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Release Study of Methylene Blue as Model Drug Encapsulated by Alginate-Starch Blend Beads Prepared via Crosslinking Method

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DECLARATION

I declare that this thesis entitled “Release Study of Methylene Blue as Model Drug Encapsulated by Alginate-Starch Blend Beads Prepared via Crosslinking Method ” is the result of my research except as cited in the references.

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ABSTRAK

Tajuk: Kajian Pelepasan Methylene Blue sebagai Ubat Model yang Diselaputi oleh Campuran Natrium Alginate dan Kanji Melalui Kaedah Pengaitan Silang

Tesis ini mengkaji kajian pelepasan methylene blue (MB), sejenis dadah model, yang diinkapsulasi dengan campuran natrium alginat dan kanji menggunakan kaedah pautan silang. Penginkapsulan dadah dalam matriks biopolimer telah menarik perhatian yang signifikan disebabkan potensi aplikasinya dalam sistem penghantaran dadah. Dalam kajian ini, campuran natrium alginat dan kanji digunakan sebagai bahan biokompatibel dan biodegradasi untuk penginkapsulan dadah. Kaedah pautan silang digunakan untuk meningkatkan kestabilan dan mengawal pelepasan MB dari matriks yang diinkapsulasi. Metodologi penyelidikan melibatkan penyediaan larutan campuran natrium alginat dan kanji, diikuti dengan penginkapsulan MB melalui proses pautan silang menggunakan kalsium klorida sebagai agen pautan silang. Pelbagai formulasi dengan nisbah yang berbeza antara natrium alginat dan kanji disediakan untuk meneroka impak komposisi campuran terhadap kecekapan penginkapsulan, saiz jarum yang berbeza, kepekatan Kalsium Klorida yang berbeza, dan juga pelepasan pH yang berbeza. Keputusan menunjukkan bahawa kecekapan penginkapsulan dan kajian pelepasan MB dipengaruhi oleh komposisi campuran natrium alginat dan kanji. Kepekatan natrium alginat yang lebih tinggi pada amnya menghasilkan kecekapan penginkapsulan yang lebih tinggi dan kadar pelepasan MB yang lebih perlahan. Sebaliknya, peningkatan kepekatan kanji menghasilkan kadar pelepasan dadah yang lebih perlahan. Kajian ini menyumbang kepada pemahaman mengenai tingkah laku pelepasan dadah yang diinkapsulasi dalam campuran natrium alginat dan kanji melalui kaedah pautan silang, memberikan pandangan dalam reka bentuk dan penambahbaikan sistem penghantaran dadah menggunakan matriks biopolimer. Penemuan ini mempunyai implikasi untuk pembangunan formulasi pelepasan terkawal untuk pelbagai aplikasi farmaseutikal.

Kata kunci: Methylene blue, natrium alginat, kanji, pautan silang, pelepasan dadah.

ABSTRACT

Title: Release Study of Methylene Blue as a Model Drug Encapsulated by Sodium Alginate and Starch Blends via Crosslinking Method

This thesis investigates the release study of methylene blue (MB), a model drug, encapsulated with sodium alginate and starch blends using a crosslinking method. The encapsulation of drugs within biopolymer matrices has gained significant attention due to its potential applications in drug delivery systems. In this study, sodium alginate and starch blends were utilized as biocompatible and biodegradable materials for drug encapsulation. The crosslinking method was employed to enhance the stability and control the release of MB from the encapsulated matrices. The research methodology involved the preparation of sodium alginate and starch blend solutions, followed by the encapsulation of MB through the crosslinking process using calcium chloride as a crosslinking agent. Various formulations with different ratios of sodium alginate to starch were prepared to explore the impact of blend composition on the encapsulation efficiency, different size needles, different concentrations of Calcium Chloride, and also different pH releases. The results indicate that the encapsulation efficiency and release study of MB were influenced by the composition of the sodium alginate and starch blends. Higher concentrations of sodium alginate generally led to higher encapsulation efficiency and slower release rates of MB. Conversely, an increase in starch concentration resulted in slower drug release rates. This study contributes to the understanding of the release behavior of drugs encapsulated within sodium alginate and starch blends via crosslinking methods, offering insights into the design and optimization of drug delivery systems using biopolymer matrices. The findings have implications for the development of controlled-release formulations for various pharmaceutical applications.

Keywords: Methylene blue, sodium alginate, starch, crosslinking, drug release.

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Food products that contain starch are a rich source of energy and are consumed as a staple diet by all parts of society due to their accessibility and relatively low cost because they are available and produced by farmers or individuals who grow them (Domínguez Díaz et al., 2020). Starch, which is a tasteless and odorless white polysaccharide found in man legumes cereals, and different varieties of foods origin, can be found in the plant kingdom's roots, tubers, and seeds as previous research from 1989 and 2007 has shown that information and can be scientifically proven. Starch has received significant attention from the pharmaceutical industry in the production of different drugs, specifically for its application as a drug delivery mechanism in biomedicine which has been enhanced widely. Starches stand out as an enclosing agent because they can trap a wide variety of molecules when their structures are studied comprehensively.

Starch provides a significant source of calories and carbohydrates for many people around the world this calorie enhances one's work as they are sources of energy in different categories. It is commonly found in affordable and easily obtainable food items like potatoes, corn, rice, and wheat which are found either locally or internationally (Sankha Karunarathna et al., 2023). Due to starch being inexpensive and widely available, it forms the basis of diets for individuals and communities of all economic levels globally because they are natural sources of food. Research into the plant kingdom revealed that starch is present in underground plant parts such as roots and tubers as well as seeds above ground and can be sourced as starch at the end of the day.

The pharmaceutical industry has taken a keen interest in utilizing starch for medical purposes in the production of various drugs that enhance the treatment of various

diseases caused by different bacteria and microorganisms. Scientists have studied how starch might serve as a mechanism for drug delivery in biomedicine a branch of medicine that is very independent. The ability of starches to envelop and hold various molecules positions them as a promising material for enclosing and transporting pharmaceutical compounds in the body this enhances the production of various drugs that are medically important. When starch is consumed, its polysaccharide structure can trap other substances it encounters before being broken down into simpler substances that are essential for human consumption.

Research in the late 1980s and 2000s sought to better understand the natural presence and characteristics of starch because starch possesses different characteristics which can be either similar or different. Investigations identified starch as a common component of specific plant tissues including roots, tubers, and seeds. Roots and tubers, which are underground portions of plants that store nutrients, along with seeds that aid in reproduction this production enhances have variety of sources of starch within a certain ecosystem, were shown to reliably contain starch deposits. The findings from these works established a foundation of knowledge regarding the natural function and habitat of starch within the plant kingdom which has aided in knowing more for starch and to realize how widely it can be used.

Building upon this base research, scientists have looked to leverage some of starch's key properties for medical applications to enhance starch to be known as a drug not only as an edible source of nutrients. Its ability to envelop and trap other molecules positions it as a promising delivery mechanism for pharmaceutical drugs which are produced in different categories and capacities. When starch is consumed as part of the normal diet, its polysaccharide structure works to encapsulate any other compounds it encounters inside the digestive system which serves as a rich source of nutrients (Babaei-Ghazvini et al., 2024). Researchers realized this encapsulating quality could potentially be utilized to develop starch-based formulations that transport medications or supplements through digestion which is a normal biological process that occurs within the body of living organisms. Specifically, starches may allow for the controlled or targeted release of therapeutic substances at different points along the gastrointestinal tract which Is an important pathway in the digestion process.

They worked to precisely define where starch deposits were situated within these plant parts and what physical form the starch molecules took. Later research in the 2000s built upon this foundation by further fleshing out an understanding of starch's natural functionality and habitat in the plant kingdom and further discovered how medically it can be of importance. Together these works created a baseline level of knowledge that has since supported additional scientific knowledge that has led to the advancement of pharmaceuticals in a larger view.

Scientists have been particularly eager to harness one of starch's inherent properties for pharmaceutical applications - its ability to encapsulate other molecules. When starch is consumed as a regular part of the diet, its polysaccharide structure functions to envelop any other compounds it meets in the digestive system. Researchers realized this entrapment quality could potentially facilitate the development of starch-based drug delivery formulations. Such formulations may permit controlled or timed release of therapeutic substances at different points along the gastrointestinal tract. This offers possibilities for improved medication absorption and targeting of specific problem areas. Continuous studies since the 1980s have helped advance the understanding of starch on both fundamental and applicative levels.

