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Preparation and evaluation of carboplatin biodegradable polymeric nanoparticles

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ABSTRACT

The present study was designed to evaluate targeting efficiency of carboplatin anticancer drug. Drug was encapsulated in natural biodegradable polymer sodium alginate. The nanoparticles were prepared by the ion gelification technique and evaluated for encapsulation efficiency, loading capacity, *in vitro* release pattern and targeting efficiency. Drug encapsulation efficiency was about 52.24–68.70% for different formulations. In vitro release profile showed duration of drug release was also increased (more than 12 h) by nanoparticulate formulation as compared to pure drug (up to 3 h). The formulations were parenterally administered to laca mice and the drug was detected in body organs like liver, lungs and spleen. In case of free drug, less amount of drug was found in liver, lungs and spleen as compared to drug encapsulated nanoparticles. Thus sodium alginate nanoparticles can be used for targeting carboplatin and it can be a promising tool in the delivery of anticancer drugs.

1. Introduction

The use of biodegradable polymers as drug carriers has long been of interest in controlled-release technology because of the ability of these polymers to get metabolized in the body. The field of biodegradable polymers is progressing rapidly, so that researchers now have substantial number of degradable polymers with a range of degradation rates. Micro- and nanoparticulate systems formulated with these polymers have shown wide applicability of oral delivery, subcutaneous injection and sustained delivery of lipophilic and some hydrophilic drugs. Nanoparticles can be employed as carriers for targeting of drugs, thereby increasing the relative bioavailability of encapsulated drugs and also for increasing the antifungal activity of drug as in case of nanoparticles containing drug amphotericin B (Shanmugassundaram et al., 2007).

Nanoparticles can passively target tumor tissue through enhanced permeation and retention effect (Monsky et al., 1999; Stroh et al., 2005). Nanoparticles can be delivered to distant target sites either by localized catheter-based infusion (Song et al., 1998) or by attaching a tissue-specific targeting ligand to nanoparticle surface (Kaul and Amiji, 2005).

Nanoparticles made of polyelectrolytes complexation have shown potential for use as drug delivery systems. Polyelectrolyte complexes (PEC) are formed when oppositely charged polyelectrolytes are mixed and interact via electrostatic interactions. Chitosan and alginate are polycation and polyanion polyelectrolytes respectively, which can be used to form a polyelectrolyte complex to deliver proteins and peptidic drugs (Coppi et al., 2001). The interaction between alginate in dilute solution with Ca^{2+} occurs at a certain ion concentration (Rajaonarivony et al., 1993). A pre-gel state results with stirring, avoiding the gel point and forming a continuous system. Subsequent addition of an aqueous polycationic solution (chitosan) results in a polyelectrolyte complex, stabilizing the alginate pre-gel nucleus into individual sponge-like nanoparticles (Sarmento et al., 2005).

Alginate (ALG) is a water soluble linear polysaccharide extracted from brown sea weed and is composed of alternating blocks of 1-4 linked α-L-guluronic and β-D-mannuronic acid residues. ALG has been reported to be mucoadhesive, biodegradable and biocompatible and has potential for numerous pharmaceutical and biomedical applications such as drug delivery system and cell encapsulation (Gombotz and Wee, 1998; Smidsrod and Skjakbraek, 1990). Alginate micro- and nanoparticles can be obtained easily by inducing gelation with calcium ions (Pan et al., 2002; Mladenovska et al., 2007). Such easy-gelling property can be used to produce a pre-gel consisting of very small aggregates of gel particles, followed by the addition of an aqueous polycationic solution to make a polyelectrolyte complex coating (De and Robinson, 2003). Poly-L-lysine (PLL), a cationic natural polymer, has been used to combine with ALG to prepare nanoparticles.

Carboplatin (cis-diamine (1,1-cyclobutanedicarboxylato)-platinum (II)), a cisplatin analog, is an antineoplastic drug with an activity profile similar to cisplatin. It is recommended for chemotherapy of ovarian cancer, head, neck and lung cancer

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(Smith et al., 1985; Vaughn, 2000; Zatloukal and Petruzelka, 2002; Rose et al., 2003). However, the toxic effects of carboplatin include dose related myelosupression with severe thrombocytopenia and leucopenia, especially in older patients with renal impairment or who have previously received chemotherapy (Shimizu et al., 1996). Thus, it is important to be able to prepare carboplatin nanoparticles to prevent or reduce its side effects.

