Novel artificial cell microencapsulation of a complex gliclazide-deoxycholic bile acid formulation: a characterization study

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Abstract: Gliclazide (G) is an antidiabetic drug commonly used in type 2 diabetes. It has extrapancreatic hypoglycemic effects, which makes it a good candidate in type 1 diabetes (T1D). In previous studies, we have shown that a gliclazide-bile acid mixture exerted a hypoglycemic effect in a rat model of T1D. We have also shown that a gliclazide-deoxycholic acid (G-DCA) mixture resulted in better G permeation in vivo, but did not produce a hypoglycemic effect. In this study, we aimed to develop a novel microencapsulated formulation of G-DCA with uniform structure, which has the potential to enhance G pharmacokinetic and pharmacodynamic effects in our rat model of T1D. We also aimed to examine the effect that DCA will have when formulated with our new G microcapsules, in terms of morphology, structure, and excipients’ compatibility. Microencapsulation was carried out using the Büchi-based microencapsulating system developed in our laboratory. Using sodium alginate (SA) polymer, both formulations were prepared: G-SA (control) at a ratio of 1:30, and G-DCA-SA (test) at a ratio of 1:3:30. Complete characterization of microcapsules was carried out. The new G-DCA-SA formulation was further optimized by the addition of DCA, exhibiting pseudoplastic-thixotropic rheological characteristics. The size of microcapsules remained similar after DCA addition, and these microcapsules showed no chemical interactions between the excipients. This was supported further by the spectral and microscopy studies, suggesting microcapsule stability. The new microencapsulated formulation has good structural properties and may be useful for the oral delivery of G in T1D.

Keywords: type 2 diabetes, bile acids, gliclazide, polymer

Introduction
Diabetes mellitus is a metabolic disorder classified as type 1 diabetes (T1D) or type 2 diabetes (T2D). T1D is an early-onset autoimmune disease marked by the destruction of β-cells of the pancreas, resulting in a partial or complete lack of insulin production and the inability of the body to control glucose homeostasis.1 T2D is a metabolic disorder with later onset and is most common in the overweight population.2 T2D is caused by genetic and environmental factors, with recent studies showing that loss of function gene variants in GPR120 have a strong association with increased risk of T2D complications.3,4 Gliclazide (G) is an antidiabetic drug used in T2D to enhance insulin secretion, and has beneficial extrapancreatic effects that render it potentially useful in T1D.5 In general, controlled absorption of G from the gut is required in order to prevent sharp fluctuations in the blood glucose levels after food intake. About 30% of a G dose undergoes enterohepatic recirculation, which may contribute to the observed high bioavailability, but also high interindividual variability in its absorption after an
oral dose. Thus, bile acids (BAs) may play an important role in enhancing G ileal absorption and optimize its efficacy and safety profiles.

BAs are known to act as permeation enhancers for antidiabetic drugs through the ileal mucosa and through the blood–brain barrier. BAs have also shown potential health benefits in diabetes treatment through their endocrinological, metabolic, energy expenditure, and other known and unknown effects. Combining BAs with G is anticipated to optimize G’s antidiabetic effect. Our studies have shown the significant antidiabetic effects of the combination in a rat model of T1D. One of the potential applications of BAs on G is through enhancing its permeation. A recent study in our laboratory has demonstrated that the BA, deoxycholic acid (DCA), enhanced G permeation through the blood–brain barrier in T1D rats. In order to design this microencapsulated formulation of gliclazide-deoxycholic acid-sodium alginate (G-DCA-SA), a suitable polymer is needed.

Commonly used polymers in drug microencapsulation technology include sodium alginate (SA), chitosan, and pectin. They are biocompatible and present no signs of clinical toxicity. SA is the salt of alginic acid, a natural polysaccharide derived from seaweed, and consisting of variable percentages of (1→4)-linked β-d-mannuronic acid and α-l-guluronic acid residues. In order to design a novel microencapsulated formulation that targets the lower intestine, low-viscosity SA (LVSA) is a good choice.

This study aimed to design a novel G-DCA-SA microencapsulated formulation, using LVSA, that is uniform, biocompatible, and thermally stable and which has the potential for optimized G delivery.

