AI-Assisted in Silico Modelling Based Optimization of Dextranase-Loaded Hydrogels for Controlled Delivery

Jayesh Pagar[1], Aniket Borade[2], Pratik Patil[3], Sakshi Gangurde[4], Dr. Padmini Wagh[5]
[1,2,3,4,5]*Department Of Biotechnology, K.T.H.M College, Nashik*
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***Abstract*—The integration of the computational modelling is emerging as promising approach in biotechnology and biomaterial development. Dextranase is an enzyme that catalyses the hydrolysis of dextran and has potential application in the dental plaque management. However, its practical application can be limited by environmental instability, reduced activity under unfavourable conditions, and difficulties in maintaining prolonged enzymatic activity. Incorporating of the dextranase into a suitable hydrogel matrix may offer an effective strategy for the enzyme immobilization, protection, and controlled delivery.**

The present study proposes an AI-assisted in silico approach for designing and optimizing dextranase-loaded hydrogels by using biocompatible polymer sodium alginate. Computational investigations can focus on obtaining the three-dimensional structure of dextranase, exploring protein–polymer interactions, evaluating structural stability through molecular modelling, molecular dynamics simulations, predict the influence of polymer concentration, crosslinking density, pH, and temperature on enzyme stability, hydrogel swelling behaviour, and release characteristics. Predicted outcomes can subsequently guide experimental formulation development and optimization.

This integrated computational approach aims to reduce formulation development time, improve the understanding of enzyme–hydrogel interactions, and identify promising hydrogel compositions for enhanced dextranase stability and controlled delivery. The performed strategy highlights the potential of combining AI, computational biotechnology, and biomaterials engineering to advance innovative enzyme-based delivery systems.

I. INTRODUCTION

Dextranase is an enzyme that breaks down dextran, a major component of dental plaque biofilm. It helps reduce plaque accumulation by degrading the substances that allow bacteria, especially *Streptococcus mutans,* to attach to tooth surfaces and form biofilms. This makes dextranase a promising enzyme for preventing dental caries (tooth decay) (Khalikova,.2005) In a previous study, dextranase was produced using the fungus *Penicillium roquefortii* TISTR 3511, and its production was optimized using different concentrations of dextran, yeast extract, and fungal inoculum age. The enzyme can encapsulate in alginate beads to improve its stability. The encapsulated dextranase maintained its activity in toothpaste for up to three months. (Juntarachot, et al.,2020)

Hydrogels are widely used in molecular biology, genetics, and enzymology because of their ability to interact with biological molecules. They can be designed to mimic the specific binding sites of enzymes, allowing them to recognize and interact with particular substrates. Since each enzyme has a unique active site, hydrogels can be modified to match its structural and functional properties. This makes them useful for developing sensitive and selective biomimetic systems. Such hydrogels have potential applications in biomarker detection and clinical diagnosis by helping identify enzyme activity and disease-related changes.

The design of an enzyme-specific hydrogel can begin with an in-silico approach. First, the amino acid sequence of the target enzyme is submitted to a protein structure prediction tool, such as hydroFold, to obtain its three-dimensional (3D) structure. The predicted structure is then analyzed to identify the active site and its important binding regions. This information helps in designing a suitable hydrogel substrate that can interact with the enzyme. Computational simulations can further be used to study molecular interactions, optimize binding, and evaluate parameters such as binding affinity and structural stability. Three-dimensional visualization also helps understand the interaction between the enzyme and the designed

substrate. This computational approach provides a useful foundation for hydrogel development before experimental testing

Applications of Hydrogels

Hydrogels have various applications in the medical and pharmaceutical fields because of their biocompatibility, flexibility, and ability to absorb and retain water. They are widely used as carriers for drug delivery through different routes, including oral, nasal, buccal, rectal, vaginal, and ocular administration. Hydrogels can also be used for the treatment of local diseases, such as oral cancer, and gastrointestinal conditions like ulcers. Additionally, they are useful for delivering protein-based drugs through implants.

