BIOAVAILABILITY OF SULFATHIAZOLE FROM FLOCCULATED AND DEFLOCCULATED SUSPENSIONS AND ITS IMPLICATIONS

D. RAMBHAU*, V. R. GUDSOORKAR AND Y. MADHUSUDAN RAO

Department of Pharmaceutical Sciences,
Nagpur University, Nagpur - 440 010

(Received on March 17, 1983)

Summary : Flocculation is commonly used to stabilize pharmaceutical suspensions. Flocculated and deflocculated suspensions of sulfathiazole were administered to healthy human volunteers. Bioavailability from these two types of suspensions was studied from urinary free drug excretion. Bioavailability was significantly lower from flocculated suspensions. The study indicates the necessity of studying all flocculated drug suspensions for bioavailability data.

Key words : sulfathiazole, suspensions, flocculated, urinary excretion, bioavailability, deflocculated

INTRODUCTION

Controlled flocculation is commonly employed to stabilize pharmaceutical suspensions. Since there is a change in physical structure and interfacial properties of suspended particles in flocculated state it is instructive to study the effect of flocculation on dissolution and bioavailability. Earlier, dissolution of sulfathiazole from its suspension (composition: sulfathiazole 2 g%, dioctyl sodium sulfosuccinate 0.2%, sodium carboxymethtylcellulose 0.02%, distilled water upto 100 *ml*) was found to be retarded (2), when flocculation was induced by using aluminium trichloride (0.064 m). This paper deals with the biovailability of sulfathiazole from flocculated and deflocculated suspensions, based on urinary excretion data.

MATERIAL AND METHODS

Five healthy male volunteers, weighing between 50 to 60 *kgs*, who had no history of renal disease or hypersensitivity to the sulphonamides participated in the study after overnight fasting.

*Present address : University College of Pharmaceutical Sciences, Kakatiya University, Vidyaranyapuri, Warangal - 506 009 (A.P.), India.

Deflocculated suspension was administered at 8 a.m. (in volume equivalent to 300 *mg* of sulfathiazole)) with 200 *ml* of water. No food and water were allowed for the following 3 hours. Voided urine samples were collected and measured at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hrs. Free sulfathiazole in urine was estimated by following the method of Bratton and Marshall (1). After a week's rest the flocculated suspension was similarly administered and studied.

Relative bioavailability of sulfathiazole from the two suspensions was calculated by the method suggested by Oser *et al.* (5).

RESULTS

Figure 1 shows the amount of free drug excreted after the administration of deflocculated and flocculated suspensions. It will be seen that the suspensions exhibited

