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Development of a controlled release neem capsule with a sodium alginate matrix, crosslinked by glutaraldehyde and coated with natural rubber

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Abstract At present, the use of huge quantities of synthetic pesticides in conventional agriculture has lead to some major environmental problems. Natural pesticide are now being developed to avoid such problems. Neem (Azadirachtin A) seed oil hereafter designated as neem Aza-A, is one such natural pesticide known to be a powerful insect antifeedant and growth-regulating substance yet limited in application because of its rapid degradation in the environment. Therefore, encapsulation of neem Aza-A within membranes to control its release and improve its stability in the environment may improve its effectiveness. Controlling the release of the pesticide was achieved by utilization of glutaraldehyde–alginate gel capsules modified by coating with a natural rubber (NR) layer. The optimization of the properties of the neem Aza-A containing beads was achieved by changing variables such as the extent of crosslinking, the amount of loading and NR layer. The SEM data indicated that the walls of the beads are smooth and nonporous. The swelling results indicated that swelling of the polymeric beads decreased with increasing exposure time to glutaraldehyde and reduced the rate of release of the pesticide. The data on the rate of release of neem Aza-A from the differently prepared capsules into an aqueous environment was analyzed by HPLC and fitted into an empirical equation to estimate the kinetic parameter. The degree of release of neem Aza-A from capsules was controlled by their condition of formation.

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Introduction

The use of synthetic pesticides in the world began in the 1930s and became widespread after World War II. By 1950, pesticides had been found to increase farm yields far beyond pre-World War II levels [1]. Since then farmers have depended heavily on synthetic pesticides to control insects in their crops. Today, it is one of the most common methods used to control insects but pesticides can have a relatively high toxicity and a high environmental impact. Thus, the use of natural pesticides is being promoted to help solve this problem as they should leave no toxic residues in the environment.

Neem (*Azadirachta indica* A. Juss.), a tree belonging to the Meliaceae family is widely distributed in South Asia, South-East Asia, and some other tropical areas [2–7]. The neem seed kernels contain Azadirachtin-A (Aza-A), a major insecticidal tetranortriterpenoid. Neem Aza-A is a powerful insect antifeedant and growth-regulating substance and exhibits considerable promise as an insecticide [2]. It can control at least 200 species of agricultural and storage insect pests belonging to different orders. It also has a short environmental persistence, and causes negligible hazards to nontarget organisms including humans. Its short environmental persistence is due to the presence of sensitive moieties such as *p*-electrons, ester linkages, and an epoxide ring. Thus, Aza-A is highly photolabile, either breaking down or isomerizing under sunlight. Thus, the photodegradation of Aza-A in sunlight is the major problem limiting its use in agriculture because the insecticide has to persist long enough to cause the death of the insect. Many workers have tried to solve this problem. The two major approaches to controlling its stability are by the addition of an antioxidant to a neem solution and encapsulation of neem in a polymer matrix. For example, the addition of UV light absorbers can enhance the photostability of Aza-A [4]. The addition of ferulic acid, gallic acid, and rutin can provided a moderate degree of photostabilization of Aza-A [4]. A current patented invention relates to an improved granular formulation of neem seed extract containing neem Aza-A having enhanced storage stability [8], and the ability for gradual release of neem Aza-A for application to the plant rhizosphere. The formulation consists of an inert particulate compound as a carrier, at least one lipophilic substance as a deactivator/binder, optional colorant and neem seed extract containing neem Aza-A [8]. The formulation provides for the gradual release of neem Aza-A at the point of application. This patent also relates to a process for the preparation of the formulation by coating the carrier with a lipophilic substance, subsequently impregnating the coated carrier with neem seed extract such as by spraying and drying at a temperature below 50 °C [8].

The second method is by microencapsulation which packages the sensitive ingredients within a coating or wall material [9–16]. The wall material protects the sensitive ingredient (or core) against adverse reactions, prevents the loss of volatile ingredients, and can control the rate of release of the ingredient. In addition,

microencapsulation can convert liquids into free-flowing powders, so that they can be more easily handled.