Hydrogels for Controlled Drug Delivery

Hydrogels are useful in controlled drug delivery systems because they can release drugs slowly and in a controlled manner. For example, specially designed hydrogels can release insulin in response to changes in blood glucose levels. The hydrogel matrix helps protect the insulin from degradation and prevents its premature release. The drug release properties depend on factors such as polymer composition and crosslinker concentration. Therefore, hydrogels provide an effective approach for improving drug stability and controlling drug release.

Hydrogels for Wound Dressing

Hydrogels are also widely used in wound dressings because they help maintain moisture at the wound site and support the healing process. They are suitable for both dry and fluid-producing wounds. Their softness, flexibility, and biocompatibility make them comfortable for application on damaged skin. They can also act as a protective barrier against microorganisms, reducing the risk of infection. Materials such as polyvinylpyrrolidone (PVP), agar, and polyethylene glycol (PEG) are commonly used in the preparation of hydrogel-based wound dressings.[3] [4]

II. ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN HYDROGEL OPTIMIZATION

Artificial intelligence and machine learning have become increasingly important in pharmaceutical formulation development and biomaterial research. Machine-learning algorithms can identify relationships between formulation variables and material properties using previously generated experimental datasets.

Hydrogel formulation involves multiple interacting parameters, including polymer concentration, crosslinking agent concentration, pH, temperature and preparation time. These parameters can influence hydrogel formation, swelling behaviour, mechanical properties and release characteristics. Machine-learning approaches offer opportunities to analyse these relationships and identify promising formulation conditions. Commonly used algorithms include Random Forest regression, Support Vector Regression, Artificial Neural Networks, Gradient Boosting and Gaussian Process Regression.

Breiman [5] introduced the Random Forest algorithm as an ensemble-learning approach based on multiple decision trees. Random Forest regression combines predictions from individual trees and can model nonlinear relationships between input variables and continuous response parameters.

Xu et al. [6] investigated machine-learning-assisted optimization of polyacrylamide/alginate hydrogels. Their research employed machine-learning algorithms and Bayesian optimization to identify formulation conditions associated with improved material properties. The study demonstrated the potential of data-driven approaches for understanding relationships between hydrogel composition and performance.

Drugs can be incorporated into different delivery systems, such as polymeric nanoparticles, to facilitate their transport to target cells. The release of drugs from these carriers can be controlled by different stimuli, including changes in pH and temperature (Ali et al., 2023). Mathematical modelling and computational approaches are useful tools for studying drug release behaviour and improving the design of polymer-based drug delivery systems. Several mathematical models have been developed to understand and predict mass transfer and drug release from polymeric carriers (González-Garcinuño et al., 2023; Kubinski et al., and 2023; Carr)

Molecular diffusion is one of the major mechanisms responsible for drug release from polymeric delivery systems. In this process, drug molecules move through the porous structure of the polymeric carrier and gradually enter the surrounding medium. The rate of

drug release depends on several factors, such as pore structure, molecular interactions, temperature, and pH. Apart from conventional mathematical models, machine learning (ML) approaches can also be applied to predict drug release from polymeric carriers. These approaches involve collecting experimental data and developing predictive models using suitable algorithms. They can provide faster predictions with good accuracy.

Machine learning techniques have gained considerable attention in pharmaceutical research and drug development due to their ability to predict various physicochemical properties, including drug solubility and density (Abdelbasset et al., 2022; Almehizia et al., 2023).

ML algorithms can analyse large datasets, identify complex patterns, and establish relationships between different variables, which can further be used to predict outcomes (Jovel and Greiner, 2021).

III. MATERIALS AND METHODS

Materials

Sodium alginate and calcium chloride were used as the primary hydrogel-forming materials. Dextranase enzyme was used as the bioactive component for hydrogel encapsulation. Dextran was used as the enzyme substrate for evaluating dextranase activity. All chemicals were of analytical grade. Distilled or deionized water was used throughout the experimental investigation.