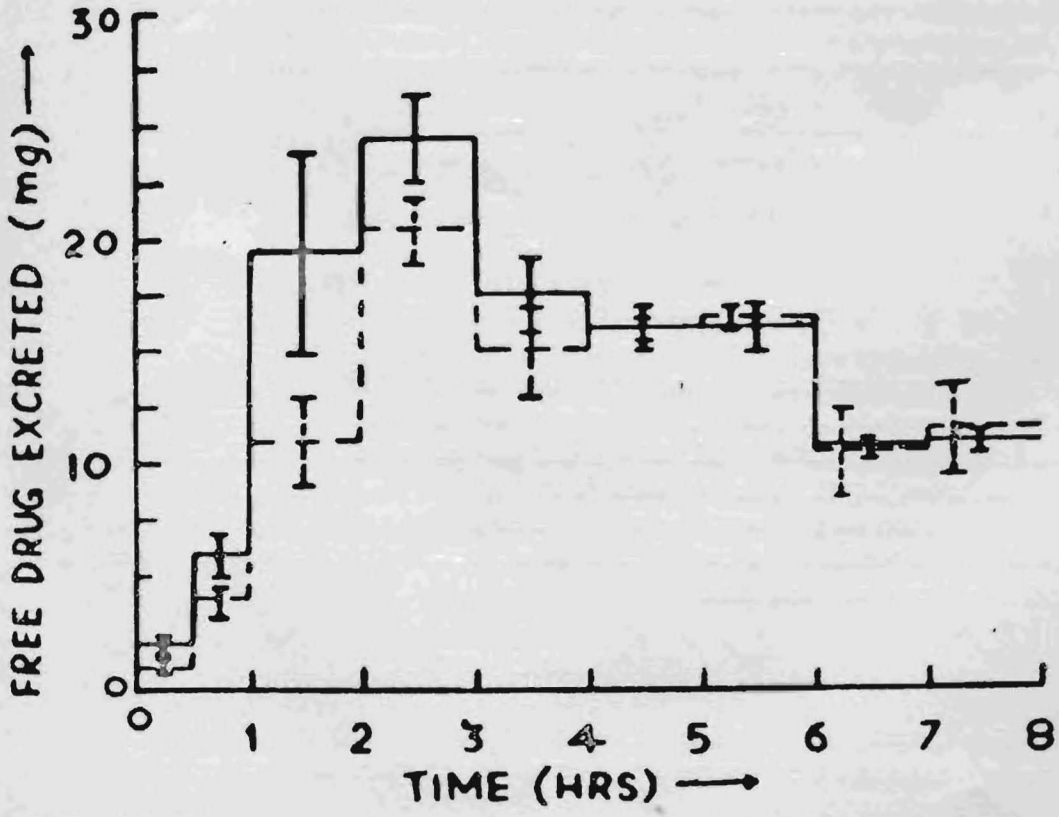

Fig 1 : Excretion of free sulfathiazole in urine after administration of deflocculated (—) and flocculated (– – – –) suspensions (see text for details). Values are means from 5 human volunteers. Vertical bars indicate s.e.m.). The difference in the mean excretion of the drug from the two systems was significant ($P<0.01$) upto a period of 4 hrs.

a marked difference in first 4 hrs as far as the rate of urinary excretion of free drug is concerned. Amount of free drug excreted was significantly more in case of deflocculated suspension. In each case free drug excretion was at peak at the end of 3 hrs. The peak concentration of drug excreted from deflocculated and flocculated suspensions was 24.669 *mg* and 20.712 *mg* respectively. Relative bioavailability of drug from flocculated suspension was 14.5% less than that from the deflocculated suspension. The difference was statistically significant ($P<0.1$).

DISCUSSION

As sulfathiazole is very hydrophobic, its release from aqueous suspensions would be poor. For such a poorly soluble drug absorption is dissolution rate-limited. Therefore, any factor which can retard the release of drug from suspension, would consequently become responsible for poorer absorption.

Important changes occur in total surface area and physical structure of flocculated drug particles. Thus drug particles are entrapped in a network of floccule and their effective surface area exposed to gastrointestinal fluids is reduced. Decrease in dissolution rate due to decrease in effective surface area of dissolving drug particles complies with the postulation of the Noyes and Whitney's equation (4), that :

$$\frac{dc}{dt} = \frac{SD}{Vh}(C_s - C)$$

where $\frac{dc}{dt}$ rate of dissolution

S = effective surface area

D = diffusion coefficident of the dissolved drug

V = volume of dissolution medium

h = thickness of diffusion layer

C_s = concentration of saturated solution of free drug

C = drug concentration at time 't'.

The flocculated suspension of the present study was developed on the basis of chemical bridging mechanism proposed by Wilson and Ecanow (7). According to these workers, the binding forces that developed between particles of a floccule are much strong and maintain integrity of the floccule-structure. Hence it could be surmised that such

floccules may not be disturbed under the usual conditions existing in the gastrointestinal tract (3, 6), thus accounting for reduced absorption and consequently, reduced excretion seen for first 4 hrs in this study. It is also possible that the formation of hydrophobic aluminium dioctyl sulfosuccinate barrier at the particle interface may have reduced absorption of drug from flocculated suspensions.

There are good number of flocculated suspensions of drugs in the market. From results of the present study we suggest that these suspensions need to be tested for bioavailability (or at least for *in vitro* drug release) to improve predictability of therapeutic results.

REFERENCES

1. Bratton, A.C. and E.K. Marshall. A new coupling component for sulfanilamide determination. *J. Biol. Chem.*, **128** : 537-550, 1939.
2. Gudsoorkar, V.R. and D. Rambhau. Influence of flocculation on dissolution of sulfathiazole suspension. *Indian Drugs*, **17** : 215-216, 1980.
3. Levy, G. Effect of certain tablet formulation factors on dissolution rate of active ingradients-I. *J. Pharm. Sci.*, **52** : 1039, 1963.
4. Noyes, A.A. and W.R. Whitney. The rate of solution of solid substances in their own solutions. *J. Am. Chem. Soc.*, **19** : 930, 1897.
5. Oser, B.L., D. Melnick and M. Hochberg. Physiologic availability of vitamins. *Ind. Eng. Chem. Anal Ed.*, **17** : 405, 1945.
6. Swarbrick, J. In : Biopharmaceutics - Current concepts in the pharmaceutical sciences. 1st-ed., Philadelphia, Lea and Febiger, p. 265, 1970.
7. Wilson, R.G. and B. Ecanow. Powdered particle interactions. Suspension flocculation and Caking-I and II. *J. Pharm. Sci.*, **52** : 757-762 and 1031-1038, 1963.