Prolonged exposure of cells to cytotoxic concentration is critical to achieve maximum cytotoxic activity. The short half-life and low bioavailability is the reason for ongoing research for effective formulation. Protection of carboplatin from fast degradation and elimination has been investigated by encapsulating the drug into pharmaceutical carriers. The low oral absorption and poor tissue specificity requires carboplatin to be delivered as nanoparticles. To avoid these problems associated with the oral administration, parenteral administration of the nanoparticles may be a suitable alternative.

The aim of the present study was to use the ion gelation technique to produce surfactant-free nanoparticles of sodium alginate. The influence of drug concentration, types of cross-linking agent and also the targeting efficiency of carboplatin-containing nanoparticles in different tissues, such as lung, spleen, liver, kidney, and serum, after intravenous administration to mice have been investigated. These results may provide some practical information for the development of nanoparticles delivery system which will enhance the targeting ability of carboplatin.

2. Materials and methods

Carboplatin (CP) (purity >99%) was purchased from Cipla Pharmaceutical Pvt. Ltd., Mumbai. Sodium alginate of low viscosity (0.02 Pa s) for a 1% solution at 20 °C was purchased from Krishna Divine, Delhi. Poly-L-lysine, Chitosan (MW is 750,000, degree of deacetylation is 80%) was acquired from Sigma Inc., USA. All other chemicals and reagents used were of analytical grade.

2.1. Preparation of carboplatin loaded alginate/chitosan nanoparticles

Both the sodium alginate and calcium chloride solutions were prepared by dissolving the chemicals in distilled water. The pH of the sodium alginate solution was adjusted to 5.1 using hydrochloric acid. Briefly, a known amount of chitosan was dissolved in 1% acetic acid solution and pH was modified to 5.4 using NaOH. The method used to prepare the nanoparticles is a two-step method adapted from Rajaonarivony's method of preparing alginate–poly-L-lysine nanoparticles (Rajaonarivony et al., 1993). Aqueous calcium chloride was added drop wise to 10 ml aqueous sodium alginate while stirring for 30 min (XK97-2 two-way homoisothermy magnetic stirrer, 1200 rpm), and then 4 ml chitosan solution was added into the resultant calcium alginate pre-gel and stirred for an additional 1 h. The resultant opalescent suspension was equilibrated overnight to allow nanoparticles to form uniform particle size (Ping et al., 2008). Same procedure was followed while preparing drug loaded nanoparticles (F1–F3) with drug amount ranging from 10 to 30 mg (Table 1).

2.2. Preparation of carboplatin loaded alginate/poly-L-lysine nanoparticles

2 ml of calcium chloride was added to 38 ml of sodium alginate to induce gelification. Then 16 ml of poly-L-lysine was added to form a polyelectrolyte complex. The nanoparticles suspension obtained was stirred for 2 h and kept overnight for stabilization. The nanoparticles were separated by ultra centrifugation at 20,000 rpm for 45 min and dried under vacuum to form a flaky mass. Same procedure was followed while preparing drug loaded nanoparticles (F4–F6) with drug amount ranging from 10 to 30 mg (Table 1).

2.3. Particle size and surface morphology

Particle size analysis was done by scanning electron microscopy (SEM) using a JEOL JSM-T330A scanning microscope. A cleaned brass specimen stud was used for mounting the samples. Wet solvent paint was applied on these studs and while the paint was wet, the pellets were placed on each stud and allowed to dry, and then the sample was observed.

2.4. Determination of drug loading and encapsulation efficiency

The dried 10 mg of carboplatin nanoparticles were dissolved in 50 ml of phosphate buffer pH 7.4. An aliquot of this suspension was added to the sample reservoir and centrifuged for 10 min at 12,000 rpm. The supernatant filtrate was assayed to determine the concentration of the unencapsulated drug. Another aliquot of the suspension was added to methanol (1:10, v/v) and sonicated for 10 min in a bath sonicator to release the encapsulated molecules, which were quantitated to determine the total drug concentration. Encapsulation efficiency (%) was calculated by the following formulae:

$$\text{Encapsulation efficiency \%} = \left[1 - \left(\frac{\text{Un-encapsulated drug}}{\text{total drug}}\right)\right] \times 100.$$

The drug loading (DL) was expressed as

$$\text{DL}(\%) = \left[\frac{\text{Weight of drug loaded in nanoparticles}}{\text{Total weight of nanoparticles}}\right] \times 100.$$

2.5. In vitro release studies

After separation of the free drug, the nanoparticle preparation was transferred to a dialysis tube and subjected to dialysis with the dialysis tube immersed in a phosphate buffer saline pH 7.4 (100 ml). At different time intervals, samples were withdrawn from the receptor compartment and the drug content was determined spectrophotometrically at 235 nm. An equal volume of phosphate buffer saline replaced the samples that were withdrawn (Nisha and Pramod, 2007).