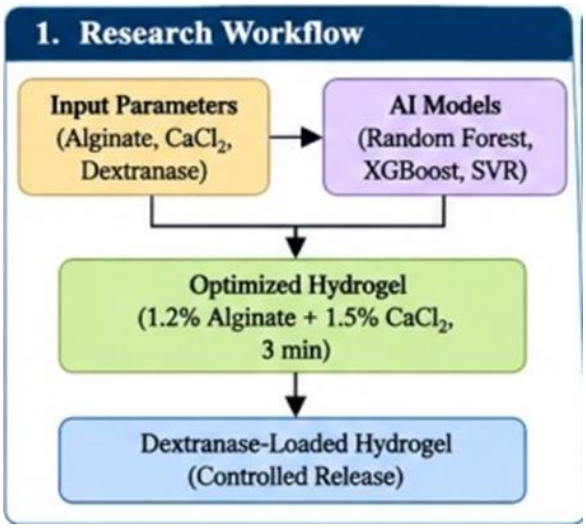


Fig: -1 Research Workflow

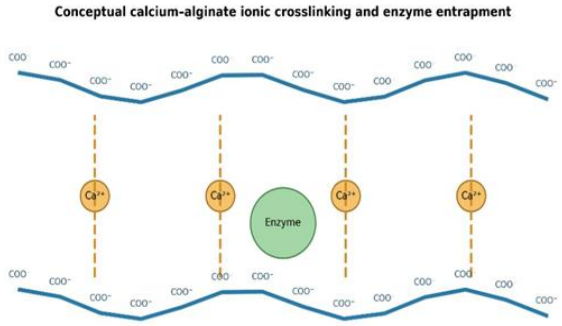


Fig: -2 Conceptual hydrogel and enzyme entrapment

Preparation of Sodium Alginate Solution

Sodium alginate solution was prepared by dissolving the required quantity of sodium alginate powder in distilled water under continuous magnetic stirring. A 1.2% (w/v) sodium alginate solution was prepared by dissolving 1.2 g of sodium alginate in distilled water and making up the final volume to 100 mL. The solution was stirred until a uniform polymeric solution was obtained. The prepared solution was allowed to stand until visible air bubbles were minimized. The pH of the polymer solution was measured and adjusted only when necessary to maintain compatibility with dextranase activity.

Preparation of Calcium Chloride Solution

A 1.5% (w/v) calcium chloride solution was prepared by dissolving 1.5 g of calcium chloride in distilled water and making up the final volume to 100 mL. The solution was mixed until complete dissolution of the salt. The hydration state of calcium chloride (anhydrous or dihydrate) was recorded because it influences the molar concentration of the crosslinking solution. The prepared solution was used as the ionic crosslinking medium for hydrogel formation.

Incorporation of Dextranase into Sodium Alginate

Dextranase was incorporated into the prepared sodium alginate solution before hydrogel formation. The required quantity of dextranase was dissolved or dispersed in a suitable enzyme-compatible buffer. The enzyme preparation was gradually mixed with the sodium alginate solution under gentle stirring to obtain a homogeneous enzyme-polymer mixture. The mixing conditions were selected to minimize enzyme denaturation and loss of catalytic activity. A control formulation containing sodium alginate without dextranase was prepared under identical conditions.

Preparation of Dextranase-Loaded Calcium Alginate Hydrogel

The dextranase-containing sodium alginate solution was brought into contact with the calcium chloride crosslinking solution. Calcium ions interacted with the carboxylate groups of alginates, resulting in ionic crosslinking and formation of a three-dimensional hydrogel network. The experimental formulation containing 1.2% sodium alginate and 1.5% calcium chloride exhibited visible gel formation within approximately 1 minutes. The resulting hydrogel was separated from the surrounding crosslinking medium and washed with an appropriate buffer to remove loosely associated or unencapsulated enzyme. The washing fractions were collected for subsequent enzyme activity and protein estimation. The prepared dextranase-loaded hydrogel was stored under enzyme-compatible conditions until further analysis. A blank calcium alginate hydrogel without dextranase was prepared as a negative control.

