Dissolution Rate of *p*-Aminobenzoates from Solid Xylitol Dispersions

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Abstract □ Xylitol was studied as a carrier in solid dispersions because of its low melting point and stability up to 180°. It is more stable than sucrose and does not enter into Maillard reactions. Solid dispersions were prepared from esters of *p*-aminobenzoic acid and xylitol by the melting method and were compressed into tablets. The *p*-aminobenzoate dissolution rates were determined by a modified beaker method. The increase in the dissolution rates was greatest at the lowest drug levels. When the dispersion drug content exceeded 20–30%, the dissolution rate per unit area remained nearly constant. In the latter case, the increase in the dissolution rate was primarily due to an increase in area. When the carbon chain length was increased in the homologous series, the dissolution rate from the xylitol dispersions showed a nearly linear decrease.

Keyphrases □ *p*-Aminobenzoic acid—rate of dissolution from solid xylitol dispersions □ Xylitol—carrier, solid dispersions of *p*-aminobenzoic acid esters □ Dissolution rate—*p*-aminobenzoic acid esters from solid xylitol dispersions □ Dosage forms, solid—dispersions, *p*-aminobenzoic acid esters in xylitol, dissolution rate

Solid dispersions have been used to increase the dissolution rate and bioavailability of drugs that are only slightly water soluble. The carriers used have been physiologically inert compounds that are readily water soluble. To reduce sulfathiazole particle size, eutectic mixtures, for example, have been prepared from urea and slightly water-soluble sulfathiazole by the melting method (1). However, the high temperatures required by the melting method may cause either the drug or the carrier to decompose.

p-Aminobenzoic acid esters, particularly the higher homologous ones, are only slightly soluble in water (2). Xylitol was studied as a carrier for solid dispersions of *p*-aminobenzoates because of its low melting point and stability up to 180°. Xylitol is almost equal to sucrose in water solubility and is more stable chemically; when xylitol is heated in the presence of amino groups, it does not undergo the Maillard ("browning") reaction (3, 4).

The melting range of xylitol is 93–94.5°, and it begins to decompose at 179–186° (3). When xylitol is used as the dispersing medium, the dissolution process is endothermic. The relatively high negative heat of xylitol solution is 145.7 J/g (3).

EXPERIMENTAL

Materials—The *p*-aminobenzoic acid esters studied were methyl *p*-aminobenzoate[1], ethyl *p*-aminobenzoate[1] (benzocaine), propyl *p*-aminobenzoate[2] (risocaine), and butyl *p*-aminobenzoate[1] (butamben). Xylitol[3] was used as a carrier.

Solid Dispersion Preparation—Solid dispersions were prepared using the direct melting method (1). A physical mixture of the drug and xylitol was made, and this mixture was heated in an IR bath[4]. The mixture of xylitol and methyl *p*-aminobenzoate was heated to 114°, and the other mixtures were heated to 96–98°. The molten mixture was cooled quickly by pouring it onto a stainless steel plate in an ice bath. The mixture was left to stabilize for 24 hr at room temperature.

Sample Preparation—The dispersion used in the tablets was pulverized to 0.71-mm particles. For dissolution rate determination, the solid dispersions were compressed into cylindrical tablets (18 mm in diameter; 750 mg) using a hydraulic press[5] in the same way as potassium bromide disks are prepared for IR spectroscopy. Pure drug tablets were prepared using the same pressure, 400 MPa.

Dissolution Rate Determination—The dissolution rates were determined using a modified beaker method (5). Each determination was run in 600 ml of distilled water in a 800-ml beaker at 37°. The tablet was placed on a sieve net (mesh 2.0 mm) positioned 2 cm from the bottom of the beaker. A sieve net basket (4 × 4 × 1 cm) was placed over the tablet (6). A three-blade stirrer[6] was placed 5 cm from the bottom of the beaker. The stirring speed was 60 rpm.

