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Oral bioavailability of vancomycin solid-state emulsions

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Abstract

Vancomycin was incorporated within water-in-oil-in-water (w/o/w) emulsions prepared from solid-state emulsions. Vancomycin, which is not normally orally absorbed, was significantly absorbed, i.e., 30% ± 0.56 (SE) after 36 h in rats ($N = 3$). The vancomycin concentration-time profile indicated that sustained release of vancomycin was very reproducible. Vancomycin was detected in serum by fluorescence polarization immunoassay (TDx, Abbott).

Keywords: Oral absorption; Peptide; Solid-state emulsion; Reconstitutable emulsion; Vancomycin

A method to prepare oil-in-water (o/w) and water-in-oil-in-water (w/o/w) type solid-state emulsions (Myers and Shively, 1992) and relevant physical properties (Shively, 1993; Shively and Myers, 1993) have been reported. Although the physical stability of these systems has been found to be unique, nothing is known about the physical stability in vivo or the in vivo characteristics of drug absorption from w/o/w emulsions prepared from solid-state emulsions.

A great deal of interest has focused on multiple emulsions (w/o/w) as a means of facilitating the gastrointestinal absorption of water-soluble compounds that are not normally subject to absorption as a result of instability in the presence of certain physiological pH values and/or enzymatic environments, e.g., peptides and proteins (Engel et al., 1968; Shichiri et al., 1974). The current understanding is that highly lipid materials, e.g., oils, fats and lipophilic drugs, are not absorbed through the portal system but by a lymphatic mechanism (Charman, 1992). In principle, conventional multiple emulsions, i.e., those containing at least two different emulsifying agents, have been shown to be potential drug delivery systems, but significant physical stability issues have limited their application (Florence and Whitehall, 1981; Davis et al., 1985).

The objective of this study was to determine if the oral bioavailability of a water-soluble drug, normally not absorbed in the GI tract, can be enhanced by incorporation within the interior aqueous phase of w/o/w solid-state emulsions.

Due to its recent use as a model peptide (Geary and Schlameus, 1993), vancomycin was chosen as the model compound for this study. Vancomycin, a glycopeptide, is administered intravenously for systemic gram positive infections to patients who are allergic or who are not responding to penicillins or cephalosporins. In con-

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trast to the spectrum of activity attained upon systemic administration, orally administered vancomycin has been shown to be only effective against gastrointestinal infections, such as staphylococcal enterocolitis (Conte and Barriere, 1988).

The procedure to prepare the vancomycin solid-state water-in-oil-in-water (w/o/w) emulsion is analogous to that described previously (Myers and Shively, 1992). The primary emulsion utilized in this study was comprised of 73.5% (w/w) sesame oil, 1.5% (w/w) monoglycerol stearate and 25% (w/w) aqueous phase. The primary emulsion's (w/o) aqueous phase contained vancomycin (pH 4.5, 200 mg/ml vancomycin HCl (Sigma Chemical Co.)) and was made isotonic with sodium chloride. Vancomycin is reported to have a shelf-life of 17 days when dissolved in saline (pH 3.8) and stored at 24°C in glass or plastic (Gupta et al., 1986). Sucrose was utilized as the matrix material at a ratio (w/w) of 3.5:1 sucrose/primary emulsion. The resultant w/o/w solid-state emulsion contained 11.1 mg vancomycin per g of solid.

Sprague-Dawley, male rats (Sasco, IA) weighing 400–470 g were surgically implanted with an indwelling jugular catheter to allow intravenous blood sampling and allowed to recover from surgery for 7 days before administration of vancomycin solutions. To prevent the influence of circadian rhythm, all experiments were initiated between 6:30 and 7:00 a.m. Rats were fasted for 12 h prior to the administration of vancomycin.

A commercial intravenous solution, a commercial oral suspension or a vancomycin solid-state emulsion was administered. The intravenous solution (Vancocin I.V.®, 5 mg vancomycin per ml in normal saline) was infused into the tail vein over a period of 45 min. The dose delivered was 10 mg/kg, at a rate of 2 ml/kg per h. At the end of the infusion, the infusion tubing was flushed with normal saline. The oral formulations of vancomycin were administered (50 mg/kg vancomycin delivered in a volume of 3 ml/kg) through a feeding tube to conscious rats. The tube was flushed subsequently with an equal volume of 5% dextrose. The commercial oral suspension (Vancocin®, Lilly Laboratories) was diluted and used as per the manufacturer's instructions. For the vancomycin solid-state emulsion formulation, a predetermined quantity of powder was dissolved in distilled water to achieve a final vancomycin concentration of 16.7 mg/ml.

