



Development of Sodium Alginate/(Lignosulfonicacid-g-Acrylamide) IPN Micro Beads for Controlled Release of an Anti-Malarial Drug

E. Chandra Sekhar¹, K. Madhusudana Rao², S. Eswaramma³, K.S.V. Krishna Rao^{3*},
R. Ramesh Raju^{1*}

¹Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur, A.P. India.

²Nano Information Materials Laboratory, Department of Polymer Science and Engineering, Pusan National University, Busan, South Korea. 609 735.

³Department of Chemistry, Yogi Vemana University, Kadapa. Andhra Pradesh, India. 516003.

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ABSTRACT

In the present work NaAlg/(LSA-g-Am) interpenetrating polymeric network micro beads were developed by graft polymerization using calcium chloride as crosslinker. Pyronaridine drug was loaded into these microbeads via blending method. Various formulations were prepared by varying the ratios of LSA/AAm/NaAlg, crosslinker and % of pyronaridine loading. Micro beads were characterized by Fourier transforms infrared spectroscopy (FTIR), differential scanning calorimetric (DSC), X-ray diffraction (X-RD) and Scanning electron microscopy (SEM). DSC and X-RD studies were performed to understand the crystalline nature of drug after encapsulation into semi IPN micro beads. SEM images gave the beads with smooth surface. FT-IR spectroscopy of microbeads confirms the formation of co-polymerization and grafting of the polymers. The encapsulation efficiency was found up to 68 %. Drug release profiles of the IPN micro beads at pH 7.4 confirmed that micro beads formed are pH-sensitive, resulting controlled release of drug during in vitro dissolution experiments. Both encapsulation efficiency and release patterns are found to be dependent on the nature of the cross-linking agent, amount of drug loading and % of LSA/Am/NaAlg. The release was extended up to 12h and release rates were fitted to an empirical equation to compute the diffusion parameters, which indicated non-Fickian or anomalous trend release of pyronaridine.

Keywords: Sodium alginate, Lignosulfonicacid, Micro beads, drug release, Pyronaridine.

1. INTRODUCTION

The objective of the present study was to develop the multi particulate delivery system for site specific delivery of pyronaridine using pH sensitive sodium alginate and lignosulfonicacid microbeads. The goal of designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. Recent research is very much focused on the natural polymers as drug carriers to sustain the action [1-2].

Alginate (polysaccharide) is obtained from marine brown algae and alginates are random anionic, linear polymers consisting of glucuronicacid, manuronic acid and mannuronic-glucuronic block units in it. Salts of alginate are formed when metal ion reacts with glucuronic or manuronicacid groups in the alginate. Alginate has been used in many biomedical applications including drug delivery system, as they are biodegradable and

biocompatible [3]. Alginates, which are naturally occurring substances, found in brown algae have received much attention as a vehicle for controlled drug delivery [4-7].

Alginates are natural poly electrolytes that comprise a family of polysaccharides which contain 1,4-linked β -D-mannuronic and α -L-glucuronic acid and mannuronic-glucuronic (MG) block residues arranged block wise and in non-regular order along the chain. Cation specific affinity of the alginate gel and its fundamental physicochemical and rheological properties are determined by this arrangement [8]. Coordination sites of two homo polymeric glucuronic chains are aligned to accommodate divalent cations easily according to the well-known "egg-box model" [9]. Some studies showed that mainly ion-exchange are responsible for this, whereas other studies reported the sorption through complexation in addition to the ion-exchange [10-14]. Alginate has been used in many biomedical applications, including drug delivery system, as they are biodegradable and

*Corresponding Author:

Email: drksvkrishna@yahoo.com,

rrraju1@gmail.com

biocompatible [2]. Alginates are easily gelled in presence of a divalent cation such as calcium ion. The gelation or crosslinking is due to the stacking of the glucuronic acid blocks of alginate chains [15].

Little research has gone through the preparation of lignin based polymers. Lignin based polymers have two-fold advantage. One is that they are abundantly available as tons of lignin is thrown off as a waste product in pulp and paper industries. Secondly, lignin is completely biodegradable; hence it is a prospective biodegradable polymer. Lignin is extracted from the waste wood chips of a paper industry. This method is effective in both utilizing the waste product and in reducing the price of the product itself. Lignin is a complex phenolic compound found abundantly in the cell wall of plants in association with cellulose and hemicellulose. The water absorption of the films increase with the increase in lignin content. It is also notable that water absorption increases with increase in pH [16].

Lignosulfonates are complex polymers derived from trees. The wood from trees is mainly composed of three macromolecular components – cellulose, hemicellulose and lignin. The extraction of lignin from wood is performed after hydrolysis with sulfuric or other acids. After the hydrolysis some structural changes occurred in the lignins. From the solution lignin is extracted with aqueous HCl and dioxane mixture [17]. In the sulfite pulping process, the lignins are sulfonated so they become water-soluble and thus can be separated from the insoluble cellulose. The soluble lignins are called lignosulfonates. Pyronaridine tetraphosphate is an anti-malarial agent and is a benzo-naphthyridine derivative. The nucleus of the pyronaridine was synthesized from mepacrine [18]. The drug is sparingly soluble in water and very slightly soluble in other solvents.

