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INVESTIGATION OF THE EFFECT OF ADDITIVES ON THE DISSOLUTION RATES OF ASPIRIN AND PARACETAMOL USING A FACTORIAL DESIGN

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ABSTRACT

The effects of glycine, taurine and sorbitol on the intrinsic dissolution rate of paracetamol and aspirin were investigated using a 2^n factorial design. It is shown that all three additives decreased the dissolution rates of the two analgesics. There was no evidence of interactions between the additives except between sorbitol and glycine at the low levels (5%) and between taurine and glycine at the high levels. The decrease in dissolution rates observed was ascribed to increase in the viscosity of the dissolution medium by the additives.

INTRODUCTION

Aspirin and paracetamol are two of the most widely used mild analgesics and in most of the clinical conditions involved, rapid onset of pain relief is desirable. For this reason, numerous attempts have been made to improve the rate of absorption of aspirin and paracetamol[1-6]. Aspirin, for example, is known to be susceptible to

dissolution rate-limitation in its absorption and for this reason, soluble and buffered formulations are widely used. Likewise with paracetamol, formulation as a soluble tablet has been reported to provide faster absorption than co-formulation with accelerants, of gastric-emptying, such as metoclopramide[7]. Soluble formulations are however not always convenient and for this reason, mouth dispersible products have been introduced. It was against this back-ground that the present study was initiated to investigate the effect of a number of formulation additives on the dissolution rate of paracetamol. As single factor studies are expensive when there is a need to investigate a number of such factors and because potential synergism were also of interest to the product formulator, a factorial design was adopted.

MATERIALS AND METHODS

Factorial Design

2^3 factorial designs were used throughout the study with three factors A, B and C each at two levels and with the usual notation : 1, a, b, ab, c, ac, bc and abc 1 refers to all the factors at their low levels. The intermediate notations are self-explanatory. Two sets of experiments were carried out for each drug in order to optimise use of the six-station dissolution equipment available to us. One set uses 0% of the additive as the low level and 5% at the high level and the second set uses 5% as the low level and 10% as the high level. Factor A refers to taurine, factor B to glycine and factor C to sorbitol.

Determining Dissolution Rates

An automated dissolution testing apparatus consisting of a Caleva Model 7ST water-bath fitted with a variable speed stirring unit, and 1 litre flat-bottomed dissolution flasks were used throughout. 300mg paracetamol or aspirin tablets were prepared using an infra-red disk 13mm punch and die hydraulic press

assembly (Research and Industrial Instrument, UK). The tablets were compressed for 10 minutes under vacuum at 7000kg.

Dissolution was from one exposed tablet surface with the other wide surface stuck with hard paraffin wax to the flat base of the basket holder of a stirring rod as shown in Figure 1a. The edges of the tablet were also sealed with hard paraffin wax. Dissolution was carried out at 100 r.p.m. with 1 litre of pH 6.8 McIlvaine buffer heated to 37°C serving as dissolution medium and adjusted to 1M ionic strength. An alternative system consisting of a tablet held in a perspex holder (Figure 1b) was also used and the results checked with those using the rotating tablet system (Figure 1a).

The drug concentration was monitored continuously using a flow-through system pumping solution through an LKB 4052 Ultrospec spectrophotometer set at 290nm for paracetamol and 250nm for aspirin.

The effects of additives were investigated by adding appropriate amounts to the basic dissolution medium so that the final concentrations were as required.

RESULTS AND DISCUSSION

Figure 2 illustrates the dissolution profiles for paracetamol in the presence and absence of the different additives in the dissolution medium. 5 or 10% w/v of each additive were used in those experiments. It is clear that instead of the claimed increase in dissolution rate, the additives actually produced a decrease in each case. The actual values are shown in Table 1. Statistical analysis (Table 2) shows that each of the main effects were significant but there was no significant interaction in the effects of the additives except for combinations of glycine and sorbitol (θ_{BC}). Similar results were also seen with paracetamol at the higher levels of additives (Figure 3). In this instance however, a significant interaction was seen with taurine and glycine (Table 3 and 4). Both amino acid still have significant main effects.