Blood was drawn from the indwelling jugular catheter (0.2 ml/sample) immediately prior to administration and 0.25, 0.92, 1.22, 1.45, 1.90, 2.90, 3.90, 4.90 and 5.90 h after administration of intravenous vancomycin and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0 and 36 h for orally administered samples. Blood was collected into Microtainer® tubes containing serum separator gel and serum was fractionated therefrom. Vancomycin was detected (detection limit = 1 μg/ml) in serum using a fluorescent polarization immunoassay (TDx, Abbott Diagnostics, Abbott Park, IL) according to the manufacturer's instructions. The rationale for the use of such an assay has been discussed (Schwenzer et al., 1983)

Vancomycin concentration-time profiles for each animal and dosage regimen were analyzed individually by compartment independent methods, i.e., moment analysis (RSTRIP®, ver. 4.05, MicroMath Scientific Software, Inc., Salt Lake City, UT).

In agreement with that anticipated, no detectable quantity of vancomycin was observed for the commercial oral suspension (Fig. 1). In contrast, vancomycin was detected in the serum of rats receiving the solid-state formulation of vancomycin (Fig. 1). Despite the small number of animals utilized for each treatment group, the reproducibility of absorption ofthe solid-state emulsion formulation is remarkable. It is also important to note that the observed concentration-time profile for the solid-state emulsion regimen is consistent with the sustained release of vancomycin. Due to our more modest expectations and the unexpected prolonged duration of the vancomycin concentration in the blood, only the area under the curve (AUC) at 36 h could be calculated (Table 1). These results are consistent with the 'typical idealized' concentration-time profile of a highly lipophilic drug (Charman, 1992). Absorption of vancomycin as a result of irritated gastrointestinal mucosa is thought to be remote since sucrose and sesame have not been reported to cause any GI irritation.

Table 1
Pharmacokinetic analyses of vancomycin administered to conscious rats intravenously, orally in a commercial suspension or orally in a solid-state emulsion

Parameter	Intravenous	Oral suspension	Oral solid-state
Dose (mg)	4362 ± 131	21250 ± 220	22630 ± 365
Body weight (g)	435 ± 14	438 ± 6	452 ± 7
Area under the curve AUC (0–36) (mg h ml^{-1})	67.35 ± 9.93	0	101.62 ± 1.01
Percent absolute bioavailability (F) [a]	100.00	0	30.00 ± 0.56 [b]

[a] Absolute bioavailability (F) was calculated as the ratio of ($AUC_{oral}/AUC_{i.v.}$) × 100.
[b] Experiment terminated after 36 h. Data represent the mean ± SE from three animals.

The absolute bioavailability of vancomycin within solid-state emulsions was determined by comparing the AUC obtained for the solid-state emulsion at 36 h to the AUC of an intravenous dose of vancomycin (Data not shown). On the basis of this information, apparently 30% of the vancomycin from the orally administered solid-state emulsion was absorbed in the 36 h collection period (Table 1) whereas there was no evidence that the commercial suspension was orally absorbed.

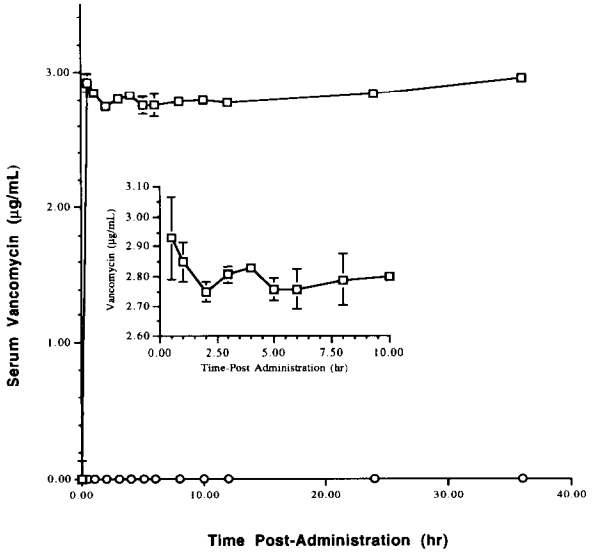

Fig. 1. Serum concentrations of vancomycin in conscious rats following administration of vancomycin formulated in a commercial suspension or a solid state emulsion. A total dose of 50 mg/kg vancomycin was administered orally to rats. Serum levels of vancomycin were measured immediately prior to administration ($t = 0$) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 36 h after administration. Data represent the mean ± SE obtained in three animals. (○) Commercial (Vancocin®) suspension;, (□) solid-state emulsion formulation.

These findings are significant in that a w/o/w solid-state emulsion formulation permits the gastrointestinal absorption of vancomycin and thereby represents a potential method of treating systemic infections. What is more important is that these results suggest that solid-state emulsions should be considered and evaluated further for the oral delivery of drugs that, due to incompatibility with gastrointestinal processes or lack of absorption, must presently be administered by the intravenous route.

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