

Research Article

Physicochemical Development and Characterization of a Hydroxyapatite-Biocompatible Polymer Matrix for Controlled Insulin Release

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Abstract

This study investigates the controlled release of insulin from composite matrices based on hydroxyapatite and Eudragit® polymers, with the aim of developing an efficient and tunable oral or implantable insulin delivery system. Hydroxyapatite was synthesized by chemical precipitation method with a Ca/P molar ratio of 1.66, closely mimicking the stoichiometry of biological apatite, and subsequently thermally treated at 800°C to enhance its crystallinity, mechanical strength, and structural stability. Two distinct matrix formulations were developed using Eudragit® RSPM and Eudragit® RS100, two pH-independent, water-insoluble polymers known for their controlled permeability properties, and were thoroughly characterized in terms of their technological and pharmacotechnical properties. Evaluation demonstrated good matrix cohesion, adequate hardness, and full compliance with mass uniformity requirements according to pharmacopoeial standards. In vitro release studies conducted under physiologically relevant conditions revealed clearly differentiated kinetic profiles depending on both the formulation type and the insulin loading dose. The first batch exhibited a classical first-order release kinetics, achieving complete insulin release over an extended period of seven days, suggesting a diffusion-controlled mechanism. In contrast, the second batch displayed a sigmoidal release profile accurately described by the Boltzmann equation ($r^2 = 0.99$), characterized by a marked acceleration phase beginning on the third day, indicative of a more complex release mechanism. These findings demonstrate that insulin loading significantly influences the release mechanism and overall kinetics, highlighting the strong potential of hydroxyapatite-polymer composite matrices for the rational design of advanced controlled insulin delivery systems.

Keywords

Composite Matrix, Hydroxyapatite, Eudragit, Polymers, Insulin, Controlled Release

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1. Introduction

An active pharmaceutical ingredient alone does not constitute a medicinal product; it generally requires an appropriate pharmaceutical carrier or delivery system to ensure effective administration within the body [1]. Medication intake and patient compliance with prescribed dosing regimens depend on several factors, among which the most common are dosing frequency [2], treatment duration, route of administration, and the occurrence of adverse effects.

In many cases, poor treatment adherence is associated with repeated drug administration, which frequently leads to missed doses that may compromise therapeutic efficacy or delay, and in some instances negate, the intended therapeutic outcome. In this context, the development of novel pharmaceutical formulations could contribute not only to improving drug efficacy but also to enhancing patient adherence throughout the treatment period, notably by reducing dosing frequency and/or minimizing adverse effects. With respect to reducing dosing frequency, controlled-release drug delivery systems represent a particularly promising approach.

With the aim of developing devices capable of controlled drug release, we designed systems intended to ensure the sustained and continuous delivery of an active molecule, namely insulin. The objective of the present study was therefore to develop novel formulations and to evaluate the controlled release of insulin from a hydroxyapatite-based matrix. Hydroxyapatite is a ceramic material with a chemical composition similar to that of bones and teeth, which confers excellent biocompatibility and makes it a suitable excipient for the controlled delivery of active pharmaceutical substances [3–5].

2. Materials and Methods

2.1. Laboratory Materials

The equipment used for the preparation of the delivery systems and for the investigation of drug release profiles included a porcelain mortar (EGEC 124-65), plastic molds with a diameter of 12 mm (Aventis Pharma, Dakar, Senegal), 10 mL and 100 mL Pyrex glass graduated cylinders (Prolabo, Paris, France), graduated pipettes of 1, 5, and 10 mL (Suprema, Prolabo, Paris, France), a 500 μ L Eppendorf precision pipette, adjustable Finn timer micropipettes (50, 100, 150, and 200 μ L), a Mettler H16 analytical balance, a D135-I drying oven (Kowel), Pyrex volumetric flasks of 50, 100, 250, 500, and 1000 mL (Prolabo, Paris, France), a mercury thermometer (–40 to 250°C) (Prolabo, Paris, France), a heated magnetic stirrer (Fisher Scientific, USA), Pyrex Erlenmeyer flasks (Prolabo, Paris, France), a 50/0.1 cm³ Aspin burette, a Volca 33-55 muffle furnace (Prolabo, Paris, France), a UV-visible spectrophotometer (Jenway 6300), Pyrex vacuum flasks (Prolabo, Paris, France), test tubes (16 $\times$ 150 mm) (Deltalabo, Barcelona, Spain), alumina crucibles (Prolabo, Paris, France), porcelain Büchner funnels (Prolabo, Paris, France), and Whatman filter

papers.