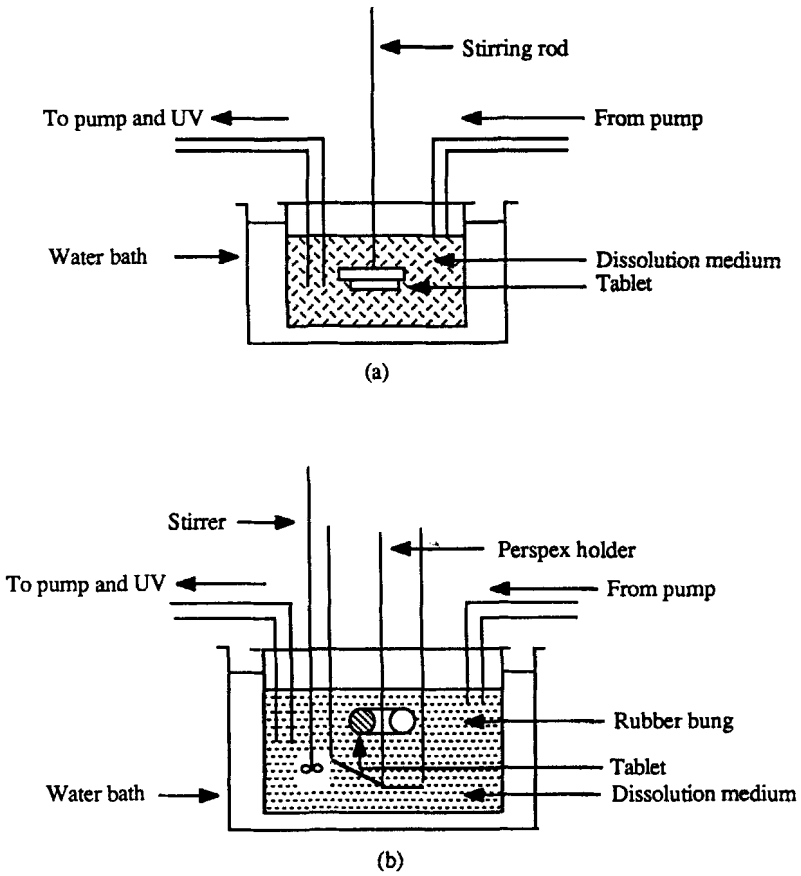

FIGURE 1
Schematic diagram of the dissolution assembly, (a) the rotating disk method and (b) the perspex method.

The interaction which was small at the low level of additives of up to 5%, became insignificant at the higher (5 to 10%) levels (Tables 2 and 4).

With aspirin, results which mirror those seen with paracetamol were observed (Figure 4). As shown in Tables 5 and 6, the main effects were also significant with aspirin as the candidate drug. Of the interaction terms only that with taurine and glycine was significant, an observation which is in tune with those seen with paracetamol and the additives at the high levels.

