Chapter

Preparation and Characterisation of Niosomal Emulsions as Novel Drug Delivery Vehicle Derived from Natural Seaweeds

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Abstract

Biomedical field uses polysaccharides for the last one half of the century due to its remarkable applications. Nature is an abundant source for natural polysaccharides made its use widely in this field. In this present chapter study, the potential of alginate-κ-carrageenan and alginate-gelatin hydrogel beads for encapsulating curcumin was investigated. The evaluation of different combination of combinations of alginate/κ-carrageenan and alginate/gelatin hydrogel beads were developed and drug release properties were compared using curcumin as a model drug. Alginate/κ-carrageenan hydrogel beads with 50:50 weight ratio exhibited higher swelling and better drug release percentage than compared to other beads. Antibacterial activity of curcumin released from hydrogel beads against *B. cereus* was established by disc assay. This nanosized vehicles with increases the efficacy and to control the delivery of biologically active substances at their specific site is as important as the drug activity itself.

Keywords: κ-carrageenan, alginate, niosome, hydrogel, drug delivery

1. Introduction

Revolution changes and modifies the conservative systems existing in the entire zones of the world. Medicinal chemistry and nanotechnology in that sense practices a revolutionary idea that promises healthy life to every human being. One such important category belongs to drug delivery is the use of natural sources as drug carriers [1]. A number of therapeutic agents show potentiality against cancer, HIV, Tuberculosis, and other kind of diseases, but most of them are not having the potential to overcome the biological barriers inside the body and this causing least effect than actual [2]. This appeal the production of a new system that can able to reduce the typical hitches associated with drugs. We need safe, secure and efficient measures to dose new generation diseases that threatening the life of living beings [3].

Accordingly, among the new discovered diseases, cancer leads as a number one killer disease because of the versatile nature and failure of therapeutic potential against the disease [4]. Recent years witnessed discovery of efficient therapeutic agents but its actual challenge is to overcome the biological barriers inside the body [5]. Most of the drugs are potent to the particular disease but the properties limited

due to its hydrophobic nature, non-specificity, toxicity to normal cells, less stability, etc. [6]. So the researchers move to deliver these available potent drugs to the pathological site by diminishing all these factors through entrapment in a biocompatible polymers as carriers [7]. They were trying to develop smart drug carriers to enhance the efficiency of drugs at its specific site with controlled delivery [8].

Drug delivery is a term that refers the successful delivery of therapeutic agents at the specific site with specific time without any kind of degradation [9]. The problem associated with available drugs in the market includes hydrophobic nature, higher toxic nature, nonspecific release, in vivo degradation and short circulating half-lives [10]. Drug delivery systems emerging from the significance of controlled release of therapeutic agent on the affected part in the effective time with least side effects [1, 11]. Natural polymer based drug carriers is the central focus due to biocompatible nature, nontoxicity, low cost, ease of use and biodegradability [10]. Specificity [12] of drug molecule can be improved using ligands at the surface of delivery systems which in turn termed targeted drug delivery to the affected area of the body [13]. Targeting can be through either passive or active [14]. Major types of drug carriers falling under

- Niosomes,
- Liposomes,
- Polymeric micelles,
- Microspheres,
- Nanostructures,
- Nanofibers,
- Protein-DNA complexes,
- Protein-drug conjugates,
- Erythrocytes,
- Virosomes,
- Dendrimers.

Utilization of drug delivery systems is a promising methodology for creating efficient therapeutic agents. Among these kinds of carrier's polymeric micelles, dendrimers, liposomes [15] are the growing area because of their outstanding properties and smart drug delivery potential [16]. Polymer based systems must meet some important features to become a good delivery vehicle such as; the backbone should be biocompatible; the term biocompatible in the sense explains capacity of a polymer to act with proper host reaction as well as the polymers are biodegradable without the formation of any kind of harmful by-products inside the body [17–19]. The polymer must soluble in various solvents and versatile in chemical, structural and in application, etc. [3, 9]. The exploitation of micelles prepared from amphiphilic copolymers for solubilization of ineffectively solvent medications has drawn in much consideration. Natural polysaccharide gets much attention towards the preparation of drug delivery systems because of their exceptional

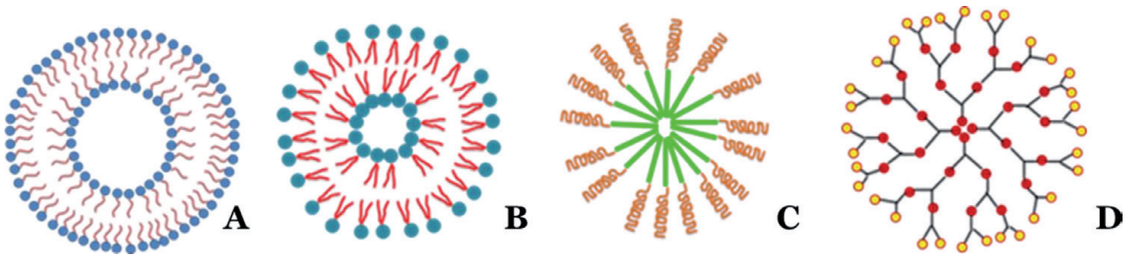

Figure 1.
(A) Niosome, (B) liposome, (C) polymeric micelles and (D) dendrimers.

hydrogel forming ability [20]. These are derived from plants, sea weeds shells of crustaceans and microorganisms [21].