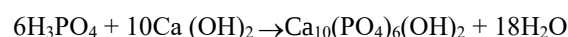
The insulin used in this study was Actrapid® HM, a human insulin produced by Novo Nordisk using recombinant DNA (rDNA) technology in *Saccharomyces cerevisiae*. Following subcutaneous administration, its maximum plasma concentration is typically reached between 1.5 and 2.5 hours. Actrapid® HM is indicated for the treatment of type I diabetes mellitus.

Hydroxyapatite powder was used as the main excipient for the development of the controlled-release systems. The polymers Eudragit® L100 and Eudragit® RS PM were also employed in the formulation of the matrices.

2.2. Methods

2.2.1. Preparation of Hydroxyapatite

Hydroxyapatite was prepared by direct precipitation by adding, under continuous stirring, a 0.3 M phosphoric acid (H₃PO₄) solution at a flow rate of 25 mL·min^{–1} to a freshly prepared 0.5 M calcium hydroxide (Ca(OH)₂) suspension, according to the following reaction [4–7]:

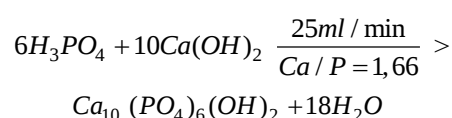


The Ca/P molar ratio was fixed at 1.66. The precipitation reaction was carried out under continuous stirring, either at 20°C (sample no. 1) or at a temperature ranging between 80 and 95°C (sample no. 2).

When precipitation was performed at 20°C, stirring was maintained for 45 min after completion of phosphoric acid addition. The resulting suspension was then allowed to age for 24 h. The precipitate was recovered by filtration and dried in an oven with a gradual temperature increase from 40 to 80°C over 24 h, followed by a holding period of 5 h at 80°C. Heating the precipitate at 80°C allowed the formation of stoichiometric hydroxyapatite [6–8].

When precipitation was carried out at elevated temperatures (80–95°C), both stirring and heating were maintained for 20 min, after which heating was stopped while stirring was continued for an additional 25 min. The suspension was then aged for 24 h, and the subsequent steps (filtration and drying) were identical to those described above.

The obtained hydroxyapatite powder samples were subsequently calcined at 600°C, 800°C, 1000°C, and 1200°C for 3 h, with a heating rate of 4°C·min^{–1} (Table 2), in order to promote hydroxyapatite crystallization and to obtain powders with different granulometries [4, 5].



2.2.2. Characterization

X-ray diffraction (XRD)

The samples were characterized by X-ray diffraction using a D500 diffractometer (Siemens, Karlsruhe, Germany) equipped with a front quartz crystal monochromator (Co $K\alpha_1$ = 0.178897 nm). The characteristic diffraction peaks of hydroxyapatite (JCPDS file No. 9-432) were observed in the XRD patterns of all samples.

However, the diffraction patterns of sample 2 exhibited significantly sharper and better-defined peaks compared to those of sample 1, indicating a higher degree of crystallinity. In addition, the continuous background was lower for sample 2,

suggesting a reduced proportion of amorphous phase relative to sample 1. Furthermore, diffraction peaks corresponding to tricalcium phosphate $\text{Ca}_3(\text{PO}_4)_2$ (α -TCP) were absent after calcination in sample 2, whereas they were still detected in sample 1 (Table 1) [4, 9-11].