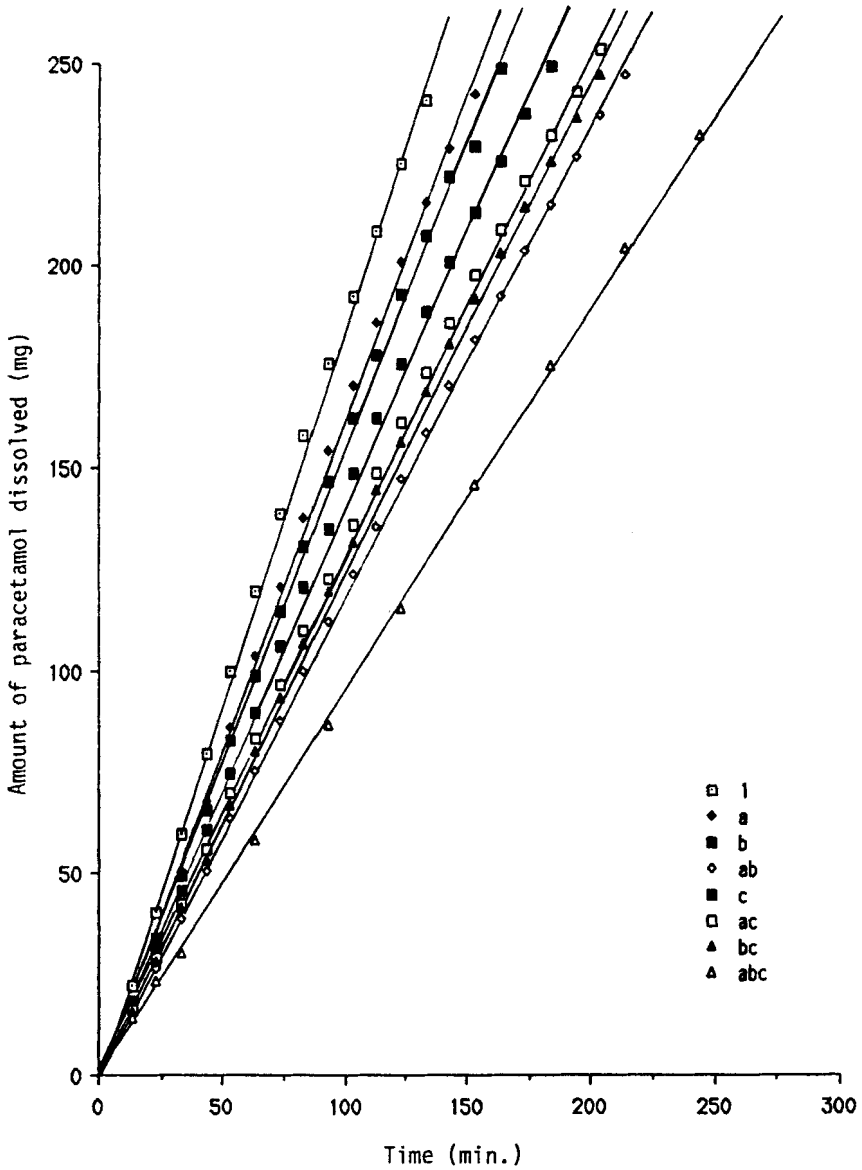

FIGURE 2

The dissolution profiles of paracetamol as a function of time using a 2^3 factorial design.
Low levels 0% and High level 5%. Key: 1 = control (all factors at low levels); a = Taurine; b = Glycine; c = Sorbitol.

TABLE 1

Effect of Additives on the Dissolution Rate of Paracetamol at Levels of 0 and 5% w/v

	Treatments							
Duplicate	1	a	b	ab	c	ac	bc	abc
Dissolution rates	1.750	1.524	1.295	1.168	1.436	1.239	1.211	0.914
mg min^{-1}	1.796	1.492	1.331	1.068	1.535	1.195	1.160	0.966
Mean	1.773	1.508	1.313	1.118	1.486	1.217	1.186	0.940

Factor A - Taurine; **Factor B** - Glycine; **Factor C** - Sorbitol.
Level 1 = 0%; **Level 2** = 5%.

TABLE 2

Main Effects and Interaction Terms for the Different Factors

Estimated effects	Magnitude	t ratio
θ_A	-0.2435	10.98
θ_B	-0.3568	16.09
θ_C	-0.2210	9.97
θ_{AB}	-0.0233	1.05
θ_{AC}	-0.0135	0.61
θ_{BC}	-0.0683	3.08
θ_{ABC}	-0.0118	0.53

Critical t value at a significance probability of 0.05 = 1.860.
θ_A = effect of factor A. Other subscripts to θ refer to appropriate factor or combination of factors.