Niosomes are one of the excellent drug carriers, composed of non-ionic surface in addition to cholesterol or its derivatives. Niosomes can overcome the disadvantages of the liposomes [22, 23]. Liposomes firstly proposed by Alec Bangham called Bangosomes in 1965, the first generation liposomes the entrapped drugs are leaked out because of the membranes are not much stronger. In the case of niosomes, the hydrophilic and hydrophobic parts influence the entrapment of drug molecules, where as in the liposomes, lipophilic domain influences in it [5, 24, 25]. Non-ionic surfactants Tween, Brij, Span, etc. are mostly used for the noisome preparation. Hydrophilic-lipophilic balance (HLB) is a dimensionless parameter which can direct the entrapment efficiency for the drug and controlled release [26]. These values are varies between the non-ionic surfactant nature [27–30]. Surfactants with a HLB number between 3 and 8 are compatible with preparation bilayer surfaces and refer to water-in-oil (W/O) emulsifier [2, 31]. The additives in the niosomes include cholesterol and charge inducer. The cholesterol reduces the HLB value and charge inducer like dicetyl phosphate (DCP), produce surface charge leads to the stabilization of the bilayer [32, 33]. Applications of niosomes mainly related to the systemic delivery of hydrophobic drug molecules. More clearly niosome is used to improve the stability and physical properties, controlled release of drug molecules and for targeting and retention of drug in blood circulation. Niosomes offer various advantages over other drug delivery devices and have found applicability in pharmaceutical field. Niosomes are exceptionally powerful drug delivery instruments for construction/focusing of different remedially dynamic moieties and the responsibility lies on future researchers to viably outfit its potential in assorted application zones to support humanity [34].

Hydrophilic interpenetrating polymeric networks like hydrogels represent excellent carrier for hydrophobic drug encapsulation. In comparison to hydrophilic nano systems widely used in drug delivery, hydrogels show better swelling property and biocompatibility [35, 36]. Hydrogels derived from natural polymers like polysaccharides, alginates, gelatin polysaccharide conjugates exhibit a gradual change in swelling properties upon variation in temperature, pH, and ionic strength. 3D polymeric network derived from hydrogels represent flexible tissue-like material for efficient delivery of hydrophobic drugs [37] (**Figure 1**).

2. Natural polysaccharides

The use of nanotechnology for the delivery of therapeutic agents was put forward by Paul Enrich [6], the proponent of drug loaded magic bullets. Biomedical field uses polysaccharides for the last one half of the century due to its remarkable applications [38]. Nature is an abundant source for natural polysaccharides made its use widely in this field. Most of the drugs used for different types of diseases

cause dangerous side effects. These problems can be reduced by the use of natural biocompatible polymer/polysaccharides as carriers for the drug. Seaweeds provide a better source for available polysaccharides such as carrageenan (iota, kappa, and lambda), alginate, and agar [39].

Monosaccharides combine to form polysaccharides with number of reactive groups that can be easily modified to get various types of polysaccharides. Typical sources of polysaccharide include algae, microorganisms, animals, etc. The positive features of polysaccharides such as higher molecular weight, changing chemical composition and large number of reactive groups gave diversity in its function. Adaptable chemical composition delivers its variety in structure and also in property. Medicinal field exploits these best properties of polysaccharides for the betterment of drug delivery. Drug carriers from polysaccharides make sustainable, cost effective and biodegradable drug carriers. Modification of polysaccharide chains opens a way to target drug to the affected site, altering the solubility, biocompatibility, moisture resistant and particularly reduce the severe side effects from therapeutic agents. Polysaccharides can perform bio adhesion through hydrophilic groups such as carboxyl, hydroxyl and amino groups by making non covalent interaction with biological tissues that elongates residing time. By this the absorption of drug at the particular area can be easily made. In this chapter we discuss niosomal emulsions of alginate, κ-carrageenan and gelatin as drug carrier [38, 40, 41].

