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EFFECT OF A SURFACTANT ON ABSORPTION OF AN ANTIBIOTIC FROM NON-AQUEOUS PARENTERAL SUSPENSIONS

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ABSTRACT

Attempts to modify the absorption of a monocyclic beta-lactam antibiotic from an oily suspension formulation were made by incorporation of the non-ionic surfactant sorbitan trioleate. Time to serum peak concentration was increased with increased level of surfactant and there appeared to be more efficient clearance of the antibiotic from the depot with increase in level of surfactant in the formulation. The second effect may be explained in terms of the physical characteristics of the formulations whereas the alteration in time to serum peak concentrations may be due to an effect of the surfactant on transport of drug through tissue.

INTRODUCTION

The formulation of beta-lactam antibiotics as ready-for-use preparations is complicated by the poor stability of these agents in aqueous media due to hydrolysis of the

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beta-lactam ring[1]. Aqueous formulations, whether solutions or suspensions can be expected to lose potency over a matter of only a few weeks under ambient storage conditions, such as to make ready-for-use aqueous formulations commercially non-viable. Hence, many manufacturers market beta-lactam antibiotics for aqueous formulations such as syrups in the form of powders for reconstitution with a short shelf life after reconstitution. Therefore, when a ready-for-use preparation is desired, for example, in veterinary work where a large number of animals need to be treated and reconstitution prior to use is not convenient, alternative formulation strategies need to be considered.

Formulation of the drug in a non-aqueous medium such as a thin vegetable oil or ethyl oleate is an alternative formulation choice for an intramuscular injection product. Suitable choice of a low viscosity oil can make handling of the product as easy as for an aqueous product and yield the benefit of good product stability.

With water-soluble drugs such as beta-lactam antibiotics a suspension formulation results. Such a formulation may give rise to an undesirable depot effect on administration and additives may be required to enhance the release of the drug. Surfactants have been added to aqueous parenteral formulations previously and both promotion and reduction in absorption have been detected. Non-ionic surfactants promoted absorption of the polypeptide antibiotic enduracidin from intramuscular injections, either by increasing capillary permeability to the drug or by preventing precipitation at the injection site[2]. A reduction in the absorption of some water-soluble drugs from aqueous intramuscular injection solutions was explained[3] in terms of reduction in the transport rate of the drug through the extracellular space and connective tissue.

In the present work we have examined the effect of a non-ionic surfactant sorbitan trioleate, on the serum concentration-time profile of a monocyclic beta-lactam antibiotic administered as an oily suspension to rabbits.

EXPERIMENTAL

Materials

Ethyl oleate was from Fisons, Loughborough U.K. and sorbitan trioleate was obtained from Atlas Chemical Industries, Leatherhead, U.K. The drug substance studied was a monocyclic beta-lactam antibiotic [3 S(Z)]-2-Amino-α(methoxyimino)-N-[2-oxo-1-[[1H-pyrazol-1-ylsulfonyl)amino] carbonyl]-3-azetidinyl]-4-thiazoleacetamide sodium salt, obtained from the Squibb Institute for Medical Research, Princeton, New Jersey, U.S.A. The antibiotic was size reduced in an air jet mill to give a mean particle size of 10μm as determined by Coulter Counter.

Pharmacokinetic Study

Suspensions of antibiotics were prepared at 100 mg ml^{-1} in ethyl oleate containing 0, 0.5 and 5.0% w/v of sorbitan trioleate. The formulations were evaluated *in vivo* in a cross-over design study. For each leg of the study six New Zealand white rabbits (2-3kg) were administered 13.5mg kg^{-1} of the drug in the form of one of the suspensions. Blood samples were taken at 0, 5, 10, 15, 30, 60, 90, 120, 210 and 360 minutes. After clotting the serum was separated by centrifugation and drug in the serum was determined by microbiological assay. The serum was extracted with acetone and the extract appropriately diluted with pH 6.0 phosphate buffer. Antibiotic Medium, Number 1 agar (Oxoid) was employed and the test organism was *Escherischia coli* SC12155 (Squibb).