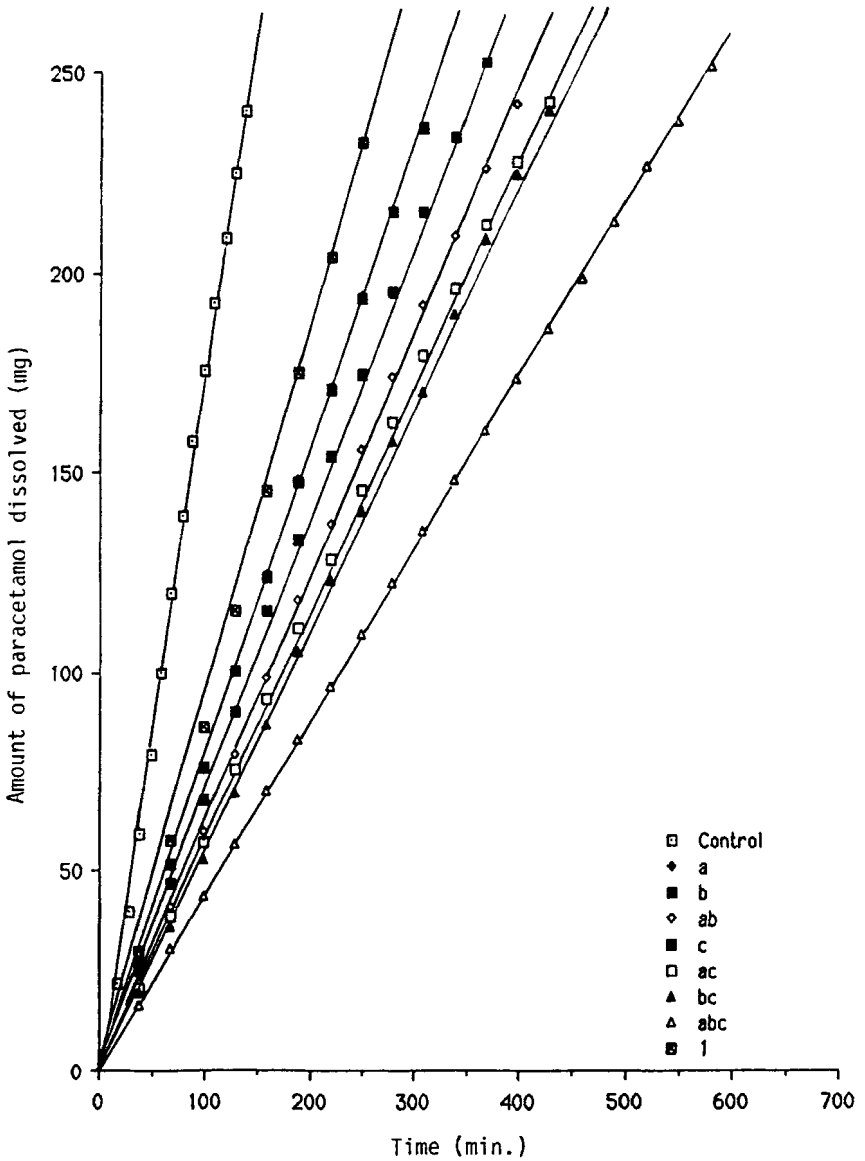

FIGURE 3

The dissolution profiles of paracetamol as a function of time, using a 2^3 factorial design.
Factor levels: Lot 5% and High 10%. Key: Control = all factors at low level;
a = Taurine; b = Glycine; C = Sorbitol (a,b,c, at high levels).

TABLE 3

Effect of Additives on the Intrinsic Dissolution Rate of Paracetamol at Levels of 5% and 10% w/v

	Treatments							
Duplicate	1	a	b	ab	c	ac	bc	abc
Dissolution rates	0.914	0.701	0.654	0.571	0.725	0.538	0.545	0.453
mg min^{-1}	0.966	0.787	0.697	0.612	0.758	0.568	0.566	0.410
Mean	0.940	0.744	0.6755	0.5915	0.7415	0.553	0.5555	0.4315

Factor A - Taurine; **Factor B** - Glycine; **Factor C** - Sorbitol.
Level 1 = 5%; **Level 2** = 10%.