Alginates are naturally derived polysaccharide block copolymers composed of β-D-mannuronic acid monomers (M-blocks), α-L-guluronic acids (G-blocks) and regions of interspersed M and G units [38, 42]. Divalent cations such as Ca^{2+} can induce hydrogel formation by polysaccharide chain association in alginates [20]. Carrageenans represent a family of sulphated linear polysaccharides consisting of (1 → 3)-linked β-galactose and (1 → 4)-linked α-D-galactose units mainly extracted from certain red seaweeds of Rhodophyceae family particularly from *Chondrus crispus*, *Eucheuma gigartina*, *Stellate iridaea*, *Hypnea*, *Solieria agardhiella and Sarconema*, which are variously substituted and modified to the 3,6-anhydro derivative, depending on the nature of origin and extraction conditions [43]. Three main types of carrageenans are known: kappa-*κ*, lambda-*λ* and iota-*i*, depending on the number and the position of the ionic sulphate groups. The presence of a suitable cation, typically potassium, or calcium is an absolute requirement for gelation of the carrageenans, especially kappa [44]. Gelatin is a protein derived from denatured collagen that contains high levels of hydroxyproline, proline and glycine. It is useful as a thermally reversible gelling agent for encapsulation [45].

However, we go through the development and characterization of alginate/*κ*-carrageenan and alginate/gelatin hydrogel beads and its application in encapsulation of a model hydrophobic potential drug, curcumin. Hydrogel beads were developed via ionotropic gelation. Alginate/*κ*-carrageenan beads were cross-linked with $CaCl_2$-KCl salt solution and alginate/gelatin beads with $CaCl_2$ solution. Drug release behaviour of alginate/*κ*-carrageenan and alginate/gelatin hydrogel beads was compared employing curcumin, which is a natural polyphenolic compound isolated from rhizome of turmeric (*Curcuma longa*) as a model drug [46]. Curcumin is widely known to possess antioxidant [47], antitumor [48], and anti-inflammatory [49] activity. Swelling of the beads and in vitro release of curcumin were studied in phosphate buffered saline (PBS, pH 7.4).

3. Materials and methods

Sodium alginate (RM 7494), κ-carrageenan (22,048, Sigma Aldrich), Gelatin, phosphate buffer saline pH 7.4 (PBS, Sigma Aldrich) and curcumin (C1386, Sigma

Materials	Weight ratio (w/w)	Polymeric concentrations (%)	Salt type	Salt concentration (%) (w/v)
Alginate/κ-carrageenan	50:50	1	$CaCl_2$·KCl	2
	70:30	1.5		
	80:20	2		
		2.5		
Alginate/gelatin	50:50	1	$CaCl_2$	2
	70:30	1.5		
	80:20	2		
		2.5		

Table 1.
Weight ratio percentage concentrations of polymeric solutions.

Aldrich) were used without further purification. $CaCl_2$ and KCl were commercial products of analytical grade. Single distilled water (Labsil Water Distiller, Model: OPTI-M4) was used in all experiments.

3.1 Preparation of alginate/κ-carrageenan and alginate/gelatin hydrogel beads and curcumin loading

Alginate, κ-carrageenan and gelatin solutions were prepared separately by dissolving each of the biopolymers in distilled water and heated up at 50°C (for alginate), 60°C (for κ-carrageenan) and 40°C (for gelatin) under constant stirring from 30 min to 1 h until complete dissolution [50]. Ionotropic method was used for the preparation of hydrogel beads. Polysaccharide mixture composed of 50:50, 70:30, 80:20 (weight ratio) with concentrations varying from 1 to 2.5% (given in **Table 1**) were prepared by mixing under constant stirring at 30°C for 30 min. Briefly the hydrogel beads were prepared by dropping the mixture through a plastic syringe (5 ml) into an aqueous salt solutions stirred magnetically. For the preparation of alginate/κ-carrageenan hydrogel beads, the salt solution was composed of 100 ml of 2% (w/v) KCl and 100 ml of 2% (w/v) $CaCl_2$ and for alginate/gelatin hydrogel beads, 200 ml of 2% $CaCl_2$ solution. To complete gelation, beads were maintained in the solution for 30 min then filtered, followed by washing with distilled water and then allowed to dry overnight at 37°C.

For curcumin loading, 10 mg/ml curcumin prepared with ethanol was mixed with each of the alginate/κ-carrageenan and alginate/gelatin mixtures and stirred until complete evaporation of ethanol. Curcumin loaded beads were prepared by dropping the mixture through a 5 ml syringe into a stirred salt solution which was composed of 100 ml of 2% (w/v) KCl and 100 ml of 2% (w/v) $CaCl_2$ in the case of alginate/κ-carrageenan and 200 ml of 2% (w/v) $CaCl_2$ for alginate/gelatin and kept in the solution for 30 min, filtered, washed with distilled water and dried overnight at 37°C.

3.2 Morphological analysis

Scanning electron microscopy (SEM, LEO 1430 V) was used to analyse the morphology of hydrogel beads.