Alginates have established themselves as one of the most versatile biopolymers, being used in a wide variety of applications (Teng et al., 2021). The conventional use of alginate as an excipient in drug products generally relies on its ability to thicken, form gels, and provide stabilization. However, the need for prolonged and improved control over drug administration has increased the demand for tailored polymer designs. Hydrocolloids like alginate can play a significant role in developing controlled-release products. At low pH, alginic acid hydrates result in the formation of a high-viscosity acid gel. Alginate can also easily be gelled through the presence of the divalent cation calcium ion. Once dried, sodium alginate beads reswell upon rehydration, creating a diffusion barrier and decreasing the migration of small molecules. Alginate's unique property of forming two different gel types dependent on pH, namely an acid gel and ionotropic gel, gives it properties distinct from neutral macromolecules. Furthermore, the molecule can be customized for several applications. To date, over 200 distinct alginate grades have been manufactured along with several alginate salts. The potential use of these various qualities as pharmaceutical excipients has yet to be fully evaluated, but alginate is likely

to make an important contribution to the development of polymeric delivery systems. This natural polymer has been adopted by the European Pharmacopoeia and can be obtained in an ultra-pure form suitable for implants. This review discusses the current use and future possibilities of alginate as a tool in drug formulation.

Encapsulation technology stands out as an option for its simplicity in application and the wide variety of substances that can be encapsulated. The product created through encapsulation takes the form of a powder. Materials that could be protected include polymers or biopolymers like dyes, catalysts, cosmetic medicines, curing agents, and even plasticizers. While encapsulation offers versatility, one of its most significant challenges is that a unique design tailored to each administration route is required to manage attributes such as particle size, shape, toxicity, and release kinetics of the encapsulated therapy.

Encapsulation can generate different structural forms which each impact release properties. A monocoque or reservoir structure consists of an active ingredient dispersed or dissolved within a polymeric matrix. In a multicore form, several active-loaded cores are encapsulated within an additional polymeric shell. For matrix encapsulation, the active is uniformly dispersed within the polymer material. Coated monocoque-type capsules feature a polymer-coated singular core while coated matrix designs have a polymer coating applied over a homogenously filled matrix system.

Previous research from 2016 explored these various encapsulation architectures and their release implications. The monocoque design offers a reservoir that releases its contents over time through diffusion out of and erosion of the polymeric shell. Multicore capsules can provide controlled release as the outer layer degrades and exposes the individual cores. With matrix encapsulation, active ingredients are released through simultaneous diffusion and polymer degradation processes.

Proper selection of encapsulation type depends on the targeted administration route and desired release profile because different drugs can be administered differently depending on the target. For example, oral delivery may require coatings that protect therapeutics from stomach acidities and control dissolution location from the body's normal physiological process like the gastrointestinal tract. The structure must also

account for attributes such as particle dimensions suitable for the administration method which serves in important role when administering such drugs, safe toxicity, and stability during storage. Achieving the right encapsulation design is paramount given each application's distinct needs but offers flexibility in formulation in understanding the type or form in which the drug can be used.

Encapsulation presents a straightforward technology that is widely employed in drug technology, simply requiring dispersion or dissolution of actives into polymeric carriers to generate powdered micro- or nanoparticles which offer the important structure in which the drugs should be administered. However, one must tailor the encapsulation structure and composition to each administration route to ensure the safe and effective delivery of encapsulated substances. Prior studies provided insights into release behaviors for common encapsulation types like monocoque reservoirs, multicore particles, matrix systems, and coated variants. Selecting the appropriate encapsulation design allows for modulating release kinetics and overcoming delivery challenges like protecting therapeutics from degradation. Continued optimization of encapsulation techniques will expand their application across drug, food, cosmetic, and other material deliveries.

Blending different polymers presented a novel approach to enhancing the qualities of polymers. There exist numerous techniques for polymer blending one method being crosslinking. Calcium chloride can act as a crosslinking agent when combined with sodium alginate, allowing for the molecular chains of sodium alginate to become more tightly interconnected. This generates a stronger synergistic effect where the interactions between chain chains ultimately form a three-dimensional grid structure in a beads state. The tensile strength, thickness, and flexibility of any resulting film are improved. Additionally, the overall performance of such a film is greatly augmented.

Prior studies have examined preparing sodium alginate-starch blends using calcium chloride as a cross-linker according to a specific molar ratio. The concentration of the cross-linker and diameter of any needles used impact the formation of beads from such blended polymer solutions. When calcium chloride is introduced to a solution containing both sodium alginate and starch biopolymers, crosslinking reactions occur between the calcium ions and the alginate chains. This causes the molecular structure to transform from long independent strands into a tightly woven network with the chains

linked together at multiple points. As more crosslinking takes place, the individual polymer molecules become extensively associated, ultimately creating a solid three-dimensional structure.

The crosslinked blended polymer network exhibits enhanced material qualities compared to either standalone component. The tensile strength is increased as the covalent bonds between polymer chains strengthen the material. Crosslinking also results in a thicker film or beads due to the compactness of the interwoven polymer structure which offers an essential factor in its application. Flexibility is improved because of the distribution of stress throughout the network under deformation thus its effectiveness is enhanced and promoted. These performance gains arise from the synergistic combination of properties from each component along with the structural reinforcement from multiple crosslinking junctions which are in between its structures. Both concentrations of the calcium chloride cross-linker and the diameter of needles used to form beads can impact outcomes because of their molecules, with optimization needed for desired results at the end of its knowledge and its application.

Through crosslinking, polymer blending presents an effective approach for modulating material attributes which are very essential in their structure and application. The interactions between sodium alginate and starch are augmented by calcium ions facilitating linkage between molecular chains when they interact with each other. This transforms the system from individual polymer strands into an intricately woven three-dimensional network due to their interaction with each other when they are interacting chemically. The denser, more robust structure conveys heightened tensile strength, thickness, and flexibility between the structures of independent elements. Performance is further bolstered through property combinations from each component. Overall, crosslinking polymer blends provide a tailored methodology for developing materials with enhanced qualities suited for a variety of applications.

Sodium alginate and starch are commonly utilized polymers in drug delivery sy, biodegradability, and natural abundance. The selection of polymer depends on factors such as drug solubility stems due to their biocompatibility between its molecules due to chemical interactions, desired release profile, and compatibility with the targeted administration route. The drug loading capacity for sodium alginate and starch is an

important parameter to quantify the amount of drug that can be incorporated into the delivery system. Release studies are influenced by aspects including polymer concentration, drug-polymer interactions, and manufacturing techniques that are used when trying to manufacture these particular drugs. Sodium alginate additionally demonstrates pH responsiveness owing to its ionization behavior under changing pH conditions when undergoing various chemical interactions. These inherent properties and considerations lay the groundwork for investigating drug release behaviors of systems composed of sodium alginate and starch.

Sodium alginate and starch are naturally derived polymers commonly used in drug delivery system formulations which particularly differ from one another. They offer favorable qualities such as compatibility with living systems, the ability to break down harmlessly, and widespread sourcing enhancing it to be widely employed. Selection of the polymer carrier depends on matching factors like the drug's solubility properties, preferred release profile over time and space, and compatibility with the intended delivery pathway into the body. The maximum drug loading, or carrying capacity, of sodium alginate and starch carriers requires determination to quantify how much activity can feasibly be included in the delivery system which differs from one polymer to another. Release performance is influenced by polymer traits such as concentration, interactions between drug and polymer, and manufacturing process parameters. Sodium alginate also exhibits pH-dependent behavior attributable to its ionization in response to acid-base conditions. However, analytical methods, test parameters, and study goals for particular evaluations may reasonably differ based on practical and intended application needs which enhances the widespread of applications at different pharmaceuticals.

1.2 Problem Statement

The production of encapsulated formulations using natural polymers has seen widespread application in fields such as biomedicine, food processing, and cosmetic or personal care products where most of the applications use these products especially regarding the scale of beads manufactured. While sodium alginate possesses properties that make it suitable for some uses which is one of the reasons why it is mostly applied, it also demonstrates limitations that need to be considered as a way of increasing the

efficiency of this process. Sodium alginate can exhibit brittleness lacking sufficient mechanical strength or resilience to withstand notable stresses or deformation making it a better option in this process and it is the main reason why it is mostly selected during manufacturing.

Starch also struggles with sensitivity to moisture and temperature variances, which influence stability and structural integrity. Fluctuations in humidity or temperature during storage or handling can induce physical property changes in starch-based products which can impact drug release behavior and overall performance making this condition an influencing factors that need to be considered during manufacturing. Such instability presents the potential for reduced quality control and this has a negative impact on the overall quality.

Sodium alginate delivery systems sometimes exhibit an initial burst release, where a significant drug amount rapidly disperses upon environmental contact. This burst effect can lead to sub-therapeutic drug concentrations and diminish treatment efficacy. The research aims to investigate how combining alginate and starch may create a superior bead formulation regarding properties such as oxygen and water vapor barrier abilities, mechanical characteristics, and optical parameters. Specifically, evaluating bead outcomes from various alginate-starch ratios, calcium chloride concentrations, and needle diameters used during production. Additionally, examining release profiles under different pH environments and responsiveness to temperature changes will provide insight into natural polymer delivery systems triggered by such conditions to target specific sites. The production of stable, consistent beads must account for the inherent sensitivities of constituent polymers while balancing desired protective and release qualities. Optimizing fabrication techniques and material choices presents an opportunity to overcome individual material limitations and better regulate drug administration for improved patient outcomes. Continued evaluation of combined alginate-starch systems may establish a robust, versatile encapsulation platform translating to diverse applications.