TABLE 4

Main Effects and Interaction Terms for the Different Factors

Estimated effects	Magnitude	t ratio
θ_A	-0.1531	9.15
θ_B	-0.1811	10.82
θ_C	-0.1674	10.00
θ_{AB}	-0.0441	2.64
θ_{AC}	-0.0082	0.49
θ_{BC}	-0.0274	1.64
θ_{ABC}	-0.0119	0.71

Critical t value at a significance probability of 0.05 = 1.860.
θ_A = effect of factor A. Other subscripts to θ refer to appropriate factor or combination of factors.

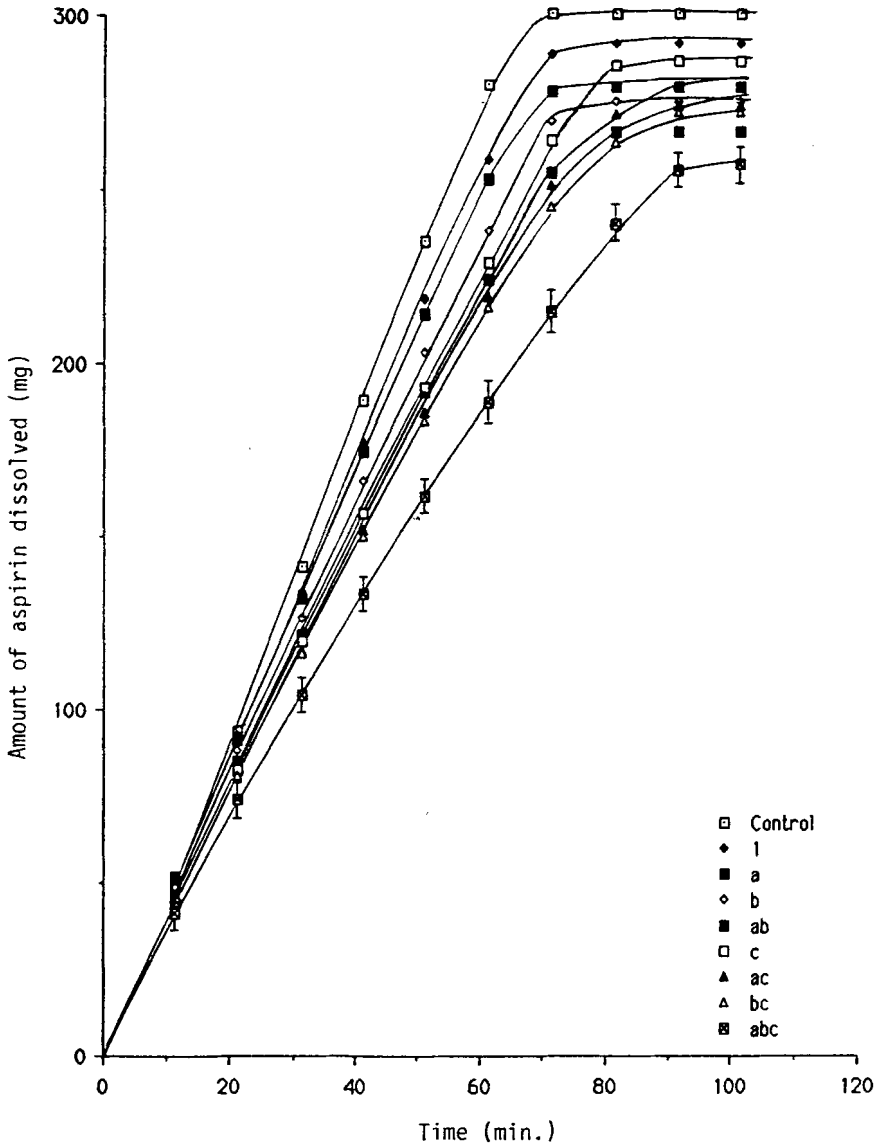

FIGURE 4

The dissolution profiles of aspirin as a function of time, using a 2^3 factorial experiment.
Factor levels in medium: Low 5% and High 10%. Key: Control = all factors at low level;
a = Taurine; b = Glycine; C = Sorbitol (a,b,c at high levels).