3.3 Swelling behaviour

The swelling degree (SD) was determined gravimetrically as follows: Both the hydrogel beads were immersed in phosphate buffered saline (PBS, pH 7.4) at 37°

C. The swelled samples were taken from the PBS at selected time intervals of 1, 2, 3, 4, and 10 up to 24 h, wiped with tissue paper, weighed and placed again in PBS. The SD, in percentage, was calculated using Eq. (1)

$$SD = \frac{Ws - Wd}{Wd} * 100\ (\%) \quad (1)$$

where Ws and Wd are the weights of swollen and dry beads, respectively.

3.4 Release study of curcumin

The cumulative release of curcumin from hydrogel beads was carried out through incubating samples while shaking at 100 rpm in 20 ml of buffer solution (PBS) at pH 7.4 (1, 2, 3, 4, 10 up to 24 h incubation) at 37°C. After incubation, 3 ml sample was taken out from the buffer solution and analysed by UV-Vis spectrophotometer (Lambda 25-PerkinElmer UV-vis spectrophotometer) at λ_{max} of 430 nm. The withdrawn volume of the sample was replaced with equal volume of fresh buffer solution to keep the volume of release fluid constant. The percentage drug release was calculated by using the following formula,

$$\text{Percentage drug release} = (\text{Amount of drug released}/\text{Amount of drug loaded}) * 100 \quad (2)$$

4. Results and discussion

4.1 Morphological analysis of hydrogel beads

Image of the swollen beads is shown in **Figures 2** and **3**. Beads obtained has diameter of 0.50 cm. Morphological features of curcumin loaded and unloaded beads were analysed through SEM images shown in **Figure 4**.

The morphological features of curcumin loaded and unloaded beads were analysed by recording the SEM images as shown in **Figure 4**.

Hydrogel beads containing alginate were smoother and more spherical compared to the beads consisting of alginate and carrageenan. This effect can be attributed to the higher cross linking ability of alginate relative to carrageenan. This cross linking takes place instantaneously upon dropping sodium alginate into the cross linking solution (consisting of Ca^{2+}) leading to geometrically stable particles.

In the case of formulations containing carrageenan, the beads were less spherical, having rough and folded surfaces. This behaviour could be attributed to the low concentration of K^+ in the hardening solution, and also to the reduced cross-linking efficiency of carrageenan as compared to alginate, which led to the production of non-spherical and less physically stable beads. The alginate-gelatin hydrogel beads show a smooth and homogeneous morphology, suggesting component miscibility and blend homogeny.

4.2 Swelling degree

4.2.1 Effect of alginate, κ-carrageenan and gelatin ratios on swelling

In the case of alginate-gelatin and alginate/κ-carrageenan hydrogel beads, the effect of sodium alginate on swelling of the hydrogel beads has been studied by varying its amount in the polymer blend in the range 50–80% (w/w). The results shown in **Figures 5** and **6**, clearly indicates that initially at 50% of alginate

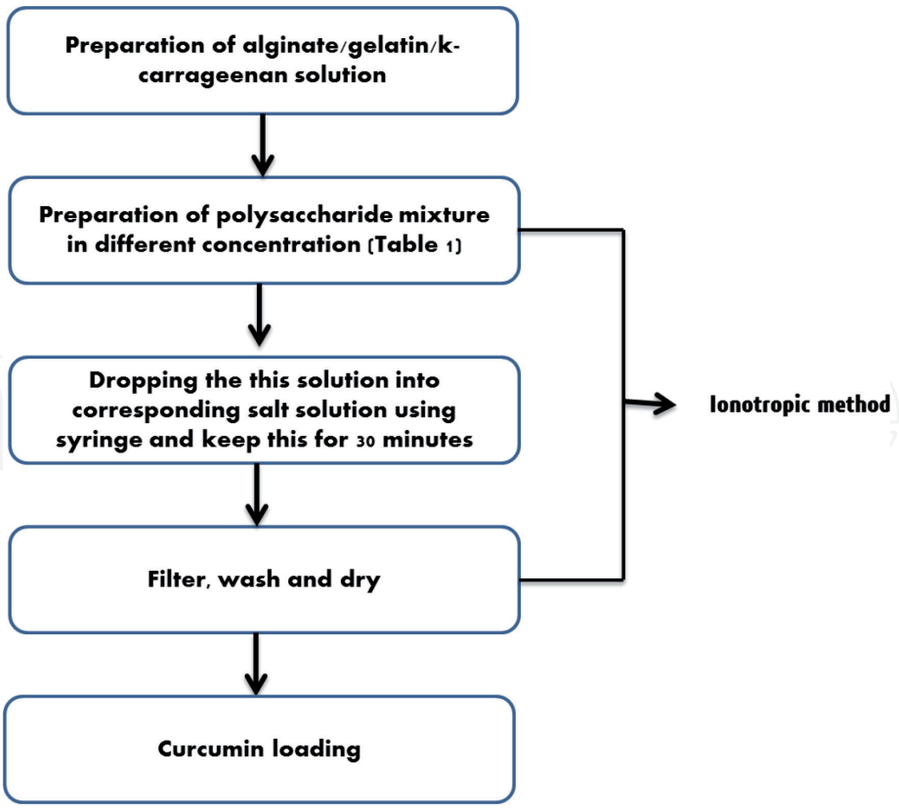

Figure 2.
Preparation of hydrogel beads and drug loading.