2. MATERIALS AND METHODS

2.1. Materials

An analytical reagent grade sample of sodium alginate (NaAlg) was purchased from central drug house New Delhi, India; lignosulfonicacid (LSA) from Sigma Aldrich, ; methanol and acryl amide (Am) was received from Merck, India; calcium chloride (CaCl₂) was received from Qualigens fine chemicals bombay,India; potassium per sulfate (KPS) was purchased from sd fine-chem, Mumbai, india and pyronaridine. all chemicals were used without further purification and double distilled water was used throughout the experiment.

2.2. Preparation of NaAlg/(LSA-g-Am) interpenetrating polymeric network micro beads loaded with Pyronaridine:

The beads were prepared in two steps by ionic gelation method using calcium chloride as counter ion. Briefly, in the first step sodium alginate dispersion was prepared in distilled water stirred by overnight and then pyronaridine was added to the NaAlg solution. Second step is to prepare the poly (LSA-g-Am) by adding the lignosulfonicacid in 5ml of distilled water, and then acrylamide was added followed by KPS as initiator and stirred at 65 °c for polymerization until the clear solution obtained. This graft polymer was added to the NaAlg solution under the constant stirring. The drug-polymer dispersion was added drop wise via a 22-gauze needle in to 1:4 ratio of calcium chloride/methanol solution. The CaCl₂ concentrations were used as 2%, 3% and 4% w/v for each formulation. The droplets were gelled in to discrete, spherical beads upon contact with CaCl₂. Each batch of beads was left for 20 min to strengthen in CaCl₂ solution. Here Na⁺ ions are replaced by Ca²⁺ ions to form the three dimensional network. The CaCl₂ was decant followed by washing twice with 200 ml of distilled water, and then dried in hot air oven at 40 °C for 24 hours [19, 20].

2.3. Estimation of drug loading and encapsulation efficiency:

The encapsulation efficiency (EE) of pyronaridine in the micro beads was determined spectrophotometrically. About ~10 mg of the drug-loaded micro beads were placed in 10 mL of buffer solution and stirred vigorously for 48 hours to extract drug from the beads. The solution was filtered and assayed by UV spectrophotometer (Lab India, Mumbai, India) at fixed λ_{max} value of 270 nm. The results of % drug loading and encapsulation efficiency were calculated, using by following Eqs. (2), (3), respectively. These data are compiled in Table 1,

$$\% \text{ Drug loading} = \left(\frac{\text{Amount of drug in microbeads}}{\text{Amount of microbeads}} \right) \times 100 \quad (1)$$

$$\% \text{ of EE} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}} \right) \times 100 \quad (2)$$

2.4. Swelling studies

The swelling behavior of crosslinked micro beads were measured based on the solvent uptake by the beads. The dry microbeads were suspended in 20 ml of double distilled water at room temperature. Further, microbeads were wiped with tissue paper to remove water from the surface of the beads. The 'weight change' was monitored at different time intervals until the beads showed constant weight. The micro beads were then weighed (W₁) on an electronic microbalance (ADAM AFP-210L England accurate to ± 0.0001 g). The micro beads were dried to a constant weight (W₂) in an oven maintained at 40 °C for 5 hrs. Swelling experiments were repeated thrice for each sample and average

values were used in data analysis. The standard deviations (S.D.) in all cases were < 5 %. The fractional weight change was transferred to a percentage using the following empirical relationship:

$$\% \text{ Wateruptake} = \left(\frac{(W_1) - (W_2)}{(W_2)} \right) \times 100 \quad (3)$$

2.5. *In vitro* release studies

In vitro release studies were carried out using Tablet dissolution tester (LAB INDIA, Mumbai, India) equipped with eight baskets. Measurement of dissolution rates at 37 ± 0.5 °C at constant speed of 100 rpm. Drug releases from the micro beads were carried out in pH 1.2 and 7.4 phosphate buffer solution at 37 °C. Sample aliquots were withdrawn at regular intervals of time, and analyzed by using UV spectrophotometer (Lab India, Mumbai, India) at the fixed λ_{max} value of 204 nm. After each sample collection, the same amount of fresh medium at the same temperature was added to the release medium to maintain the sink condition. All measurements were carried out in triplicate and the values were plotted with standard deviation errors.

2.6. *Fourier transforms infrared spectroscopy (FTIR)*

Infrared spectroscopy is one of the most powerful analytical tools, which provides the possibility of chemical identification. It provides information regarding the structure of a molecule. FT-IR is based upon the simple principle that a chemical substance shows selective absorption in the infrared region giving rise to absorption bands called an IR absorption spectrum, over a wide wavelength range. The NaAlg/(LSA-g-AAm) IPN micro beads were finely ground with spectroscopic grade KBr to prepare pellets using a hydraulic pressure of 600 kg/cm². Different bands are present in the IR spectrum, which will correspond to the characteristic functional groups and bonds present in the chemical substance. The infrared absorption spectra of the NaAlg/(LSA-g-AAm) micro beads were obtained using a FTIR spectrophotometer (Perkin Elmer Spectrum Two, UK).

