The Forgotten Material: Gelatin-Based Inhalable Microcapsules Formulated By A Simple Ionic Complex Approach As A Platform For Controlled Pulmonary Drug Delivery

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INTRODUCTION

The development of inhalable controlled release platforms is of great interest in aerosol science due to the need for multiple dosing when treating chronic diseases such as asthma and COPD. However, the number of excipients used for inhalation is limited compared to the parenteral route making it difficult for any technology based on non-approved polymers to reach the market. From this restrictive list of excipients, gelatin (Figure 1) is a biodegradable polymer used for controlled release formulations and accepted by the FDA at high doses in the lung (100 mg daily) [1]. The last is probably because gelatin is released to some extent after piercing the capsules containing the formulation during the actuation of dry powder inhalers. Therefore, gelatin rises as a promising candidate for developing a new generation of controlled release inhalable formulations with rapid regulatory approval. To our knowledge, several research publications are available on manufacturing spray-dried gelatin microparticles for controlled drug release. However, this is the first time gelatin has been proposed as a matrix system for delivering inhalable drugs using the ionic complex formation interaction. The study proposes using a drug-gelatin ionic complex approach to encapsulate the drug and control its release from the matrix using as crosslinkers either the drug itself or calcium carbonate (also accepted for inhalation by the FDA). Gelatin type A was used to generate a positively charged carrier for drugs. SC is a drug that has been used for the treatment of chronic diseases such as asthma. However, its half-life is short (< 2 hours) and requires between three to four daily doses to achieve a therapeutic effect. Therefore, this study selected this drug to evaluate the ionic complex formation with positively charged gelatin.

STUDY AIM

To determine if the ionic complex approach allows for the formulation of gelatin microcapsules capable of reducing the diffusion rate of sodium cromoglycate (SC) more efficiently. Additionally , the swelling properties of the gelatin will be evaluated as an alternative mechanism to escape from the macrophage uptake.

EXPERIMENTAL METHODS

Preparation of inhalable gelatin microcapsules by spray drying:

Carrier-free inhalable formulations of SC encapsulated on gelatin were prepared by spray drying after an optimization process using a DOE Box-Behnken approach (data not shown). Gelatin A has an isoelectric point of pH= 9 and carries an overall positive charge when dispersed on distilled water (pH 5.5). On the other hand, gelatin B has a lower isoelectric point of pH = 5 and is negatively charged when exposed to basic media [2]. To promote the anionic state of gelatin B, the pH of the media was raised to 7.4 using sodium hydrogen carbonate. SC was used as a drug model since it has the potential to work as a crosslinker by itself after interacting with positively charged gelatin. However, calcium carbonate was also used as an additional crosslinker as part of the ionotropic interaction strategy. All the formulations used FDA-approved excipients under their daily limit dose (table 1).

Table 1: Formulations prepared to evaluate the effectiveness of the ionic complex strategy on the controlled release of the ionic drug model

Formulation	Content
SC	Sodium cromoglycate
GA + SC	Gelatin A + sodium cromoglycate
GB + SC	Gelatin B + sodium cromoglycate
GA + SC +CC	Gelatin A + sodium cromoglycate + calcium carbonate
GB + SC +CC	Gelatin B + sodium cromoglycate + calcium carbonate

The feeding solutions were prepared at 1% w/w, dissolving gelatin type A or B in distilled water (pH 5.5). For gelatin type A, sodium cromoglycate was dissolved immediately after, and allowed to interact with the gelatin for 30 minutes. For gelatin type B, the negatively charged form of gelatin was promoted by adding a solution of sodium hydrogen carbonate (0.3 M at 40°C), increasing the pH of the solution to 7.4. After this step, SC was added to the solution. Finally, for the crosslinked formulations, calcium carbonate was added to the solutions and allowed to rest for 10 minutes before atomization. The feeding solutions were atomized using a Büchi Mini Spray dryer B- 290 (Büchi, Labortechnik AG, Switzerland), obtaining dry powders formulations of the inhalable gelatin-based microcapsules. Spray-dried gelatin microcapsules powder were stored at 20°C in desiccated condition.