1.3 Objectives

1. To prepare alginate-starch beads using the crosslinking method.
2. To study the effect of parameters (ratio of alginate-starch, the concentration of calcium chloride, needle size) of beads.
3. To study methylene blue release in UV-Vis for 90 minutes.

1.4 Scope of Study

The research aims to formulate blended beads utilizing sodium alginate and starch through a cross-linking fabrication method. Specifically, sodium alginate/starch beads will be prepared using various component ratio combinations along with differing concentrations of Calcium Chloride as the cross-linker. Additionally, the impact of employing distinct needle size during production will be evaluated. Parameter alterations will be systematically studied throughout experimentation.

Release dynamics will be characterized using methylene blue as a model active compound. Methylene blue possesses characteristic absorbance within the visible light spectrum cantered around 660 nm, allowing for quantification based on the Beer-Lambert law relating absorbance to concentration in solution. By measuring the absorbance of solutions containing methylene blue released over time using a UV-Vis spectrophotometer, concentration values can be derived. This will permit determination of the release rate profile for methylene blue over 90 minutes from the formulated beads.

Spectrophotometric analysis provides a label-free, non-destructive analytical technique suitable for tracking release kinetics. Methylene blue was selected as a representative active due to its simple, inexpensive nature along with distinctive light absorption facilitating concentration measurements. Characterizing release under various formulation and processing conditions aims to elucidate parameter impact. Comparative evaluation of methylene blue concentrations liberated from the beads in aqueous environments over an extended time interval will yield release rate dynamics.

Through systematically preparing blended alginate-starch beads while varying material ratios, cross-linking agent levels, and production needle sizes, the research seeks

to explore processing parameter influence. Calcium chloride concentration is being investigated as the cross-linking agent bridging alginate and starch polymer chains. Release studies employing methylene blue and UV-Vis absorbance measurements will enable quantification and comparison of release profiles for the formulated bead types because elucidating relationships between fabrication conditions and resulting release behaviors can support optimization efforts.

1.5 Significances of Study

Sodium alginate and starch are naturally occurring polymers that are biocompatible, non-toxic, and abundantly sourced worldwide where these attributes render them suitable for applications involving biological systems such as drug delivery. Their compatibility with living tissues helps reduce risks of adverse reactions or toxicity issues when employed clinically making them a better option because of the availability and strength they have when used in the manufacturing process. Alginate-starch beads additionally provide versatility in the formulation and drug incorporation capacities. Properties such as composition ratios, sizes, and crosslinking densities can be readily modulated to customize beads according to specific drug profile needs.

These beads are also capable of encapsulating an array of active compounds which is inclusive of both hydrophilic and hydrophobic drugs. Encapsulation within alginate-starch beads protects drugs from degradation and enzymatic breakdown. This proves particularly important for actives that are sensitive to environmental conditions or enzymatic metabolism within the body. The beads serve as a physical barrier safeguarding drugs until reaching target sites. Sodium alginate and starch are also relatively inexpensive and widely available starting materials. Production of alginate-starch beads demonstrates lower costs compared to alternative drug delivery systems hence rendering them an economically practical option for pharmaceutical applications.

Characterization of these blended beads fabricated under controlled conditions can provide formulation design guidance. Release kinetics elucidation from the model methylene blue compound translates to profile predictions for diverse encapsulated actives. On the other hand, optimizing fabrication parameters like polymer ratios and

crosslinking levels could lead to tailored release behaviors meeting specific therapeutic needs. Lastly, establishing structure-function relationships between processing variables and resulting encapsulation performance carries broader significance.

CHAPTER 2

LITERATURE REVIEW

2.1 ENCAPSULATION

Encapsulation is the extensive process of completely enveloping or entrapping one substance within a protective or controlled barrier material (Xu et al., 2022). Within the specialized field of controlled pharmaceutical delivery applications, encapsulation refers to enclosing an active therapeutic agent or targeted drug compound entirely within a customized carrier formulation (Xu et al., 2022). This carrier material, commonly characterized as the protective delivery matrix or vehicle structure, can be an intricately designed polymer construct, lipid molecular arrangement, or another optimized biocompatible material composition. It functions as an impermeable defensive barricade surrounding the packaged drug payload, preventing breakdown or destabilization from external degradative interactions while simultaneously regulating the drug's controlled temporal distribution profile.

According to Mamusa et al., (2021), specialized carrier formulation that encapsulates the active drug compound is designed through extensive research and testing to provide defense of the delicate medication from the harsh and unpredictable environment of the human digestive system as the encapsulated drugs are intended for oral administration and must pass through the stomach acids and enzymes of the gastrointestinal tract without premature degradation or dissolution before reaching the intended absorption site in the lower intestines where the carrier formulation is engineered to safely and selectively release the encapsulated drug payload at just the right location and time according to the designed pharmacokinetic parameters.

The customized encapsulating carrier materials whether comprised of synthetic polymers, natural lipids, or other biocompatible components are intricately engineered at the nanoscale level through the utilization of sophisticated fabrication techniques and technologies including nanospray drying, nanoemulsion, lipid nanoparticle formation, and more to construct the optimal protective barrier structure with desired properties including complete encapsulation of the active drug, impermeability to degradation, and precise control over drug release kinetics and timing which are all critical factors in developing effective drug delivery systems for conditions requiring tightly regulated dosing schedules to achieve therapeutic drug concentrations at sites all over the body for various applications from cancer treatment to management of chronic diseases to vaccinations and beyond (Diltemiz et al., 2021).

The encapsulation procedure can be accomplished through a variety of highly specialized technological strategies such as micro-scale containment fabrication, nano-scale delivery vehicle construction, or the formation of macro-scale encapsulated bead or capsule geometries. for optimizing drug delivery outcomes (Grgić et al., 2020). Encapsulation offers innumerable advantages in production and enhance therapeutically advanced drugs to be used set different categories of administration, , improve solubility for enhanced absorption incorporation of the drug within one's body thus enhanced drug compatibility within the body leading to more adaptability of the drug to one's body cells, prolong the duration of effective drug presence to minimize dosing frequency requirements which can come as a result of either higher intake of particular drugs leading to encapsulated drugs being the best and better method of oral administration of a drug, and crucially allow for targeted localization of drug accumulation precisely at prioritized treatment sites which can finally enhance the drug to attain its medical importance that has been prescribed by the medical practionaire (Mohammed et al., 2020). This maximizes therapeutic effectiveness while minimizing potential off-target interactions and systemic side effects. encapsulation plays a pivotal role in properly designing targeted delivery systems by providing a means to fully envelop and safeguard drug cargos while precisely governing bioavailability kinetics to optimize therapeutic impact leading to the enclosure of all drug components within the system so that it can offer medical importance value to the target.

Encapsulation technologies accomplish many integral objectives for advancing tailored pharmaceutical delivery approaches which differ from individual to individual as there are different delivery methods of the drugs (Jiang et al., 2020). Primarily, encapsulation offers complete protective shielding of drugs from degradation which could lead to a drug losing its original constituents which could be a disadvantage, enzymatic breakdown processes, or otherwise unfavorable environmental conditions within diverse anatomical regions for the case of polio vaccinations in African regions (Wagle et al., 2020). The customized carrier formulation acts as an impenetrable physical barricade thus not allowing any material from the external environment to contact with the drug, fully guarding the packaged drug payload from compromising exterior factors which are the major constituents of that drug. Encapsulation permits meticulously regulated extended-term controlled liberation of the completely encapsulated therapeutic cargo over prolonged durations so that the drug can reach its desired destinations safely. The carrier architecture can be deliberately engineered to gradually discharge the drug in a precisely timed manner to maintain therapeutic concentrations longitudinally without necessitating frequent redosing intervals so that the drug can work effectively within the body of an individual. The ability of encapsulation techniques to entirely envelop active drug compounds within personalized carrier formulations designed for maximum defense of the medication and precision dosing control has revolutionized drug delivery mechanisms solving prior compliance issues with more regular dosing regimens while also improving patient outcomes through stabilized therapeutic levels of the pharmaceutical agent being delivered to its destination target site for treatment which is a co-factor and the aim of different manufacturers, this serves as major confident model in ensuring the drug reach the target safely.

2.2 MATERIAL FOR ENCAPSULATION

A diversity of naturally occurring and synthetically formulated polymers have been investigated as potential encapsulating materials for controlled drug delivery applications these materilas are designed in a way that they can easily dissolve leading delivery of the drug (Ma et al., 2022). Both nature-inspired and engineered options provide unique properties suiting varied pharmaceutical needs which are the key developing features in the drug ecosystem. Alginate,

extracted from brown seaweed, forms ionically crosslinked hydrogel networks capable of entrapping drug payloads so that they can be delivered safely. Its swelling and diffusion-mediated release behaviors can be modulated through bioinspired structural modifications thus resulting in safe delivery of the drug constituents within one's body. Chitosan, obtained from crustacean exoskeletons from marine life, demonstrates mucoadhesive properties advantageous for mucosal drug absorption within the gastrointestinal tract (Mura et al., 2022). Its cationic character also enables interactions with anionic therapeutic agents as well as gene complexes. Hyaluronic acid, a principal component of human connective tissues, forms viscoelastic hydrogels through non-covalent interactions between repeating disaccharide units and serves widely are good and compatible materials for the encapsulation of these drugs (Di Mola et al., 2022). These adaptive natural polymers offer low immunogenicity and sustainable sourcing thus they don't induce any severe immune response.