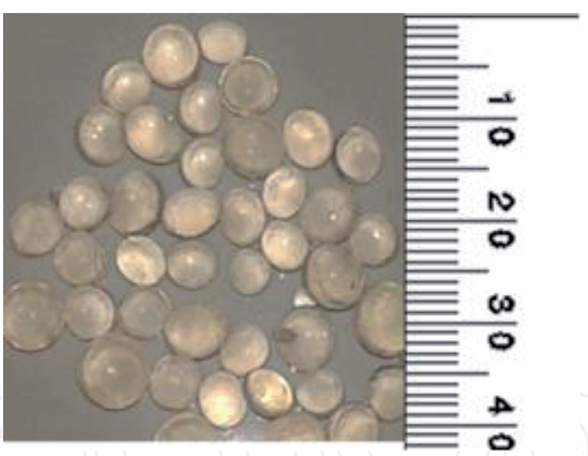

Figure 3.
Image of the swollen beads.

content in the hydrogel beads, the swelling ratio is high, while beyond this amount (70–80%) a fall in swelling degree is observed. The observed initial increase in the swelling degree could be attributed to the fact that since alginate is a linear anionic hydrophilic polymer, its increasing amount in the hydrogel beads cause an increased hydrophilicity of the polymer network with fixed ionic charges and enhanced repulsion among the polymer chains. This leads to greater swelling. However the decrease in swelling degree observed beyond 50% can be attributed to the fact that increase in alginate content results in a compact polymer network. This will form small pore sizes that slow down the diffusion of water molecules into the hydrogel beads and consequently the swelling degree decreases.

The effect of gelatin on the swelling degree of the alginate/gelatin hydrogel beads has been studied by varying the amount of gelatin in the polymer blend in the range 20–50% (w/w). **Figure 5** clearly indicates that, an increase in swelling