Physical Properties of Formulations

Viscosity of suspensions was determined on a Deer Rheometer using a cone and plate. Apparent viscosities were calculated from the curves obtained. Interfacial tension between the vehicle and distilled water was determined using a White Electrical Instruments torsion balance equipped with a 13mm diameter platinum ring. Satisfactory values for distilled water were confirmed prior to each interfacial tension determination. Five determinations for each vehicle were carried out and the mean value calculated. For each determination a fresh interface was prepared and the interface was allowed to equilibrate for fifteen minutes before the determination was made. This was to allow for the known slow diffusion of non-ionic surfactants such as sorbitan trioleate to interfaces [4].

The wettability of the drug powder by the vehicles was investigated by use of the drop height contact angle method. Drug compacts (60mg) were prepared on a Manesty 'F' single punch tablet machine equipped with 6.29mm diameter flat-faced punches. The compression pressure was 70 MPa . A drop of vehicle was placed on the upper, unlubricated face of the compact and the contact angle measured directly via a travelling microscope.

RESULTS AND DISCUSSION

The serum concentration-time profiles for the three formulations (Fig. 1) show a distincteffect of increasing the amount of the surfact sorbitan trioleate in the formulation. The serum peak concentration time was delayed with increasing level of sorbitan trioleate but for the two sorbitan trioleate-containing formulations there was little difference in the peak concentration achieved.

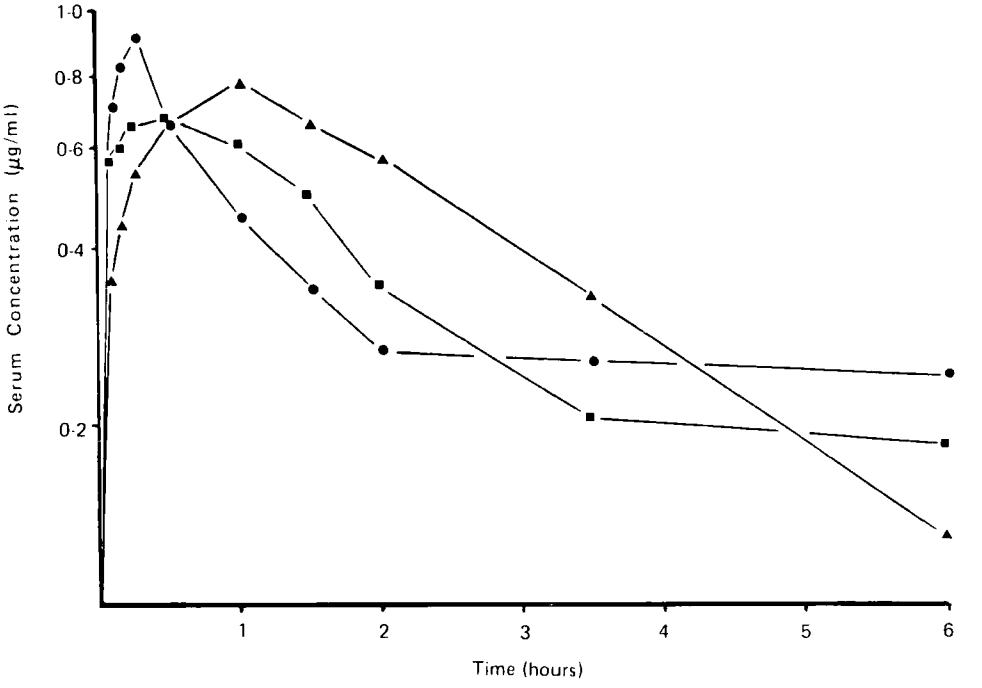

Fig. 1. Serum Concentration-time Curves for a Monocyclic Beta-lactam Antibiotic Formulation Containing Sorbitan Trioleate

- ● ethyl oleate vehicle
- ■ ethyl oleate vehicle + 0.5% sorbitan trioleate
- ▲ ethyl oleate vehicle + 5.0% sorbitan trioleate

A more noticeable effect is in the shape of the serum concentration-time profiles after 120 minutes. For the surfactant-free formulation a plateau is seen with a relatively constant serum concentration of approximately 0.3 µg ml^{-1} at all time points examined.