The hydroxyapatite obtained after calcination of sample 2 at 600°C, 800°C, 1000°C, and 1200°C was well crystallized and free of detectable impurities (Figure 1). Consequently, this sample was selected for the development of controlled-release systems. For this reason, all subsequent characterizations were performed exclusively on sample 2.

Table 1. Crystalline phases identified by X-ray diffraction as a function of precipitation temperature and maturation time, after a 3-hour dwell at different calcination temperatures [4].

Sample	Precipitation temperature (°C)	Maturation time (h)	80 °C	600 °C	800 °C	1000 °C	1200 °C
Sample 1	20	24	Apatite + amorphous phase	Apatite + amorphous phase	Apatite	Apatite + α -TCP	Apatite + α -TCP
Sample 2	80-95	24	Apatite + amorphous phase	Apatite	Apatite	Apatite	Apatite

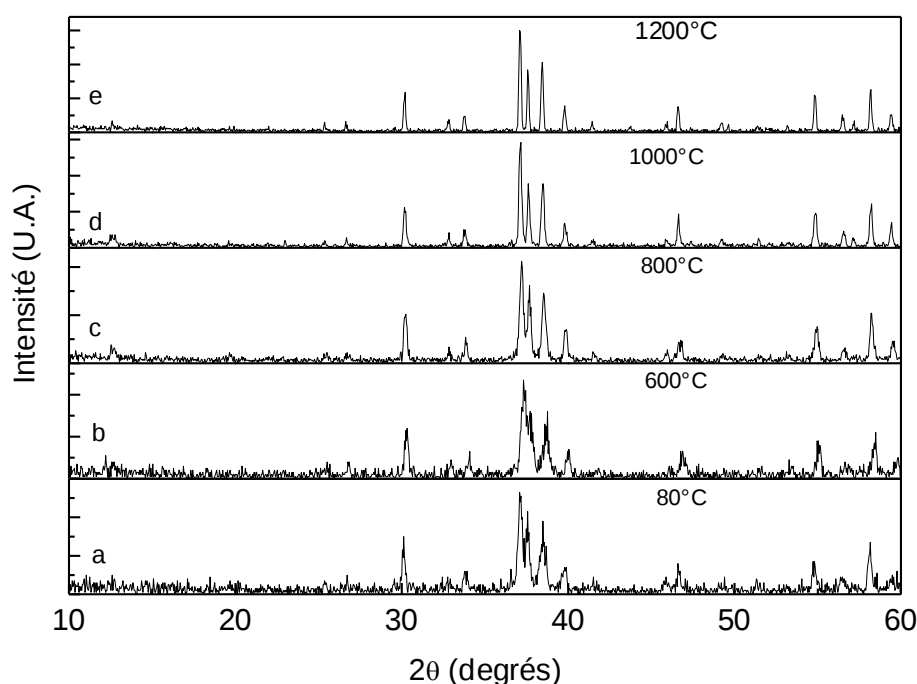


Figure 1. X-ray diffraction patterns of thermally treated hydroxyapatite (Sample 2).

XRD patterns of hydroxyapatite precipitated at 80-95°C and dried at 80°C (a), after calcination in air for 3 h at 600°C (b), 800°C (c), 1000°C (d), and 1200°C (e), showing progressive improvement in crystallinity [4].

Infrared Spectroscopy (FTIR)

FTIR spectra of Sample 2 before and after calcination were obtained using an ATI Mattson Genesis Series FTIR™ spectrophotometer (GMI, Strasbourg, France). All spectra closely

matched that of standard synthetic hydroxyapatite (Figure 2), confirming the preservation of the apatite structure after thermal treatment. The presence of hydroxyl groups was evidenced by absorption bands at 3571 and 630 cm^{-1} , whereas

the characteristic phosphate (PO_4^{3-}) vibrational modes appeared at 571, 601, 962, and 1040-1080 cm^{-1} [10, 11].