Preparation of polymeric granules containing 20, 35 and 50% (w/w) of the natural liquid pesticide viz., *A. indica* A. Juss. (neem) seed oil (NSO) was reported by T.M. Aminabhavi and co-worker [5]. The polymer matrices used for encapsulation were urea formaldehyde crosslinked starch (UF–St), guar gum (UF–GG) and UF–(St + GG) [5]. They found that the release of the active ingredient depended on the type of matrix and its swelling ability. The percentage loading of NSO with different matrices and their density exerted an influence on the release data. Then, they studied the release kinetics and encapsulation efficiency of the urea formaldehyde (UF) crosslinked matrices of St, GG, and St + GG for the controlled release of the solid (chlorpyrifos) and liquid (neem seed oil) pesticides [6] in 2001. They indicated that variable release rates were related to the polymer type and especially the pesticide type.

An improved granular formulation of neem seed extract containing neem Aza-A has enhanced storage stability, and the ability to gradually release neem Aza-A for application in the plant rhizosphere [8]. It was found that the best formulation contained inert particulate matter as a carrier, at least one lipophilic substance as a deactivator/binder, optional colorant and neem seed extract containing neem Aza-A. The invention also required the development of a method for the preparation of the formulation by coating the carrier with a lipophilic substance, subsequently impregnating the coated carrier with neem seed extract followed by an optional coating with a colorant and finally a lipophilic substance, by spraying and drying at a temperature below 50 °C.

T.M. Aminabbavi and co-worker studied the encapsulation of a natural liquid pesticide using sodium alginate (Na–Alg) as a controlled release (CR) polymer after crosslinking with glutaraldehyde (GA) [10]. They found that the swelling of the polymeric beads decreased with increasing exposure time to the crosslinking agent. However, no significant variation in swelling was observed with different amounts of neem Aza-A loading. In addition, the rate of release of neem Aza-A from beads was very fast. Thus, in this work we have tried to apply a natural rubber coating to the sodium alginate capsule. Sodium alginate Na–Alg has been used as a controlled release matrix material in medicine [17–19], membranes [20–22] and agriculture [10, 23, 24] after crosslinking it with calcium chloride. Alginate polysaccharides are known to be haemocompatible and do not accumulate in any organs of the human body. It has been reported that glutaraldehyde (GA) solution and alginate can react together by coacervation due to the chemical reaction between the hydroxyl groups of Na–Alg and GA.

In the work presented here we test the feasibility of encapsulating neem Aza-A in a matrix made from sodium alginate that produces a product with good end-use properties. To the best of our knowledge, this is the first study of its kind showing the effect of a natural rubber coating of a capsule obtained from sodium alginate on the release of neem Aza-A. The effect of physically modifying the hydrophobicity of alginate beads was also investigated. The optimum conditions for release of neem Aza-A from such capsules were investigated.

Experimental

Materials

Neem seed kernels were purchased locally in Thailand; neem Aza-A extract was prepared according to the procedure previously described [1]. Sodium alginate, glutaraldehyde (25% w/v) solution and AR grade methanol samples were all purchased from Fluka agent, Thailand. The concentrated NR latex used in this study is a high ammonia latex received from Jana company, Co., Ltd. (Songkhla, Thailand).

Methods

Preparation of capsule beads and efficiency of entrapment

A 4% w/v sodium alginate solution in distilled water was prepared in a heating mantle. After complete cooling neem Aza-A (7,000 ppm) was added at different concentrations and mixed thoroughly using a magnetic stirrer. The polymer solution containing neem Aza-A was added dropwise into methanol containing 1% w/v glutaraldehyde as a crosslinking agent and 0.1% w/v of 1 N HCl as a catalyst, using a 25-ml hypodermic syringe (0.8 mm diameter) with constant stirring. The beads formed were removed from methanol containing HCl after 10, 20 and 30 min proving to degree crosslinking between glutaraldehyde and sodium alginate. The beads were washed with water and then dried. The efficiency of entrapment was calculated as the ratio between the initial mass of neem Aza-A to be encapsulated and its mass in the final product. About 20 mg of the exactly weighed microcapsule sample was mixed in distilled water (250 ml) to form a homogeneous suspension. The total neem Aza-A in the solution was extracted with a 50/50 w/w MeOH/H_2O mixture for 48 h and the amount was determined by HPLC (PerkinElmer LC).