2.7. *Differential Scanning Calorimetry (DSC)*

DSC curves of pure micro beads, pyronaridine, and drug loaded micro beads were recorded using TA instruments sequential thermal analyzer (Model-SDT Q₆₀₀, UK). The sample was weighed between 10 to 12mg. The temperature maintained between 50 °C to 400 °C for the analysis of samples. Analysis of the samples was performed at heating rate of 10°C/min under N₂ atmosphere at a purging rate of 100 mL/min.

2.8. *X-ray Diffraction Studies (XRD)*

X-ray diffraction measurements were recorded using a Rigaku diffractometer (Cu radiation, $\lambda = 0.1546$ nm) running at 40 kV and 40 mA and were recorded in an angle of 5-60 °C at a speed rate of 5°/min to estimate the crystallinity of the sample.

2.9. *Scanning Electron Microscopy (SEM)*

To analyze the particle size and size distribution, drug loaded micro beads were taken on a glass slide and their sizes were measured using an optical microscope under regular polarized light. SEM images of micro beads were recorded using a JSM 6400 SEM (JEOL Ltd., Akishima, Tokyo, Japan) at X50 and X500 magnifications. Working distance of 8.5-9.5 mm was maintained and the acceleration voltage used was 10 kV, with the secondary electron image (SEI) as a detector. The sample and an inert reference placed in a temperature controlled chamber and the heat flow required to maintain the sample and the reference at the same temperature is measured. These results are regarding either absorption of heat (endothermic reaction) or a release of heat (exothermic reaction) [21].

3. RESULTS AND DISCUSSIONS

3.1. *Fourier transforms infrared spectroscopy (FT-IR) analysis*

Figure (1.A) the FT-IR spectrum of the starting lignosulfonates contains peaks at 3434 cm⁻¹ due to OH stretching in phenols; aromatic skeletal vibrations peak observed at 1607 cm⁻¹ in LSA; the peak at 1032 cm⁻¹ is the result of OH stretching of primary alcohols. Peaks at 1124 and 513 cm⁻¹ are due to the S=O stretching in sulfonic acids and SO₂ scissoring, respectively. In the case of Figure (1.B); finding a new characteristic peak at 1668 cm⁻¹ for stretching vibration of C=O confirmed the formation of amide bond, and furthermore the absorption band at 1592 cm⁻¹ which is consigned to N-H bending vibrations conformed that AAm was successfully grafted on to the LSA. Figure (2.A) illustrates the changes signifying a successful crosslinking reaction. In case of NaAlg, a characteristic broad peak appearing at 3434 cm⁻¹ corresponds to O-H stretching vibrations of NaAlg. A sharp peak at 1607 cm⁻¹ corresponds to the carbonyl group of COONa moiety present in NaAlg.

In Figure (2.C) the shift of the peak of amide I from 1593 cm⁻¹ to 1607 cm⁻¹ was observed in the formation of crosslinked micro beads. NaAlg/(LSA-g-Am) micro beads samples are similar or show some overlaps with starting lignosulfonates spectra. The peak appearing in the range of 1091-1124 cm⁻¹ in microbeads corresponds to C-O-C linkage vibrations. This band appears due to the formation of an ether linkage as a result of the reaction between

hydroxyl groups of NaAlg with sulfonated groups of lignosulfonic acid. Comparison of all NaAlg samples and the starting lignosulfonates showed overlap of FT-IR peaks indicate the presence of the template in the polymer, however in different extent. The phenolic peak is shifted to lower wavelengths in the drug loaded micro beads. In LSA, SO₂ stretching peaks are shifted to higher wavelengths and the S=O scissoring peak is present in all prepared sodium alginate micro beads. Such changes in the spectra confirmed the successful crosslinking of LSA with both natural polymers. Figure (3.C) represents the no frequency changes occurred in the plain crosslinked microbeads and drug loaded microbeads indicates the uniform dispersion of drug occurred into micro voids of NaAlg-gt-(LSA-gt-AAm) microbeads.

3.2. Differential Scanning Calorimetric (DSC) studies:

The DSC thermal analysis was carried out, accumulation to know the thermo-mechanical properties of proposed NaAlg/(LSA-gt-AAm) microbeads and to identify any achievable chemical interactions between the drug and polymer backbone. DSC curves for drug-loaded microbeads, plain micro beads and pyronaridine drug are shown in Figure (4). The curve of pure beads which exhibits endothermic peak at 270 °C indicates the crosslinking of Ca⁺² between LSA and sodium alginate. The drug pyronaridine exhibits a sharp peak at 236 °C due to polymorphism and melting. However, this peak is not appeared in the curve of drug loaded micro beads, suggesting that most of the drug was uniformly dispersed in polymer matrices at molecular level.

3.3. X-ray Diffraction Studies:

The X-RD study facilitates to identification of crystalline or amorphous nature of interior materials in polymeric matrix. The X-ray diffraction analysis of pyronaridine, plain NaAlg/(LSA-gt-AAm) micro beads and drug loaded NaAlg/(LSA-gt-AAm) micro beads are depicted in the Fig (5). Crosslinked plain micro beads of NaAlg/(LSA-g-AAm) showed no intense peaks implying the amorphous nature of polymers. Pyronaridine has shown characteristic intense peaks at 2θ of 14°, 18°, 20°, 23° and 38° suggesting its crystallinity. Drug loaded micro beads were exhibits low intense peaks at 14°, 22°, and 40°. The X-RD pattern of the physical mixtures showed no changes in the crystalline nature of the individual components, but their peaks were more diffused in bead formulations, possibly due to changes in the degree of crystallinity of the drug that might have confirmed its dispersion in the polymer matrix of the beads [22].

