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Increased oral absorption enhancement of insulin by medium viscosity hydroxypropyl cellulose

Mounir Mesiha *, Madiha Sidhom

Division of Pharmaceutics, A & M Schwartz College of Pharmacy, Long Island University, 75 DeKalb Av., Brooklyn, NY 11201, USA

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Abstract

The hypoglycemic effect of orally given insulin was studied on rabbits, using two different absorption promoters, and two different carriers. The effects of hydroxypropyl cellulose (HPC) of different degrees of substitutions (Klucel® GF, MF, and HF), and consequently of different viscosities, on the oral bioavailability of insulin have been studied. The fatty acid-Brij® system was not affected by the HPC studied, while the salicylate-cellulose system resulted in a significantly better absorption of insulin in the presence of the medium viscosity Klucel®. More than 70% reduction in blood glucose levels was achieved for rabbits, treated with the salicylic acid-Klucel MF-Avicel® system containing 5 units of insulin per kg of animal weight.

Keywords: Peptide transport; Insulin; Hydroxypropylcellulose; Viscosity; Absorption site clearance; Bioadhesive

1. Introduction

Oral insulin therapy might offer a means of improving portal levels of insulin, in order to mimic the physiological route of insulin secretion. The peripheral hyperinsulinaemia associated with other insulin regimens was claimed to be an important factor in the development of artherosclerosis in long-term treatment (Gwinup et al., 1990; Kennedy, 1991). Many attempts to improve oral bioavailability of insulin have been reported, including the addition of enhancers (Mesiha and El-Bitar 1981; Nishihata et al., 1981; Lee and Yamamoto, 1990) and enzyme inhibitors (Morishita et al., 1992). The rapid clearance of the administered dose from the site of administration is another barrier limiting the absorption of peptide and protein drugs (Lee, 1991). The available literature pays little attention to the effect of vehicles on oral absorption of insulin (Mesiha, 1981; Cho and Flynn, 1989). The purpose of this study was to maximize insulin oral absorption by extending the contact time at the site of absorption, using viscosity controlling additives.

2. Materials and methods

2.1. Materials

Porcine regular insulin solution (Iletin®-R U-100, Eli Lilly), hydroxypropylcellulose (HPC;

* Corresponding author.

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Klucel® GF, MF and HF, Hercules) and microcrystalline cellulose (MCC; Avicel® PH-102, FMC) were used. Other chemicals were analytically pure grade.

2.2. Animals

Male white rabbits weighing 2850 ± 200 g were fed with pelleted chow. All animals were fasted overnight before test, but water was provided *ad libitum*.

2.3. Blood glucose determination

The Glucometer® II (Ames) was used to measure rabbits' blood glucose content through standardized glucose oxidase strips (Glucostix, Ames).

2.4. Preparations

Two different systems were prepared for the study containing granular particles of screen size 12/14 and 10% w/w of HPC. The HPC grade GF low viscosity, MF medium, and HF high viscosity were used alternatively. The first system contained 10% w/w sodium salicylate as the absorption promoter in an MCC matrix. The second system contained HPC of different viscosity grades in stearic acid medium, using 5% Brij®-35 as the absorption promoter.

The concentration of the HPC was arbitrarily chosen. In the first system, MCC was thoroughly mixed with HPC and granulated with the insulin solution containing the sodium salicylate. The stearic acid system was prepared by melting the stearic acid with the surfactant and allowed to congeal, then mixed with the HPC. The insulin solution was incorporated into the mix by simple trituration in a small glass mortar.

Similar systems containing all ingredients and devoid of insulin served as control. One formulation was prepared with HPC MF grade and no absorption enhancer was prepared for testing the enhancing effect of HPC on insulin absorption.

2.5. Hypoglycemic effect

12 California rabbits were investigated in a cross-over latin square design. Animals were fasted over 18 h before starting the test. The insulin delivery systems were accurately weighed into dry stomach tubes, flushed by 5 ml of air, followed by 10 ml of water through a syringe attached to the stomach tube. The insulin dose was 5 U/kg.

Insulin absorption was monitored by its effect on blood glucose level. Blood samples were obtained from the external marginal ear vein before the test and at 30 min intervals over a 2 h period. Blood glucose level was determined immediately after sample withdrawal, using the Glucometer®, and was expressed as a percentage of the initial level.

Student's t-test was used to compare the hypoglycemic effect of different formulations with the control data at the same time intervals. A p value of 0.05 or less was considered significant.

