Sodium Carboxymethyl Cellulose Loaded with Vildagliptin for Diabetic Delivery: In Vitro and In Vivo Evaluation of Nanoparticles

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ABSTRACT SUMMARY
Vildagliptin-loaded mucoadhesive nanoparticles using sodium carboxymethyl cellulose were prepared by spray drier to retain the drug in the stomach for a prolonged period of time and provide sustain release. The SEM of the nanoparticles was found to have smoother surface with shriveled shape. Drug loading and the percentage recovery were 92.2 ± 0.5 and 93 ± 0.4 respectively. Particle size was found to be 580 nm. The percent swelling of formulation was found to be 172±6%. In vivo studies in rats suggest that the vildagliptin was retained in the GIT for prolonged period of time (~12 h).

INTRODUCTION
Diabetes is now one of the utmost common non-communicable diseases universally. At present oral antidiabetic drugs do not directly restore the complex secretory role of the islet cells, and are also limited by side effects. Vildagliptin is a DPP-4 inhibitor considered most methodically in clinical trials Regrettably, one of the main weaknesses of using vildagliptin is its biological half-life of ~2 hours and is eliminated rapidly, it is recommended that patients need to be adhered strictly to the dosing intermission with two doses of 50mg per day. Mucoadhesive drug delivery systems announce abundant benefits that arise from localization at a specified target site, including the minimization of oscillations in drug concentrations in the blood and lengthy residence time at the site of drug absorption. Many scientists have confirmed the possible use of sodium carboxymethyl cellulose as mucoadhesive agents, which retain the drug in the abdominal for an extended period of time and provide controlled release. In accepting of the above evidences, experiments were carried out to develop and evaluate sustained release mucoadhesive formulations of vildagliptin.

EXPERIMENTAL METHODS
Nanoparticles were prepared BUCHI nano spray dryer with 1% solution of sodium carboxymethyl cellulose and vildagliptin. The spray nozzle was 7 µm; inlet and outlet temperature was maintained at 120 °C and 35°C respectively. The percentage recovery and drug loading efficiency were calculated according to the formulas below.

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\text{Percentage recovery} = \frac{\text{Amount of nanoparticles}}{\text{Sum of initial materials}} \times 100
\]

\[
\text{Drug loading efficiency (％)} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100
\]

The surface morphology of the nanoparticles was characterized by scanning electron microscope (SEM). The particle size distribution was determined using a Malvern Zetasizer Nano Series Nano-SZ. The mucoadhesive of nanoparticles was confirmed according to methods described previously and our published data. Concisely, a freshly cut piece of intestine of rabbit were obtained. A known quantity of nanoparticles was placed on mucosal surface. Successively, nanoparticles were washed with phosphate buffer solution (pH 7.4) at the rate of 5 ml/min using a peristaltic pump. The time required for separating all the nanoparticles from mucosal surface of the rabbit intestine was documented by visual inspection.

In vitro release profile of formulations was studied using conventional dialysis method. Known quantity of spraydried vildagliptin nanoparticles were placed in dialysis membrane (MWCO 12–14 KDa, Sigma-Aldrich), and dialyzed against 500mL of PBS pH 7.4. At predetermined time intervals samples were withdrawn and analyzed by LC-MS.
G.I.T. Distribution Studies was carried out by using Sprague Dawley strains of male rats (6 – 8 months, 200 ± 10g) were selected GIT distribution studies. The animals were equally divided into six groups of five animals each. One group served as a control and received 3.0mg /kg. The other groups received equivalent amount of drug in formulation. The doses were given orally using a rubber tube. After 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, and 12 h, the animals were cut and GIT were isolated and residue in stomach was removed cautiously by tweezers and drug concentration analysed by LC-MS method.

RESULTS AND DISCUSSION
The drug loading and the percentage recovery were 92.2 ± 0.5 and 93 ± 0.4 respectively. In comparison with old-fashioned approaches spray dryer gives maximum possible yields of fine particles. Particle size of the formulation was found to be 580 nm. The particle size consistency is very essential because the target region of the nanoparticles including the drug is influenced on the size of the particle, bioavailability and the plasma drug concentration will fluctuate if the size deviation is varied.

The surface morphology was visualized by SEM studies and found to be smoother surface with shriveled shape nanoparticles might be due to lack of surfactant. Since, the formulation considered staying in GIT for extended time; we did not use a surfactant in our preparation due to the possible toxic residue upon oral administration in gastro-intestinal tract (GIT). Vildagliptin-loaded sodium carboxymethyl cellulose nanoparticles display an important drug release (24 ± 5%) in the first 30 min corresponding to a significant initial burst effect followed by a slow release up to 12 h (97 ± 0.5%). The release mechanism followed peppas model with R² = 0.9925. The percent swelling of CVN formulation was found to be 172±6%.

The mucoadhesive result of formulation and pure drug in rats were evaluated at different time intervals. When vildagliptin solution (standard) was given orally, the drug concentration decreased to 98.4% within 3 hours which was significantly low. On the contrary, the formulation of vildagliptin started to decrease from the 0.5 hour (24%) and this decrease continued up to the 12th hour (97%). The results indicated that sodium carboxymethyl cellulose due to its acrylic acid backbone, high molecular weight and negatively charged carboxyl groups on the side chains forces the molecules to form very sticky fluids in the presence of mucin and extended the residence time of the nanoparticles in the GIT.

CONCLUSION
Mucoadhesive drug delivery is a valuable means of directing drugs to the GIT and can be used for delivery of effective anti-diabetic therapy. Our outcomes can also be used to cultivate an operative blueprint for targeted stomach-specific drug delivery, and can be explored further in vivo with other drugs, using a slight alteration in the procedures used here for preparation of the nanoparticles.

REFERENCES

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