Table 1
Formulation table showing quantity of each ingredient used in formulation.

Formulation	Drug	Sodium alginate	Calcium chloride	Poly-L-lysine	Chitosan
F1	10	0.3%; w/v (10 ml)	0.33%; w/v (2 ml)	–	0.08%; w/v (4 ml)
F2	20	0.3%; w/v (10 ml)	0.33%; w/v (2 ml)	–	0.08%; w/v (4 ml)
F3	30	0.3%; w/v (10 ml)	0.33%; w/v (2 ml)	–	0.08%; w/v (4 ml)
F4	10	0.12%; w/v (38 ml)	18mM (2 ml)	0.1%; w/v (16 ml)	–
F5	20	0.12%; w/v (38 ml)	18 mM (2 ml)	0.1%; w/v (16 ml)	–
F6	30	0.12%; w/v (38 ml)	18 mM (2 ml)	0.1%; w/v (16 ml)	–

2.6. In vivo drug targeting studies

Fifteen laca mice were divided into 3 groups, a constant day and night cycle was maintained and they were fasted for 12 h. Carboplatin nanoparticles (alginate/chitosan and alginate/poly-L-lysine) were given intravenously after redispersing them in sterile phosphate buffer saline solution and pure carboplatin by injection, at a dose of 15 mg/kg body weight via the tail vein.

After 2 h the mice were sacrificed and their liver, lungs and spleen were isolated. The individual organs of each laca mice were homogenized separately and centrifuged at 15,000 rpm to obtain the supernatant. The supernatant was filtered through an ultra filter membrane of pore size 0.2 μm and subjected to extraction procedure.

2.6.1. Extraction procedure

Ultra filtrate samples were mixed with a known amount of 10% solution of diethyldithiocarbamic acid (sodium salt DDTC) in sodium hydroxide and incubated at 37 °C for 1 h and then chilled. The drug chelate was then extracted with chloroform and evaporated to dryness and redissolved in PBS pH 7.4. The drug content was estimated using UV-spectrophotometer at 235 nm (Bhadra et al., 2003).

2.7. Stability studies of carboplatin nanoparticles

The formulated nanoparticles were separated into three portions. One portion was kept at room temperature, the second at 45 °C and the third at 4 °C for 1 month. After 30 days drug content of all samples were determined by the method discussed previously in entrapment efficiency section. *In vitro* release study of formulation F-2 and F-5 was also carried out after 30 days storage (Balasubramanium et al., 2002).

3. Results

3.1. Preparation of alginate/chitosan and alginate/poly-L-lysine nanoparticles

The preparation method of nanoparticles produced well formed nanoparticle with good morphological characteristics. The alginate/chitosan and alginate/poly-L-lysine nanoparticles are carried out at ambient temperature; preparation is simple, rapid, and reliable. Both types of nanoparticles are obtained spontaneously under very mild conditions. The preparations of carboplatin loaded nanoparticles are relatively difficult because of gelling nature of sodium alginate which gives nanoparticles only at particular concentration of polymer. In fact, calcium ions react with guluronic acid units on alginate to form an 'egg-box' structure. It is proposed that nanoparticles can be formed by enveloping the negatively charged calcium alginate complex in pre-gel state with cationic polymer, and the pre-gel state is essential to enable the ionic interactions between alginate, calcium, and cationic polymer to form nanoparticles (Li et al., 2007).

3.2. Particle size and surface morphology

Electron microscopy analysis confirmed the presence of nanoparticles and provided morphological information of the typical carboplatin loaded nanoparticles. With the SEM, particles were seen to be spherical, distinct and regular (Figs. 1–6). Average particle size of nanoparticles of carboplatin was 266–310 nm, 300–350 nm, 335–388 nm, 185–209 nm, 240–270 nm and 290–324 nm respectively for formulations F1–F6. The particle size varies depending on the experimental parameters used to