Materials and methods

Materials

G (99.92%), LVSA (99%), and DCA (99%) were purchased from Sigma-Aldrich Co (St Louis, MO, USA). Calcium chloride dihydrate ([CaCl$_2$.2H$_2$O] 98%) was obtained from Scharlab SL (Barcelona, Spain). All solvents and reagents were supplied by Merck (Darmstadt, Germany), and were of high-performance liquid chromatography (HPLC) grade and used without further purification.

Drug preparation

Stock suspensions of G (20 mg/mL) and DCA (1 mg/mL) were prepared by adding the powder to 10% Ultra-soluble gel of 100 mL HPLC water. The CaCl$_2$ stock solution (2%) was prepared by adding CaCl$_2$ powder to HPLC water. All preparations were mixed thoroughly at room temperature for 4 hours, stored in the refrigerator, and used within 48 hours of preparation.

Preparation of microcapsules

Microcapsules of G-loaded LVSA were prepared using a Büchi-based microencapsulating system that operates through jet-flow microencapsulation. Parameters were set in a frequency range of 1,000–1,500 Hz and a constant flow rate of 4 mL/min. Polymer solutions containing SA and G with or without DCA were made up to a final concentration (of G-DCA-SA) in a ratio of 1:3:30, respectively. This ratio was based on our previously published work and was found to exhibit maximum consistency and best morphology. Two formulations were prepared, one with G (1 mg/mL) in SA solution (30 mg/mL) and the other with G (1 mg/mL) and DCA (3 mg/mL). Microcapsules were collected from our microencapsulating system and, for each formulation, three independent batches were prepared and tested separately (n=3). All microcapsules (G-loaded and G-DCA-SA-loaded microcapsules) were prepared and treated in the exact same way. Microencapsulation efficiency was calculated as a percentage based on the total amount of G recovered, divided by total G used.

Characterization of loaded microcapsules

Morphology, size analysis, and chemical characterization of microcapsules

All microcapsules were freshly made, stored in the refrigerator, and used within 48 hours of preparation. The appearance and size of microcapsules were examined using light microscopy followed by scanning electron microscopy (SEM) and energy dispersive X-ray (EDXR) spectrometry. The particle size distribution and mean particle size diameter were calculated using SmartSEM V05.03NV software (Carl Zeiss AG, Jena, Germany).

SEM and EDXR spectroscopy

The surface morphology of the microcapsules was examined using SEM (Zeiss Neon 40EsB FIBSEM; Carl Zeiss AG) with 0.8 nm calibrated resolution. The chemical characterization of the microcapsules was examined using EDXR (AztecEnergy EDS Analysis Software, Oxford Instruments, Oxfordshire, UK). Electron micrographs of G and G-DCA-SA microcapsules were obtained using SEM, and their chemical characterization was obtained using EDXR. The samples were mounted on a glass stub with double-sided adhesive tape and coated under vacuum with platinum (5 nm) in an argon atmosphere prior to examination. Micrographs with different magnifications were recorded to study the morphological...
and surface characteristics of the microcapsules. Multiple images at various scales and angles were taken, and those that best captured the details of the surface morphological changes were used.

**Determination of dispersing media viscosity**

Fifteen milliliter aliquots (n=3) of both preparations (G-SA and G-DCA-SA) were taken from freshly prepared solutions, and the viscosity was measured at room temperature using a Visco 88 viscometer (Malvern Instruments Limited, Malvern, UK). The temperature remained constant at 23°C throughout the experiment (monitored by the Visco 88).

**Differential scanning calorimetry (DSC) analysis**

DSC thermograms of G, DCA, and LVSA powders, their physical mixture, and their microencapsulated formulations were carried out on a DSC instrument (DSC 8000; Perkin-Elmer Inc., Waltham, MA, USA). Five milligram samples were placed in sealed aluminum pans and heated at 20°C/min under a nitrogen atmosphere (flow rate 30 mL/min) in the 35°C–240°C range. An empty aluminum pan was used as a reference. The equipment was calibrated for baseline and temperature with zinc metal.

**Fourier transform infrared spectroscopy (FTIR) studies**

FTIR spectra of the pure components, their physical mixture, and the microcapsules were recorded via an attenuated total reflectance FTIR spectrometer (Spectrum Two™; PerkinElmer), and infrared measurements were performed in transmission in the scanning range of 450–4,000 cm⁻¹ at room temperature. The same G to SA and G to DCA to SA ratios as those analytically determined in the microcapsules were used for preparing the different physical mixtures that served as controls.