The shape of this curve may be explained in terms of the mechanism of the release of the drug from the

vehicle. Studies by Crommelin and de Blaey [4] on the *in-vitro* release of drugs of low water solubility from mineral oil-based suspensions indicated that, at low drug concentrations, the release was determined by transport of particles to the oil-water interface. At high drug concentrations the release was determined by the intrinsic dissolution rate of the drug. For the compound studied here, water solubility is low at less than 20 mg g^{-1} and solubility in the vehicles used is negligible. The observed serum concentration time profile may be explained in that once the drug at the oil interface is depleted due to absorption an equilibrium situation is achieved governed by transport of solid drug to the interface. This transport to the interface may be physical migration of particles or regression of the interface due to clearance of the oil. When surfactant is added the plateau phase is reduced with 0.5% sorbitan trioleate and abolished with 5.0% sorbitan trioleate. This effect may be explained in terms of the reduction in interfacial tension due to surfactant (Table 1) and also by improved wetting of the powder by vehicle when surfactant is present (Table 2). The contact angle method used does not appear to be sufficiently sensitive to indicate differences between the two surfactant-containing formulations which was expected due to their different interfacial tension values against distilled water. The test however does indicate improved wetting when sorbitan trioleate is present compared with the surfactant-free formulation. The reduced interfacial tension and enhanced wetting of the drug would facilitate transfer of the drug across the oil interface.

An apparently more efficient clearance of the drug from the depot is suggested by the elimination of the

TABLE I

Interfacial Tension of Vehicles Used for Preparation of Injections

Vehicle	Interfacial tension (dynes cm^{-1})
Ethyl oleate	15.7
Ethyl oleate + 0.5% sorbitan trioleate	14.4
Ethyl oleate + 5.0% sorbitan trioleate	8.2

TABLE II

Contact Angle for Vehicles on Drug Compacts

Vehicle	Contact Angle
Ethyl oleate	12.1°
Ethyl oleate + 0.5% sorbitan trioleate	8.4°
Ethyl oleate + 5.0% sorbitan trioleate	8.5°

low, relatively constant serum level of drug after 120 minutes for surfactant-containing formulations. Although this can be explained by the physical parameters determined for the formulations, these factors do not explain the shift in time to serum peak concentration. Whilst interaction between drug and surfactant in the vehicle cannot be completely ruled out, this is unlikely in the

TABLE III

Apparent Viscosity of Antibiotic Suspension Formulations

Vehicle	Viscosity (cP)
Ethyl oleate	23
Ethyl oleate + 0.5% sorbitan trioleate	25
Ethyl oleate + 5.0% sorbitan trioleate	25

non-aqueous medium. Water in the vehicle could result in the formation of reverse micelles which may trap small amounts of the water soluble drug but water levels in the vehicle were so low as to make such an effect insignificant. Changes in the viscosity of the formulation on surfactant incorporation are slight and would not explain the differences between 0.5% and 5.0% sorbitan trioleate formulations (Table 3).

More likely is a direct effect of the surfactant on tissue permeation by the drug, this having been previously reported [3] for the absorption of water-soluble drugs from aqueous intramuscular injection solutions containing non-ionic surfactants. The effect was related to the level of surfactant present and differences in the rate of clearance of drug and surfactant from the injection site helped support this observation.

The present report indicates the same negative effect of surfactant on drug absorption from an intramuscular injection, the observation in this case being extended to oily suspension injections with the time to peak serum concentration being delayed further with increasing

surfactant concentration. In the case studied a useful effect of the inclusion of the surfactant is seen in that more efficient clearance of the drug from the depot is apparently achieved.

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