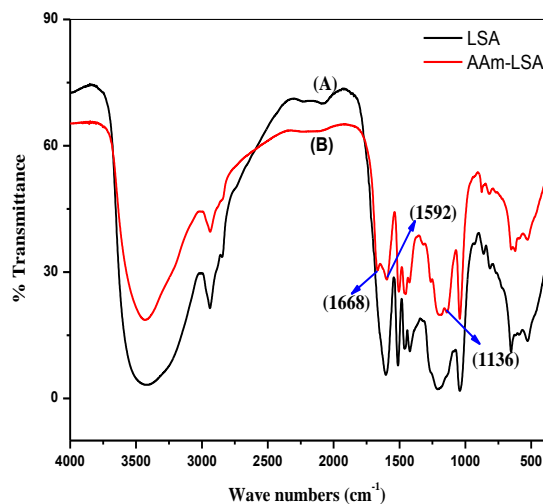


Figure 1. FTIR Spectrum of (A) pure NaAlg, (B) Am-g-LSA and (C) crosslinked micro beads of NaAlg-co-(LSA-g-Am).

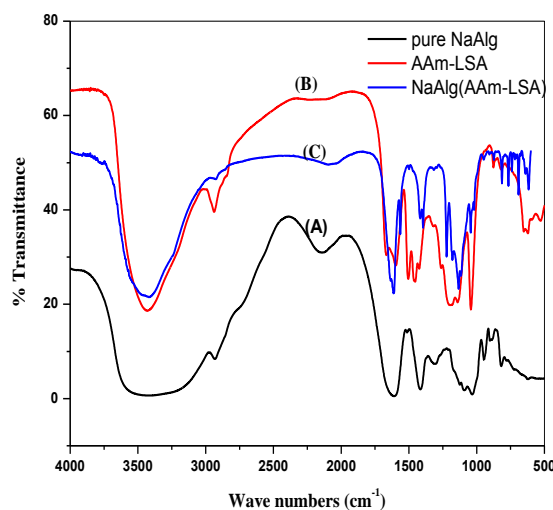


Figure 2. FTIR Spectrum of (A) pure Pyronaridine, (B) NaAlg/(LSA-g-Am) and (C) drug loaded NaAlg/(LSA-g-Am) micro beads.

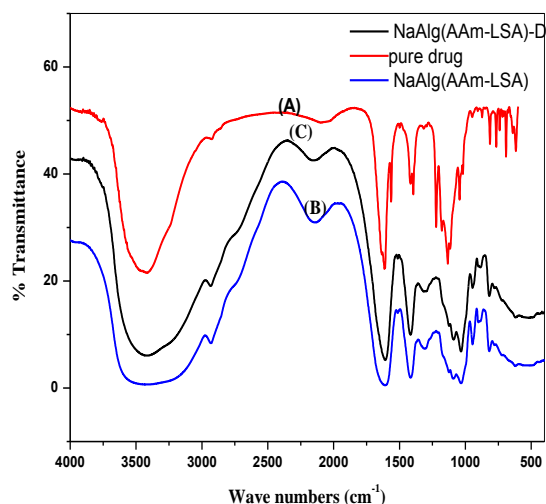


Figure 3. FT-IR Spectrum of (A) pure Pyronaridine, (B) NaAlg/(LSA-g-Am) and (C) drug loaded NaAlg/(LSA-g-Am) micro beads.

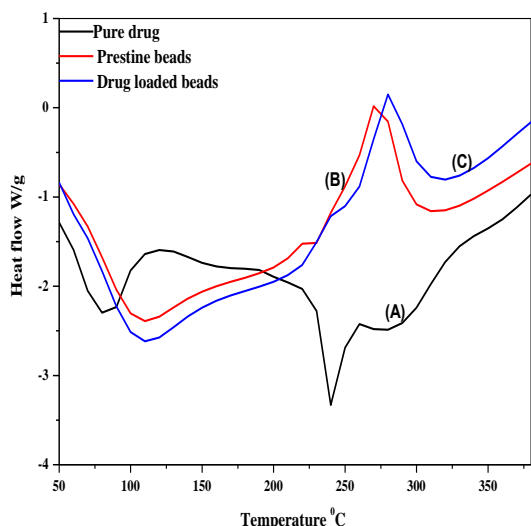


Figure 4. DSC thermo grams of (A) pure pyronaridine, (B) pristine NaAlg-LSA micro beads and (C) pyronaridine loaded NaAlg-LSA micro beads.