Coating of capsules with NR

The concentrated NR latex used in this study is a high ammonia latex received from Jana company, Co., Ltd. (Songkla Thailand).

The % total solid content (TSC) of latex is defined as the percentage by weight of the concentrated latex which is non-volatile at a definite temperature in an open atmosphere. The % TSC of concentrated NR latex in this study was determined by using the method described in ASTM D107688 as shown in Eq. 1.

$$\%\,\mathrm{TSC} = (W/Wt) \times 100 \tag{1}$$

where W, weight of dry NR sample (g); Wt, weight of NR latex sample (g).

The % dry rubber content (DRC) of latex is defined as the percentage by weight of the concentrated latex which is precipitated by acetic acid. The % DRC of concentrated NR latex was determined (Eq. 2) by using the method described in ASTM D1076-88.

$$\%\,\mathrm{DRC} = (Wx/Wt) \times 100 \tag{2}$$

where *Wx*, weight of dry NR coagulum (g); *Wt*, weight of NR latex sample (g).

Five grams of dried natural rubber were dissolved in toluene (50 ml) in a beaker (250 ml). The capsules (5 g) were dipped into the toluene solution then removed and dried at room temperature.

Briefly, the dried capsules of crosslinked sodium alginate mixed with neem Aza-A (7,000 ppm) were dipped into a toluene solution of natural rubber (5% w/w). Then, the coated capsules were dried at 30 °C for 24 h. Multiple coatings were prepared by immersion of the single-coated neem capsules into the natural rubber with a 30% DRC. Thereafter, the procedure was the same as during the preparation of the single-coated neem capsules. The third-coated neem capsules were derived by dipping the double-coated neem capsules into a natural rubber with 30% DRC followed by the same methodology as that given above. Fourth-coatings were prepared by immersion of the third-coated neem capsules into a natural rubber with a 60% DRC and dried at 60 °C until its weight was constant.

Bead size measurement

Five samples of the completely dried beads from the different formulations were selected and their sizes were measured using a micrometer screw gauge (Sargent, USA) with an accuracy of ±0.01 mm.

Swelling study of the individual beads

The swelling property of the beads was subjected to a measurement of their swelling ratio in an aqueous medium as a function of time. The bead samples exposed to GA for different times at 26 ± 2 °C were selected and incubated with distilled water in a watch glass. The mass of all bead samples was taken at measured time intervals and the average value was calculated. During this process, care was exercised during handling of the swollen beads to avoid any weight loss due to breaking or erosion of the beads. All the weight measurements of the swollen beads were taken on a Mettler single pan balance with an accuracy up to the fifth decimal. The percentage swelling ratio of the beads was calculated as in Eq. 3.

$$\%\,\text{swelling ratio} = \frac{(\text{wet weight} - \text{dry weight}) \times 100}{\text{dry weight}} \tag{3}$$

Scanning electron microscope (SEM)

The aim of the SEM study was to obtain a topographical characterization of the beads. The sample was deposited on a brass hold and sputtered with gold. SEM photographs were taken with a JSM 6400 Scanning Microscope (Japan) at the required magnification at room temperature.

Content uniformity, dissolution and releasing studies

Beads were evaluated for their neem content by refluxing a known mass of the beads with 100 ml of methanol at 65 °C. Refluxing was continued for 1 h to ensure complete extraction of neem from the beads. The absorbance of the methanol solution containing the extracted neem was measured at 211 nm in a HPLC (PerkinElmer LC) using pure methanol as a blank.

The dissolution study was carried out in 250-ml conical flasks containing the dissolution medium (0.1% Tween-80 solution in distilled water) with closure caps and kept at 35 °C in an incubator (WTB Binder, Germany). Two or three beads weighing about 10 mg were taken added to the dissolution medium. At definite time intervals of time, the conical flasks were well shaken well and a 10-ml aliquot was taken for the analysis of neem Aza-A using HPLC (PerkinElmer LC) at 211 nm. Experiments were performed in triplicate in order to minimize the variation error. The cumulative release of neem Aza-A from the capsule beads was estimated using an empirical equation to estimate the value of n as follows (Eq. 4)

$$M_t/M_\infty = Kt^n \text{ or } \log(M_t/M_\infty) = \log(K) + n\log(t) \tag{4}$$

where M_t/M_∞ is the released fraction at time t, n is the release exponent, and K is the release factor. From the slope and intercept of the plot of log (M_t/M_∞) against log (t), the kinetic parameter n was calculated.