The tablet was placed on the sieve net, and the solvent was poured into the beaker. The dissolution test time was 3 min. Samples were taken at the stirring blade level through a filter[7] using a peristaltic pump which let the sample solution into the spectrophotometer flow-through cells[8]. The sample solution absorbance was registered automatically at 284 nm. Xylitol did not interfere. The dissolution rate was determined per tablet unit area (milligrams per square centimeter per hour).

RESULTS AND DISCUSSION

At a low drug content (<10%), the molten mixture solidification was slow. When the drug content was increased, however, the dispersion solidified quickly. A solid dispersion of xylitol–*p*-aminobenzoates increased

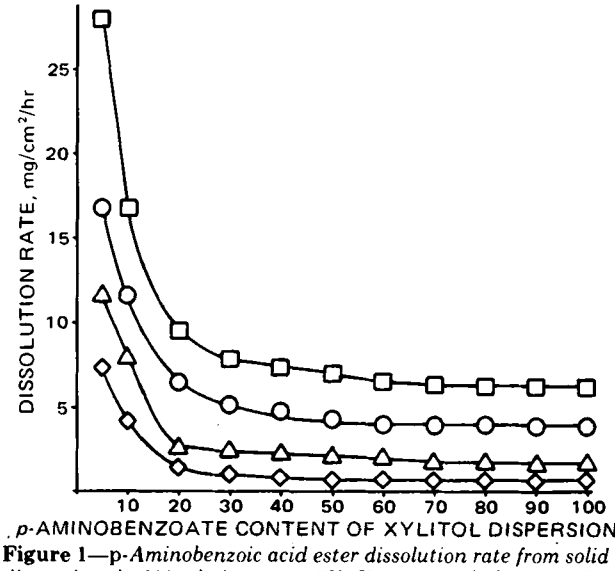

Figure 1—p-*Aminobenzoic acid ester dissolution rate from solid xylitol dispersions in 600 ml of water at 37°. Key:* □, *methyl* p-*aminobenzoate;* ○, *ethyl* p-*aminobenzoate;* △, *propyl* p-*aminobenzoate; and* ◇, *butyl* p-*aminobenzoate.*

[1] Purum, Fluka AG.
[2] ICN Pharmaceuticals.
[3] Pharmaceutical grade, Sokerikemia Oy, Xyrofin Ltd.
[4] Ströhlein, Düsseldorf-Stuttgart, West Germany.
[5] Matra-Werke G.M.B.H., type M 177.2, Frankfurt, West Germany.
[6] Nalgene 6160.
[7] Millipore, 0.22 μm.
[8] Unicam SP. 800A, Unicam Instruments Ltd.

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the *p*-aminobenzoate dissolution rate. The difference between several dissolution rate tests was less than ±5% during the first 3 min of dissolution when the surface areas of the tablets were still nearly identical. The dissolution rate was calculated over the portion of the dissolution profile that followed zero-order kinetics.

The increase in the dissolution rate as compared with that of pure drug tablets was greatest when the drug content was lowest. The dissolution rate of a xylitol dispersion containing 5% butyl *p*-aminobenzoate was about 10 times, per unit area, the pure drug dissolution rate. When the increase in area caused by dispersion of the drug with xylitol (1:20) was considered, the dissolution rate of a 5% dispersion was about 200-fold that of the pure drug. The dissolution rate of the methyl *p*-aminobenzoate dispersion was fivefold per unit area, which corresponds to a 100-fold increase in the dissolution rate of the pure drug when the increase in area is considered. When the dispersion drug content was 20–30%, the changes in the dissolution rate per unit area decreased. In this case, the increase in the dissolution rate was primarily due to an increase in area.

A curve depicting the dissolution rates as a function of the drug content of the dispersion was of nearly the same shape for each compound (Fig. 1). When the *p*-aminobenzoic acid ester alkyl group carbon chain was increased, the xylitol dispersion dissolution rate showed a nearly linear decrease.