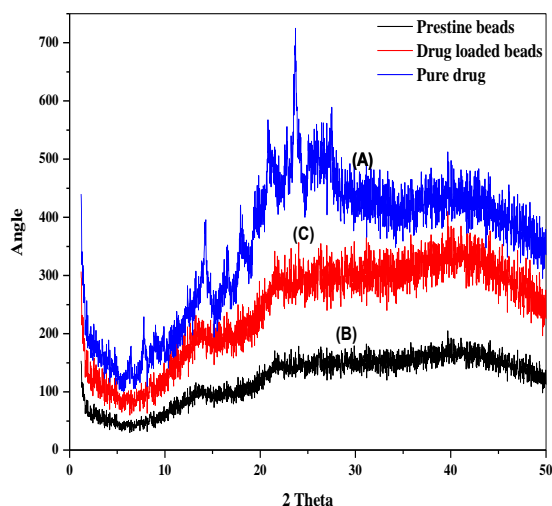


Figure 5. X-RD Spectra of (A) pure pyronaridine, (B) pristine NaAlg/(LSA-g-Am) micro beads and (C) pyronaridine loaded NaAlg/(LSA-g-AAm) micro beads.

3.4. Scanning Electron Microscopy Studies:

The SEM Photographs of dried drug loaded NaAlg/(LSA-g-Am) micro beads and their surface morphology have shown in Fig: (6). The average size of micro beads (490 μm) was calculated from the optical microscope as well as from scanning electron microscopy. It was found that morphology of the NaAlg/(LSA-g-AAm) micro beads is discrete and spherical in shape with slightly rough outer surface and visible large wrinkles and pores have a sandy appearance because of the surface-associated crystals of pyronaridine drug. In case formulated micro beads with NaAlg/(LSA-g-AAm) has more spherical, smooth surface, there is no wrinkles and also complete entrapment of drug crystals inside the matrices.

3.5. Swelling studies:

The swelling kinetics of alginate gels were investigated by several groups [23-28] but to the best of our knowledge has yet to be quantified. Draget et al.; showed that both the molecular weight and the bead size affect the swelling kinetics of high alginic acid gels [23]. Martinsen et al.; referred that the swelling behavior as the “gel beads resistance to volume changes” and found that above a certain Ca^{+2} concentration (depending on alginate type) and with storage times that exceed a certain value, the gel beads are relatively stable to volume changes [24]. According to the Fig.8 with increase of NaAlg concentration equilibrium swelling is also increased due to ultimate absorbance of water.

3.6. In-vitro release studies

3.6.1. Effect of Cross-linking agent

The formation of NaAlg-LSA micro beads significantly depends on the CaCl_2 (crosslinker) concentration. The % swelling ratio and drug release from the beads also influenced by crosslinker variation. Fig (8.A) reveals that; at higher concentration of crosslinker (NaAlg-LSA-5 with 4% of CaCl_2), the equilibrium swelling is less when compared to NaAlg-LSA-3, NaAlg-LSA-4. It was found that 5 % CaCl_2 considered as the highest crosslinking content and the swelling is decreased

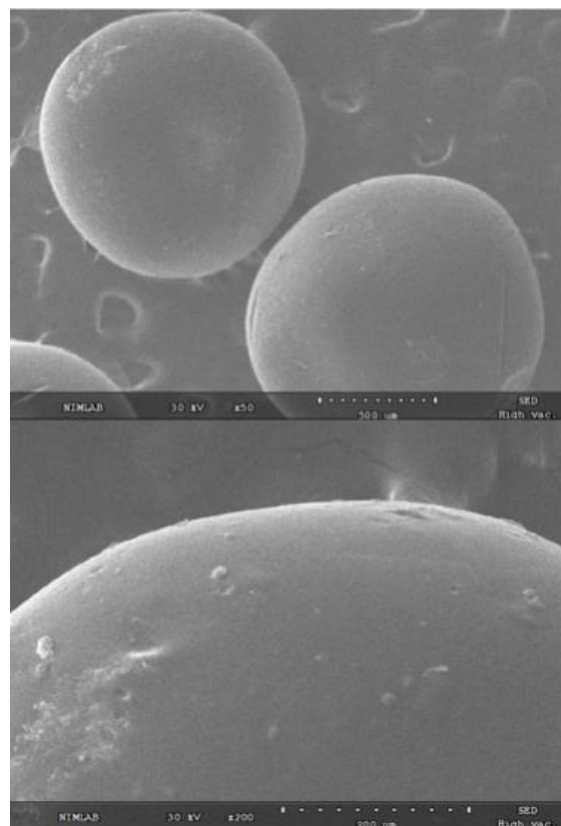


Figure 6. Scanning Electron Micrographs of NaAlg/(LSA-g-Am) micro beads at different magnifications.