Results and discussion

Preparation of neem capsules

The encapsulation of neem (herein called capsule) was prepared using sodium alginate as a controlled release polymer after crosslinking with glutaraldehyde, and then the capsule was coated with natural rubber solution. The optimum condition for encapsulation of neem such as the time left in the glutaraldehyde solution was investigated. In order to optimize the drying conditions, some samples of the beads of equal weights but with different extents of crosslinking were selected for their testing rate of drying.

The percentage entrapment efficiency was altered by varying the time of exposure to the crosslinking agent. It was found that the percentage entrapment efficiency decreased drastically with a decrease in the aqueous suspension medium. Beads produced in 0.1% w/v HCl in methanol at 298 °C and exposed for 10 min showed the highest entrapment efficiency i.e., 91.2% and the lowest entrapment efficiency i.e., 73.6% was observed using 0.1% w/v HCl in methanol at 298 °C and again exposed for 30 min (Table 1). Neem Aza-A is soluble in aqueous media, thus increasing the time of exposure to glutaraldehyde in the presence of HCl as catalyst decreased the entrapment efficiency and increasing the concentration of Neem Aza-A did increase the amount bound but the entrapment efficiency was reduced.

Table 1 Effect of the time of exposure to glutaraldehyde and the neem Aza-A content on bead diameter and entrapment efficiency of capsules

Time of exposure to 5% GA (min)	Neem Aza-A loading (%)	Bead diameter (mm)	Entrapment efficiency (%)
10	5	1.11 ± 0.12	91.2 ± 1.2
	10	1.25 ± 0.12	89.1 ± 1.3
	20	1.28 ± 0.14	85.2 ± 1.1
20	5	1.28 ± 0.22	89.7 ± 1.3
	10	1.32 ± 0.13	88.8 ± 1.4
	20	1.48 ± 0.12	83.7 ± 1.4
30	5	1.35 ± 0.22	80.6 ± 1.5
	10	1.43 ± 0.15	78.4 ± 1.4
	20	1.45 ± 0.17	73.6 ± 1.6

Swelling ratio of capsule

The effect of crosslinking on the percentage of swelling ratio by beads exposed for various times to glutaraldehyde is shown in Fig. 1. All the beads show a maximum uptake of water during the first hour, but beads formed by exposing them for only 10 min to the crosslinking agent absorbed more water than the beads formed by exposing them for 20 and 30 min. Equilibrium swelling ratio was achieved in 10, 50 and 180 h after crosslinking with glutaraldehyde for 10, 20 and 30 min, respectively. The particles produced in this work were analyzed for their sizes using the light scattering method. Aza-A release from the beads was measured after subjecting them to a number of physical and chemical parameters including those

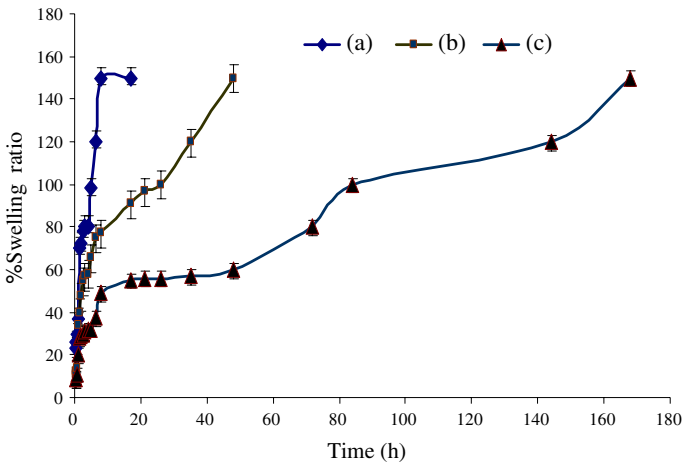

Fig. 1 Effect of crosslinking on the percentage of swelling ratio by beads at (**a**) 10, (**b**) 20 and (**c**) 30 min exposure to glutaraldehyde

related directly to the release medium and those resulting from changes to the characteristics of the structures controlling release (beads). The capsule bead at 30 min of storage time in glutaraldehyde solution was selected for NR coating study due to its lower swelling ratio comparing the other sample.