**Results and discussion**

**Morphology, size analysis, and chemical characterization of microcapsules**

Microcapsules were obtained using LVSA polymer, G, and DCA at a constant ratio of 30:1:3, respectively. Using our microencapsulation system, we were able to form microcapsules of a similar size. The mean diameters ranged from 1,000 to 1,150 µm for all batches of both formulations. The mean particle size was not significantly affected by the presence of DCA (Figure 1). Microencapsulation efficiency remained similar, at 93±5% for G-SA and 90±7% for G-DCA-SA.

**SEM**

SEM studies of a G-SA microcapsule (Figure 2) and G-DCA-SA microcapsules (Figure 3) represent randomly selected microcapsules from a few freshly made batches. SEM results show microcapsules of consistent uniformity and well-defined spherical shapes. G-SA microcapsules (Figure 2) appeared slightly larger in size than the G-DCA-SA microcapsules (Figure 3). The microcapsule size difference between different formulations was not statistically significant. Due to the high-resolution images, we were able to conclude that the surfaces of the microcapsules were rough but consistent from one microcapsule to another in the sample used for all analyzed batches (Figures 2B–D and 3B–D).

![Figure 1 G-SA microcapsules (A) and G-DCA-SA microcapsules (B).](image)

**Abbreviations:** G-DCA-SA, gliclazide-deoxycholic acid-sodium alginate; G-SA, gliclazide-sodium alginate.
These high-resolution images also revealed ridges on the surface of the microcapsules with small crystal depositions. The small crystals distributed throughout the microcapsule surfaces were believed to be sodium chloride (NaCl), which was confirmed by EDXR spectroscopy studies, as discussed below (Figures 4 and 5).

**EDXR spectroscopy**

In order to further analyze the composition of the microcapsule surface for the G-DCA-SA formulation, EDXR was used to identify the various surface crystal depositions and microcapsule composition including, various ions present on the surface of the microcapsules. Analysis of
crystal depositions on the microcapsule surfaces (Figure 5) revealed high levels of Na and Cl ions, confirming that there were small crystals of NaCl on the surface of G-DCA-SA microcapsules; this was expected, given sodium chloride is a by-product of the ionic-gelation methodology of microcapsule production.\textsuperscript{16,19,20} Both formulations showed high levels of sulfur, oxygen, and carbon, confirming the presence of G within the polymer matrix for the formulation, although carbon and oxygen are also common to DCA and SA. As for the microcapsule surface composition, EDXR revealed high levels of calcium, carbon, and oxygen, which were expected, given the microcapsule wall structure and DCA-reinforced calcium alginate matrix system.
The EDXR assessment of G-SA microcapsules is shown in Figure 4, which reveals the surface where analyses were done. Figure 4A shows the core of the G-SA microcapsule with the corresponding EDXR spectrum (Figure 4C). The spectrum shows a high concentration of the sulfur (S) atom, unique to the drug G, as no other excipient in the formulation contains S atoms. The spectrum also reveals high concentrations of calcium (Ca) and oxygen (O), which are likely to correspond to the surrounding calcium alginate membrane. Figure 4B, on the other hand, is an analysis of the surface, with the corresponding EDXR spectrum shown in Figure 4D. Figure 4D shows predominant Ca and O activity corresponding to the general surface composition, with some S detected, likely due to the deposition of small drug crystals nearby or to the penetration of electron rays in the membrane deep enough to detect the encapsulated drug.

An example of an EDXR assessment of G-DCA-SA microcapsules is shown in Figure 5A, with the respective spectrum of the microcapsule surface. In Figure 5C, the microcapsule surfaces were not perfectly homogenous, thus varying crystal depositions could occur at selected sites across the microcapsule surface. Figure 5A exemplifies the core of the G-DCA-SA microcapsules, and Figure 5C shows a high concentration of S atoms, which is expected from G molecules. Figure 5B illustrates the surface surrounding the drug in the G-DCA-SA microcapsules, and Figure 5D shows a high concentration of Cl and Ca atoms, which are expected to adhere to the surface of the microcapsules. These atoms derive from the used vehicle carrying the formed microcapsules (CaCl₂). Furthermore, Figure 5C and D show the chemical characteristics of the microcapsules, with dominant ions (Na, O, Ca, and Cl) that are expected for typical G-DCA-SA microcapsules prepared via ionic-gelation methodology.

