ENHANCED ABSORPTION AND LYMPHATIC TRANSPORT
OF MACROMOLECULES VIA THE RECTAL ROUTE

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INTRODUCTION

The rectal route has long been known as a specific absorption means for the delivery of lipophilic small molecules. In general rectal delivery exhibits several advantages as summarized in Table 1.

Orally administered polypeptide drugs are degraded or metabolized by acid and/or enzymes in the stomach and small intestine, or are absorbed poorly, and thus have lowered bioavailability. By contrast, bioconversion of polypeptides hardly occurs in the lower digestive tract due to low enzymatic activity and neutral pH. However, the normal adult lower intestine is an impermeable barrier to the uptake of macromolecules (Dalmark, 1968; Warshaw et al., 1977; Taniguchi et al., 1980), and for effective drug therapy, the form of the drug must be modified to improve absorption, and to make delivery safe and efficient.

CHARACTERISTICS OF ENHANCED ABSORPTION BY PROMOTERS

Various investigations are being made presently towards enhancing the rectal absorption of poorly absorbable drugs, (for example see Nishihata et al. (1981)). Our first report in 1977 showed that the absorption of heparin through the large intestine was greater than that through the small intestine if aided by an adjuvant; a lipid-bile salt mixed micellar system (Muranishi et al., 1977).

At the beginning of the study we intended to apply the potential adjuvant effect to oral medication, but our results strongly suggested

Table 1. Advantages of Rectal Administration

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<td>1.</td>
<td>Safe and convenient administration, painless</td>
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<td>2.</td>
<td>Possible way to reduce drug degradation in gastrointestinal tract</td>
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<td>3.</td>
<td>By passing of the liver to avoid &quot;first pass&quot; elimination of high clearance drugs</td>
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<td>4.</td>
<td>Convenience to administer a large dose</td>
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S. S. Davis et al. (eds.), *Delivery Systems for Peptide Drugs* © Springer Science+Business Media New York 1986
that rectal administration was more suitable for inducing the absorption of macromolecules. Although we have used an aqueous solution or colloidal suspension of the promoters in animal experiments, a dosage formulation for rectal administration can be designed for therapeutic use as shown in Fig. 1.

![Fig. 1. Strategy for getting potential absorption of macromolecules](image)

When the designed suppository is administered to the rectal cavity, the macromolecular drug and promoter are released to be in close contact with the rectal and colonic mucous membranes. The promoters, such as monoolein, oleic acid, linoleic acid, capric acid, salicylic acid or their salts can act on the epithelial cells to allow permeation of the macromolecules. The molecules can then pass through the cells and enter both the blood and lymph capillaries.

Most promoters are lipophilic compounds which have a small hydrophilic moiety such as a carboxyl group. Some seem to have a surfactant action on the biomembrane (the mucous surface) and thereby modify the epithelium. However, it is evident by many experimental results that the absorption enhancing effect by these safe adjuvants is essentially different from the action of surfactants. Microscopic observations have failed to show severe damage such as disruption and loss of the surface of the mucosal cell membrane, on exposure to the promoters. As shown in