TABLE 5

Effect of Additives on the Intrinsic Dissolution Rate of Aspirin at Levels of 5% and 10% w/v

	Treatments							
Duplicate	1	a	b	ab	c	ac	bc	abc
Dissolution rates	4.084	4.004	3.785	3.434	3.504	3.340	3.340	2.845
mg min^{-1}	4.027	3.820	3.645	3.406	3.550	3.404	3.069	2.714
Mean	4.0585	3.912	3.715	3.420	3.527	3.372	3.2045	2.7795

Factor A - Taurine; **Factor B** - Glycine; **Factor C** - Sorbitol.
Level 1 = 5%; **Level 2** = 10% **Diameter of disk** = 1.3cm.

TABLE 6

Main Effects and Interaction Terms for the Different Factors

Estimated effects	Magnitude	t ratio
θ_A	-0.2546	5.19
θ_B	-0.4369	8.90
θ_C	-0.5549	11.30
θ_{AB}	-0.1054	2.15
θ_{AC}	-0.0354	0.72
θ_{BC}	-0.0206	0.42
θ_{ABC}	-0.0296	0.60

Critical t value at a significance probability of 0.05 = 1.860.
θ_A = effect of factor A. Other subscripts to θ refer to appropriate factor or combination of factors.

In an attempt to investigate the reason behind the observed decrease in paracetamol and aspirin dissolution rate the viscosity of the medium was measured in the presence and absence of the additives and the results are shown in Table 7. The stagnant layer theory[8] predicts that the dissolution rate R is related to the diffusivity D of the diffusant according to equation 1

$$R = \frac{DC_s}{h} \qquad \text{Equation 1.}$$

where C_s is the drug solubility and h is the effective diffusion layer thickness. Plots of any one of the variables in equation 1 against R does not usually give a straight line because of simultaneous variation in one or both of the other two variables. An alternative approach[9, 10] is to use an empirical equation of the form

$$R = k\eta^{-\beta} \qquad \text{Equation 2.}$$

where η is the viscosity of the medium and k and β are system parameters[11]. The usefulness of empirical equations has been illustrated by Florence, Elworthy and Rahman[12] in their work on the dissolution rate of soluble salts in solutions of varying viscosities. The authors drew addition to the difference between microscopic viscosity and the effective viscosity of the medium. More recently, Nelson and Shah[11] developed a convective diffusion model of the form

$$R = 2.16D^{2/3}C_s\alpha^{1/3}r^{2/3} \qquad \text{Equation 3.}$$

for spherical particles where α is the shear rate at the interface and r is the radius of the exposed surface.

TABLE 7

The Intrinsic Dissolution Rates of Paracetamol and the Kinematic Viscosities of the Media with Various Additives Incorporated

Factor	Intrinsic dissolution rate of paracetamol ($mg/cm^2/min$)	Intrinsic dissolution rate of aspirin ($mg/cm^2/min$)	Kinematic viscosity
Control	1.336	3.290	0.970
1	0.7082	3.057	1.390
a	0.561	2.948	1.530
b	0.510	2.800	1.550
ab	0.446	2.577	1.899
c	0.559	2.658	1.770
ac	0.417	2.541	1.990
bc	0.419	2.415	2.300
abc	0.326	2.095	2.340

The dissolution experiment was carried out using the rotating disk method at 37°C.

Factor levels: Low 5% and High 10%
1 = concentrations of all factors at their low levels
a = 10% Taurine
b = 10% Glycine
c = 10% Sorbitol