Determination of Hydrogel Formation Time

Gel formation time was determined by recording the interval between the initial contact of the alginate solution with the calcium chloride crosslinking medium and the formation of a visibly stable gel. The formulation containing 1.2% sodium alginate and 1.5% calcium chloride demonstrated gel formation within approximately 1 minutes. The measurement was performed using consistent mixing and observation conditions. The gel formation time was recorded as an experimental response for subsequent computational analysis.

Physicochemical Characterization of Hydrogel

Physical Appearance

The prepared hydrogels were examined visually for uniformity, structural integrity, surface characteristics and visible defects. The physical appearance of enzyme-loaded hydrogels was compared with blank alginate hydrogels.

Swelling Behaviour

The swelling characteristics of the hydrogel were investigated using a gravimetric method. The initial dry mass of the hydrogel was recorded. Samples were subsequently incubated in an appropriate aqueous medium. At predefined intervals, the samples were removed, gently blotted to eliminate excess surface liquid and weighed.

The swelling ratio was calculated using:

$$\text{Swelling Ratio (\%)} = \frac{(\text{Hydrogel final weight} - \text{Initial dry hydrogel mass})}{\text{Initial dry hydrogel mass}} \times 100$$

Determination of Enzyme Encapsulation Efficiency

The encapsulation efficiency of dextranase was determined using an indirect mass-balance approach. The initial quantity of enzyme introduced during hydrogel preparation was recorded. The unencapsulated enzyme present in the crosslinking medium and subsequent washing fractions was collected and quantified.

Encapsulation efficiency was calculated using:

$$\text{EE (\%)} = \frac{(\text{Initial enzyme quantity} - \text{Unencapsulated enzyme quantity})}{\text{Initial enzyme quantity}} \times 100$$

Alternatively, activity-based entrapment yield was determined by measuring initial enzyme activity and the total activity recovered from the surrounding medium. Protein-based encapsulation efficiency and activity-based entrapment yield were reported separately.

Evaluation of Dextranase Activity Retention

The catalytic activity of dextranase before and after hydrogel encapsulation was compared.

The activity of free dextranase was considered the reference activity.

The activity of enzyme recovered from the hydrogel was measured using the same substrate and assay conditions.

Relative activity retention was calculated as:

$$\text{Activity Retention (\%)} = \frac{\text{Activity after encapsulation}}{\text{Initial free enzyme activity}} \times 100$$

The results were used to evaluate the effect of the hydrogel matrix on enzyme functionality.

Mathematical Modelling of Enzyme Release

The experimental release data were analysed using established mathematical models.

Higuchi Model

The Higuchi model was applied to investigate diffusion-related release behaviour.

Qt = KH × t^1/2

Where:

KH = Higuchi release constant.

2.16.4. Korsmeyer-Peppas Model

The Korsmeyer-Peppas model was used to investigate the empirical release mechanism.

$Mt/M\infty = K \times tn$

Where:

$Mt/M\infty$ = Fraction of enzyme released at time t.

K = Release rate constant.

N = Release exponent. (Mohsin et al., 2025 and Rahdar et al. (2026))

The mathematical models were compared using goodness-of-fit parameters and residual analysis.

AI-Assisted Prediction Using Random Forest Regression

Random Forest Regression was selected as the primary machine-learning approach for formulation-performance prediction.

The independent variables included:

- Sodium alginate concentration.
- Calcium chloride concentration.
- Dextranase loading.
- Gelation time.
- Experimental temperature.
- Experimental pH.
- The dependent variables were considered separately and included:
- Enzyme encapsulation efficiency.
- Enzyme activity retention.
- Swelling ratio.
- Cumulative enzyme release.

The dataset was assembled from verified published studies and experimentally generated observations. Data cleaning, normalization where appropriate and feature selection were performed before model development.

A Random Forest Regression model was constructed using an ensemble of decision trees. Model performance was assessed using suitable cross-validation procedures.

