BIOADHESIVE GEL PREPARATIONS FOR RECTAL DRUG DELIVERY

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Many attempts have been made to use hydrogel as delivery systems for various drug and vioactive materials to prolong and control their pharmacological activities.

Rectal administration of drugs by using hydrogel bases, such as poloxamer ABA block copolymer (Pluronic F-127) gels, polyacrylic acid (Carbomer 934, 940, or 941) aqueous gels,and polyvilyl alcohol gels, have been reported on the preparation and potential suppository use of new gels(Eudragit L, Eudragit S, and Eudispert) that are block copolymers of methacrylic acid and methyl methacrylate.[1-6] These hydrogel and xerogel preparations, especially Eudispert hv gels, show excellent staying and bioadhesive effects in the lower part of the rectum in rats and rabbits compared with those of polyethylene glycol (PEG)2000 and Witepsol H-15(or S-55) suppositories. Visual and optical microscopic observation of rectal membrances indicated no irritation or abnormality after administration of Eudispert hv tydrogel and xerogel.

Anatomically, the superior rectal vein drains via the inferior mesenteric vein into the portal vein, and the inferior and middle rectal veins drain directly into the inferior vena cava via the internal pudendal vein and the internal iliac vein. Accordingly, active drug loss caused by first-pass metabolism may be avoided by rectal administration. Accordingly, drug administration in the lower part of the rectum is almost nonhepatic route for high-clearance drugs.

This presentation will show that the hepatic first-pass elimination could be avoided to a maximal degree when Eudispert hv hydrogel preparations containing a drug such as (I) lidocaine, (II) prooopentofylline,or (III) salicylamide were

administered in rabbits. Furthermore, rectal absorptions of (IV) 5-fluorouracil (5-FU), a typical hydrophilic drug which is poorly absorbable from the intestine, were studied by administering Eudispert gels with or without fatty acid rectally in rats.

(I) Rectal Gel preparations for Sustained-Release and Avoidance of Hepatic First-Pass Metabolism of Lidocaine.

After an oral administration of lidocaine HCI solution, the plasma concentration of lidocaine was considerably lower than that after intravenous administration for all time periods. The absolute bioavailability was 5.63%. For the Witepsol S-55 and PEF 2000 suppositories, the plasma levels of lidocaine were higher than those for the oral preparation, and Cmax and area under the plasma concentration-time curve (AUC) values significantly improved respectively. On the other hand, Eudispert hv hydrogel and xerogel preparations showes the characterstics of a sustained-release preparation, especially the xerogel preparation with 5 mEq NaOH. Absolute bioavailability for hydrogel and xerogel preparations increased significantly ($p<0.05$) by approximately 1.7-3.4 folds compared with those of Witepsol S-55 and PEG 2000 suppositories.

(II) Rectal Gel Preparation for Sustained Release and Avoidance of Hepatic First-Pass Metabolism of Propentofylline

Eudispert hv gels containing propentofylline, a new cerebral microcirculation-improving agent, were prepared and tested for avoidance of the first-pass metabolism of propentofylline through the liver and for sustauned release of propentofylline. The absolute bioavailability of propentofylline after oral administration was only 4% in rabbits. The relative bioavailabilities of propentofylline from PEG 2000 and Witepsol H-15 suppositories were approximately 8 and 16-fold, respectively, compared with oral administration. Furthermore, the absolute bioavailability of propentofylline from Eudiispert hv hydrogel and xerogel preparation was almost 100%. The results indicate that, in principle, drug loss caused by first-pass

metabolism may be avoided completely by placing Eudispert hv hydrogel and xerogel formulations in the lower part of the rectum for long periods.

(III) Rectal Gel Preparations for Sustained Release and Avoidance of Gastrointestinal and Hepatic First-Pass Metabolism of Salicylamide

Eudispert hv hydrogel and xerogel preparations containing salicylamide displayed sustained-release plasma profiles when compared with other conventional rectal preparations. The absolute bioavailability of salicylamide was 97.3% for the hydrogel preparation and 98.4% for the xerogel preparation. These results may arise because the gel preparation stays at the application site, the lower part of the rectum, over a fairly long period because of its bioadhesive force. Furthermore, the gastrointestinal and hepatic first-pass elimination of salicylamide can be avoided completely by rectal administration of these preparations.

(IV) Improvement of Rectal Bioavailability of 5-FU from Eudispert hv Rectal Gels

Following oral and rectal administration, 5-FU show an incomplete bioavailability, with may be due to the poor biomembrane permeability characteristics of the drug, as indicated by its high polarity (n-octanol/aqueous pH 7.4 buffer partition coefficient: log P = -0.96).
Absolutely and xerogel preparations increased to approximately 2.5 times those of Witepsol H-15 and PEG 2000 suppositories. Using n-carpric acid or linolenic acid as an absorption enhancer, absolute bioavailabilities of 5-FU improved to 1.85 or 2.24 folds for Witepsol H-15, 4.86 or 4.99 folds for PEG 2000 and 2.76 folds for 2.36 folds for Eudispert hv hydrogel preparations, respectively. The absolute bioavailability of 5-FU for Eudispert hv hydrogel with n-capric acid improved to nearly the same that for intravenous preparations (Frect = 95.55%).

It was suggested that the absorption enhancing effects Eudispert hv gels could be explained by solvent drag effect and addition of n-capric acid or linolenic acid in the hydrogel preparations might incease 5-FU permeability of

the rectal membrances. The cumulated in the rectal tissue homogenates showed the increasing tendency with the decrease of the bioavailabilities of 5-FU.

Accordingly, Conventional suppositories of 5-FU might be useful in the treatment of the colonal cancer, and Eudispert hv hydrogel with n-capric acid containing 5-FU administered rectally could be expected to aim at the systemic effects on carcinoma.

In conclusion, the hydrogel and xerogel preparations presented here are useful for rectal administration and highly valuable as the drug delivery systems. A varity of medicinal components, including those poorly absorbable as well as those easily inactivated by the first-pass effects of the liver, can be embedded in these hydrogel and xerogel preparations.

References

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