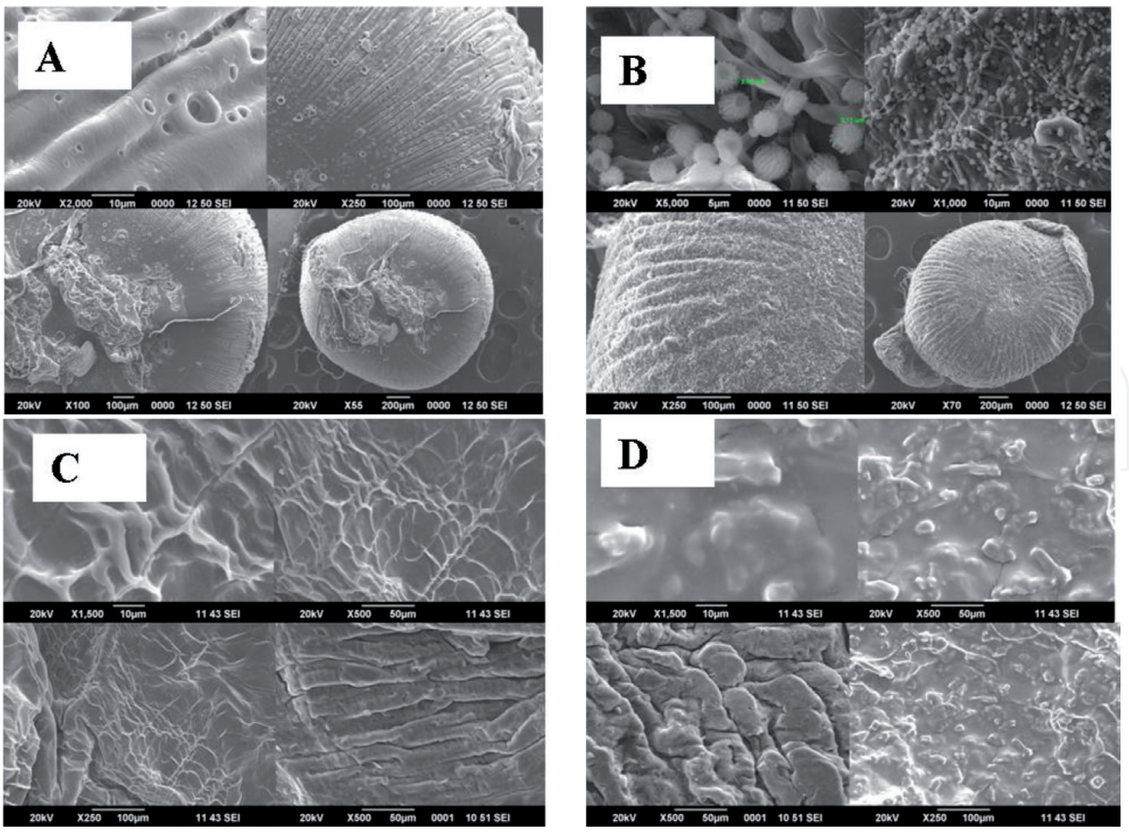

Figure 4.
*SEM micrographs of unloaded (A) alginate/κ-*Car*, (B) alginate/gelatin hydrogel beads and curcumin loaded, (C) alginate/κ-*Car*, (D) alginate/gelatin hydrogel beads.*

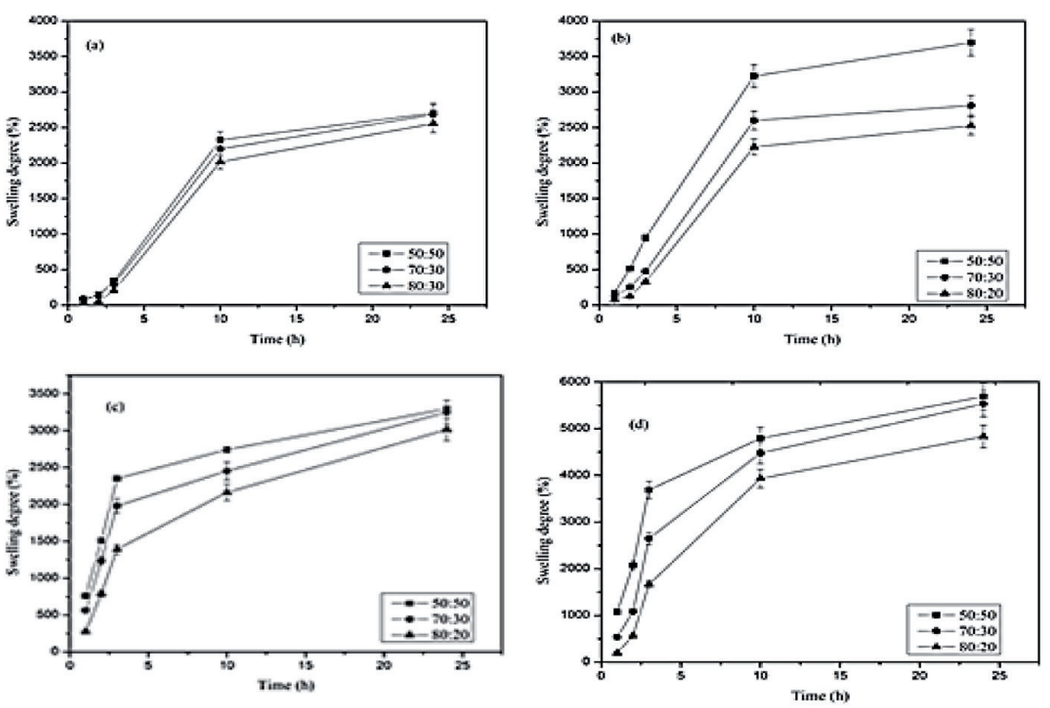

Figure 5.
Effect of alginate/gelatin weight ratio's on the swelling of the alginate/gelatin composite hydrogel beads at different polymer concentrations (a) 1%, (b) 1.5%, (c) 2%, (d) 2.5%.

degree is observed with increase in gelatin content. An increase in the amount of gelatin in hydrogel beads enhances the hydrophilicity of polymer network and leads to higher swelling degree. The effect of κ-carrageenan on swelling degree of