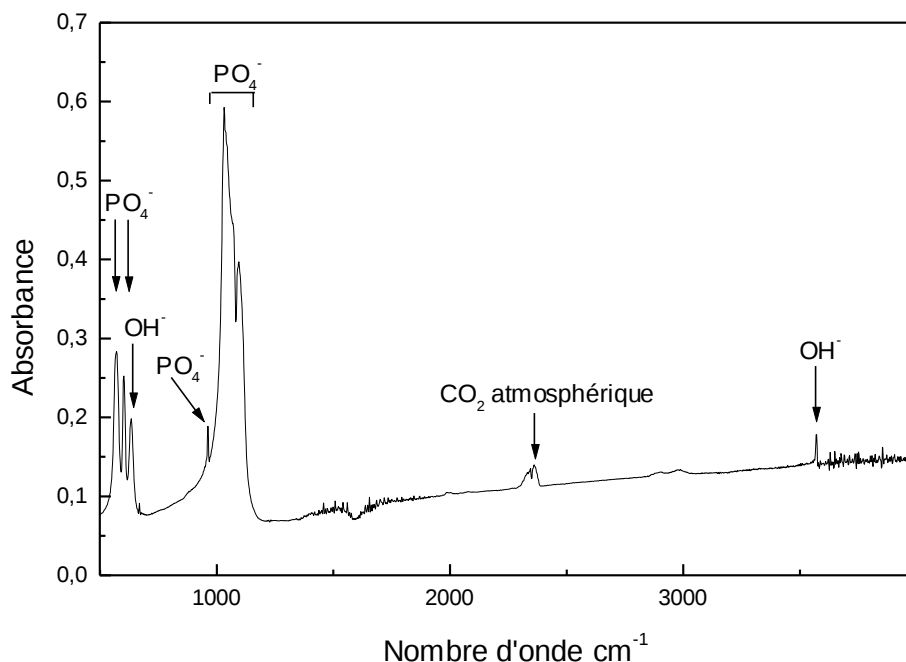


Figure 2. FTIR absorption spectrum of the hydroxyapatite sample calcined at 800°C for 3 h [4].

Specific surface area of powders

The specific surface area of Sample 2 and of the powders obtained after thermal treatment of Sample 2 (Table 1) was determined by nitrogen adsorption using the BET method with

a Sorpty 1750 apparatus (Carlo Erba Strumentazione, Milan, Italy). The results show that the specific surface area increases with increasing calcination temperature up to 800°C, beyond which a marked decrease is observed.

Table 2. Variation of the specific surface area of the powder precipitated at 80-95°C as a function of thermal treatment temperature (BET method).

Annealing temperature (°C)	80	600	800	1000	1200
BET surface area (m^2/g)	40	50	75	7	5

Selected Powder Samples

The powder selected for the preparation of the hydroxyapatite-polymer composite system intended for the controlled release of insulin was calcined hydroxyapatite (CHA). This material was obtained from non-calcined hydroxyapatite, which was first filtered and dried in an oven at 80°C for 24 h, followed by calcination at 800°C for 3 h.

The resulting calcined hydroxyapatite exhibited a specific surface area of 75 m^2/g and consisted of particles with sizes ranging from 100 to 200 nm. Prior to use, all powder samples were sieved through a mesh with a nominal aperture size of 250 μm to ensure particle size homogeneity.

Preparation of the Controlled Release Systems

The controlled release of active pharmaceutical ingredients from hydroxyapatite-based matrices relies on the ability of this material to adsorb and retain bioactive compounds. Numerous studies have demonstrated the relevance of hydroxyapatite for the development of controlled release systems, either in the form of tablets intended for oral or buccal administration or as cement-based systems for bone-related applications [4, 12-18].

In this context, insulin-controlled release systems were developed using calcined hydroxyapatite in combination with

Eudragit®-type polymers. The resulting formulations consisted of hydroxyapatite, the active ingredient (insulin), and polymeric binders, namely Eudragit® RS PM and Eudragit® RL 100, the latter being used as an external-phase binder.

The manufacturing process was based on the prior adsorption of insulin onto hydroxyapatite, followed by homogeneous mixing with the selected polymers. The resulting mixtures

were then molded into plastic cavities and dried at room temperature. This protocol enabled the preparation of two distinct batches, each consisting of ten hydroxyapatite-polymer-drug systems intended for the evaluation of insulin-controlled release behavior.