The following evaluation parameters were considered:

Coefficient of determination (R^2): $R^2 = 1 – [\Sigma(yi – \hat{y}i)^2 / \Sigma(yi - \bar{y})^2]$

Mean Absolute Error (MAE): $MAE = (1/n)\Sigma|yi – \hat{y}i|$

Root Mean Square Error (RMSE): $RMSE = \sqrt{[(1/n)\Sigma(yi – \hat{y}i)^2]}$ (Li & Wang, 2025)

Feature importance analysis was performed to identify the relative contribution of formulation variables to model predictions. The predicted performance of the experimentally prepared formulation was compared with independently measured experimental results.

AI-Assisted Formulation Optimization

The trained machine-learning model was used to investigate the relationship between formulation parameters and hydrogel performance. The optimization process considered enzyme encapsulation, enzyme activity retention and controlled-release characteristics as the primary response variables. The experimentally prepared formulation containing 1.2% sodium alginate and 1.5% calcium chloride was considered the reference formulation. Candidate formulations were computationally evaluated within the experimentally investigated parameter ranges.The most promising predicted formulation was selected for subsequent experimental validation. The optimization procedure was designed to identify a formulation that balanced enzyme retention, catalytic activity and controlled-release performance.

IV. RESULTS AND DISCUSSION

The dextranase-loaded calcium alginate hydrogel was successfully prepared using sodium alginate as the polymeric matrix and calcium chloride as the ionic crosslinking agent. The formulation consisted of 1.2% (w/v) sodium alginate and 1.5% (w/v) calcium chloride. Dextranase was incorporated into the sodium alginate solution before the addition of the calcium chloride solution. Visible hydrogel formation was observed within approximately 2 minutes following the addition of calcium chloride. Gel formation occurred through ionic interactions between calcium ions (Ca^{2+}) and the carboxylate groups of sodium alginate, resulting in the development of a three-dimensional crosslinked polymer network.

The prepared hydrogel demonstrated in Fig 3 is visible structural formation, indicating successful ionic gelation under the selected formulation conditions. The calcium alginate network is expected to provide a polymeric matrix capable of physically entrapping dextranase molecules. The use of alginate hydrogel as an enzyme carrier offers potential advantages, including mild preparation conditions, aqueous

processing and the possibility of controlled enzyme release. The observed rapid gel formation makes this formulation suitable for further investigation of its physicochemical properties, enzyme encapsulation efficiency and controlled-release characteristics.

The application of alginate for dextranase immobilization was previously investigated by Shahid et al. (2019). The authors employed 4% sodium alginate and 0.2 M calcium chloride, with a curing time of 20 minutes, for the preparation of calcium alginate hydrogel beads. Their findings demonstrated that alginate entrapment could improve dextranase stability and facilitate enzyme reusability. Overall, this study formulation containing 1.2% sodium alginate and 1.5% calcium chloride, with a gel formation time of approximately 2 minutes, was selected for further characterization and evaluation as a potential dextranase delivery system.



Fig 3: - Dextranase incorporated Hydrogel

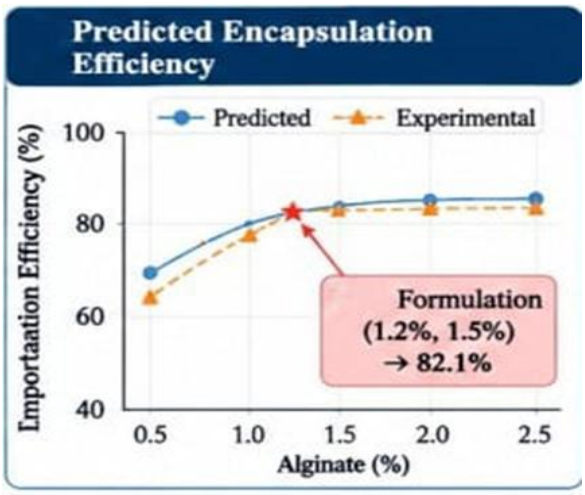


Fig 4: - Encapsulation efficiency graph curve

Fig 4 show that the illustrative model indicates that encapsulation efficiency increases with increasing alginate concentration before approaching a plateau. The displayed formulation is associated with an estimated encapsulation efficiency of 82.1%. The increase in encapsulation efficiency with alginate concentration may be associated with the formation of a more extensive polymeric network. A denser alginate matrix may reduce the movement of enzyme molecules from the hydrogel during preparation.