Alginate-derived capsules can encapsulate both hydrophilic and hydrophobic medications achieving extended multiphase release kinetics tunable through regulating crosslink density within the interwoven fiber network structure along with the degree of polymer chain entanglement which enables it to respond to either charge within one self-body, molecular weight characteristics and patterning of copolymer composition during biosynthesis also is a key factor to consider when looking for better encapsulating materials. Chitosan's mucoadhesive excipient properties prove highly beneficial for localized targeting of mucosal tissues allowing therapeutic payloads to more effectively adhere to epithelial cell surfaces for absorption while also forming a protective barrier preventing premature drug dissolution and maintaining stable concentrations at the delivery site which is the major and key target principle when dealing with this drugs. Hyaluronic acids dynamic hydrogel assembly engages in reversible physical bonding between carboxyl and hydroxyl functional groups along the long unbranched polysaccharide backbone giving rise to a high swelling capacity aqueous gel with customizable porosity and pore size dependent on molecular weight and concentration variables enabling precise tailoring of drug diffusion parameters and release time.

Synthetic polymers offer engineered tunability as encapsulation matrices through chemical synthesis techniques this polymers can naturally release these drugs once they reach the target sites. Biodegradable polyesters like polylactic acid and polyglycolic acid have received FDA approval for various medical implant and drug delivery applications due to their adjustable erosion kinetics permitting accurate programming of drug liberation schedules to match pharmacokinetic needs across all boards once dealing with these particular drugs when enhancing their effectiveness. Poly-ε-caprolactone forms semicrystalline hydrophobic matrices proven biocompatible with prolonged degradation over two years when formulated as micro and nanoparticle carriers for sustained release injectables which are used in administering these same drugs to a particular individual at this matter. Poly(ortho esters) generate carboxylic acid by-products of low toxicity upon hydrolysis making them attractive options for localized drug release within one's body thus not causing any harm or contraindications. Their hydrolytic degradation produces non-toxic metabolites eliminating concerns for long-term accumulation within the individual normal physiological functioning.

Advancements in polymer chemistry now enable highly customized macromolecular design with control over the molecular weight of different compounds and elements that serve to encapsulate this particular drugs, composition, sequence, topology, and functionality at the individual monomer level yielding next-generation tunable delivery platforms which play a key important function when dealing with this particular drugs Dalal Mohamed Alshangiti et al., 2023). Combinatorial biomaterial libraries facilitate high-throughput evaluation of structure-property relationships guiding material optimization which can enhance better drug absorption. Rapid prototyping and 3D printing technologies provide automated fabrication of complex multi-scale architectures with the spatial distribution of distinct encapsulated cargos for personalized therapies, this aids in studying various methods and structures to enhance the solubility of these particular drugs. Advanced surface modification techniques introduce stimuli-responsive elements and target ligands permitting environmental or location-specific activation, this ligands serve as attachment sites of this drug to enhance proper drug delivery. Continued cross-disciplinary developments at the interface of polymer and pharmaceutical sciences hold tremendous promise

to revolutionize drug delivery through rational material engineering resulting in development of better and compatible materials when dealing with these particular drugs.

Synthetic alternatives like PEG, PLGA, PCL, and PVA empower precisely customized encapsulation designs through tunable chemical compositions and configurations which offer a variety of alternatives when issuing drugs and their possible compartment structures. PEG boasts exceptional biocompatibility and is often employed to formulate stealth liposomes and polymeric micelles through amphiphilic self-assembly with essential drug-loading cores and core when handling these particular drugs.. The biodegradable polyester PLGA completely degrades into non-toxic metabolic products which are not harmful to the individuals taking that same particular drug, presenting sustained drug release over weeks to months depending on the ratio of lactic to glycolic acid monomers which are particularly and specifically used in this type of binding drugs. Hydrophobic PCL provides a slower degradation rate suited for prolonged implants so that the drug can be absorbed and released in small bits resulting in this particular method.

Advanced material engineering may enable even greater control over encapsulation parameters like degradation kinetics, loading capacity, targeting abilities, and controlled unpacking of delicate drug payloads which in due course can change either in their concentration or at some point could lead to toxicity and poisoning (Han et al., 2020). Both natural and synthetic polymers continue making contributions through nanocarrier design which is used as a primary drug enclosing method, stimulation-responsive hydrogels, and 3D printable scaffolds – expanding the reach of personalized controlled release formulations leading to a drug safely delivery its constituents to the target site. Optimization of existing encapsulating agents as well as designing new platform technologies holds promise for enhancing patient quality of life across diverse therapeutic applications without causing any contraindication to the individuals using that particular drug.

Precise manipulation of polymer composition through recombinant techniques and atom transfer radical polymerization now permits definition of macromolecular structure at the

individual monomer scale providing unprecedented command over a range of tunable properties which can be interpreted by reading this atom through technological methods (Chen et al., 2020). By introducing stimuli-reactive side chains or end groups sensitive to specific environmental triggers like temperature, light, magnetic fields or chemical signals, material engineers design prodrugs that remain inert until activated exclusively at the target destination by local stimuli which is produced by oneself body of the individual who is indented to have that particular drug. This enables controlled unpacking of the drug payload only following encapsulated nanocarrier accumulation at diseased tissues or cellular uptake within desired cell populations while preventing premature release of the drug resulting to the drug not performing medically indented functions.

Capsules and device components with intricate multi-scale porous architectures and spatial patterning of diverse encapsulated compounds also can be used to safeguard this kind of drugs (Zhang et al., 2022). Loaded hydrogel scaffolds are being designed to gradually biodegrade while stimulating new tissue growth and revascularization within ones body at a particular time. This maximizes therapeutic effectiveness while minimizing potential off-target interactions and systemic side effects. Implantable devices with millimeter scale reservoirs, micron sized delivery channels and sub-micron encapsulated payloads promise personalized therapies through programming of multiple release kinetics, combinations, and dosing schedules. Emerging “4D printing” expands such capabilities with shape-shifting programmability, allowing transient device designs optimized for non-invasive therapeutic deployment and removal.

Nanotechnology developments including DNA origami, lipid vesicles and polymer-protein conjugation continue advancing nanocarrier design. DNA origami techniques utilize the sequence-specific self-assembly of DNA to construct nanostructures with addressable surfaces and cavities for encapsulating diverse cargos. Lipid-coated DNA nanocages show potential for intracellular delivery of nucleic acids or chemotherapeutics. Liposomes engineered with stimuli-responsive components may achieve controlled content release through structural transformations. Polymer-protein conjugation generates biohybrid systems integrating targeting ligands with tunable polymeric carriers. Selective cellular internalization and intracellular trafficking can be achieved through conjugation of cell penetrating peptides to stimuli-sensitive nanogels (Zhang et al., 2022).

Besides protective containment and regulated temporal distribution profiling, encapsulation further facilitates targeted shipment of drugs exclusively to prioritized anatomical sites within the body. The customized carrier design can bear specialized signature targeting properties that actively promote accumulation solely at prioritized treatment tissues or cellular populations. This maximizes therapeutic effectiveness while minimizing potential off-target interactions and systemic side effects which can occur as a result of this interactions between the drug and the body. Encapsulation designs can moreover improve the solubility and absorption incorporation of hydrophobic drug payloads poorly soluble in aqueous physiological milieus that occurs depending on one's physiological processes that are taking place within one's body. Their solubility and bioavailability can be substantially enhanced. Encapsulation allows for the simultaneous delivery of complex multidrug therapeutic regimens Equally within one body. To finalize, encapsulation accomplished using comprehensively optimized nanoscale vehicle designs such as customized polymeric particulate constructs, amphiphilic lipid bilayer vesicle configurations which is a doubled charged membrane is a fatal layer when, or other advanced biomaterial matrices, forms an impermeable protective shell surrounding the active drug payload to conduct regulated liberation profiling while facilitating targeted delivery to enhance therapeutic efficacy which is very essential when knowing the percentage of drug adaptability within the body of individual (Chen et al., 2020).

2.3 Methods for Encapsulation

Drug delivery seeks to optimize health outcomes through diverse science which is used in administering drugs into the body of an individual (Adepu & Ramakrishna, 2021). Encapsulation techniques merit thoughtful consideration to uphold ethics while advancing compassionate innovation due to advancement in technology. Natural and engineered polymers each offer benefits, like seaweed-sourced alginate facilitating controlled hydrogel release this particular drugs when administered onto the body of an individual. Synthetics too permit tailored designs which vary in different forms and categories, from PEG's non-fouling carriers to PLGA's tunable

degradation to release this particular drugs into the body system. A diversity of methods likewise empowers personalized approaches which at some point vary from one form to another.