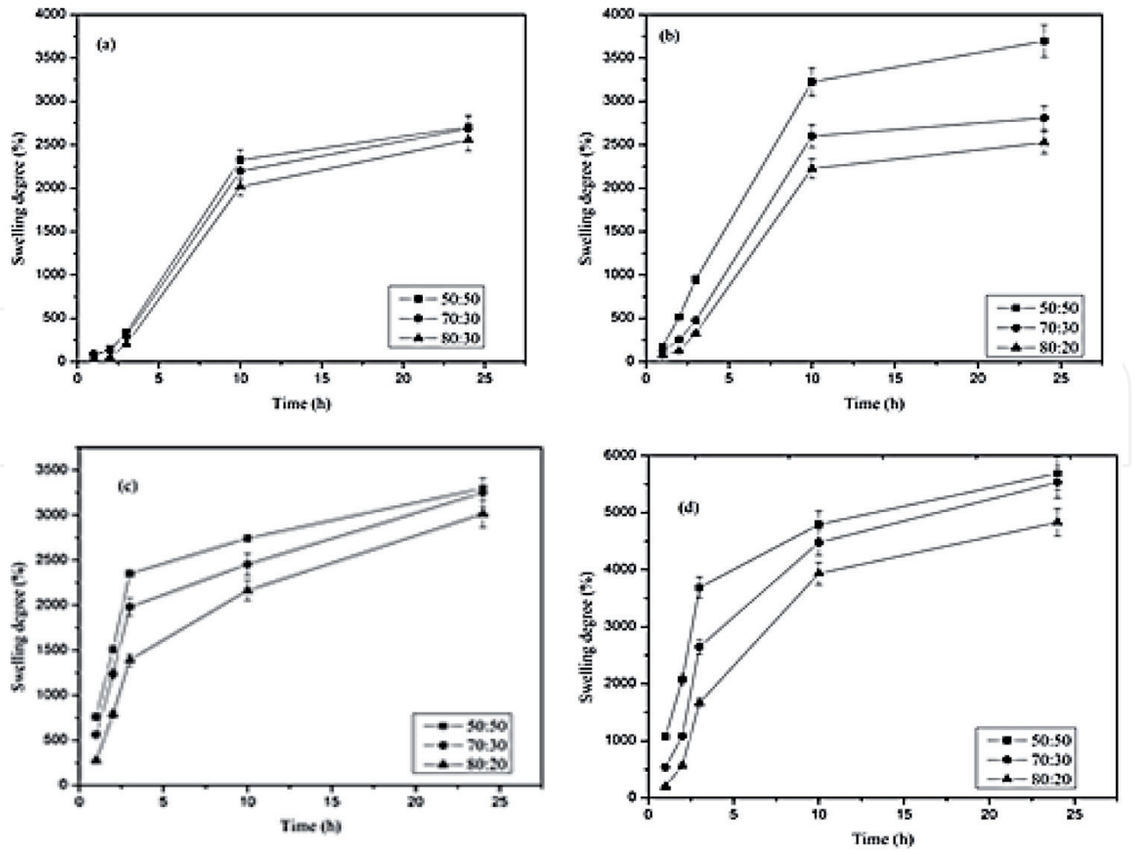

Figure 6.
Effect of alginate/κ-carrageenan weight ratio's on the swelling of the alginate/κ-carrageenan hydrogel beads with polymer concentrations (a) 1%, (b) 1.5%, (c) 2%, (d) 2.5%.

alginate/κ-carrageenan hydrogel beads has been studied by varying the amount of κ-carrageenan in the range 20–50% (w/w). The results showed in **Figure 6** shows the swelling degree of alginate/κ-carrageenan hydrogel beads increases with increase in carrageenan content. With increase in carrageenan content, the beads become less compact in structure and large pores and surface cavities were observed in the hydrogel beads. The alginate/κ-carrageenan (50:50) hydrogel beads show a higher degree of swelling than the alginate/gelatin (50:50) hydrogel beads. Swelling behaviour of hydrogel beads were examined by varying polymer concentration (1, 1.5, 2, 2.5%). As shown in **Figures 5** and **6**, increase in polymer concentration leads to enhancement in the swelling degree of both hydrogel beads. In both cases, hydrogel beads with polymer concentration 2.5% show the highest swelling. Comparison of the swelling degree of alginate/κ-carrageenan hydrogel beads with alginate/gelatin hydrogel beads shows that the former one with polymer concentration 2.5% and weight ratio 50:50 has higher degree of swelling than latter alginate/gelatin hydrogel beads with polymer concentration 2.5% and weight ratio 50:50.

4.3 Curcumin release study

4.3.1 Effect of alginate on curcumin release

Curcumin release studies were carried out in PBS (pH 7.4). Upon variation of sodium alginate ratio in the range 50–80% (w/w) in the polymer blend, the amount of curcumin released was found to diminish with time. This observation could be explained on the basis of swelling behaviour of hydrogel beads as discussed earlier. Moreover, by increasing the amount of alginate content, volume fraction of alginate