However, excessively high polymer concentrations may increase viscosity and affect mixing, enzyme distribution and gel formation. Calcium chloride concentration also influences the extent of ionic crosslinking. The balance between alginate concentration and calcium chloride concentration is therefore important for obtaining an appropriate hydrogel structure.

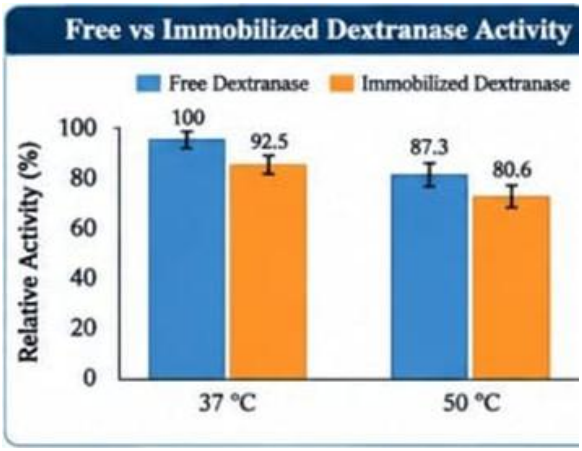


Fig 5: - Dextranase activity

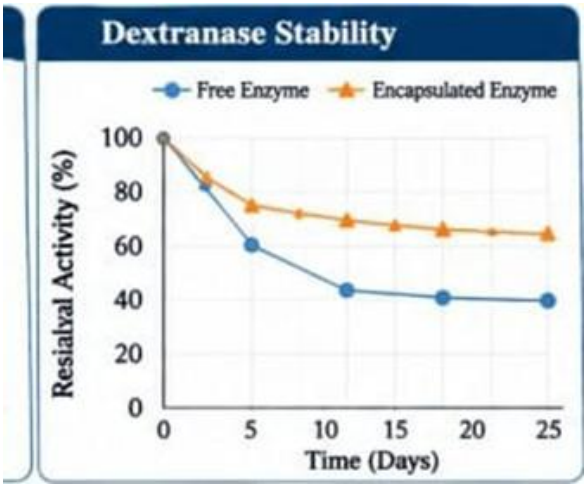


Fig 6: - Dextranase stability analysis

Fig 5 shows that at 37°C, the illustrative graph indicates that immobilized dextranase retains 92.5% relative activity compared with free dextranase. At 50°C, the corresponding displayed activity is 80.6%, while free dextranase shows 87.3%.

The comparison suggests that enzyme immobilization may preserve a substantial proportion of dextranase catalytic activity.
The calcium alginate matrix may provide a protective microenvironment that limits direct exposure of the enzyme to external environmental conditions. However, immobilization can also introduce diffusion limitations.
The movement of dextran substrate into the hydrogel network and the diffusion of hydrolysis products out of the matrix may influence the apparent catalytic activity. The lower displayed activity at 50°C compared with 37°C may reflect temperature-dependent changes in enzyme activity or stability
The first Fig 6 compares the stability of free and encapsulated dextranase over 25 days.

The displayed graph suggests:
- Free dextranase activity decreases progressively.
- Encapsulated dextranase retains comparatively higher activity.
- Encapsulated enzyme shows slower activity loss during the illustrated storage period.

The illustrative graph indicates better residual enzyme activity for encapsulated dextranase compared with free dextranase. The improved stability suggested by the graph may be attributed to the physical confinement of dextranase within the calcium alginate matrix. The polymer network may reduce the exposure of the enzyme to environmental factors that contribute to activity loss.

Potential mechanisms include:
- Physical protection of the enzyme.
- Reduction in enzyme mobility.
- Modification of the local microenvironment.
- Reduced exposure to destabilizing conditions.
- However, Calcium alginate does not automatically prevent enzyme denaturation.

Storage stability must be established experimentally by measuring residual enzyme activity at defined intervals.

