Chitosan-Sodium Alginate Biocomposite, Blended with Nanoclay Cloisite 30B for Controlled Release of an Anti-Diabetic Drug
Syzygium cumini (Jamun) Seed Powder

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Abstract
The release of drugs as per physical command of requirements in a matrix is a potential smart drug delivery system in pharmaceutical sciences. The release of drugs out of polymeric matrix can be controlled by a simple diffusion process and a prolonged therapeutic capability can be attained. Adding to advantages the frequency of dosing can be reduced contributing to an improved compliance. In our research work, a biopolymer- biocomposite of Chitosan and sodium alginate (an alginate salt) was blended with Nanoclay Cloisite 30B. Jamun seed powder as an anti-diabetic drug was incorporated to the polymer nanocomposite matrix. The drug release kinetics was investigated. The kinetics of the drug delivery system has been systematically studied. Drug release kinetics was analyzed by plotting the cumulative release data vs. time by fitting to an exponential equation which indicated non-fickian type of kinetics. The drug release was examined at different pH medium and it was found that the drug release also depends upon the pH medium as well as the Nature of Matrix.

Keywords: Chitosan; Sodium Alginate (SA); Nanoclay Cloisite 30B; Jamun Seed Powder (JSP); Controlled Drug Delivery; Drug Release Kinetics

Introduction
A short review on controlled drug delivery
The foremost days when the “controlled drug delivery” (CDD) field began. The pioneers who launched this exciting and important field, and the key people who came after them. It traces the evolution of the field from its origins in the 1960s to the 1970s and 1980s. When a large number of microscopic “Controlled drug delivery (DD) devices and implants were designed for delivery as mucosal inserts. When microscopic degradable polymer depot DD systems (DDS) were commercialized to the currently very active and nanoscopic era of the targeted nano-carriers., in a sense bringing to life Ehrlich’s imagined concept of the “Magic Bullet”. For administrating a pharmaceutical or novel product to a patient, since decades drug delivery system is functioning as a carrier or medium with targeted delivery of drugs specifically with sufficient dosage of drugs as per requirement in a controlled release process [1]. Nanotechnology has been a great boom like nanoparticles, nanoshells, nano robots and dendrimers which are potential carrier systems and has been showing a precise delivery of drugs. With all advanced carrier systems a controlled drug delivery is a major concern in research which seeks all in-lab experimental and physiological approach for betterment of human healthcare.

Structure of chitosan
Chitosan is a hydrophobic biopolymer obtained industrially by hydrolyzing the amino acetyl groups of chitin, which is the main component of shells of crab, shrimp and many crustaceans, by an alkaline treatment. It is a polysaccharide of linear structure with repeating units (Figure 1) of β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). It is made by treating the chitin shells of shrimp and crustaceans for demineralization and deacetylation by an alkaline solution (Figure 2). Chitosan is emerging as a therapeutic drug delivery system with very less toxicity and with increased biocompatibility and bioavailability [2].
Sodium alginate

Sodium alginate is a natural polysaccharide product extracted from brown seaweed which develops in cold water regions. The chemical compound is the sodium salt of alginic acid. It is having molecular formula as \((\text{NaC}_6\text{H}_{12}\text{O}_6)^n\). Its solubility is in both hot water and cold water with prolonged agitation. Without the need of heat, sodium alginate forms a gel in presence of calcium which makes it highly compatible with chitosan \([3]\). We used Sodium alginate obtained from A.B. enterprises, Shradanand, Building, and Mumbai.

Jamun Powder

*Syzygium cumini*, commonly known as "Jamun" (Figure 3) is of family myrtaceae. *Syzygium cumini* is being spread overseas from India by Indian emigrants. It cures many health problems like diabetes, Ulcers etc. This fruit is also known as black berry. It has much cultural and medicinal value. Its leaves are used in marriage pedal decorations. It is more widely consumed by diabetes patients in powder form \([4-8]\).

We used Jammu seed powder obtained from Indian worldwide Herbs, Chennai, India (Figure 4).

**Figure 4: Purified jamun seed powder.**

**Nanoclay Cloisite 30B**

Nanoclay Cloisite 30B is an organically modified sodium in montmorillonite (MMT) with Quaternary ammonium Salt (where T is tallow; 65%C_{18}, 30%C_{16}, and 5%C_{14}) for controlled release of Jamun Seed Powder. The composites 2.5% Cloisite 30B has been Compound with jamun Seed powder and controlled release of drug has been evaluated. Drug delivery systems using of jamun seed powder has also been studied at different levels of pH and drug loading. For our work, Cloisite 30B was purchased from southern clay products, Austin, Texas.