Emulsion techniques disperse actives across Solvent-Phase matrices so that the drug can be fully emulsified into a needed solution (Park et al., 2021). Extrusion and injection confer uniformity through precise shaping. Electrostatic layering utilizes oppositely-charged interactions to steadily structurize payloads. Spray drying atomizes solutions for efficient particulate forming, while self-assembly organizes components through intrinsic molecular attractions. Crosslinking generates strengthened networks via chemical, physical or radiative bonding between linear chains. Hydrogels interesting especially their permeability and responsiveness aim to safely conduct therapeutics as native tissues do. Optimization across scales seems key, from molecular modifications enhancing biocompatibility to process refinements ensuring batch consistency.

2.4 Drug in Encapsulation

During the developmental stages of delivering therapeutic aid to those in need, it is imperative to fully investigate each element comprising the treatment methodology. A profoundly integral component herein involves selecting an appropriate pharmaceutical agent to capsule within the carrier material.

Myriad factors are required for thorough consideration when determining the opposite drug to incorporate within the encapsulation framework. Firstly, and foremost the intended biochemical function of the medicinal substance must be apt for addressing the pathology intending resolution. The drug's intended mechanism of action whether operating excitatory, inhibitory, or modulatory capacities necessitates exact accommodation within the formulation parameters.

Additional logistical aspects intrinsic to the drug compound include yet are not restricted to assessing its water solubility properties to ensure suitable dispersion and dissolution behaviours requisite for efficient therapeutic absorption profiles over desired durations (Park et al., 2021). Hydrophobic agent's proclivity for nonpolar partitioning while hydrophilic drugs water solubilizing tendencies each must accurately align with the carrier networks affinities. Furthermore, investigating the drugs physical and chemic stabilities when subjected to varying environmental conditions such as temperature, pH, oxidative, and light exposures helps ascertain encapsulation processing parameters and subsequent storage handling guidelines.

The drugs molecular weight, size, shape, charge characteristics, and isomeric form all influence its payload packaging proclivities and release kinetics from formulations. Larger more conglobated drugs may necessitate porous matrices with wider mesh sizes while minutely diminutive molecules require matrices with selective permeabilities. Ionized drugs electrostatic forces can govern its interactions with oppositely charged carriers permitting modulation of its release timing. Chiral isomers containing identical elemental compositions yet divergent spatial geometries may exhibit differing solubility necessitating dedicated carrier systems.

Moreover, examining the drugs pharmacological and pharmacokinetic properties elucidates optimal dosing schemes and schedules for attaining and maintaining therapeutic concentrations at destination sites and tissues. Narrow therapeutic index agents requiring stringent plasma level regulations demand sophisticated encapsulation designs affording highly tuned liberation profiles. Extended action medications necessitate sustained steady state administrations from depot formulations. Localized or targeted delivery platforms require compounds exhibiting binding affinities for intended cellular and macromolecular receptors.

Lastly, assessing the medications production and purification methods can impact encapsulation processing workflows and economics. Synthetically manufactured compositionally homogenous small molecule drugs facilitate mass manufacturing encapsulation while biotechnologically derived structurally intricate protein and nucleic acid based medications require

specialized encapsulating with additional stabilizing excipients added. Natural product extraction derived drugs heterogeneous and complex compositions necessitate extensive analytical testing to ensure batch to batch quality consistencies. Cost efficiencies stem from leveraging encapsulation techniques compatible with diverse drug fabrication techniques.

Therefore, thoroughly evaluating intrinsic physicochemical properties, pharmacologic attributes, and production particulars of candidate therapeutic agents serves to inform rationale drug substance selections optimally configured for accomplishing targeted sustained delivery objectives. Pairing drugs complementary encapsulation-amenable qualities with carrier system design attributes customized for drugs inherent traits and functions streamlines formulations advancements toward advancing patient wellbeing applications. The drugs identity proves profoundly pivotal in driving formulation frameworks achieving exceptional clinical translations.

2.5 Release Study in Encapsulation

Investigating encapsulation formulation release properties through assiduous analytical experimentation provides indispensable structure-function insight bankable for clinical translations. Purposeful release kinetics optimization from tailorable delivery platforms proves instrumental in addressing diverse therapeutic dosing necessities (Ibrahim et al., 2022).

Initial release profiling entails subjecting encapsulated drug samples to non-destructive dissolution testing under physiologically simulative conditions while dynamically monitoring liberation quantities throughout predefined elapse durations (Ibrahim et al., 2022). Continuous agitation maintains sink conditions favouring drug diffusion from carrier matrices into surrounding media mimicking in vivo circulation dynamics and various systemic distribution and elimination flows. Interval sampling for analysis by descriptive analytical methods such as ultraviolet and fluorescence spectroscopies afford quantitative determinations into escaping drug masses versus time dependencies from which release kinetics modelling may be parameterized.

Influential formulation attributes emerge from comparative evaluations between resultant release curves among varied carrier composition types and fabrication techniques. Hydrophobic synthetics exhibiting slowed chain segmental motions tend toward hindered diffusion mediated controlled release while hydrophilic polymers rapid swelling and relaxation under aqueous submersion incur Encapsulation offers innumerable advantages initially heightened yet transiently waning liberation profiles. Ionically cross-linked hydrogels dynamic structural reorganizations in response to solvent interactions and pH or ionic strength fluctuations further enable tunable release triggering or modulation through environmental stimuli (Ibrahim et al., 2022).

Moreover, matrix morphologies dramatic impacts emerge from investigative modifications within fabrication parameters (Ibrahim et al., 2022). Monolith devices impermeable barriers impose linear diffusion restricted release while micron scale particulate dispersions colloidal stabilities and surface areas determine release. Porosities extent and interconnectivity impose size dependent restrictions on liberated molecules permeability's thus facilitating modulated liberty escalations. High internal phase emulsion derived carriers continuous structures confer multi-dimensional release avenues outweighing monolithic analogues.

Additionally altered drug loading concentrations exert release influences through mass transport constraints, whereas drug-carrier interactions such as electrostatic complexations or molecular entanglements can induce release retardation. Molecular weights, hydrodynamic radii, and polar substituent presences of encapsulated drugs further influence liberated mobilities and pathways. Release kinetics discernments thereby inform design avenues including modulated loading amounts, adjusted matrix porosities and morphologies optimization toward formulating desired dosing durations and kinetics.

Quantitative characterization aids formulation enhancements directed toward addressing diverse clinical applications. Microparticle suspensions apt for bolus injections require initial burst releases followed by sustained levels maintenance. Implantable necessitate longevity for prolonged therapeutic provisions. Stimuli-tuned platforms enable targeted release activations at

disease sites. This indispensable field of kinetic analysis under simulated physiological conditions thereby serves pivotal advancements in customized controlled delivery systems formulations.

CHAPTER 3

MATERIALS AND METHODS

3.1 Materials

Sodium Alginate (SA) (Natrium Alginate) Chemically Pure (C.P) from R&M Chemicals, Starch from Potato Soluble (ST) (EX Potato) AR from HmbG Chemicals, and Methylene Blue (MB) C0533 from HmbG Chemicals and Calcium Chloride (CaCl) as crosslinker.

3.2 Methods

The preparation of Sodium Alginate (SA) / Starch (ST) blends loaded with Methylene Blue (MB) were prepared in 3 different ratios, 3 different size of needle, 3 different pH release. So in total we prepared 12 samples at the end of this experiment. Those sample was detailed in Table 1 below.

First of all we need to weigh 3g of SA and 3g of ST and 2.5g of CaCl. CaCl need to dissolve in 100 ml of distilled water while 3g of SA and 3g of ST need to dissolve in 100 ml of distilled water without any lumps. Dissolved mixture will added with 0.002g/ml of methylene blue as model drug load. As following segment, mixture will be aspirate into 18G size needle, then expelled into CaCl solution to form beads.

Formed beads will be drained out from the solution. Drained beads will be added into 1.2 pH of distilled water solution. Those beads will be let spinned in magnetic stirrer at 1000rpm for 90 minutes. With a use of dropper sample solution will be collected in different time period such

as after 3 minutes, 5 minutes, 15 minutes, 30 minutes, 60 minutes and 90 minutes be to study the release rate under Uv-Vis. All these steps will be repeated according to table 1.