3. Results and discussion

The hypoglycemic effect of the studied preparations was taken as a monitor for insulin absorption in its physiologically active form. Control experiments devoid of insulin did not differ from the normal blood glucose-time profiles of the fasted rabbits under similar conditions. Orally given insulin solution with no additives at the same or double the dose showed no reduction in blood sugar. Insulin is not absorbed due to the penetration and enzymatic barriers (Lee and Yamamato, 1990). Salicylate-insulin preparations, containing no HPC, have been tested on a limited number of animals, two rabbits. The two rabbits tested suffered from gastric bleeding and the experiment was discontinued. The local irritating effect of salicylates is well documented in the literature.

The rapid clearance of protein drugs from the site of absorption was considered to be another barrier for insulin absorption (Lee, 1991). This was illustrated in nasal protein drug delivery research, where desmopressin absorption was greater with the more viscous carriers (Harris, 1986). Hydroxypropylcellulose was chosen for this study because of its solubility and gel formation properties. The Brij®-stearic acid system has been

Table 1
Hypoglycemic effect of oral insulin given to rabbits, 5 U/kg in Brij®-stearic acid dispersions containing hydroxypropylcellulose of different viscosity grades

Viscosity grade of HPC	Percent of blood glucose level relative to initial level after time (min)				n
	30	60	90	120	
Control	99 ± 1.17	108 ± 2.96	114 ± 1.04	93 ± 6.69	5
GH (low)	83 ± 1.52 [a]	95 ± 0.98	75 ± 1.78 [b]	76 ± 7.90	6
MF (medium)	54 ± 2.27 [b]	64 ± 6.06 [b]	88 ± 0.71 [b]	113 ± 17.07	6
HF (high)	68 ± 5.25 [b]	90 ± 13.65	120 ± 12.56	116 ± 15.52	6

[a] $p < 0.05$;
[b] $p < 0.01$ compared with the control data at similar time intervals.
Data represent the mean ± standard deviation. GH, MF, and HF are viscosity grades for Klucel® brand of HPC.

studied before (Mesiha and El-Bitar, 1981). The incorporation of HPC into the system did not provide much advantage over the previous system in terms of hypoglycemic effect (Table 1). Reduction of the irritating effect of the surfactant enhancer might be an advantage, which needs to be studied further.

The effect of viscosity inducing HPC was significant in the case of the salicylate-cellulose system (Table 2). The rate and extent of oral insulin absorption from systems with HPC were dependent on the viscosity grade. Significant reduction ($p < 0.01$) of blood glucose level was recorded during the first 30 min after the medium viscosity grade (MF) preparation, with the salicylate enhancer, was administered. This effect extended with the same significant hypoglycemic effect over the 2 h of the test. Insignificant reduction in blood glucose level was recorded with insulin formulations containing low or high viscosity grades of HPC during the first 30 min after oral administration. The high viscosity (HF) system exhibited a lag time of 30 min followed by a steady slow rate of insulin release resulting in a gradual reduction in blood sugar. This might be due to diffusion-controlled release, which depends on the diffusion coefficient of insulin in the viscous film, its concentration gradient and the thickness of the film (Grass and Robinson, 1990). This same correlation explains the faster effect of the medium viscosity grade system (MF), with the expected higher diffusion rate than the HF system, and relatively slow clearance rate from the absorption site. The mobility of the GF or low viscosity grade system resulted in less absorption enhancing effect for insulin, due to faster clearance and the lower concentration gradient at the site of absorption.

We can conclude from the above data that combining the oral insulin absorption enhancer with a bioadhesive substance of medium viscosity can increase the bioavailability of oral insulin.

Table 2
Hypoglycemic effect of oral insulin given to rabbits, 5 U/kg in salicylate-MCC dispersions with hydroxypropylcellulose of different viscosity grades

Viscosity grade of HPC	Percent of blood glucose level relative to initial level after time (min)				n
	30	60	90	120	
Control	98 ± 6.25	116 ± 9.36	120 ± 12.39	122 ± 13.50	6
MF, no salcilyate	85 ± 15.29	96 ± 8.85	97 ± 1.78 [a]	101 ± 3.50 [a]	4
GH (low)	86 ± 9.25	88 ± 6.94 [a]	95 ± 3.35	86 ± 8.22	6
MF (medium)	64 ± 3.66 [b]	57 ± 8.14 [b]	57 ± 2.58 [b]	43 ± 17.07	6
HF (high)	97 ± 5.88	92 ± 8.65	96 ± 9.47 [a]	86 ± 5.89 [a]	5

[a] $p < 0.05$;
[b] $p < 0.01$ compared with the control data at similar time intervals.
Data represent the mean ± standard deviation. GH, MF and HF are viscosity grades of Klucel® brand of HPC.

Fatty acid dispersions are not affected, probably because of a different mechanism of absorption promotion.

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