Evaluation of Gastrointestinal Mucoadhesive Patch System (GI-MAPS) Containing Caffeine as a Model Drug in Human Volunteers

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Introduction

A new oral delivery system, gastrointestinal mucoadhesive patch system (GI-MAPS) has been developed to overcome the problem of very low oral bioavailability of peptide/protein drugs. In our previous study, GI-MAPS preparations had improved the oral bioavailability of a model protein drug, granulocyte colony-stimulating factor (G-CSF) in beagle dogs. Therefore, the evaluation of the efficiency of GI-MAPS as a new oral delivery system was studied in human volunteers.

Methods

GI-MAPS preparations: GI-MAPS preparations were composed of three layers: 1) backing layer, made of water-insoluble polymer, ethylcellulose (EC), was prepared spreading 20% w/v EC solution on a teflon plate and dried at room temperature 2) adhesion site-controlling layer (enteric polymer membrane) was prepared from 20% w/v Eudragit L 100 by using the same method and 3) mucoadhesive drug-carrying layer prepared by mixing caffeine (50 mg), sodium salicylate (40 mg), HCO-60 (150 mg), 0.5 N NaOH (100 μl), deionized (DI) water (400 μl), and Carbopol (50 mg). Muco-adhesive drug-carrying layer was weighted and uniformly spread on backing layer, then covered with enteric polymer membrane. These three layers were sealed and cut into circular patches of 3 mm diameter, by a heat-sealing punching equipment. The patches (120 pieces) were filled into an enteric capsule (HP 55) along with effervescent powder. A solution of caffeine (50 mg), sodium salicylate (40 mg), DI water (400 μl) and 0.5 N HCl (100 μl) was filled into an enteric capsule (HP 55) as control.

In vitro release studies: The studies were performed by using USP XXI paddle apparatus (50 rpm) with 900 ml of pH 7.4 phosphate buffer maintained at 37.0 ± 0.5 °C as the release medium.

In vivo absorption studies: Three healthy human volunteers 23-33 years of age were participated in the study. The studies were carried out under both fasting and fed state. Saliva samples were collected for 1 min interval at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after administration of the test preparations.

Saliva caffeine assay: Analyses using HPLC system. The analytical column was chemcosorb 5-ODS-H. The mobile phase consisted of pH 3.5 phosphate buffer and acetonitrile (80:20 V/V). The detection wavelength was 275 nm and the flow rate was 0.8 ml/min.

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Pharmacokinetic parameters:
Pharmacokinetic parameters were determined from the salivary caffeine excretion rate vs. time data. The time when salivary caffeine excretion rate reached its maximum, T\text{max}, the maximum salivary caffeine excretion rate, R\text{max}, and the first appearance time of caffeine into the saliva, T\text{i}, were obtained from the authentic salivary excretion rate vs. time data. The area under the salivary caffeine excretion rate vs. time curve (AUC) and the area under the first moment curve (AUMC) after oral administration of the test preparations were calculated using trapezoidal rule up to the last measured point. The mean residence time after the first appearance of drug in saliva (MRT\text{i}) was calculated by dividing AUMC by AUC and then subtracting with the first appearance time of caffeine in the saliva.

Results
The release of caffeine from GI-MAPS was rapid in the in vitro study. GI-MAPS demonstrated a significantly (p<0.05) higher AUC (11.36±5.26 μg·h/min) and longer MRT\text{i} (4.79±0.29 h) than the control (AUC= 3.79±2.44 μg·h/min, MRT\text{i}= 2.04±0.66 h) under fasting state. A higher AUC (8.43 ± 5.66 μg·h/min) and a longer MRT\text{i} (3.21 ± 1.48 h) value with GI-MAPS preparation compared to the control (AUC = 3.59 ± 0.58 μg·h/min, MRT\text{i} = 1.93 ± 0.39 h) were obtained under fed state. However, we couldn’t find any significant difference (P<0.05) between the average AUC and MRT\text{i} values of GI-MAPS and the control preparation. However, the influence of food on MRT\text{i} and AUC of GI-MAPS preparations was clearly obtained in two volunteers. MRT\text{i} values were decreased from 5.04 to 2.62 h and 4.46 to 2.29 h and AUC values were decreased from 17.44 to 11.91 μg·h/min and 8.26 to 4.23 μg·h/min in subjects 1 and 3, respectively.

Discussion
The increase in AUC and MRT\text{i} of salivary caffeine excretion rate is ascribed to the increased resident time of GI-MAPS at the absorption membrane as a result of bioadhesion. The mucoadhesive polymer, Carbopol, was thought to form gel structure in the small intestine and adhere to the intestinal wall. The prolonged residence time of GI-MAPS by sticking to the mucus layer at the site of absorption resulted in high drug concentration gradient between the system and the enterocytes thereby increasing the drug diffusion through trans cellular and paracellular routes. The lower AUC and MRT\text{i} values obtained under fed state study might be explained by the complexation of the mucoadhesive polymer with food contents. The increase in pH of GI tract after food intake also might have influenced the surface charge of both mucus membrane and polymer and it might have affected the degree of hydration and viscosity of mucoadhesive polymer that could reduce the adhesive strength between mucus membrane and polymer.

Conclusions
1) Significantly higher AUC and MRT\text{i} with GI-MAPS than with the control establish the superiority of GI-MAPS as a oral drug deliver system.
2) Food intake may affect the delivery efficiency of GI-MAPS.