NO	SAMPLE NAME	RATIO OF SODIUM ALGINATE : STARCH (g)	CONCENTRATION OF CALCIUM CHLORIDE (g/ml)	SIZE OF NEEDLE (G)	RELEASE pH
1	3SA/3ST/0.25CaCl/18G	3g : 3g	0.25	18 G	1.2
2	3SA/3ST/0.25CaCl/24G	3g : 3g	0.25	24 G	5
3	3SA/3ST/0.25CaCl/26G	3g : 3g	0.25	26 G	7.4
4	3SA/3ST/0.5CaCl/18G	3g : 3g	0.5	18 G	1.2
5	3SA/3ST/0.5CaCl/24G	3g : 3g	0.5	24 G	5
6	3SA/3ST/0.5CaCl/26G	3g : 3g	0.5	26 G	7.4
7	3SA/6ST/0.5CaCl/18G	3g : 6g	0.5	18 G	1.2
8	3SA/6ST/0.5CaCl/24G	3g : 6g	0.5	24 G	5
9	3SA/6ST/0.5CaCl/26G	3g : 6g	0.5	26 G	7.4
10	3SA/9ST/0.5CaCl/18G	3g : 9g	0.5	18 G	1.2
11	3SA/9ST/0.5CaCl/24G	3g : 9g	0.5	24 G	5
12	3SA/9ST/0.5CaCl/26G	3g : 9g	0.5	26 G	7.4

Table 1 : SAMPLE PREPARATION

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Results

In this chapter, we will analyze and discuss the results obtained from the experiment on the release study of methylene blue as a model drug encapsulated by alginate/starch blend beads prepared via crosslinking method. The data provided consists of the sample names, the ratio of sodium alginate to starch, the concentration of calcium chloride, the size of the needle used, and the release pH. Additionally, UV-Vis intensity measurements for methylene blue at different time intervals and pH values are also provided.

4.2 Discussion

When the ratio of sodium alginate to starch was 3g:3g, at a calcium chloride concentration of 0.25g/ml, and a needle size of 18G, the release of methylene blue showed the highest intensity at a pH of 1.2, gradually decreasing with increasing pH values. This observation suggests that the release behaviour of methylene blue from the alginate/starch blend beads is influenced by the composition of the beads and the pH of the release medium.

The highest release intensity of methylene blue at pH 1.2 can be attributed to the interaction between the drug and the blend beads. At this pH level the alginate chains in the beads are protonated which is the main reason for the increased swelling and porosity of the beads as it is observed from the results. The enhanced swelling observed in the experiment plays a crucial role in facilitating the diffusion and release of drugs. This change in size before and after the experiment

can be attributed to this mechanism. Additionally, the presence of calcium ions that are introduced through the calcium chloride crosslinking process further promotes the release of methylene blue by destabilizing the bead structure which contributes significantly to the results obtained during the experiment.

As the pH of the release medium increases the alginate chains undergo ionization process that has an impact on the size of the alginate (Sreya et al., 2023). This ionization process is responsible for the decrease in swelling and porosity of the beads. Additionally, the reduced swelling limits the diffusion of methylene blue from the beads which is responsible for the gradual decrease in the release intensity. These observations emphasize the importance of considering pH conditions when designing drug delivery systems using alginate/starch blend beads. Therefore, from the results obtained from the experiment the pH values of 5.0 and 7.4 in particular highlight the significant impact of pH on drug release.

The choice of a calcium chloride concentration of 0.25g/ml and a needle size of 18G also influences the release behavior. The concentration of calcium chloride directly affects the crosslinking density of the beads (Girón-Hernández et al., 2021), which subsequently impacts their structural integrity and drug release properties. In the case of a lower concentration (0.25g/ml), the crosslinking network is less dense, allowing for easier diffusion of methylene blue out of the beads. Conversely, a higher concentration (0.5g/ml) leads to a more compact and rigid structure, resulting in a reduced release rate of the drug. It is imperative to consider these factors, such as calcium chloride concentration and pH conditions, when designing drug delivery systems utilizing alginate/starch blend beads. These considerations will greatly influence the release behavior and efficacy of the drug delivery system.

The needle size used in the experiments determines the size of the pores formed during the bead formation process (Girón-Hernández et al., 2021). A smaller needle size would result in smaller pores and potentially slower drug release due to restricted diffusion. In contrast, a larger needle size could lead to larger pores and a faster release rate due to the large size of the pores making movement easier unlike when the pores are of small sizes. However, in these experiments the needle size did not show a significant effect on the release behaviour, suggesting that the chosen

needle sizes (18G, 24G, and 26G) were within a range that did not strongly influence the diffusion properties of methylene blue.

Therefore, the results demonstrate that the ratio of sodium alginate to starch as well as the pH conditions play crucial roles in the release behavior of methylene blue from alginate/starch blend beads. A ratio of 3g:3g of sodium alginate to starch, a calcium chloride concentration of 0.25g/ml, and a needle size of 18G resulted in the highest release intensity of methylene blue at pH 1.2. These findings provide valuable insights into the design and optimization of drug delivery systems using alginate/starch blend beads. Further research is necessary to explore the underlying mechanisms and optimize the formulation parameters to achieve desired drug release profiles.

Similarly, at a ratio of 3g:3g but with a calcium chloride concentration of 0.5g/ml and needle sizes of 18G, 24G, and 26G the release intensity followed a similar pattern with the highest intensity at a pH of 1.2 and decreasing intensity at higher pH values. This observation reinforces the pH-dependent nature of the release behaviour of methylene blue from the alginate/starch blend beads.

The highest release intensity at pH 1.2 can be attributed to the favourable conditions for drug diffusion and release (Bialik-Wąs et al., 2021). At this low pH level, the alginate/starch blend beads exhibit increased swelling and porosity allowing for enhanced drug permeability. The presence of calcium ions from the crosslinking process further facilitates the release of methylene blue by destabilizing the bead structure.

As the pH of the release medium increases, the ionization of the alginate chains occurs, resulting in reduced bead swelling and porosity. This decrease in swelling limits the diffusion of methylene blue out of the beads which leads to a gradual decrease in the release intensity. The sustained release behaviour observed at higher pH values (5.0 and 7.4) highlights the importance of considering the pH conditions when designing drug delivery systems using alginate/starch blend beads.

When the ratio of sodium alginate to starch was increased to 3g:6g and 3g:9g the release intensity of methylene blue decreased at all pH levels that indicate a lower drug release from the beads. This decrease in release intensity can be attributed to the higher starch content in the blend beads. Starch is known for its slower release properties due to its relatively low water solubility compared to sodium alginate. The increased starch content in the beads leads to a more compact and less porous structure which impede the diffusion of methylene blue and resulting in a slower release rate.

The findings from these experiments highlight the significance of the sodium alginate to starch ratio in determining the release behavior of methylene blue from alginate/starch blend beads. A higher starch content in the blend beads leads to a decrease in the release intensity hence emphasizing the need for careful formulation design to achieve the desired drug release profiles.

In summary, the experiments conducted with a ratio of 3g:3g a calcium chloride concentration of 0.5g/ml, and needle sizes of 18G, 24G, and 26G demonstrated that the release intensity of methylene blue followed a similar pattern with the highest intensity at a pH of 1.2 and decreasing intensity at higher pH values. Increasing the ratio of sodium alginate to starch to 3g:6g and 3g:9g resulted in a decrease in the release intensity at all pH levels, indicating a lower drug release from the beads. These findings provide valuable insights into the formulation parameters that influence the release behaviour of drugs from alginate/starch blend beads and can guide the development of optimized drug delivery systems. Further research is needed to explore additional formulation parameters and elucidate the underlying mechanisms governing the release kinetics in these systems.

In addition to the ratio of sodium alginate to starch, the effect of calcium chloride concentration and needle size on the release behaviour of methylene blue from the alginate/starch blend beads was also investigated. Understanding the impact of these factors is crucial for fine-tuning the drug release properties of the beads and optimizing their application in drug delivery systems (Iman Salahshoori et al., 2024).

The calcium chloride concentration was varied from 0.25g/ml to 0.5g/ml while keeping the sodium alginate to starch ratio at 3g:3g. Interestingly, increasing the calcium chloride concentration resulted in a slightly higher release intensity of methylene blue at all pH levels. This observation suggests that the crosslinking density of the beads, which is influenced by the calcium chloride concentration, affects the release behaviour of the drug. A higher concentration of calcium chloride may lead to a more compact and rigid bead structure, limiting the diffusion of methylene blue and resulting in a slower release rate. However, the effect of calcium chloride concentration on the release behaviour was relatively minor compared to the sodium alginate to starch ratio.

Secondly, the size of the needle used during the bead formation process was investigated to determine its influence on the release intensity of methylene blue. Needle sizes of 18G, 24G, and 26G were employed while keeping the sodium alginate to starch ratio at 3g:3g and the calcium chloride concentration at 0.25g/ml. Surprisingly, the results showed that the needle size did not have a significant effect on the release behaviour. This suggests that the needle sizes used in the experiments (18G, 24G, and 26G) were within a range that did not strongly influence the diffusion properties of methylene blue. It is important to note that needle size can impact the size of the pores formed during bead formation which can subsequently affect drug release (Islam et al., 2019). However, in this particular study, the chosen needle sizes did not result in a noticeable difference in release kinetics.

The results of these experiments emphasize the predominant role of the sodium alginate to starch ratio in controlling the release of methylene blue from the alginate/starch blend beads. A higher alginate content (3g:3g) led to a more sustained release while increasing the starch content (3g:6g and 3g:9g) resulted in a decreased release rate. The calcium chloride concentration and needle size showed minor effects on the release behaviour indicating that they are secondary factors compared to the composition of the blend beads.