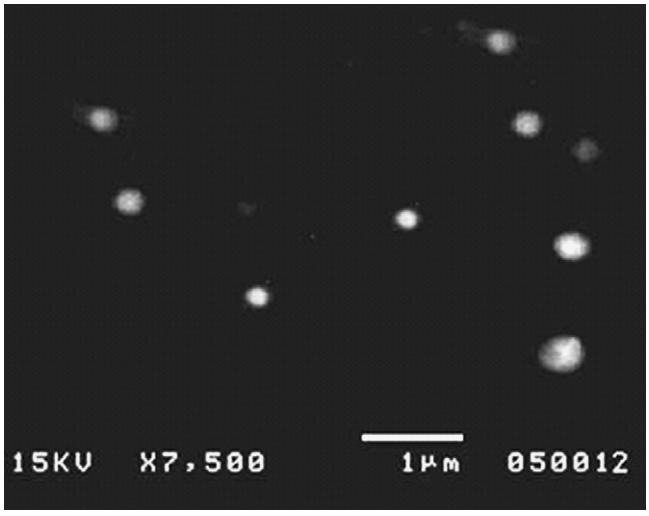

Fig. 1. Scanning electron photomicrographs of formulation 1.

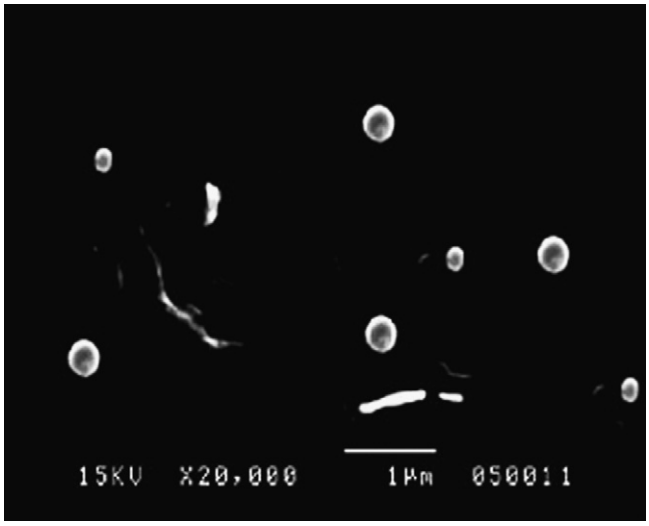

Fig. 2. Scanning electron photomicrographs of formulation 2.

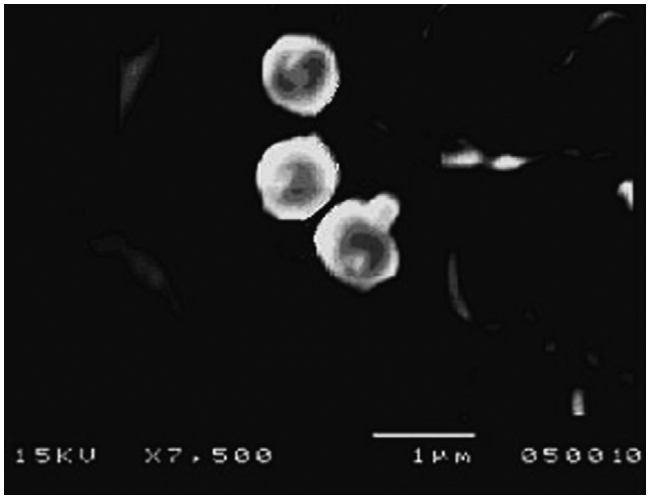

Fig. 3. Scanning electron photomicrographs of formulation 3.

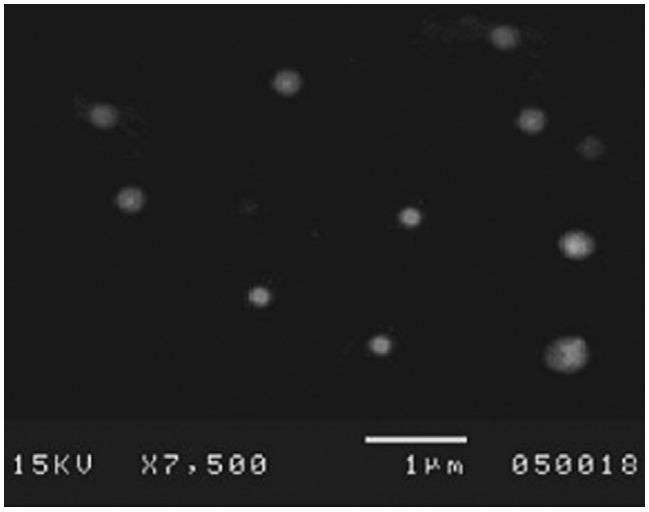

Fig. 4. Scanning electron photomicrographs of formulation 4.