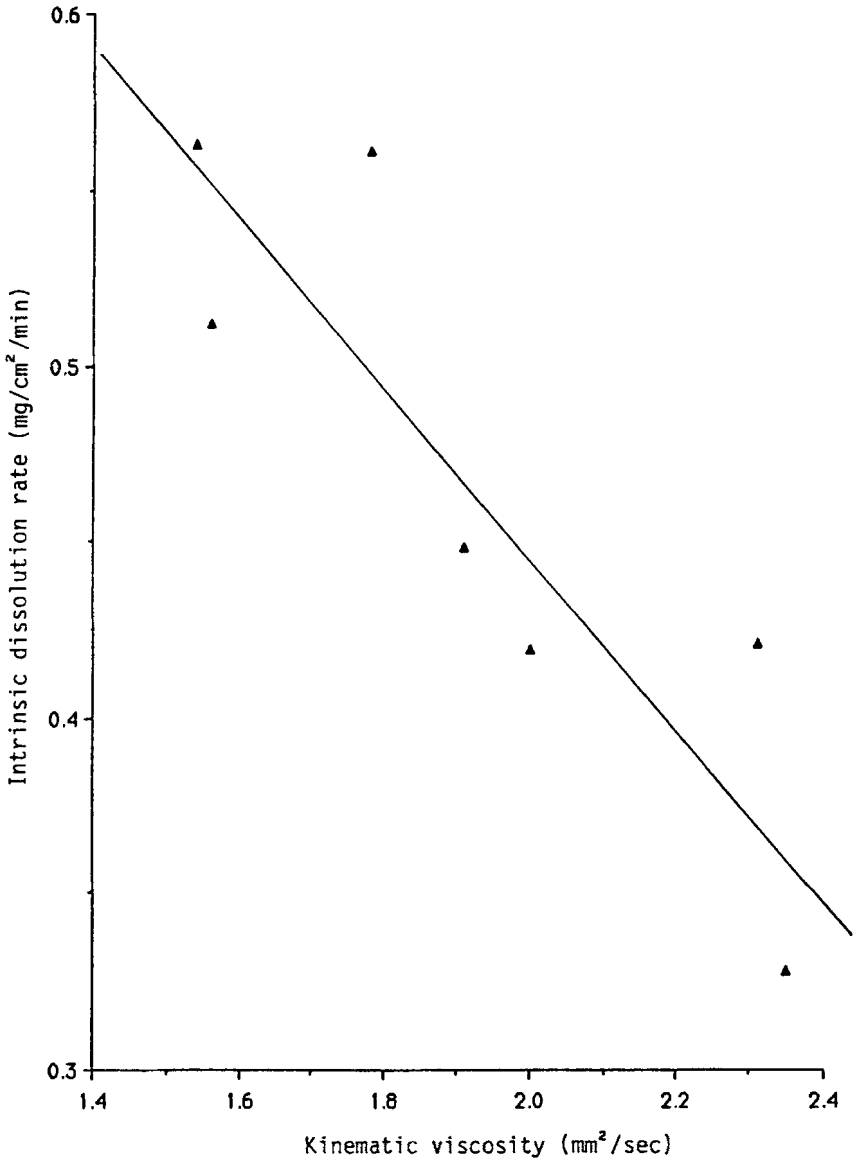

FIGURE 5

The relationship between the intrinsic dissolution rate of paracetamol and the kinematic viscosity of the dissolution medium.