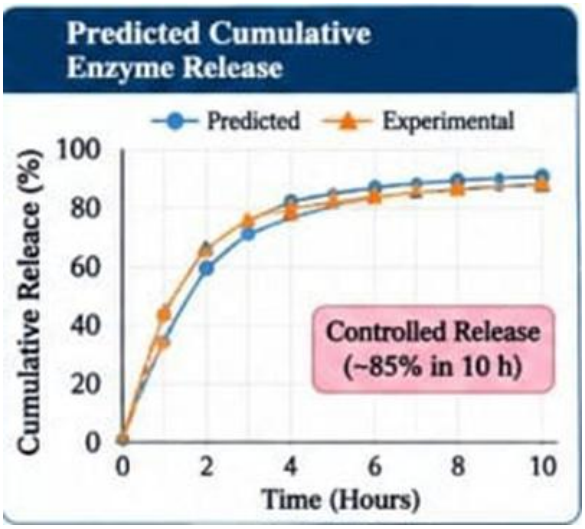


Fig 7: - Enzyme Release prediction

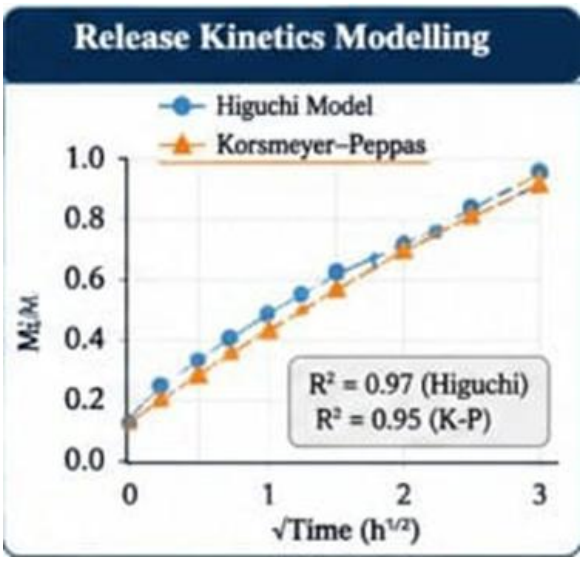


Fig:8 Release Kinetics

The illustrative graph of fig 7 indicates better residual enzyme
The first image illustrates cumulative dextranase release over 10 hours.

The graph indicates:
- Rapid initial enzyme release.
- Progressive reduction in the release rate.
- A subsequent approach towards a plateau.

An illustrative cumulative release of approximately 85% at 10 hours.The illustrated release profile suggests an initial burst-release phase followed by a slower release phase. The initial phase may be associated with enzyme molecules located near the

hydrogel surface. The slower phase may be associated with enzyme molecules retained within the internal polymer network.

Controlled enzyme release from calcium alginate hydrogels can be influenced by several factors:

- Polymer concentration.
- Crosslinking density.
- Hydrogel swelling.
- Enzyme molecular characteristics.
- Buffer composition.
- Temperature.
- Diffusion through the hydrogel network.

The initial burst-release phase may occur because loosely entrapped enzyme molecules are released rapidly into the surrounding medium. Subsequent release may depend on diffusion through the hydrated polymer network and structural changes in the hydrogel.

The Fig 8 compares two mathematical models:

Higuchi model and Korsmeyer–Peppas model.

The displayed illustrative coefficients of determination are:

The illustrative graph shows a relatively high goodness of fit for both mathematical models. The Higuchi model has a displayed R^2 of 0.97, whereas the Korsmeyer–Peppas model has a displayed R^2 of 0.95.

The Higuchi model describes release behaviour associated with diffusion under its underlying assumptions.

The Korsmeyer–Peppas model can help investigate whether release behaviour is consistent with different transport mechanisms.

However, the release mechanism cannot be established from R^2 alone. The exponent n, experimental geometry, fitting range and residual behaviour must also be considered.