These findings have important implications for the design and development of drug delivery systems utilizing alginate/starch blend beads. The ability to tailor the release kinetics of drugs by adjusting the sodium alginate to starch ratio offers promising opportunities for personalized medicine and targeted therapy. By carefully selecting the appropriate formulation

parameters, it is possible to achieve the desired release profiles for specific drugs and therapeutic applications. However, it is worth mentioning that further investigations are warranted to optimize the formulation and gain a deeper understanding of the underlying mechanisms governing the release kinetics. Additional factors such as bead size, swelling behaviour and biodegradability should also be considered. By considering these aspects researchers can continue to refine the alginate/starch blend bead systems and unlock their full potential in the field of drug delivery.

The effect of calcium chloride concentration and needle size on the release behaviour of methylene blue from alginate/starch blend beads was explored alongside the sodium alginate to starch ratio. The results demonstrated that the ratio of sodium alginate to starch played a crucial role in the release behaviour, with higher alginate content resulting in a more sustained release and increasing starch content leading to a decreased release rate. The calcium chloride concentration and needle size had minor effects on the release behaviour. These findings highlight the tunability of the alginate/starch blend beads for controlled drug release and their potential applications in drug delivery systems. However, further research is necessary to optimize the formulation parameters and gain a comprehensive understanding of the release kinetics in order to harness the full potential of these systems.

The average size before and after release varies among the different samples. Sample 7, with the highest starch content (6g), exhibited a noticeable increase in size after release indicating significant swelling of the beads. This can be attributed to the higher water absorption capacity of starch compared to sodium alginate. Conversely, sample 10, with the highest starch content (9g), showed a decrease in size after release, suggesting potential erosion or degradation of the beads.

Regarding the effect of calcium chloride concentration and needle size on the bead size, it is observed that they generally have a minor influence. Samples with different calcium chloride concentrations (0.25g/ml and 0.5g/ml) and needle sizes (18G, 24G, and 26G) exhibited similar average sizes before and after release.

These findings highlight the importance of the sodium alginate to starch ratio in determining the size and behavior of the alginate/starch blend beads (Montes et al., 2022). Other

factors such as formulation parameters, crosslinking density and swelling behavior can also impact the bead size and release kinetics. Understanding these factors is crucial for tailoring the release properties of the beads to specific drug delivery requirements.

Therefore, the average size before and after release of the alginate/starch blend beads provides valuable information about their physical changes during drug release. The data in the table suggests that the sodium alginate to starch ratio has a significant influence on the bead size and swelling behavior while the calcium chloride concentration and needle size show minor effects. These insights can guide further research and optimization of the bead formulation to achieve desired drug release profiles and enhance their potential applications in drug delivery systems.

On the analysis and discussion based on the results obtained from the experiment on the release study of methylene blue as a model drug encapsulated by alginate/starch blend beads. The experiment was conducted using different ratios of sodium alginate to starch varying concentrations of calcium chloride, and different needle sizes. The release behavior of methylene blue was evaluated at different pH levels over a period of 90 minutes.

The first set of experiments involved a ratio of 3g of sodium alginate to 3g of starch, with a calcium chloride concentration of 0.5g/ml. The release of methylene blue was tested at pH values of 1.2, 5.0, and 7.4, using needle sizes of 18G, 24G, and 26G. The results showed that at pH 1.2, the release intensity of methylene blue was the highest and gradually decreasing with increasing pH values. This suggests that the release of methylene blue from the alginate/starch blend beads is pH-dependent. The needle size did not significantly affect the release behaviour.

In the second set of experiments, a ratio of 3g of sodium alginate to 9g of starch was used, with the same calcium chloride concentration of 0.5g/ml. The release behaviour of methylene blue was again tested at pH values of 1.2, 5.0, and 7.4, using needle sizes of 18G, 24G, and 26G. The results showed a decrease in the release intensity of methylene blue compared to the previous set of experiments. This indicates that increasing the starch content in the blend beads resulted in a

slower release rate of methylene blue. The needle size did not have a significant effect on the release behaviour.

Next, we examined the effect of a lower calcium chloride concentration (0.25g/ml) on the release behaviour of methylene blue using a ratio of 3g of sodium alginate to 3g of starch. The pH values tested were 1.2, 5.0, and 7.4, with needle sizes of 18G, 24G, and 26G. The results showed that the release intensity of methylene blue was lower compared to the experiments with a calcium chloride concentration of 0.5g/ml. This suggests that a higher concentration of calcium chloride promotes a faster release of methylene blue from the blend beads. The needle size did not significantly affect the release behaviour (Montes et al., 2022).

Lastly, we investigated the effect of the same ratio of 3g of sodium alginate to 3g of starch, but with a higher calcium chloride concentration of 0.5g/ml. The release behaviour of methylene blue was evaluated at pH values of 1.2, 5.0, and 7.4, using needle sizes of 18G, 24G, and 26G. The results showed that the release intensity of methylene blue was similar to the previous set of experiments with a calcium chloride concentration of 0.5g/ml. This indicates that the higher calcium chloride concentration had a negligible effect on the release behaviour. The needle size also did not significantly influence the release behaviour.

Therefore, the results suggest that the ratio of sodium alginate to starch plays a significant role in the release behaviour of methylene blue from the alginate/starch blend beads. Increasing the starch content resulted in a slower release rate of methylene blue. The pH level of the release medium also affected the release behaviour with the highest release intensity observed at pH 1.2. The concentration of calcium chloride and the needle size did not have a substantial impact on the release behaviour.

These findings demonstrate the potential of alginate/starch blend beads as drug delivery systems, where the release of drugs can be controlled by adjusting the ratio of sodium alginate to starch. However, further research is needed to optimize the formulation and understand the underlying mechanisms governing the release kinetics.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

The primary objective of this research was to examine how methylene blue, used as a model drug, was released from beads composed of a blended matrix of sodium alginate and starch. These blend beads were formed using a crosslinking technique involving calcium chloride. A key part of the experimental design centred on evaluating the impacts of several factors on the release profile of methylene blue from the beads. Specifically, the ratio of sodium alginate to starch, concentration of calcium chloride used, needle size during bead formation, and pH level of the environment surrounding the beads during drug elution testing.

The findings demonstrated that the ratio between sodium alginate and starch within the blend beads had a notable influence over how methylene blue was discharged. Beads containing a larger portion of starch relative to alginate resulted in methylene blue having a lower release intensity, signalling a slower rate at which the drug left the beads (Montes et al., 2022). This outcome can be attributed to starch exhibiting lower solubility in water compared to sodium alginate. Starch's relatively insoluble nature leads to the beads possessing a more compact internal structure that is less porous, providing impedance to the diffusion of methylene blue moving outwards.

The pH level of the surroundings was another key factor in impacting methylene blue's release behaviour from the alginate/starch beads. The highest release intensity occurred under acidic pH conditions of 1.2, and this value gradually decreased as the pH rose. This implies that methylene blue's discharge from the beads was pH-dependent, with more suitable circumstances

for drug diffusion and escape happening in low pH environments. In pH 1.2 settings, the blend beads demonstrated amplified swelling and porosity, allowing enhanced permeability of the methylene blue. Additionally, the calcium ions participating in bead formation assisted release further by destabilizing bead composition as pH changed. As pH increased alkalically, ionization occurred along the alginate polymer chains, diminishing bead swelling and porosity. This diminished swelling limited how readily methylene blue could diffuse outward, bringing about the gradual decline in release intensity seen. The sustained release observed at higher pH 5.0 and 7.4 highlights the importance of taking the environmental pH into account when designing drug delivery systems leveraging alginate/starch blend beads.

The concentration of calcium chloride used for crosslinking and the needle dimension chosen for forming the beads were found to have a relatively minor impact on methylene blue's release behaviour in comparison to the ratio between alginate and starch. A rise in calcium chloride concentration resulted in a small upregulation of methylene blue's release intensity across all examined pH levels. This hints that adjustments to bead crosslinking density influenced by calcium chloride concentration somewhat affected the drug's release behaviour. However, the calcium chloride concentration's effect was considerably less pronounced than that of the alginate/starch ratio. Needle size utilized in the range of 18G, 24G, and 26G did not demonstrate a significant impact on methylene blue's release intensity either, suggesting the needle dimensions tested did not strongly govern the drug's diffusion properties.

In conclusion, this research initiative aimed to advance the understanding of how formulation specifics and environmental parameters related to release kinetics for a model drug encapsulated within alginate/starch blend beads. The findings offer guidance on optimizing such a delivery system by considering important factors like polymer blend composition and pH sensitivity. Continued expansion of this line of inquiry holds promise to improve clinical translation for these blend bead technologies.

5.2 Recommendations

While the study provided useful insight into how formulation specifics like sodium alginate to starch ratio, calcium chloride concentration, and needle size impact methylene blue release kinetics, expanding the parameters investigated could allow for even more precise control. Additional factors worth exploring include bead particle size, swelling behavior, and how the blend degrades over time. Evaluating these properties may uncover optimization opportunities for tailoring the release profile.

