtained for the aqueous dispersions of each suspending agent were as expected from a consideration of the properties of the agents and the influence of changes in pH on those properties. The systems exhibited varying degrees of pseudoplastic behaviour. The apparent viscosities of the dispersions at different rates of shear fell into the same ranking order at a given pH; i.e. the flow curves did not cross each other over the range of shear rates that was employed. Since the shear rates that are experienced by a dosage form in the stomach are likely to be of low order the apparent viscosity ($\eta_{app}$) of each dispersion at pH 1.2 and 37°C was calculated at a shear rate of 100 $s^{-1}$. The $\eta_{app}$ values are also shown in Table 1. In the case of the sodium alginate dispersions, which formed clumps of alginic acid gel in an aqueous dispersion medium at pH 1.2 any relationship between the release of aspirin and viscosity is likely to be more complex than with the other systems. Consequently, no attempt was made to calculate an apparent viscosity for the sodium alginate dispersion in an acidic medium.

It can be seen from Table 1 that a rank order relationship exists between the parameters obtained from the release rate studies using the dialysis method and the apparent viscosities of the suspension media, the higher the viscosity the lower the $k_F$ value and the higher the $t_{1/2}$ value. Since the complexation studies showed that there was no measurable interaction between the aspirin and any of the suspending agents at pH 1.2 it is probable that the difference between the rate constants obtained for the release of drug from the different formulations was due to the effect of viscosity. It should be borne in mind that hydrolysis of aspirin will occur concurrently with dialysis and that the rate of hydrolysis will be affected by the viscosity of the reaction medium. However, the hydrolysis rate constant of aspirin in saturated solution at 37°C is much smaller than the $k_F$ values given in Table 1 ($k_{hydrol.} = 0.00579\ h^{-1}$; Lippmann and Mattocks, 1962) so that most of the drug released from the dialysis sac in the present studies will be in the form of aspirin.

Although the dialysis method is more sensitive than the flask-stirrer method to whatever effect is caused by the suspending agents it should be borne in mind that changes that are insignificant from an in vivo point of view may give rise to significant differences in the in vitro results. Corresponding in vivo data is required in order to determine the usefulness of the dialysis method as an indicator of changes in the bioavailability of drugs from suspensions. However, enhanced sensitivity in an in vitro method is not necessarily unacceptable if the method is to be used in preformulation studies or for quality control purposes (Barr, 1972).

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REFERENCES

Barr, W.H., The use of physical and animal models to assess bioavailability. In Brodie, B.B. and Heller, M.W. (Eds.), Bioavailability of Drugs, Karger, London, 1972, pp. 67–68.

Barzilay, R.R. and Hersey, J.A., Dissolution rate measurements by automated dialysis method. J. Pharm. Pharmacol., 20 (1968) 230S.

Bates, T.R., Lambert, D.A. and Johns, W.H., Correlation between the rate of dissolution and absorption of salicylamide from tablet and suspension dosage forms. J. Pharm. Sci., 58 (1969) 1468–1470.

Bates, T.R., Rosenberg, H.A. and Tembo, A.V., Inconsistencies in rationale underlying official USP dissolution rate specifications for nitrofurantoin. J. Pharm. Sci., 62 (1973) 2057–2058.

Berlin, A., Simers, B., Agurell, S., Hiort, A., Sjorgrist, F. and Strom, S., Determination of bioavailability of diazepam in various formulations from steady state plasma concentration data. Clin. Pharmacol. Ther., 13 (1972) 733–743.

British Pharmaceutical Codex, 1973. The Pharmaceutical Press, London, p. 756.

Davis, R.E., Hartman, C.W. and Fincher, J.H., Dialysis of ephedrine and phenobarbitol from whole human saliva and simulated saliva. J. Pharm. Sci., 60 (1971) 429–431.

Duncan, D.B., Multiple range and multiple *F* test. Biometrics, 11 (1955) 1–42.

Kassem, M.A. and Mattha, A.G., Rheological studies on dispersions of polyvinylpyrrolidone. Pharm. Acta Helv., 45 (1970) 18–26.

Lippmann, I. and Mattocks, A.M., Stability of aspirin in the presence of amphetamine salts. In American Pharmaceutical Association Conference, Las Vegas, 1962.

Martindale, The Extra Pharmacopoeia, 26th edn. The Pharmaceutical Press, London, 1972, p. 1071.

Marty, J.J. and Hersey, J.A., Apparatus for measuring in vitro availability of liquid oral preparations. J. Pharm. Pharmacol., 27 (1975) 437–438.

Mitchell, A.G. and Broadhead, J.E., Hydrolysis of solubilized aspirin. J. Pharm. Sci., 56 (1967) 1261–1266.

Muranyi, A., Szalicilamide-szuspenziok hatoanyag-leadasi sebessegenek vizsgalate. Gyogyszereszet, 17 (1973) 161–165.

Poole, J.W., Some experiences in the evaluation of formulation variables on drug availability. Drug Inf. Bull., 3 (1969) 8–16.

Riegelman, S., Clinical evaluation of the effect of formulation variables on therapeutic performance of drugs. Drug Inf. Bull., 3 (1969) 59–67.

Seager, H., The effect of methylcellulose on the absorption of nitrofurantoin from the gastrointestinal tract. J. Pharm. Pharmacol., 20 (1968) 968–969.

Shah, N.B. and Sheth, B.B., Effect of polymers on dissolution from drug suspensions. J. Pharm. Sci., 65 (1976) 1618–1623.

Swarbrick, J., In vitro models of drug dissolution. In Swarbrick, J. (Ed.) Current Concepts in the Pharmaceutical Sciences; Biopharmaceutics, Lea and Febiger, Philadelphia, 1970, pp. 265–294.

Weintraub, H. and Gibaldi, M., Rotating-flask method for dissolution determination of aspirin from various dosage forms. J. Pharm. Sci., 59 (1970) 1792–1793.