The composition of the different batches is summarized in Table 3.

Table 3. Composition of the different hydroxyapatite-polymer-insulin systems expressed as weight percentages.

Batch	Annealed HAp (%)	Eudragit® internal (%)	Eudragit® external (%)	Insulin (%)
Batch 1	76.79	15.38	7.7	0.135
Batch 2	76.65	15.38	7.7	0.270

For each batch, ten units were prepared; the molds used (blister cavities) had a diameter of 12 mm and a depth of 4 mm (Figure 3).

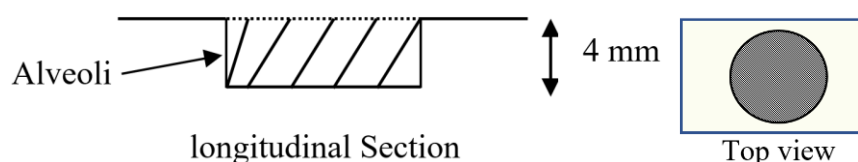


Figure 3. Schematic representation of the homogeneous systems.

All the prepared systems were weighed after oven drying, allowing the determination of the mean mass, standard deviation, as well as the minimum and maximum masses.

3. Results

3.1. Evaluation of the Systems

Mass uniformity test

All the prepared systems were weighed after drying at ambient temperature. The mean mass, standard deviation, as well as the minimum and maximum masses permitted according to pharmacopoeial requirements were then calculated.

All the studied batches were found to be compliant; indeed, we observed that:

$$m_{\text{ext}} = m_{\text{moy}} \pm 0,050m_{\text{moy}}$$

The results of these calculations are reported in Table 4.

Table 4. Pharmacotechnical parameters of the systems.

Batch	Mean mass (g)	Standard deviation (g)	Authorized maximum (g)	Authorized minimum (g)
Lot 1	0.103	$1.99 \cdot 10^{-5}$	0.10815	0.09785
Lot 2	0.104	$3.95 \cdot 10^{-5}$	0.1092	0.0988

Study of insulin release

The insulin release study was carried out in an aqueous medium. For each batch, the experiment was performed on three units of known mass. Insulin concentrations were determined

using the Biuret method.

The mean cumulative release profile was calculated from a calibration curve, as shown in Figure 4:

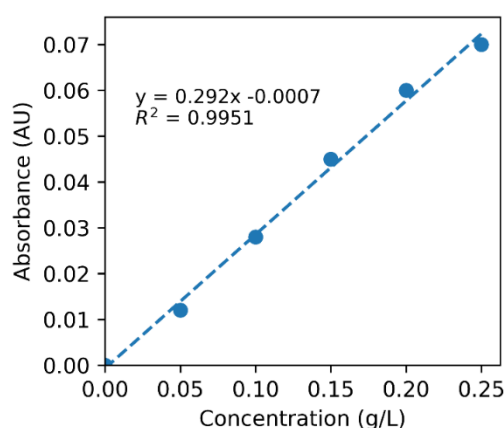


Figure 4. Calibration curve.

Insulin release was evaluated *in vitro* using a standardized protocol. The experiments were carried out in cylindrical plastic vessels with a capacity of 150 mL, containing 100 mL of distilled water and sealed with a screw cap to minimize evaporation. Representative samples from each batch were immersed in the dissolution medium without agitation and maintained at room temperature.

Aliquots of 2 mL were withdrawn every 24 h, and each sampled volume was immediately replaced with an equal volume of distilled water after homogenization of the medium by gentle inversion of the vessel. The collected samples were mixed with 5 mL of Biuret reagent, and the amount of insulin released was quantified by measuring the optical density at 550 nm using a UV-visible spectrophotometer (Jenway, model 6300).