The effect of a natural rubber (NR) layer on the percentage of swelling by beads prepared at 30 min storage time in glutaraldehyde solution are shown in Fig. 2 It seems that the release rate of neem Aza-A from the capsules can be improved by modifying the capsule structure by coating them with NR. Diffusion in polymers is an important mechanism in pharmacy for controlling the release of drugs [9]. Diffusion in polymeric systems is passive, if the driving force is purely a brownian molecular motion. However diffusion can also be modified by external effects, either by the influence of the release medium through swelling or biodegradation, or by the effects of physical forces such as electrical, osmotic or convective forces. The fundamentals of diffusion are based on Fick's laws that describe the macroscopic transport of molecules by a concentration gradient [9].

A suitable coating material must be nonreactive, essentially immiscible with the material being encapsulated and capable of being rapidly hardened to form a film. Natural rubber was selected as the coating agent of neem Aza-A-sodium alginate capsules to provide an adequate barrier wall. The dry capsules of crosslinked sodium alginate mixed with neem Aza-A (7,000 ppm) were dipped into a toluene solution of natural rubber (5% w/w). Then, the coated capsules were dried at 30 °C for 24 h. Multiple coatings were prepared by immersion of the single-coated neem

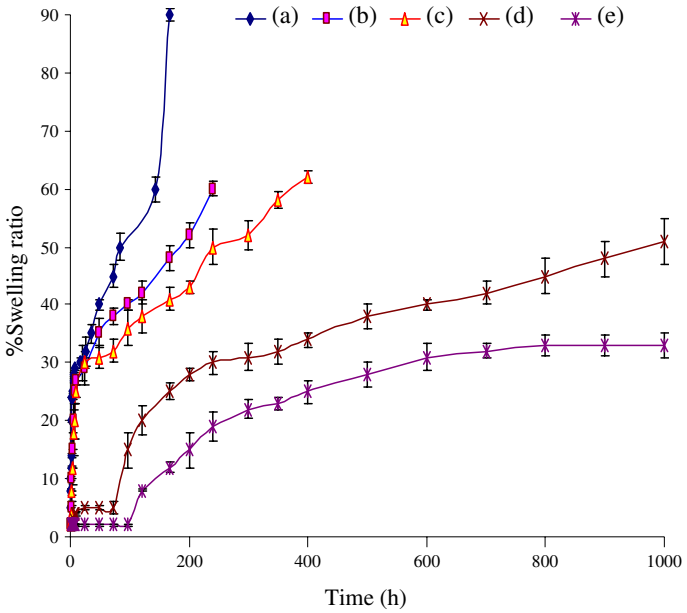

Fig. 2 Effect of adding layers of NR to capsules on the percentage of water uptake by beads (**a**) 0 (**b**) 1, (**c**) 2 (**d**), 3 and 4 NR layers

Aza-A capsules into a natural rubber with 30% DRC. Thereafter, the procedure was the same as during the preparation of single-coated neem Aza-A capsules. The three-coated neem Aza-A capsules were derived by the dipping of double-coated neem Aza-A capsules into a NR with 30% DRC and then using the same methodology as described above. A fourth-coatings were prepared by the immersion of the third-coated neem Aza-A capsules into a natural rubber with 30% DRC and dried at 60 °C until its weight was constant. It is clear that the rate of swelling decreased dramatically after coating neem Aza-A capsule with NR compared with that of the capsule without coating. When the NR layers on the capsules increased, the swelling ratio of these resulting capsules dramatically decreased, especially capsule beads with four coats of NR. The swelling ratio of neem Aza-A obtained from first-coated neem Aza-A in aqueous medium at 2, 24, 72 and 240 h of storage neem Aza-A was 10, 29, 38 and 60%, respectively. When the NR coating on capsules was increased from 1 to 3 layers, the swelling ratio of neem Aza-A obtained from first-coated neem Aza-A in aqueous medium at 2, 24, 72 and 240 h of storage neem Aza-A was increased by 2, 5, 5 and 30%, respectively.