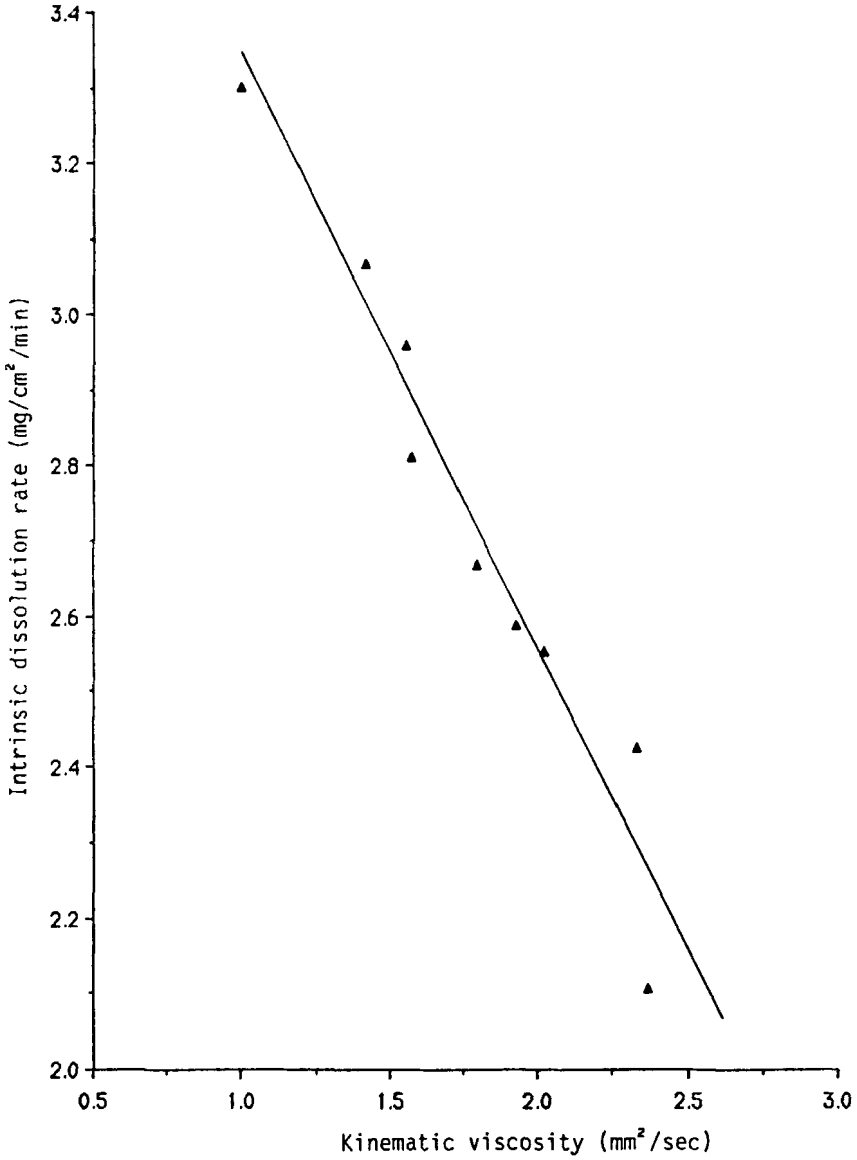

FIGURE 6

The relationship between the intrinsic dissolution rate of aspirin and the kinematic viscosity of the dissolution medium.

Figure 5 and 6 show the observed relationships between dissolution rate and kinematic viscosity. Both gave significant linear trends, an F value of 19.83 and a significance probability of 0.003 for paracetamol and an F value of 119.03 and a significance probability of less than 0.0005 for aspirin. A sharp curvature can however be seen with paracetamol and indeed logarithmic transformation of both the dependant and independant variables led to a much improved linear relationship between the paracetamol dissolution rate and the viscosity of the medium and indeed the corresponding F and significance probability are then 82.13 and less than 0.0005 respectively. It would therefore appear that the additives decrease the drugs' dissolution rates essentially by altering the viscosity of the medium.

The original motivation of this study was to investigate whether the additives enhanced the dissolution of the drugs investigated. The data reported here indicate that the dissolution rate of both aspirin and paracetamol were in fact reduced by the additives. The results however do not exclude the possibility that despite the lack of positive effects, the additives could in vivo accelerate the drugs' absorption. Glycine, for example, has been reported to increase iron absorption in vivo[13-14] Additionally, in vitro results may fail to correlate with in vivo absorption rates[15]. However what the results do show is that if enhancement in aspirin and paracetamol is observed by the addition of any of the additives studied, increased dissolution is unlikely to be the mechanism involved.

CONCLUSION

Using factorial designs, we have been able to evaluate the effect of three additives on the intrinsic dissolution rates of aspirin and paracetamol. The data suggest that all three additives reduced the dissolution rates of the drugs. Interactions between the additives were only significant with glycine and sorbitol at

the low levels and glycine and taurine at the high levels. The effect of the additives can be rationalised on the basis of their effects on viscosity of the dissolution medium.

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