3.2. Release Profiles of the Systems

Since ceramic-based controlled release systems do not release their entire active substance load within 12 hours, sampling was performed every 24 hours. The release studies conducted on the different batches were carried out over a period of 7 days. The results are presented in the form of curves and tables. The amounts of insulin released, expressed as milligrams per unit surface area Q (mg/cm²), as a function of time for the samples from batch 1 are shown in the following figure:

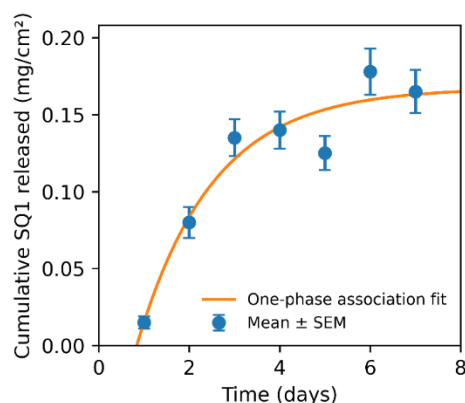


Figure 5. Insulin release profile of batch 1 expressed as mg/cm².

From analysis of the release curves, a first-order kinetic release profile can be identified. This behavior can be described by the following relationship:

$$Q = y_0 + A_1 e^{-x/t}$$

Q is the amount of insulin released per unit surface area at time t ;

y_0 is the amount of insulin released per unit surface area after seven days;

A_1 is a dimensionless constant;

t is the characteristic time constant of the release process

For both batches, a higher dissolution efficiency was observed at lower insulin loadings, except during the initial phase up to day 3, where this trend was not clearly established. By examining the shape of the release curves for batch 2, it can be observed that the release profiles can be modeled using the Boltzmann equation, which describes a sigmoidal behavior. This relationship is expressed by the following equation:

$$Q = \frac{A_1 - A_2}{1 + e^{(x - x_0)/dx}} + A_2$$

Q represents the amount of insulin released;

A_1 and A_2 are release constants corresponding to the lower and upper asymptotes of the sigmoidal curve;

x_0 is the time corresponding to the inflection point of the release curve;

dx is the characteristic time constant related to the slope of the release profile.

The amounts released, expressed as milligrams per unit surface area Q_i (mg/cm²), as a function of time for batch 2 are shown in the following figure. The modeling parameters as well as the correlation coefficient were calculated using Origin® software (version 6.1) and are also presented in Figure 7.

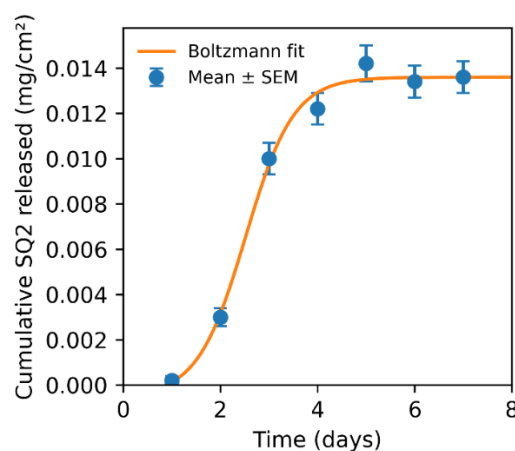


Figure 6. Insulin release profile of batch 2 expressed as mg/cm².

In Figures 7 and 8, the percentages of insulin released Q_i (%) from the matrices are presented. It can be observed that

the batches of systems containing the lowest insulin concentrations exhibit faster release compared with batches formulated with higher insulin loadings.

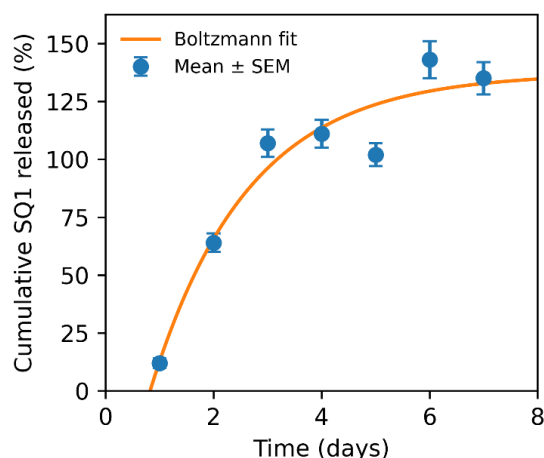


Figure 7. Percentage of insulin released from batch 1.