**Viscosity of the microencapsulated formulation**

Table 1 shows the viscosity, shear rate, shear stress, and torque force for all microencapsulated formulations under various speeds (20, 35, 61, 107, 187, 327, 572, and 1,000 rpm). The G-SA formulation was more viscous, but both formulations behaved as almost non-Newtonian fluids under shear stress. Thus, and as anticipated from our previous studies, both formulations behave as thixotropic non-Newtonian fluids under increasing stress, as evidenced by parallel reductions in their apparent viscosity. Further evidence of the thixotropic-pseudoplastic behavior of both formulations can be seen in the proportional increases in torque and shear rate following rising shear stress forces and associated decrease in the viscosity, characteristic of non-Newtonian fluid, and thixotropic behavior of the polymer. The application of the stirring rod in the solutions at increasing speeds resulted in the solutions forming rapid circular motions away from the site of centripetal force origin, suggesting that both formulations also behaved in a non-Weissenberg fashion.

**Thermal analysis of the microcapsules**

DSC is an important technology for the thermal characterization of various materials. DSC establishes a connection between temperature and specific physical properties of substances, such as crystallization and melting temperature. It is commonly used to determine the enthalpy

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**Table 1** Viscosities and related parameters of both microencapsulated formulations: G-SA and G-DCA-SA (n=3)

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Setting</th>
<th>Speed (rpm)</th>
<th>Viscosity (mPa·s)</th>
<th>Shear rate (s⁻¹)</th>
<th>Torque (mN·m)</th>
<th>Shear stress (Pa)</th>
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Abbreviations: G-DCA-SA, gliclazide-deoxycholic acid-sodium alginate; G-SA, gliclazide-sodium alginate; UD, undetected (below the instrument limit of detection).
associated with the process of microencapsulation.\textsuperscript{29} In microencapsulation, DSC measures how physical properties of G and DCA molecules change, along with temperature against time.\textsuperscript{30,31} This occurs through determining the temperature and heat flow (35°C–240°C) associated with G transitions as a function of time. DSC spectra were analyzed for G powder (Figure 6A), DCA powder (Figure 6B), SA powder (Figure 6C), G-DCA-SA powder (Figure 6D), G-SA microcapsules (Figure 6E), and G-DCA-SA microcapsules (Figure 6F).

DSC analysis of DCA powder (Figure 6B) showed a small peak at 178°C, indicative of a DCA melting point. A similar peak at 179°C was clearly observed with G analysis (Figure 6A), which is indicative of its melting point. The DSC analysis of DCA and G microcapsules (Figure 6F) showed transparent and interference-free integration of two predominant peaks - one corresponding to G, and the other a slight shift to the right when compared to individual DCA and SA powders, which could represent possible chemical interactions between SA and DCA in the microcapsule matrix, alterations in the crystallinity of DCA and SA within the temperature range used for analysis, or polymorphism leading to an endothermic shift to the right.\textsuperscript{32,33}

As for the G-SA microcapsule (Figure 6E) analysis, there was a very similar graph with two prominent peaks – one representing G (160°C), and the other the SA powder (193°C), and could represent plasticization of the polymer.\textsuperscript{34} SA powder (Figure 6C) showed a significant peak at 200°C, indicative of the endothermic thermal behavior of the polymer and in line with the SA peak observed at 200°C in G-DCA-SA microcapsules (Figure 6F).\textsuperscript{35} G was not chemically modified or did not participate in any significant reaction, as evidenced by endothermic peaks characteristic of the drug following analysis of the microcapsules.\textsuperscript{36,37} This was confirmed by the combined powders of G, DCA, and SA (Figure 6D), which showed two peaks representing the G and SA peaks, which was a slight shift from the original G peak, thus suggesting that there were no significant chemical interactions occurring between DCA, G, and SA in the powder form. However, there remains the possibility of G and DCA

Figure 6 Differential scanning calorimetry thermograms of G powder (A), DCA powder (B), SA powder (C), G-DCA-SA powder (D), G-SA microcapsules (E), and G-DCA-SA microcapsules (F).