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Pharmacokinetics of Drugs Subject to Enterohepatic Circulation

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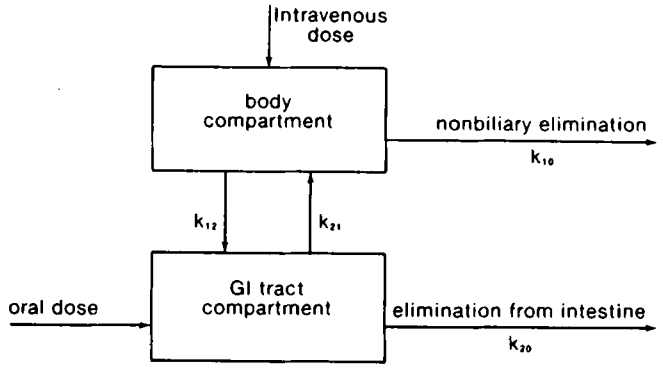
Abstract □ The influence of the changes in biliary excretion and reabsorption rates on the pharmacokinetics of drugs subject to enterohepatic circulation was examined analytically. A recently proposed two-compartment model with drug elimination occurring in each compartment was adapted to represent the body and the GI tract. Enhanced reabsorption was equivalent to biliary excretion rate reduction, except that the latter always decreased α and prolonged the α-phase half-life while the former always increased α and shortened the half-life. However, depending on the relative values of the two elimination rate constants, biliary excretion reduction (or reabsorption enhancement) could either increase or decrease the terminal drug half-life (β-phase). Whether the terminal drug half-life was prolonged or shortened, a biliary excretion reduction always increased the area under the plasma decay curve for intravenous and oral doses and also raised the steady-state drug level in the body for constant-rate intravenous infusion. As a consequence, the lethality, toxicity, or effectiveness of the drug will be increased for patients with impaired bile flow or enhanced drug reabsorption; therefore, the clinical dosage may have to be reduced.

Keyphrases □ Enterohepatic circulation—effect of biliary excretion and reabsorption rates on drug pharmacokinetics, two-compartment model □ Distribution—enterohepatic circulation, effect of biliary excretion and reabsorption rates, pharmacokinetics, two-compartment model □ Pharmacokinetics—enterohepatic circulation, effect of biliary excretion and reabsorption rates, two-compartment model

When a substance is excreted into the bile, passes through the lumen of the intestine, is reabsorbed, and then is carried to the liver *via* blood flow, it undergoes enterohepatic circulation or cycling. Many endogenous and exogenous substances (bile salts, morphine, methadone, methotrexate, digitoxin, *etc.*) can undergo enterohepatic circulation (1). Pharmacokinetic study of drugs subject to enterohepatic circulation has gained importance in recent years.

A two-compartment model representing the body and the GI tract was recently proposed by Harrison and Gibaldi (2) to describe the influence of cholestasis (bile flow reduction or discontinuance) on the elimination of drugs undergoing enterohepatic circulation. Scheme I shows the



Scheme I—Pharmacokinetic model for a drug subject to enterohepatic circulation.

pharmacokinetic model of the biliary excretion (k_{12}) and reabsorption process (k_{21}) of a drug eliminated by both compartments. Cholestasis was simulated numerically by reducing the transfer rate constant k_{12}. Results (2) suggested that cholestasis can either increase or decrease the terminal drug half-life ($T^{\beta}_{1/2}$), depending on the ratio of the two elimination rate constants k_{10}/k_{20}. If the ratio is greater than unity, cholestasis will increase β and reduce the drug half-life. The reverse is true if the ratio is less than unity. In contrast, a biliary excretion reduction will always decrease α and prolong the α-phase half-life.

Although the terminal drug half-life may be decreased, many experiments showed that drug lethality and toxicity are greater in animals with a ligated bile duct than in normal animals (1). Furthermore, since enterohepatic circulation is characterized by biliary excretion and reabsorption, the reabsorption influence on drug disposition should also be studied. In the present work, the effects of both processes on the pharmacokinetics of drugs undergoing enterohepatic circulation were examined analytically. The dependence of the drug half-lives, the area

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