**Materials and Methods**

The powdery form Chitosan was procured from Indian Sea foods, Kochi, India. Sodium alginate was obtained from A.B. enterprises, Shradianand building, Mumbai. Jamun seed powder was obtained from Indian worldwide Herbs, Chennai, India. Cloisite 30B was obtained from southern clay products Austin, Texas.

**Preparation of chitosan-sodium alginate-JSP beads**

One gram of chitosan powder was soaked in 50 ml de-ionized double distilled water and heated at 70°C to obtain a homogeneous solution and one gram of Sodium alginate was dissolved in 50 ml of de-ionized water. Nanoclay solutions with different clay compositions (1 wt%, 3 wt%, 5 wt%, 7.5 wt% and 10 wt%) were prepared by dispersing appropriate amounts of clays into 50 ml of Chitosan-Sodium alginate blend solution and then different percentage of jamun Seed powder was added with keeping under vigorously stirring for 24 hours continuously [9-12].

**Drug loading**

Jamun seed powder of different loadings, i.e. 1 wt%, 3 wt%, 5 wt%, 7.5 wt%, 10 wt% were added to Chitosan/Sodium alginate/Cloisite 30B clay solution and stirred for 1 hour and then the polymer-drug composite solution were kept at room temperature for drying.
Surface Characterization

Scanning electron microscopy was performed for comparing chitosan and chitosan-sodium alginate blended Nanoclay with jamun seed powder biocomposites with varying individual concentrations.

![Figure 5](image)

*Figure 5: From above scanning electron micrograph, we concluded that the surface of the chitosan is amorphous (in figure 5a). Gradually its roughness increases with increase in its amount of Nanoclay Cloisite 30B and percentage of Jamun Seed Powder (in figure 5b-5d).*

Dissolution experiment

Dissolution lab equipped with six paddles, experiments were performed at 370°C using the dissolution tester (disso test, paddle speed of 100 rpm. To mimic gastrointestinal tract environment of human body, 900 ml of phosphate buffer solution of pH 3.4 and pH 7.4, was used as the dissolution media. For estimating the jamun seed powder content, an amount of 5 ml of aliquot comprising polymer-drug composite was used each time at a regular fixed time interval. Using a UV spectrophotometer (Systronics, India) at the ‘k’ max value of 420 nm the amount of jamun seed powder was analyzed. The amount of water penetration, hydration, swelling and the breaking of the gelatinous layer in the matrix is effectively related to the amount of drug released from the matrices. Various proposed kinetic models relating to the drug release from matrices is shown below. However, it is worthwhile to mention here that the release mechanisms of a drug would depend on the whole dosage form as it is used.

1. Zero order kinetics: \( W = k_1 t \)
2. First-order kinetics: \( \ln(100-W) = \ln 100 - k_2 t \)
3. Hixon-crowel’s cube -Root Equation (Erosion Model): \( (100-W)^{1/3} = 100^{1/3} - k_3 t \)
4. Higuchi's square Root of Time Equation (diffusion Model): \( W = k_4 t \)
5. Power law Equation (Diffusion/Relaxation model): \( M_t / M_{\infty} = K_5 t^n \)

\( M_t / M_{\infty} \) is the fractional drug release into dissolution medium and ‘KS’ is a constant incorporating the structural and geometric characteristics of composite and drug release rate. The diffusion constant termed as ‘n’ as an exponent that describes the drug release transport mechanism [14]. At value of 0.5, it describes quasi-fickian diffusion mechanism of the drug release from the polymeric matrix. When ‘n’ value is greater than 0.5, a non-typical, non-fickian drug diffusion occurs. When ‘n’ value is equal to 1, a non -Fickian, case-II or zero-order release kinetics can be observed [15,16]. Korsmeyer, et al. had represented diffusional release mechanisms of drugs from polymeric film [17] in 1983 named as Korsmeyer-Peppas model.
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<table>
<thead>
<tr>
<th>Release exponent (n)</th>
<th>Drug transport mechanism</th>
<th>Rate as a function of time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
<td>$t^{0.5}$</td>
</tr>
<tr>
<td>0.45 &lt; n = 0.89</td>
<td>Non-Fickian transport</td>
<td>$t^{n-1}$</td>
</tr>
<tr>
<td>0.89</td>
<td>Case II transport</td>
<td>Zero order release</td>
</tr>
<tr>
<td>Higher than 0.89</td>
<td>Super case II transport</td>
<td>$t^{n-1}$</td>
</tr>
</tbody>
</table>