Abbreviations: DCA, deoxycholic acid; G-DCA-SA, gliclazide-deoxycholic acid-sodium alginate; G-SA, gliclazide-sodium alginate; SA, sodium alginate; G, gliclazide.
peaks overlapping. Overall, this indicates good stability of G and DCA in the formulated microcapsules. Interestingly, the DCA peak (Figure 6B) noted in the DCA individual powder did not appear in the G-DCA-SA powder mixture of the combined powders (Figure 6D). This may be due to a shift in the thermal capacity within the 35°C–240°C range, or to interactions or potential crystallinity.30,37 The DCA peak was absent in the G-DCA-SA microcapsules, possibly due to DCA formulated in the combined G-DCA-SA microcapsules existing in an amorphous or disordered crystalline phase as well as a solid state solution (Figure 6F).37

The shift in the thermal profile of G in the microencapsulation form (Figure 6E) suggests that the drug solubilizes in the polymer matrix via ionic interactions, while no significant chemical reaction takes place between G or any of the formulation excipients, as shown by FTIR studies (Figure 7) and previous in vivo and ex vivo work in our laboratory.14,34,38–40 Comparing all peaks, G does not apparently participate in significant crosslinking reactions, and retains its chemical integrity during the microencapsulation process, as evidenced by FTIR studies.

FTIR spectral studies

The FTIR spectra were used to confirm the chemical compatibility of G with the SA polymer and DCA in the microencapsulation formulation. FTIR spectra were analyzed for G powder (Figure 7A), DCA powder (Figure 7B), SA powder (Figure 7C), G-DCA-SA powder (Figure 7D), G-SA microcapsules (Figure 7E), and G-DCA-SA microcapsules (Figure 7F).

Figure 7 Fourier transform infrared spectra of G powder (A), DCA powder (B), SA powder (C), G-DCA-SA powder (D), G-SA microcapsules (E), and G-DCA-SA microcapsules (F).

Abbreviations: DCA, deoxycholic acid; G-DCA-SA, gliclazide-deoxycholic acid-sodium alginate; G-SA, gliclazide-sodium alginate; SA, sodium alginate; G, gliclazide; T, transmittance.
microcapsules (Figure 7E), and G-DCA-SA microcapsules (Figure 7F).

The spectrum of G-SA for the C=O band in carbonyl group shows a sharp peak at 1,707 cm⁻¹ (Figure 7A), which was consistent across both microencapsulated formulations (Figure 7E and F) and powder mixture (Figure 7D). Again, for the S=O band in sulfonamide, the G-SA spectra show peaks at 1,161 cm⁻¹, and for the amino group, peaks of 3,260 cm⁻¹ in the microcapsules and powder mixture. For DCA powder (Figure 7B), the spectrum is in line with previously published work. In G-DCA-SA microcapsules (Figure 7F) and G-DCA-SA powder (Figure 7D), there was a small shift of the G peak to the right (1,603 cm⁻¹). This may be due to the dilution of DCA concentration in the mixture, or may occur during the microencapsulation process. The more likely reason is the dilution of the powder in the G-DCA-SA mixture, which is in line with the thermal analysis above (Figure 6D). In addition, the FTIR spectrum of SA powder (Figure 7C) is consistent with the literature; however, the spectra of G-DCA-SA microcapsules and G-DCA-SA powder mixture seem to be weaker and seem to display less bond-peak activity. This may be due to the dilution of the sample, which is consistent with the thermal analysis of the G-DCA-SA powder mixture (Figure 7D). Overall, FTIR spectra of G suggest that microencapsulation of G with SA and DCA does not significantly compromise the chemical composition and structural integrity of the G molecules, as no significant chemical reaction occurred between the drug and any of the formulation excipients.

Conclusion

Microencapsulation of G and DCA is a novel and viable technique that is useful for targeted drug delivery. The new formulation designed in this study displays appropriate excipient compatibility and structural morphology with thixotropic-pseudoplastic behavior. This microencapsulated formulation is expected to ensure adequate encapsulation of labile compounds, such as primary BAs, which seem beneficial in conjunction with G, in diabetes treatment. Along with the use of microencapsulation, DCA will play a crucial role in optimizing G absorption in the ileum, which will help to further increase its antidiabetic effect. However, more work is needed to better evaluate the drug release profile from the microcapsules. The authors’ future study aims at investigating the release kinetics of the formulation in various pH and temperature values and establishing its targeted delivery characteristics, which is anticipated to have significant impact on future in vivo studies.

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Disclosure

The authors report no conflicts of interest in this work.

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