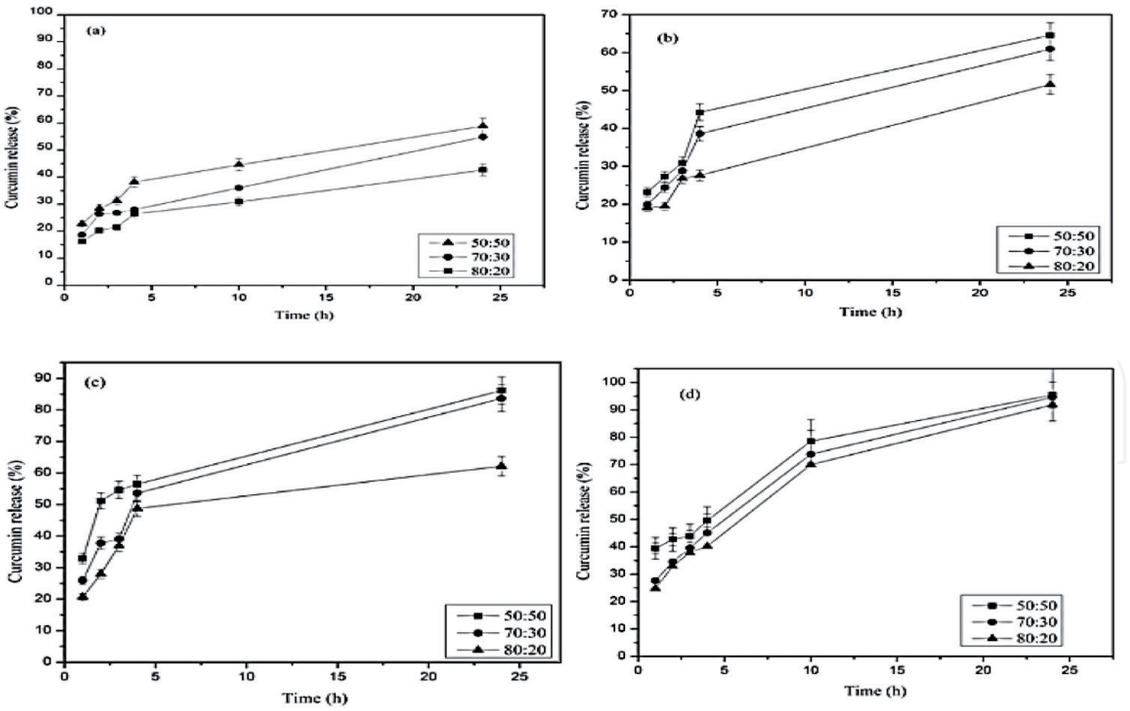

Figure 7.
Effect of alginate/gelatin weight ratio's on cumulative release of curcumin from the hydrogel beads with polymer concentrations (a) 1%, (b) 1.5%, (c) 2%, (d) 2.5%.

in the hydrogel beads increases leading to the fact that curcumin molecules has to travel a long path in order to diffuse out through the swollen beads because of its characteristic size. This causes a slow release of curcumin from both the hydrogel beads.

4.3.2 Effect of κ-Car and gelatin on curcumin release

κ-Car content on drug release has been studied by varying *κ-Car* in the range 20–50% (w/w). **Figure 4** clearly depicts that the amount of released curcumin increases with increasing *κ-Car* content. With increase in *κ-Car* content in hydrogel beads, swelling increases resulting in enhanced drug release. Alginate/*κ-Car* beads with alginate/*κ-Car* weight ratio 50:50 showed highest curcumin release percentage (95.45%), owing to the fact that the matrices were built on weak entanglements driven by the presence of *κ-Car*.

4.3.3 Effect of gelatin on curcumin release

In the case of alginate/gelatin hydrogel beads, influence of gelatin content on curcumin release was studied by varying its amount in the range 20–50% (w/w) (**Figure 7**). Drug release investigations suggests that with increasing gelatin content, release of curcumin from alginate/gelatin hydrogel beads increases and the observed curcumin release is due to the larger swelling. Alginate/gelatin hydrogel beads with 50:50 weight ratios showed 48.24% curcumin release.

4.3.4 Effect of varying percentage composition of κ-Car and gelatin on curcumin release

Drug release from the hydrogel beads was also studied by varying polymer concentration in the range 1–2.5%. In the case of both hydrogel beads, 2.5% is the best

polymer concentration for curcumin release. Curcumin release from alginate/*κ-Car* hydrogel beads shows a higher release percentage than alginate/gelatin hydrogel beads. It can be concluded that higher swelling degree of the alginate/*κ-Car* hydrogel beads leads to greater curcumin release percentage.

5. Conclusions

Present study describes the development and evaluation of natural polymer based hydrogel beads for drug encapsulation. The key role of the carrier was for the dissolution of curcumin in aqueous media. Alginate/*κ-Car* hydrogel beads with 50:50 weight ratio showed highest swelling degree having a higher of curcumin release percentage (95.45%) in PBS (pH 7.4). Observations of morphological analysis show that the amount of carrageenan content has significant content in the pore size of beads. Swelling degree of alginate/gelatin hydrogel beads were lower than compared to the swelling behaviour of alginate/*κ-Car* hydrogel beads. This reveals the role of Car in improving the swelling as well as release pattern of curcumin. Results obtained reiterate the increased efficacy of polymer blends with incorporation of *κ-Car* for hydrophobic drug encapsulation. Effective drug release is also established. In fact, the drug release and biological activity of environment friendly hydrogel beads based on natural polymers represent an innovative and adequate alternative for the development of novel therapeutic agents in drug discovery research.

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