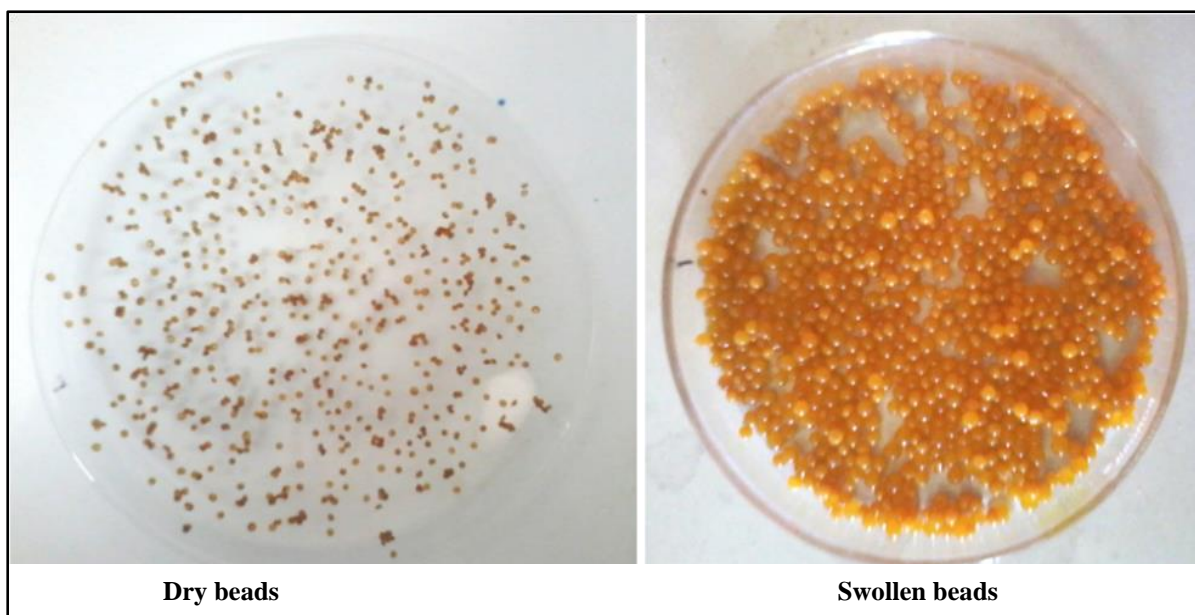


Figure 7. Photo graphs of dry micro beads and swollen micro beads of NaAlg/(LSA-gt-AAm).

as the concentration of CaCl_2 increased. The % cumulative release of pyronaridine data against time (min) plots for different concentrations of crosslinkers (2%, 3% and 4%) at constant amount of the pyronaridine (5%) are fitted in fig (8.B). The drug release is very fast at lower amount of CaCl_2 (2%) and slower at higher concentration, 100 % release was observed at 740 min. The release of pyronaridine from the formulations containing higher amount of Ca^{2+} is relatively low due to tight structure in the intermolecular chain and hence they exhibit lower water uptake. The cumulative release was lower at higher Ca^{2+} when compared with lower concentration of Ca^{2+} . As the amount of crosslinker increases the polymeric chains of NaAlg-LSA become more evidently due to the contraction of micro voids. Thus the cumulative release of pyronaridine becomes slower at higher concentration of CaCl_2 . The lower swelling is due to the counter ions (sodium ions), that shield the charge of the carboxylate anions and inhibits efficient anion-anion repulsions. As a result, a remarkable decrease in equilibrium swelling is observed.

3.6.2. Effect of monomer (LSA) content

The water absorbency of the prepared microbeads increased with increasing of LSA content in the formulations NaAlg-LSA-1 (0.1 mg), NaAlg-LSA-2 (0.2 mg) and NaAlg-LSA-3 (0.3 mg) respectively is due to increase in hydrophilic groups of NaAlg as well as amount of LSA. The amount of water uptake is a direct indicator on the pore voids of the polymer matrix and drug delivery system can also be depending upon the pore size of the polymer. However, the swelling increases in NaAlg-LSA-3 (0.3 mg). NaAlg-LSA-2 (0.2 mg) beads exhibits

moderate swelling and equal cumulative release with NaAlg-LSA-3. The figure (9.A) revealed that the equilibrium swelling is slightly increased with increasing of monomer (LSA) concentration relatively the cumulative release also increased (figure 9.B.).

3.6.3. Effect of polymer variation

The effect of NaAlg content on cumulative release of the pyronaridine was studied. The results are shown in Figure (10). The formulations NaAlg-LSA-1, NaAlg-LSA-4 and NaAlg-LSA-6 having different amount of NaAlg and cured with 2% Calcium chloride solution finally loaded with 5% pyronaridine tetraphosphate. Figure (10) clearly indicates that higher amount of NaAlg containing beads shows higher cumulative release, since the hydrophilic nature is increased with increasing amount of sodium alginate content in the microbeads. The NaAlg-LSA-6 showed maximum due to more number of hydrophilic groups caused to maximum swelling in the buffer medium (pH 7.4). Polymer to monomer ratio also influenced in the case of NaAlg-LSA-4 and NaAlg-LSA-6 compositions as almost equal up to 120 min. When the sodium alginate content increased the swelling degree also increased which causes to more cumulative release in the NaAlg-LSA-6. Therefore the release of pyronaridine increased with increase in NaAlg.