Aerodynamic performance characterization

The aerodynamic performance of the spray-dried formulations was evaluated using the Next Generation Impactor™ (Copley Scientific Limited, United Kingdom). Every formulation was aerosolized using a High-Resistance RS01 Monodose DPI (Plastiape), with an airflow of 57 L/min, generating a pressure drop of 4KPa. The powder formulations were loaded with 20 mg of the formulation. Each sample was recollected using phosphate buffer pH 7.4 and heated to 60° C to ensure the maximum dissolution of SC.

Particle swelling assessment

The swelling properties of the gelatin microcapsules were determined by laser diffraction using the Sympatec HELOS-R (Sympatec GmbH, Clausthal-Zellerfeld, Germany). The formulations were dispersed on ethanol 99% for 5 seconds to reach a homogeneous suspension. Then, the suspension was immersed into a small volume cuvette (7 mL) with buffer phosphate pH 7.4. The laser diffraction device was set to measure the particle size of the dispersion every 30 seconds for 20 minutes.

Dissolution Test (Franz diffusion cell)

The release profiles of the gelatin microcapsules were determined using Franz diffusion cell. Each formulation was analyzed in triplicate with 5 mg of the formulation. The microcapsules were placed on a glass fiber filter and loaded into the Franz diffusion cell. Buffer phosphate pH 7.4 was used as a dissolution medium at 37 °C. The concentration of SC released from the microparticles was analyzed using UV spectrophotometry at λ = 345 nm using a spectrophotometer Synergy H1M (Biotek Instruments, Santa Clara, CA, US). Standards of SC were prepared in phosphate buffer pH 7.4, and linearity over the range 1.0–20.0 µg/ml was observed (R2 = 0.999).

RESULTS

Gelatin microcapsules were highly dispersible

Overall, the FPF of all carrier free formulations was above 60% (Figure 1), showing a good correlation with the results obtained from the DOE performed with the placebo gelatin microcapsules. The theory of opposite charge interactions between the positively charged gelatin (type A) and SC obtained the highest performance. At the same time, the rest of the formulations did not present significant differences in their aerodynamic performance.

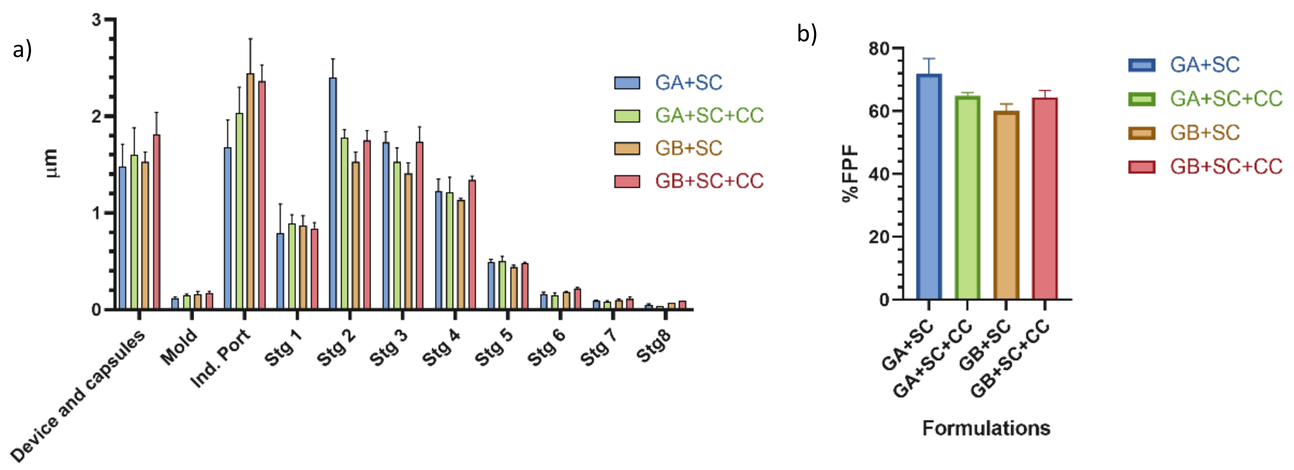

Figure 1: Aerodynamic properties of gelatin microcapsules. a) Comparison of deposition patterns in the NGI of each inhalable formulation b) Comparison of the fine particle fraction (%) of the inhalable gelatin microcapsules.

