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Note

5-Fluorouracil encapsulated alginate beads for the treatment of breast cancer

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Abstract

Alginate beads containing 5-fluorouracil (5-FU) were prepared by the gelation of alginate with calcium cations. Alginate beads loaded with 5-FU were prepared at 1.0 and 2.0% (w/v) polymers. The effect of polymer concentration and the drug loading (1.0, 5.0 and 10%) on the release profile of 5-FU was investigated. As the drug load increased, larger beads were obtained in which the resultant beads contained higher 5-FU content. The encapsulation efficiencies obtained for 5-FU loads of 1.0, 5.0 and 10% (w/v) were 3.5, 7.4 and 10%, respectively. Scanning electron microscopy (SEM) and particle size analysis revealed differences between the formulations as to their appearance and size distribution. The amount of 5-FU released from the alginate beads increased with decreasing alginate concentrations.

Keywords: 5-Fluorouracil; Alginate beads; Biodegradable polymers; Breast cancer

Polysaccharides such as alginates have been used extensively in the food, cosmetics, pharmaceutical and biomedical industries for their gel forming properties in the presence of multivalent cations. Alginate, a naturally occurring copolymer of guluronic acid and manuronic acid, is widely used in pharmaceutical applications (Pepperman et al., 1991; Sugawara et al., 1994; Aslani and Kennedy, 1996). The simple, mild, aqueous-based gel formation of sodium alginate in the presence of divalent cations such as Ca^{2+} has been used for drug delivery (Takka et al., 1998; Çalış et al., 2001). It has been reported that purified alginate is non-toxic and biodegradable (Torre et al., 1998).

The objective of this study was to increase the payload of 5-fluorouracil (5-FU) in alginate beads and its evaluation in vitro for developing an improved local delivery system for breast cancer treatment. The factors investigated were the physical appearance of the beads, the amount of 5-FU that could be encapsulated and the mean size of the beads produced. The in vitro release of 5-FU from the beads was also evaluated.

The drug 5-FU, was generously donated by Sandoz Pharma, Switzerland. Sodium alginate of

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low viscosity grade (Pronova Biopolymers, Norway), and calcium chloride dihydrate (Merck, Darmstadt, Germany) were used as supplied. All other chemicals were of analytical grade.

Sodium alginate beads were prepared by extruding 1.0 and 2% (w/v) sodium alginate aqueous solution and 5-FU through a 22-gauge needle into 100 mM $CaCl_2$ aqueous solution, and cured for 1 h. The resultant sodium alginate gel beads were washed with distilled water.

Formulation variables of the 5-FU loaded alginate beads are listed in Table 1.

Scanning electron microscopy (SEM) evaluation of the alginate beads was carried out to examine surface morphology. Beads were mounted on metal stubs with conductive silver paint and the sputtered with a 150 A thick layer of gold in a Bio-Rad apparatus. A SEM (Jeol-SEM ASID-10 Device in 80 kV) was used to evaluate surface characteristics.

Known amounts of beads were accurately weighed and added to 25 ml of pH 7.4 phosphate buffer. The sample was placed in an ultrasonic bath to ensure that all the encapsulated 5-FU was extracted by the pH 7.4 phosphate buffer. The sample was then made up to 10 ml using pH 7.4 phosphate buffer. An aliquot sample was removed through a 0.22 μm Millipore filter, and the filtrate assayed at 266 nm using an UV-spectrophotometer (Shimadzu, UV-160A, Japan). Controls consisting of blank beads were also assayed. Each determination was carried out in triplicate.

Particle size distribution of the beads was determined by sieve (Endocott Ltd., England) analysis procedure.

Release of 5-FU from alginate beads was performed by using a bath-shaker. Weighed amount of 5-FU loaded samples were put into a glass vessel containing 25 ml of phosphate buffer solution (pH 7.4). The glass vessel was then immersed into a waterbath. Temperature of the dissolution vessel was maintained at 37 ± 0.5 °C. At scheduled time intervals, 1 ml of sample was removed from the vessel and the amount of 5-FU was determined by spectrophotometer (Shimadzu UV 160A, Japan) at 266 nm.