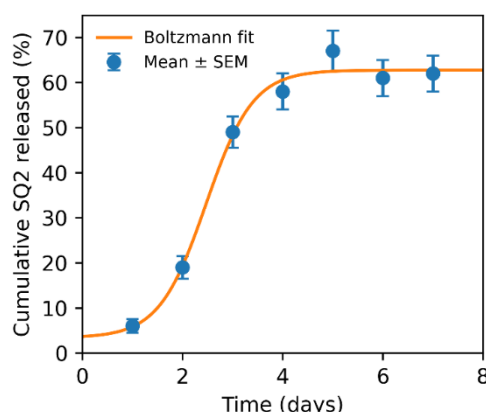


Figure 8. Percentage of insulin released from batch 2.

The mean insulin dissolution efficiencies for both batches were calculated. This parameter was proposed by Khan [20] and is defined as the ratio between the area under the dissolution curve up to time t and the area of the rectangle corresponding to 100% dissolution at the same time. For comparative purposes, identical and fixed time intervals must be selected.

$$ED(\%) = \frac{\int_0^t Q(t)dt}{Q_{100,t}} \cdot 100$$

$ED(\%)$ is the dissolution efficiency at time t ;

$Q(t)$ is the amount of active pharmaceutical ingredient released as a function of time;

Q_{100} is the total amount of active ingredient contained in the tablet.

Table 5. Mean dissolution efficiencies of the systems.

Time (days)	Cumulative SQ1 released (%)
3	10.61 ± 0.49
5	33.57 ± 1.46
7	61.95 ± 1.63

For both batches, the dissolution efficiency was found to be higher when the insulin loading was lower, except during the initial period ending on day 3.

4. Discussion

The continuous release of active pharmaceutical ingredients is currently a major focus in the pharmaceutical industry; therefore, this study investigated the release of insulin from hydroxyapatite-based matrices.

The choice of hydroxyapatite as the main excipient is justified by its mineral composition, which is close to that of bone and dental tissues, as well as by its proven suitability for the development of sustained release systems [4, 5, 12, 18]. The hydroxyapatite powder used in this work was obtained by a precipitation reaction between calcium hydroxide and orthophosphoric acid with a Ca/P ratio of 1.66, carried out at temperatures ranging between 80 and 95°C. After filtration and drying at 80°C for 24 h, the powder was calcined at 800°C for 3 h.

In addition, polymeric excipients were incorporated into the formulations, namely Eudragit® RS PM in powder form as the internal phase and Eudragit® RS100 as the external phase using absolute ethanol as the wetting liquid. Two batches of composite systems were obtained, whose individual units exhibited good mechanical consistency. Mass uniformity testing demonstrated that all systems complied with pharmacopoeial requirements.

Insulin release studies performed in an aqueous medium revealed that the release profiles followed different kinetic laws depending on the matrix composition. For batch 1, insulin release followed a first-order kinetic profile, modeled by the equation $Q = y_0 + A_1 e^{-x/t}$.

These release profiles are similar to those previously obtained with paracetamol, for which release extended over 18 days [5], whereas insulin release was completed within 7 days. This difference can be attributed to the initial drug loading. In insulin-based systems, insulin concentrations ranged from 0.135% to 0.27%, whereas paracetamol loadings reported in the literature vary between 5% and 30% [4, 5, 17, 18].

For batch 2, the release kinetics were best described by the Boltzmann equation, yielding a sigmoidal release profile. The selection of the Boltzmann model was justified by its higher correlation coefficient ($r^2 = 0.99$) compared with that obtained using first-order kinetics ($r^2 = 0.96$). In fact, batch 2 exhibited

a relatively sharp increase in insulin release around the third day, suggesting a release mechanism that may be specific to insulin and, more generally, to protein-based active substances [19-24].