*Table 1: Korsmeyer-Peppas model; Interpretation of diffusional release mechanisms from polymeric films.*

*In vitro* drug release: Effect of *pH*, time and drug loading

To investigate the effect of pH 1.2 and 7.4 media the cumulative release data was analyzed and presented in figure 6 and 7, indicate that by increasing the pH from 1.2 to 7.4, a considerable increase in the cumulative release is observed for all composites.

From above graphical results, it is seen that the 50% drug-polymer composites have shown longer drug release rates than the other composites, Release data showed that formulations containing highest amount of drug displayed fast and higher release rates than those formulations containing a small amount of drug loading. When lower amount of drug present in the matrix, the rate of release of the drug becomes much slower due to the availability of more free void spaces inside the system.

Drug release kinetics

Drug release kinetics was analyzed by plotting the cumulative release data vs. time by fitting to an exponential Equation of the type as represented below [14,15].

\[ \frac{M_t}{M_{\infty}} = Kt^n \] (a)

Here \( M_t / M_{\infty} \) represents the fractional drug release at time \( t \); \( k \) is a constant characteristic of the polymer drug system and \( n \) is the empirical parameter describing the release mechanism [16]. For all the five formulations the values of \( n \) and \( k \) were estimated by help of the least square sizing procedure and same is represented in table 2. The values of \( k \) and \( n \) have shown significance relevance on the amount of drug loading and polymer content of the matrix. The Drug carrying composites exhibited ‘n’ values range from 0.57 to 1.67 in pH 7.4 and 0.61 to 1.78 in pH 1.2 respectively. The value of less than 1 has also been recently aging, indicating a shift from erosion type release to swelling controlled, non-flow micro viscosity inside the matrix and closure of non-fickian type mechanism was reported. This may be due to a reduction in the regions of cavities during the swollen state of the polymer [18].

<table>
<thead>
<tr>
<th>Sample Code</th>
<th>Value of “k” pH 1.2</th>
<th>Value of “k” pH 7.4</th>
<th>Value of “n” pH 1.2</th>
<th>Value of “n” pH 7.4</th>
<th>Coordination Coefficient, ( R^2 ) pH 1.2</th>
<th>Coordination Coefficient, ( R^2 ) pH 7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 wt%</td>
<td>0.03</td>
<td>0.01</td>
<td>0.61</td>
<td>0.57</td>
<td>0.9451</td>
<td>0.9256</td>
</tr>
<tr>
<td>3 wt%</td>
<td>0.05</td>
<td>0.04</td>
<td>0.74</td>
<td>0.68</td>
<td>0.9521</td>
<td>0.9337</td>
</tr>
<tr>
<td>5 wt%</td>
<td>0.07</td>
<td>0.06</td>
<td>1.58</td>
<td>1.38</td>
<td>0.9676</td>
<td>0.9458</td>
</tr>
<tr>
<td>7 wt%</td>
<td>0.16</td>
<td>0.11</td>
<td>1.68</td>
<td>1.43</td>
<td>0.9751</td>
<td>0.9711</td>
</tr>
<tr>
<td>10 wt%</td>
<td>0.24</td>
<td>0.18</td>
<td>1.78</td>
<td>1.67</td>
<td>0.9756</td>
<td>0.9726</td>
</tr>
</tbody>
</table>

Table 2: Release kinetics Parameters of different formulations at pH 1.2 and pH 7.4.

Conclusion

Controlled delivery devices that utilize biodegradable polymers have a significant advantage over competing delivery systems in that there is no need for surgical removal of the device. Further, if the polymer degrades only at the surface, the drug release process is simplified in water diffusion into the bulk is minimized and drug release rate is governed by polymer degradation rate. Novel nanocomposites of Guar gum-Sodium alginate blended with Cloisite 30B were prepared and characterized by SEM studies. This blend was loaded with different amounts of anticancer drug curcumin to study the drug release behavior. The swelling studies of the nanocomposites have been reported.

Acknowledgement

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Bibliography

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