Morphology of capsules

The particles produced in this work were analyzed for their sizes using the light scattering method. The SEM photographs of capsule are shown in Fig. 3 and it is clear that the particles are shaped like an egg. The mean particle size was 0.14 mm as measured using both OM and SEM. After the capsules were coated with NR, their diameter drastically increased from 0.14 mm to be 3 mm and had a smoother capsule surface

Release rate study of neem from sodium alginate capsules

Capsules prepared using a number of different physical and chemical parameters including those related directly to the release medium, the release conditions and

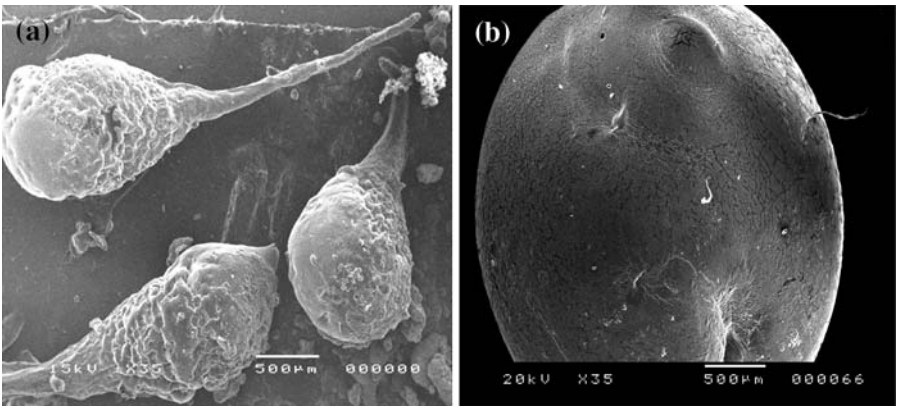

Fig. 3 Scanning electron microscopic photographs of capsule beads prepared with 30 min of storage time in glutaraldehyde solution, (**a**) without and (**b**) with NR coating

those resulting from changes to the characteristics of the release controlling device (beads) were tested for their ability to release neem Aza-A from capsule beads. The effect of the degree of crosslinking of the sodium alginate beads on the kinetics of Aza-A release is depicted in Fig. 4. The longer the exposure time to glutaraldehyde the longer it took to release neem Aza-A 100% of neem Aza-A was released in 5 h from beads exposed to glutaraldehyde for 10 min, and in 10 and 25 h from beads exposed to glutaraldehyde for 20 and 30 min, respectively. Beads with exposure to glutaraldehyde for 30 min were therefore selected for NR coating.

The n value is an empirical parameter characterizing the release mechanism [10]. On the basis of the diffusion exponent, an n value of 0.5 indicates the nutrient release mechanism approaches to a Fickian diffusion controlled release, whereas when n is equal to 1.0 this indicates the nutrient release mechanism approaches to a zero-order release. An n value from 0.5 to 1.0 indicates a reactive agent release mechanism for a non-Fickian diffusion or a chain relaxation controlled release. From the plot of log (M_t/M_∞) against log (t), release exponent (n) has been calculated (Fig. 5). The n value is in the range from 0.3515 to 0.6258. The n value with 0.3515 of sample obtained from a 30 min storage time in glutaraldehyde solution indicates that the release in this system deviates from a Fickian diffusion controlled release. The n of capsule beads obtained from 10 and 20 min of storage time was 0.599 and 0.6258, respectively, indicating that these systems exhibited non-Fickian diffusion. These results deduced that the n value of this system depends on exposure time in glutaraldehyde solution leading to different crosslinking density contents and different neem release mechanism patterns in the sample.