Photographs of beads taken showed that the beads were spherical and had rough surface characteristics (Fig. 1). As the 5-FU load increased from 1 to 10% (w/v) with respect to the total dry weight of alginate, the droplets of beads increased in size. Irregularly shaped small beads were observed when lower drug loads of less than 5% (w/v) were used. As the drug-load was increased, larger beads were obtained, in which the resultant beads contained higher 5-FU content. When less 5-FU was introduced, the dispersion of the 5-FU into gels by the stirrer was more effective, therefore the 5-FU droplets were smaller. However, as more 5-FU was introduced, the dispersive effect of the stirrer became less efficient and as a result larger droplets were obtained.

Quantitatively, there was an increase in the encapsulation efficiency with an increase in 5-FU load. The rate of increase levelled off at 10% (w/v) 5-FU load. The maximum encapsulation effi-

Table 1
Formulation variables of the 5-FU loaded alginate beads

Formulation code	Formulation variables	
	Concentration of alginate (%)	Drug loading (%)
A	1	1.0
B	1	5.0
C	1	10.0
D	2	1.0
E	2	5.0
F	2	10.0

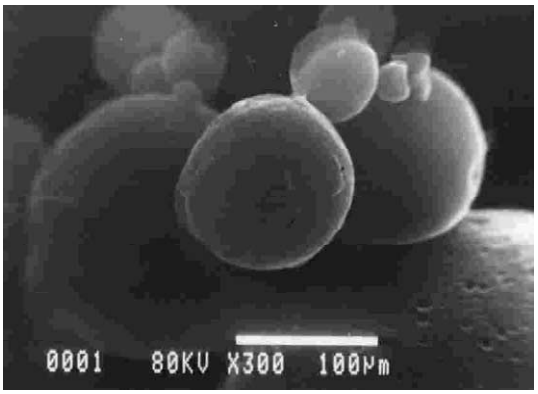

Fig. 1. SEM of 5-FU loaded beads (B coded formulation).

Table 2
Properties of 5-FU loaded alginate bead formulations

Formulation code	The mean particle size (mm ± GSD)	Encapsulation efficiency (%)	$T_{50\%}$ (h)
A	1.2 ± 1.5	3.5 ± 1.3	1.2
B	1.1 ± 1.7	7.4 ± 1.5	1.4
C	1.4 ± 0.5	10 ± 2.5	1.7
D	1.9 ± 0.5	5.0 ± 1.7	2.1
E	2.1 ± 1.1	8.4 ± 2.4	2.4
F	2.3 ± 1.4	11.4 ± 3.2	2.7

($n = 6$; $x \pm$ S.E.M.).

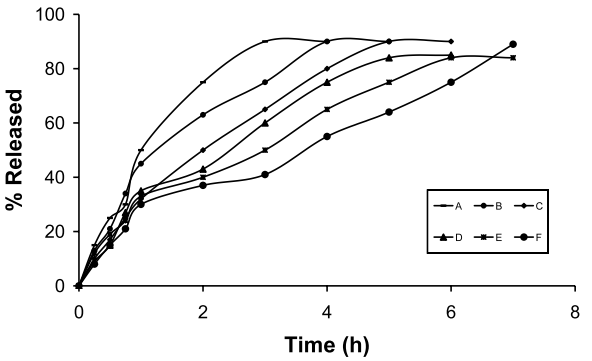

Fig. 2. In vitro release profile of 5-FU loaded alginate beads.

ciency obtainable was 10%. The encapsulation efficiencies obtained for 5-FU loads of 1.0, 5.0 and 10% (w/v) were 3.5, 7.4 and 10%. The mean size of the beads increased sharply at a high drug load of 10% (w/v). At 10% (w/v) 5-FU-load, the size distribution indicating larger mean sizes of 1.4 ± 0.5 mm (Table 2).

The amount of 5-FU released from alginate beads increased with decreasing alginate concentrations. For this reason, the result of in vitro release study showed that formulations A, B, C prepared with 1% (w/v) alginate released the drug faster than formulations D, E, F prepared with 2% (w/v) alginate. The results of in vitro release studies also exhibited that F coded formulation released the drug slower than the other formulations (Fig. 2).

As 5-FU load increased to 10% (w/v), the efficiency of agitation decreased considerably, and this resulted in a larger number of 5-FU droplets of a bigger size and, consequently, a greater number of larger beads. The developed formulations can be proposed as a promising system for the treatment of breast cancer.

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