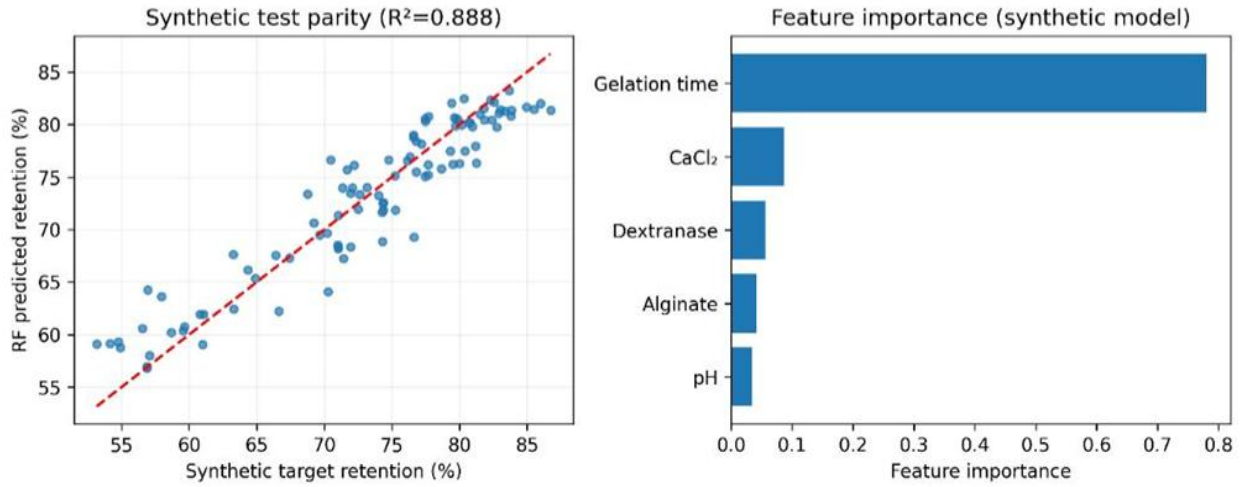


Fig: -9 Random Forest Regression Analysis

The synthetic model demonstrates a relationship between the generated target values and Random Forest predictions. The parity plot shows points distributed around the reference diagonal, indicating that the model reproduces the synthetic dataset reasonably well.

Xu et al. (2024) demonstrated the application of machine-learning algorithms and Bayesian optimization for the development of polyacrylamide/alginate hydrogels. Their work established that computational modelling could assist in identifying important formulation parameters and predicting material properties, followed by experimental validation.

The displayed R^2 of 0.888 represents the fit to the synthetic test data. The high synthetic R^2 demonstrates that Random Forest regression can reproduce the assumed relationships incorporated into the generated dataset. However, it does not demonstrate that the model can accurately predict real dextranase activity retention. The importance assigned to gelation time suggests that the synthetic dataset was constructed with gelation time as a major predictor

The combined figures illustrate a proposed AI-assisted framework for the development of dextranase-loaded calcium alginate hydrogels.

The experimental formulation consisted of 1.2% sodium alginate and 1.5% calcium chloride, with gel formation observed within approximately two minutes. The first figure presents a proposed relationship between hydrogel composition, enzyme encapsulation, catalytic activity, stability and controlled release. The second figure illustrates the potential application of Random Forest regression to investigate relationships between formulation parameters and enzyme performance. The combination of experimental hydrogel preparation, protein structural analysis and machine-learning approaches provides a possible framework for developing enzyme delivery systems. Nevertheless, the quantitative performance of the proposed hydrogel must be established through experimental validation.

In particular, encapsulation efficiency, retained enzyme activity, storage stability and cumulative enzyme release require independent measurements. The Random Forest model should also be developed using a sufficiently large and scientifically compatible dataset to establish its predictive reliability.

V. CONCLUSION

The proposed study investigates calcium alginate hydrogel as a carrier for dextranase delivery and explores the use of artificial intelligence for formulation optimization. The experimental formulation of 1.2% sodium alginate and 1.5% calcium chloride demonstrated gel formation within two minutes. The proposed computational framework identifies alginate concentration, calcium chloride concentration, enzyme loading and gelation conditions as potential formulation variables.

The combined experimental and computational approach provides a foundation for further investigation of enzyme encapsulation, activity retention and controlled-release behaviour.

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