3.6.4. Effect of drug content on drug release

Figure (11) shows the different amount of drug loading and release pattern of pyronaridine from the microbeads at different time intervals. Release data showed that formulations (NaAlg-LSA-6 (5 %), NaAlg-LSA-7 (10 %) and NaAlg-LSA-8 (20

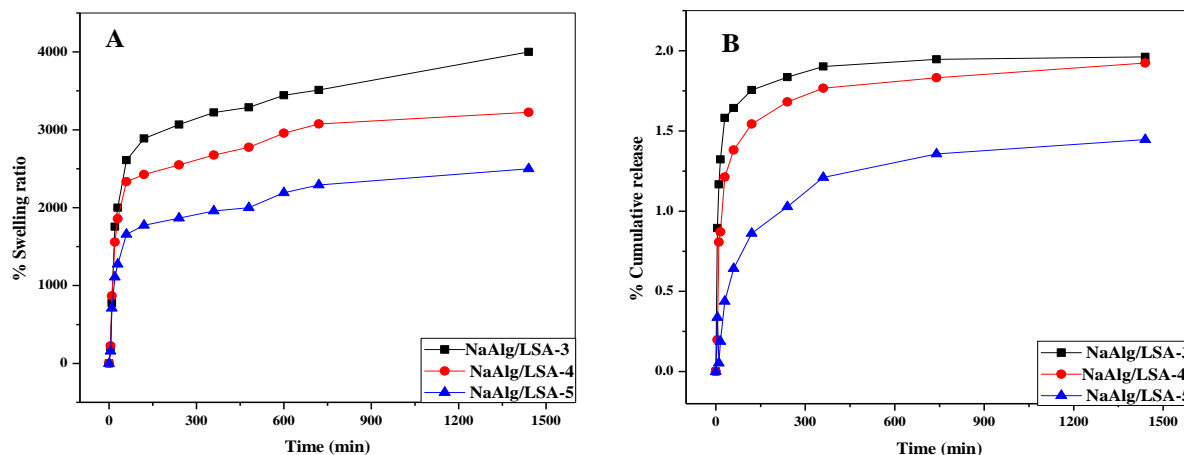


Figure 8. % Swelling ratio and % Cumulative release of Pyronaridine (5%) through NaAlg-LSA micro beads containing different amount of CaCl₂, NaAlg-LSA-3 (2%), NaAlg-LSA-4 (3%) and NaAlg-LSA-5 (4%).

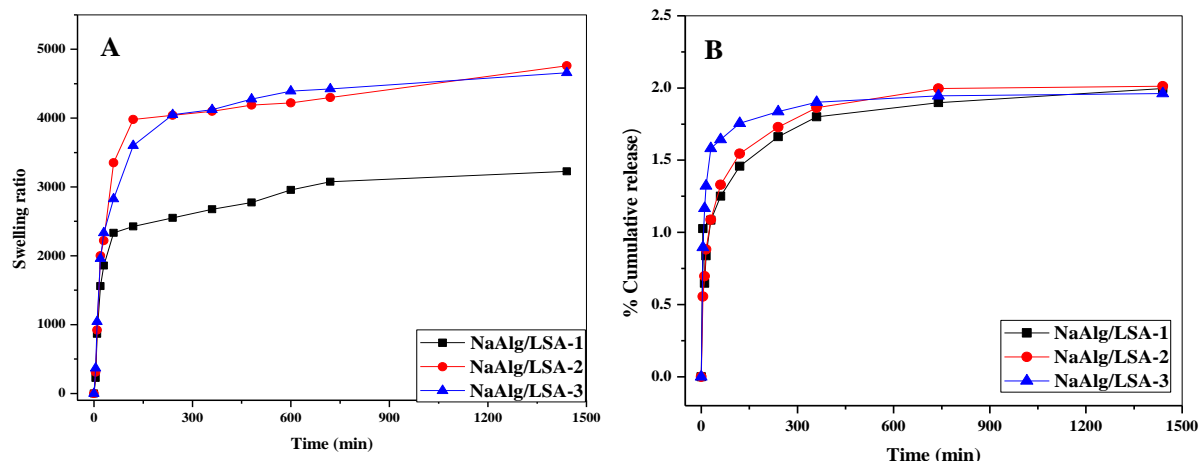


Figure 9. % Swelling ratio and % Cumulative release of Pyronaridine (5%) through NaAlg-LSA micro beads containing different amount of LSA, NaAlg-LSA-1 (0.1 mg), NaAlg-LSA-2 (0.2 mg) and NaAlg-LSA-3 (0.3 mg).

(%) containing the highest amount of drug (20 %) displayed fast and higher release rates than those formulations containing a small amount of pyronaridine. A prolonged release was observed for NaAlg-LSA-6 containing 5 % of drug. From the fig (11) it is noticed that the cumulative release pattern becomes slower at the lower amount of drug in the polymer complex and this is due to the accessibility of more free void spaces in the micro beads through which lesser number of drug molecules will transport.

3.6.5. Effect of pH on drug release

Cumulative release studies were carried out from pyronaridine loaded microbeads at pH 1.2 and 7.4 conditions at room temperature and are fitted in figure (12). The release profile reveals that highest amount of release was observed at pH 7.4 is due to the presence of the calcium ions bound to carboxylic groups of NaAlg begin to undergo ionic exchange of Na⁺¹ present in the swelling medium

[29-30]. Initially the swelling was very high at pH 7.4 and relatively the cumulative release is also high up to 5 hours, after that slowly increased and finally almost leveled off. The release of pyronaridine is higher at pH 7.4 than pH 1.2, this can be explained on the basis of higher degree of swelling due to ionization of hydroxyl groups and carboxylic groups in the networks at pH 7.4. This indicates that the micro beads having pH sensitivity.