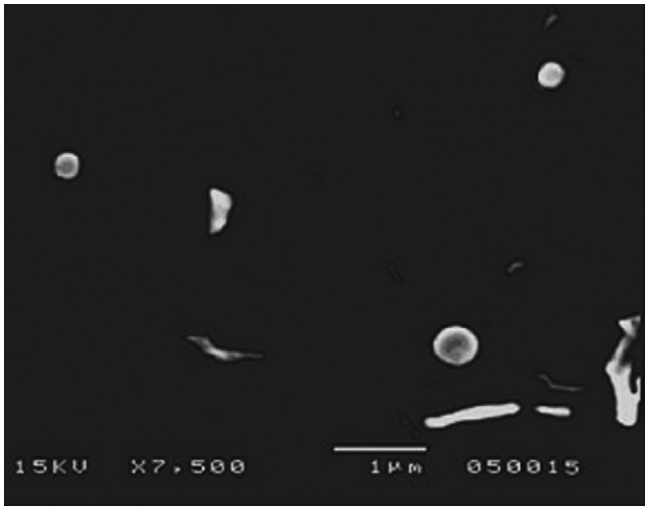

Fig. 5. Scanning electron photomicrographs of formulation 5.

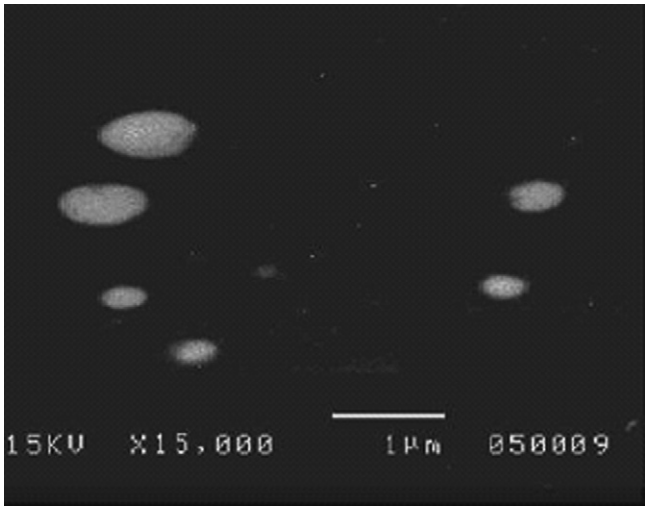

Fig. 6. Scanning electron photomicrographs of formulation 6.

Table 2
Drug loading and encapsulation efficiency of sodium alginate nanoparticles.

Formulation	Drug (mg)	Drug loading (%)	Encapsulation efficiency
F1 (alginate/chitosan)	10	3.03	52.24
F2 (alginate/chitosan)	20	6.75	62.82
F3 (alginate/chitosan)	30	10.87	64.16
F4 (alginate/PLL)	10	12.54	61.23
F5 (alginate/PLL)	20	32.22	68.70
F6 (alginate/PLL)	30	38.04	71.16

prepare them (Jacob, 1999). Particles of all formulations were in nanoparticles having smooth surface.

3.3. Drug loading and encapsulation efficiency

Drug loading and encapsulation efficiency data obtained are as shown in Table 1. Increasing the drug concentration from 10 to 30 mg in the formulation resulted in an increase in drug loading efficiency from about 3.03% to 10.87%, 12.54% to 38.04% for alginate/chitosan nanoparticles and alginate/poly-L-lysine nanoparticles respectively (Table 2). Similarly, increasing the drug concentration from 10 to 30 mg in the formulation resulted in change in encapsulation efficiency from 52.24% to 64.16%, 61.23% to 71.16% (Table 2) for alginate/chitosan nanoparticles and alginate/poly-L-lysine nanoparticles respectively.

3.4. In vitro release properties of carboplatin

Fig. 7 shows the cumulative release curves of carboplatin from alginate/chitosan and alginate/poly-L-lysine nanoparticles. 51.11%, 52.57%, 54.50% and 53.57%, 58.44%, 56.44% of carboplatin was released from alginate/chitosan and alginate/poly-L-lysine nanoparticles respectively within 10 h. The release profile was characterized by an initial burst effect, followed by a continuous and sustained release phase within 10 h. The burst release results seem to indicate that a significant amount of carboplatin initially associated with nanoparticles remained on their surfaces by weak interactions forces between polyelectrolytes and carboplatin (Sarmento et al., 2006a,b).