Ionic interaction between gelatin and CS decreases the diffusion rate

The dissolution profile of CS released from the gelatin matrix was measured using the Diffusion Franz cell system (Figure 2). Formulation SC shown a slower release from the gelatin matrix at formulation GA+SC. The release was not as slow as expected but it presents an opportunity to explore the ionic interaction.

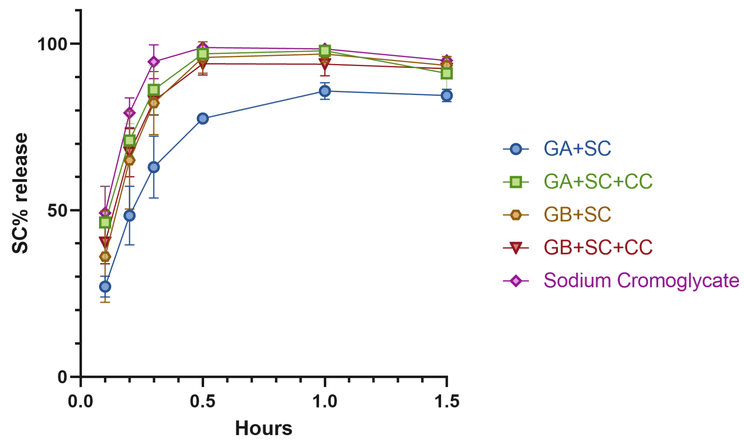

Figure 2. Dissolution test by Franz diffusion of sodium cromoglycate gelatin microcapsules and the non-encapsulated drug.

Microcapsules made of gelatin type A are capable of swelling

The swelling capacity of all formulations is summarized in figure 3. All formulations using gelatin type A presented swelling behavior during the time that the test was performed.

Overall, formulations based on gelatin B had a discrete or non-increase in particle size after five minutes of being dispersed on the buffer. The formulation of SC interacting with the positively charged gelatin type A presented a significant increase in particle size, describing a rapid swelling behavior.

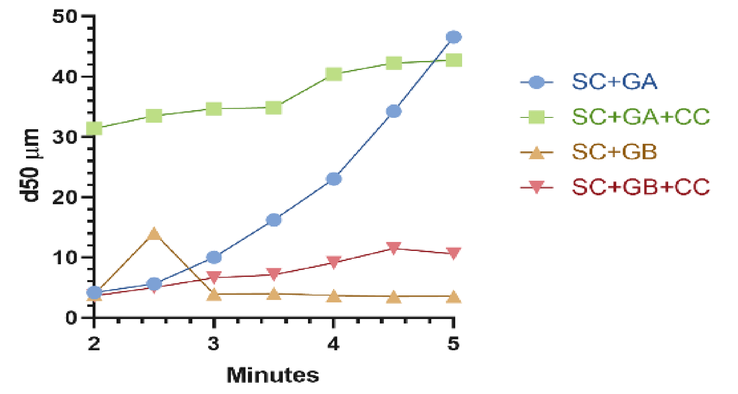

Figure 3. Particle size of gelatin-based microcapsules measured by laser diffraction when exposed to buffer phosphate pH 7,4 for five minutes. Data are presented as the d_{50} of the particle size distribution at each time point.

CONCLUSIONS

The strategy of ionic interaction between gelatin A and anionic drugs allowed to create a highly dispersible formulation with controlled release of sodium cromoglycate. These microcapsules swell rapidly when exposed to an aqueous media, which can be a mechanism to prolong their residence time on the lung.

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