The effect of release rate of Aza-A from the beads coating capsules, made by exposure to glutaraldehyde for 30 min with different layers of natural rubber on the release rate of Aza-A from the beads are presented in Fig. 6. The release profile from neem Aza-A without NR coating is also shown for comparison (Fig. 6). It is

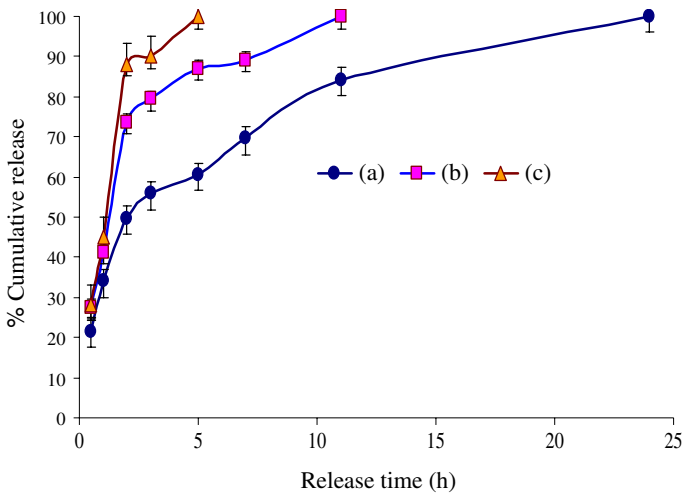

Fig. 4 Effect of crosslinking on the release of neem from capsules prepared by crosslinking with glutaraldehyde for (**a**) 10, (**b**) 20 and (**c**) 30 min without coating with NR

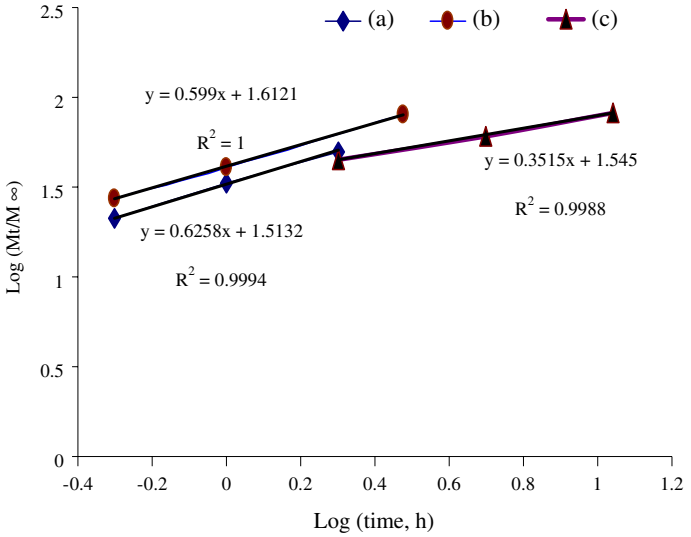

Fig. 5 Fitting of release kinetics of neem Aza-A from capsules not coated with NR and prepared by exposure to glutaraldehyde for (**a**) 10, (**b**) 20 and 30 min

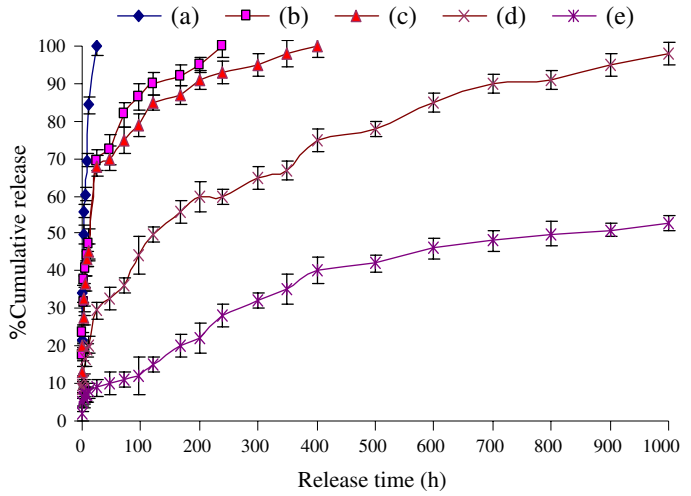

Fig. 6 Effect of NR coating on the release of neem Aza-A from capsules coated with NR (**a**) 0 (**b**) 1 (**c**) 2, (**d**) 3 and 4 layers of NR

obvious that the neem Aza-A release rate is reduced significantly by NR coating, which is consistent with the results of the swelling study. The natural rubber film is very strong, rigid and hard to swell, so the diffusion through this coating is the rate limiting step for swelling and neem-A release. The release was prolonged by additional natural rubber layers on the capsule surface. The neem Aza-A cumulative release from capsules exposed for 2, 24, 72 and 240 min in aqueous medium was