The study solely utilized calcium chloride in forming the crosslinked alginate/starch network enclosing the model drug. However, considering other crosslinking agents for their effects could broaden the system's potential. Compounds like sodium tripolyphosphate, calcium sulfate, or borax may produce distinct stability or release impacts worth scrutinizing.

Assessing blend bead performance with medicines other than methylene blue would add meaningful perspective. Drugs with varying physicochemical traits and therapeutic purposes could interact differently, offering release behavior insights. While informative for fundamental mechanistic understanding, in vitro testing alone provides limited utility. Subjecting the blend beads to in vivo studies would offer a more holistic view of biocompatibility, degradability, and effectiveness within living systems - critical factors for real-world applications.

Finally, translating the developed system into practical and affordable use demands scaling production capabilities while retaining key attributes. Optimizing mass manufacturing parameters like reproducibility, stability, and cost will influence the technology's commercial translation and accessibility. Addressing these scale-up considerations appears prudent as findings begin practical application phases.

REFERENCES

Bialik-Wąs, K., Królicka, E., & Malina, D. (2021). Impact of the Type of Crosslinking Agents on the Properties of Modified Sodium Alginate/Poly(vinyl Alcohol) Hydrogels. Molecules, 26(8), 2381. https://doi.org/10.3390/molecules26082381

Girón-Hernández, J., Gentile, P., & Benlloch-Tinoco, M. (2021). Impact of heterogeneously crosslinked calcium alginate networks on the encapsulation of β-carotene-loaded beads. Carbohydrate Polymers, 271, 118429. https://doi.org/10.1016/j.carbpol.2021.118429

Iman Salahshoori, Mahdi Golriz, Augusto, M., Mahdavi, S., Rahime Eshaghi Malekshah, Afsaneh Javdani-Mallak, Majid Namayandeh Jorabchi, Hossein Ali Khonakdar, Wang, Q., Mohammadi, A. H., Sadat, M., & Farshad Kargaran. (2024). Simulation-Based Approaches for Drug Delivery Systems: Navigating Advancements, Opportunities, and Challenges. Journal of Molecular Liquids, 395, 123888–123888. https://doi.org/10.1016/j.molliq.2023.123888

Islam, M. S., Ang, B. C., Andriyana, A., & Afifi, A. M. (2019). A review on fabrication of nanofibers via electrospinning and their applications. SN Applied Sciences, 1(10). https://doi.org/10.1007/s42452-019-1288-4

Montes, L., Santamaria, M., Garzon, R., Rosell, C. M., & Moreira, R. (2022). Effect of the addition of different sodium alginates on viscoelastic, structural features and hydrolysis kinetics of corn starch gels. Food Bioscience, 47, 101628. https://doi.org/10.1016/j.fbio.2022.101628

Sreya, E.S., Kumar, D.P., Balakrishnan, P. and Sreerag Gopi (2023). Science and Technology of Alginates: A Review. pp.1–28. doi: https://doi.org/10.1007/978-981-19-6772-6_48-1.

Babaei-Ghazvini, A., Vafakish, B., Patel, R., Falua, K. J., Dunlop, M. J., & Acharya, B. (2024). Cellulose nanocrystals in the development of biodegradable materials: A review on CNC resources, modification, and their hybridization. International Journal of Biological Macromolecules, 258, 128834. https://doi.org/10.1016/j.ijbiomac.2023.128834

Adepu, S., & Ramakrishna, S. (2021). Controlled Drug Delivery Systems: Current Status and Future Directions. Molecules, 26(19), 5905. https://doi.org/10.3390/molecules26195905

Chen, C., Ng, D. Y. W., & Weil, T. (2020). Polymer bioconjugates: Modern design concepts toward precision hybrid materials. Progress in Polymer Science, 105, 101241. https://doi.org/10.1016/j.progpolymsci.2020.101241

Dalal Mohamed Alshangiti, El-damhougy, T. K., Zaher, A., Madani, M., & Mohamed Mohamady Ghobashy. (2023). Revolutionizing biomedicine: advancements, applications, and prospects of nanocomposite macromolecular carbohydrate-based hydrogel biomaterials: a review. RSC Advances, 13(50), 35251–35291. https://doi.org/10.1039/d3ra07391b

Di Mola, A., Landi, M. R., Massa, A., D'Amora, U., & Guarino, V. (2022). Hyaluronic Acid in Biomedical Fields: New Trends from Chemistry to Biomaterial Applications. International Journal of Molecular Sciences, 23(22), 14372. https://doi.org/10.3390/ijms232214372

Diltemiz, S. E., Tavafoghi, M., Barros, N. R. de, Kanada, M., Heinämäki, J., Contag, C., Seidlits, S. K., & Ashammakhi, N. (2021). Use of artificial cells as drug carriers. Materials Chemistry Frontiers, 5(18), 6672–6692. https://doi.org/10.1039/D1QM00717C

Domínguez Díaz, L., Fernández-Ruiz, V., & Cámara, M. (2020). An international regulatory review of food health-related claims in functional food products labeling. Journal of Functional Foods, 68, 103896. https://doi.org/10.1016/j.jff.2020.103896

Grgić, J., Šelo, G., Planinić, M., Tišma, M., & Bucić-Kojić, A. (2020). Role of the Encapsulation in Bioavailability of Phenolic Compounds. Antioxidants, 9(10), 923. https://doi.org/10.3390/antiox9100923

Han, W. B., Lee, J. H., Shin, J., & Hwang, S. (2020). Advanced Materials and Systems for Biodegradable, Transient Electronics. Advanced Materials, 32(51), 2002211. https://doi.org/10.1002/adma.202002211

Jiang, T., Liao, W., & Charcosset, C. (2020). Recent advances in encapsulation of curcumin in nanoemulsions: A review of encapsulation technologies, bioaccessibility and applications. Food Research International, 132, 109035. https://doi.org/10.1016/j.foodres.2020.109035

Ma, S., Yuan, G., Zhang, Y., Yang, N., Li, Y., & Chen, Q. (2022). Development of encapsulation strategies towards the commercialization of perovskite solar cells. Energy & Environmental Science, 15(1), 13–55. https://doi.org/10.1039/d1ee02882k

Mamusa, M., Resta, C., Sofroniou, C., & Baglioni, P. (2021). Encapsulation of volatile compounds in liquid media: Fragrances, flavors, and essential oils in commercial

formulations. Advances in Colloid and Interface Science, 298, 102544. https://doi.org/10.1016/j.cis.2021.102544

Mohammed, N. K., Tan, C. P., Manap, Y. A., Muhialdin, B. J., & Hussin, A. S. M. (2020). Spray Drying for the Encapsulation of Oils—A Review. Molecules, 25(17), 3873. https://doi.org/10.3390/molecules25173873

Mura, P., Maestrelli, F., Cirri, M., & Mennini, N. (2022). Multiple Roles of Chitosan in Mucosal Drug Delivery: An Updated Review. Marine Drugs, 20(5), 335. https://doi.org/10.3390/md20050335

Park, H., Kim, J.-S., Kim, S., Ha, E.-S., Kim, M.-S., & Hwang, S.-J. (2021). Pharmaceutical Applications of Supercritical Fluid Extraction of Emulsions for Micro-/Nanoparticle Formation. Pharmaceutics, 13(11), 1928. https://doi.org/10.3390/pharmaceutics13111928

Sankha Karunarathna, I. Wickramasinghe, Truong, T., Brennan, C. S., Navaratne, S. B., & Jayani Chandrapala. (2023). Development of Low-Calorie Food Products with Resistant Starch-Rich Sources. – a Review. Food Reviews International, 1–18. https://doi.org/10.1080/87559129.2023.2204137

Teng, K., An, Q., Chen, Y., Zhang, Y. and Zhao, Y. (2021). Recent Development of Alginate-Based Materials and Their Versatile Functions in Biomedicine, Flexible Electronics, and Environmental Uses. ACS Biomaterials Science & Engineering, 7(4), pp.1302–1337. doi: https://doi.org/10.1021/acsbiomaterials.1c00116

Wagle, S. R., Kovacevic, B., Walker, D., Ionescu, C. M., Shah, U., Stojanovic, G., Kojic, S., Mooranian, A., & Al-Salami, H. (2020). Alginate-based drug oral targeting using bio-

micro/nano encapsulation technologies. Expert Opinion on Drug Delivery, 17(10), 1361–1376. https://doi.org/10.1080/17425247.2020.1789587

Xu, C., Ban, Q., Wang, W., Hou, J., & Jiang, Z. (2022). Novel nano-encapsulated probiotic agents: Encapsulate materials, delivery, and encapsulation systems. Journal of Controlled Release, 349, 184–205. https://doi.org/10.1016/j.jconrel.2022.06.061

Zhang, Y., Zhang, T., Huang, Z., & Yang, J. (2022). A New Class of Electronic Devices Based on Flexible Porous Substrates. Advanced Science, 9(7). https://doi.org/10.1002/advs.202105084

APPENDIX A

APPENDIX B

APPENDIX C