3.7. Drug release kinetics

The cumulative drug release kinetics was calculated by plotting the cumulative release against time and by fitting these data to the exponential equation [31].

$$M_t/M_\infty = kt^n \text{----- (4)}$$

Where M_t/M_∞ tells about the fractional release at time ‘t’ and the rate constant is indicated by ‘k’, ‘n’

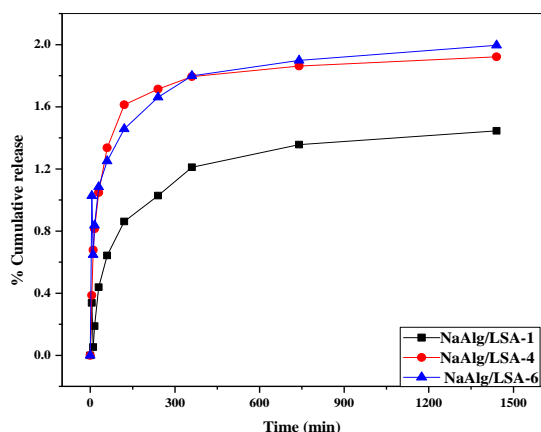


Figure 10. % Cumulative release of Pyronaridine through NaAlg-LSA micro beads containing different amount of sodium alginate, NaAlg-LSA-1 (1 mg), NaAlg-LSA-4 (1.5 mg) and NaAlg-LSA-6 (2 mg).

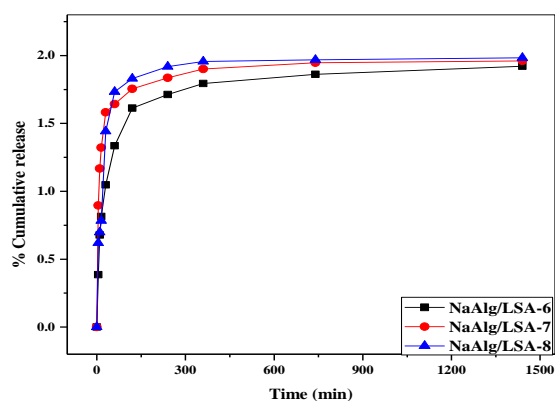


Figure 11. % Cumulative release of Pyronaridine through NaAlg-LSA micro beads containing different amount of drug, NaAlg-LSA-6 (5 %), NaAlg-LSA-7 (10 %) and NaAlg-LSA-8 (20 %).

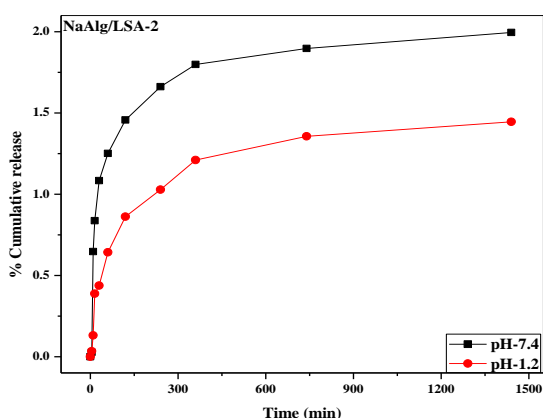


Figure 12. % Cumulative release of Pyronaridine (5%) through NaAlg-LSA-2 micro beads at pH 1.2 and 7.4.

is the diffusional exponent of the drug-polymer system. The n values provide the release mechanism and ranges from 0.5 to 1.0 and it was

the slope of the plot $\log(t) vs \ln(M_t/M_\infty)$. If ' n ' value is equal to 0.5 indicates that is Fickian diffusion (case I transport), while ' n ' values from 0.45 to 0.89 it suggests an antithetical transport due to equilibrium swelling or erosion. And if $n=1$, it is completely non Fickian diffusion or case II operative release mechanism. In the pre sent study for the pyronaridine loaded NaAlg/(LSA-gt-AAm) microbeads the ' n ' value is in the range 0.516-0.685 indicating an antithetical release mechanism (non Fickian diffusion) for the pyronaridine release [32-33]. The values of ' k ' and correlation coefficient ' r ' are calculated and included in table 2, indicating a good experimental data.

4. CONCLUSIONS

Pyronaridine loaded NaAlg/(LSA-g-AAm) micro beads were prepared by using CaCl_2 as a crosslinker. DSC and XRD studies confirmed the molecular level dispersion of drug in the micro beads. SEM pictures have shown the good compatibility of NaAlg and LSA compositions present in the micro beads with smooth surface. The encapsulation efficiency was found to vary between 57 and 68 % depending upon the blend composition, cross-linking and the amount of drug loading. Drug release studies indicated controlled release of pyronaridine for more than 10 h and potentially used for drug delivery. The NaAlg/(LSA-g-Am) micro beads showed pH-sensitive release manner. As shown in the results of release pattern at pH 1.2 less amount of drug was released from the microbeads while at pH 7.4 relatively higher amount of drug was released. The modelling of the drug release indicated that an antithetical transport mechanism. Our study showed that an anti-malarial drug release from NaAlg/(LSA-g-Am) micro beads plays an important role in the release mechanism stimulated by changes in the pH and have potential applications as controlled drug release carrier. Finally the attempt of controlled release of pyronaridine was success by all formulations as composed.

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