31, 69, 81 and 100%, respectively and when capsules were coated with 1–4 layers of NR the cumulative release of the neem Aza-A from capsules stored in the same condition changed to 8, 29, 36 and 60%, respectively. It should be noted that with an increase in NR coating, the capsule matrix becomes more dense resulting in a decrease in the rate of diffusion of neem Aza-A through the swollen beads, especially beads with a fourth-NR coating. The n values of neem Aza-A coated with NR (Table 2), have been estimated from Fig. 7. It was found that the n value of this sample obtained from 0, 1, 2 and 3 layers was 0.3515, 0.3766, 0.4476 and 0.3497, respectively at a regression of 0.9988, 0.9875, 0.9870 and 0.9991, respectively. The *n* of fourth-coated neem Aza-A capsules was not calculated due to unequilibrium state. Thus, the neem Aza-A release mechanism of beads coated with NR was by Fickian diffusion. This result is concluded that the best condition of controlling neem release from capsules for application in soil agriculture was 3 NR coating layer and 30 min of exposure time in 0.1 w/v% glutaraldehyde solution due to the

Table 2 Effect of exposure time to glutaraldehyde and NR coating on the n value of the capsules

Storage time in glutaraldehyde	NR coating number	*n*	r^2
10	0	0.6258	0.9994
20	0	0.599	1.000
30	0	0.3515	0.9988
30	1	0.3766	0.9875
30	2	0.4476	0.9870
30	3	0.3497	0.9991

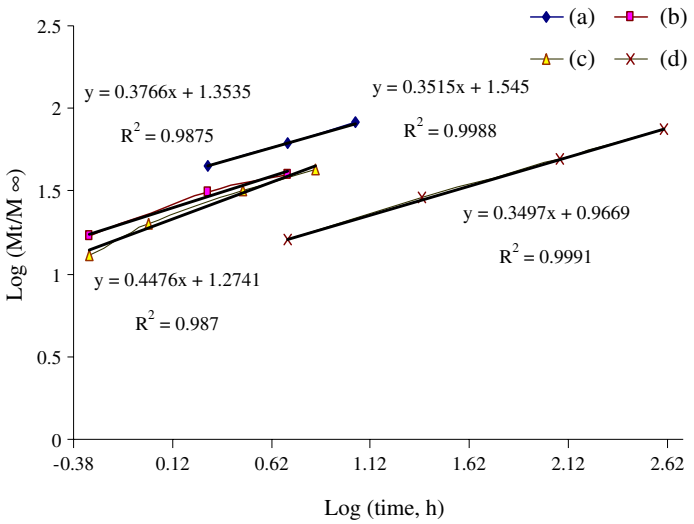

Fig. 7 Fitting of release kinetics of neem Aza-A from capsules with uncoated NR (**a**) and coated with (**b**) 1, (**c**) 2 and (**d**) 3 layers of NR

optimum controlling neem release from capsule bead, observing from n value and swelling ratio as well as neem release from them.

Conclusions

These experimental results indicate that neem Aza-A can be successfully encapsulated into the sodium-alginate capsules crosslinked with glutaraldehyde and then coated with NR. After the sodium alginate matrix capsules were coated with NR, the surface of the capsules changed from quite rough to smooth. NR coating of the neem Aza-A-sodium alginate capsules had a pronounced effect on slowing the release of neem Aza-A. The NR could be used as an adequate surface barrier to give better distribution of neem Aza-A in the sodium alginate matrix and consequently more efficient release of neem Aza-A as compared to the uncoated capsules. The rate of neem Aza-A release decreased with the increase in dipping time in the NR latex. The rate of release of neem Aza-A from capsules in aqueous medium depended on the exposure times to glutaraldehyde and the number of layers of NR on its surface. The optimum condition of controlling neem release from capsules in soil agriculture was 3 NR coating layer and 30 min of exposure time in 0.1 w/v% glutaraldehyde solution. The expected application of resulting capsule will be in soil agriculture field.

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