The analysis of dissolution efficiencies, which increased as insulin loading decreased, further confirmed that batch 1 released the entire insulin content by the third day, whereas batch 2 released only approximately 60% of its initial insulin load over the same period. These findings demonstrate that the initial insulin content plays a key role in determining the release profile of insulin from hydroxyapatite-polymer matrices [18, 25-28].

Overall, comparison of the release profiles of the two batches showed no major difference between them. The statistical significance of the observed differences was evaluated using Student's *t*-test for small independent samples, yielding a *p*-value of approximately 0.76, which is higher than the conventional threshold of 0.05 and also greater than the threshold recommended by Ronald Fisher. According to Fisher, a *p*-value greater than 0.1 indicates no evidence against the null hypothesis.

5. Conclusion

At present, one of the major challenges faced by the pharmaceutical industry is the development of new dosage forms based on existing active pharmaceutical ingredients in order to improve their therapeutic effectiveness after administration. In this context, the present work focused on the study of insulin release from a hydroxyapatite-based matrix with the aim of defining and understanding its release profile. Hydroxyapatite was selected as the main excipient. The hydroxyapatite powder used in this study was obtained by a precipitation reaction between calcium hydroxide and orthophosphoric acid with a Ca/P ratio of 1.66, carried out at temperatures ranging from 80 to 95°C. After filtration and drying at 80°C for 24 h, the powder was calcined at 800°C for 3 h. Polymeric excipients were also incorporated into the formulations, namely Eu-dragit® RS PM in powder form as the internal phase and Eu-dragit® RS100 as the external phase using absolute ethanol as a wetting agent. Two batches of composite systems were obtained, whose individual units exhibited good mechanical integrity. Mass uniformity testing demonstrated that all systems complied with pharmacopoeial requirements. Insulin release studies performed in aqueous medium showed that the release profiles followed different kinetic behaviors depending on the matrix composition. For batch 1, insulin release followed a first-order kinetic profile modeled by the equation $Q = y_0 + A_1 e^{-x/t}$ with complete release achieved within 7 days. This relatively short release duration was directly related to the initial insulin loading in the system.

For batch 2, the release kinetics were best described by the Boltzmann equation, leading to a sigmoidal release profile. The use of the Boltzmann model was justified by a higher correlation coefficient ($r^2 = 0.99$) compared with that obtained

using first-order kinetics ($r^2 = 0.96$). In this batch, a relatively abrupt increase in insulin release was observed around the third day, suggesting a release behavior that may be specific to insulin and, more generally, to protein-based active substances. The analysis of dissolution efficiencies, which increased as insulin loading decreased, confirmed that batch 1 released a large proportion of insulin from the third day, whereas batch 2 released only about 60% of its initial insulin content over the same period. These results highlight the crucial influence of the initial insulin loading on the release behavior. Overall, the findings of this study demonstrate that hydroxyapatite powder constitutes a suitable substrate for the development of hydroxyapatite-polymer matrices capable of achieving controlled and prolonged insulin release. Nevertheless, the kinetic profile observed for batch 2 requires further investigation, as the discontinuous release pattern suggests a concentration-dependent behavior that may indicate a two-phase release mechanism, characterized by an initial burst effect followed by a more gradual elution phase.

Abbreviations

XRD	X-ray Diffraction
FTIR	Fourier Transform Infrared Spectroscopy
BET	Brunauer Emmett Teller

Author Contributions

Abdou Faye: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Sidy Mouhamed Dieng: Supervision, Data curation, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing

Marie Jeanne Arlette Ciss: Validation, Visualization, Writing – review & editing

Alphonse Rodrigue Djiboune: Validation, Visualization, Writing – review & editing

Benedicte Souho: Validation, Visualization, Writing – review & editing

Mamadou Soumboundou: Validation, Visualization, Writing – review & editing

Papa Mady Sy: Validation, Visualization, Writing – review & editing

Gora Mbaye: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Mounibe Diarra: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Louis Augustin Diaga Diouf: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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