3.5. In vivo drug targeting and stability study

The average targeting efficiency of drug loaded alginate/chitosan nanoparticles, alginate/poly-L-lysine nanoparticles and pure drug in different organs like liver, lungs and spleen after intravenous administration was found to be as shown in Table 3. Nanoparticle carboplatin group was compared with pure

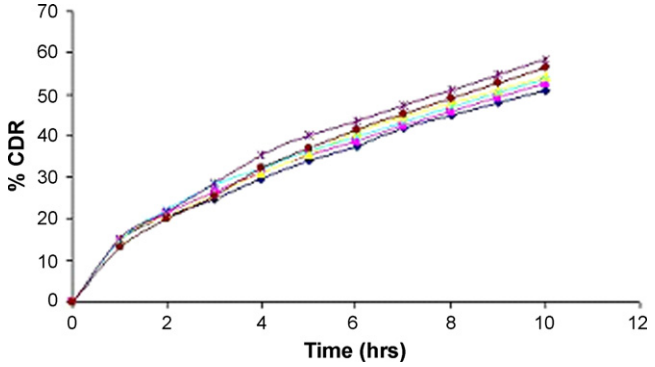

Fig. 7. *In vitro* release profile of carboplatin loaded nanoparticles F1–F6. %CDR = % cumulative drug release. ( ) %F1; ( ) %F2; ( ) %F3; ( ) %F4; ( ) %F5; ( ) %F6.

Table 3
Average targeting efficiency of nanoparticles formulation and pure drug.

Formulation	Targeting organs		
	Liver	Lungs	Spleen
Alginate/chitosan nanoparticles	39.39%	24.67%	28.57%
Alginate/PLL nanoparticles	28.57%	10.85%	14.52%
Pure drug	18.32%	8.61%	11.23%

carboplatin applying Student's *t*-test, the statistical results showed that the probability value was highly significant $p < 0.0001$.

Drug content after 30 days of storage for formulations F1–F6 was 47.61%, 60.21%, 61.02%, 55.23%, 68.45% and 63.78%. The stability studies of selected formulation F2 and F5 was done. Results that show % CDR after 30 days were 52.12%, 50.11%, 42.34% for F2 and 56.11%, 53.45%, 45.67% for F5 at 4 °C, room temperature and at 45 °C respectively.

4. Discussion

In the present research, the study reports a method to prepare alginate/chitosan and alginate/poly-L-lysine nanoparticles based on the formation of a polyionic complex between the two biopolymers. This system may have some interesting features:

Carried out at ambient temperature, preparation is simple, rapid, and reliable.
Both type of alginate nanoparticles (using chitosan and poly-L-lysine) are obtained spontaneously under very mild conditions.
Particle size for the alginate/chitosan showed the smallest particle size in different drug polymer ratios and alginate poly-L-lysine nanoparticles showed maximum drug content. The results revealed that larger particles have higher drug content, because fewer drug molecules have sufficient time to diffuse into aqueous phase.
Encapsulation efficiency was highest with alginate/poly-L-lysine nanoparticles.

The release study also showed that the formulated nanoparticle showed a sustained release. The release profile was characterized by an initial burst effect in three media, followed by a continuous and controlled-release phase.

The release results shows that cross-linking agent have effect on release profile as alginate/chitosan nanoparticles shows more sustained release of carboplatin for longer duration than nanoparticles using poly-L-lysine as cross-linking agent.

The complex protects the encapsulant, has biocompatible and biodegradable characteristics, and limits the release of encapsulated materials more effectively than either alginate or chitosan alone.

The present study shows that the targeting efficiency of loaded nanoparticles over free drug is higher, which may provide increased therapeutic efficacy. Moreover, higher concentration of drug targeted to various organs may help in the reduction of dose required for the therapy and thereby dose related side effects could also be minimized.

Targeting efficiency of alginate/chitosan nanoparticles was more than alginate/poly-L-lysine nanoparticles and more poly-L-lysine have some immunogenic effects. So poly-L-lysine is less suitable for using as cross-linking agent for nanoparticle formulation.

Stability studies results showed no change in drug amount in nanoparticles after 30 days of storage. It predicts that the suitable storage condition for the nanoparticles to be 4 °C and room temperature. Hence, it can be concluded that chitosan is better complexing agent than poly-L-lysine for preparing and delivering carboplatin in nanoparticles.

Thus desirable goals can be achieved by a systematic formulation approach in the shortest possible time with a reduced number of experiments thereby reducing the cost of development of the formulations.

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