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DISSOLUTION CONTROLLED DRUG RELEASE FROM AGAROSE BEADS

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ABSTRACT

A simple method was used for loading ibuprofen or indomethacin into agarose beads to obtain sustained release. Placebo beads were prepared by a dropwise addition of a hot aqueous agarose solution into a beaker of chilled mineral oil and water. Prior to loading, the aqueous component in the beads was replaced by repeated soakings in ethanol. Loading was accomplished at room temperature using ethanolic drug solutions. Upon drying, the beads shrank to about a third of their original size. The surface morphology of dried placebo and loaded beads was studied using electron microscopy. The release time at 37°C and pH 7.5 increased with drug loading and at 50% loading the release time was 4 hours for indomethacin and 6 hours for ibuprofen. Release of chlorpheniramine from dried and swollen beads was examined to elucidate the release mechanism. From dissolution studies it was concluded that the delay due to swelling is less than 10 minutes, chlorpheniramine release from swollen beads

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was primarily diffusion controlled, and the release mechanism for indomethacin and ibuprofen has three components: *i*) swelling of the beads, *ii*) dissolution of crystallized drug, and *iii*) diffusion of dissolved drug from the beads.

INTRODUCTION

Agarose is prepared from various species of Gelidium and other red algae.[1] It is an alternating copolymer of 3-linked β-D-galactopyranose and 4-linked 3,6-anhydro-α-L-galactopyranose[2] with a molecular weight of approximately 120,000. It is an uncharged polysaccharide having a very low content of sulfate (< 0.30 % w/w) and carboxylate groups. It is characterized by its gelling point (normally 35-45°C for a 1.5% gel). Agarose dissolves as a colloidal sol in water if heated to about 90°C and forms a solid gel upon cooling below its gelling point. Agarose gelation is thermoreversible; the gel remelts on heating to about 90°C. In the gel, the agarose molecules form double helices which are linked together by hydrogen bonding in bundles to form a network. In the bundles 10 to 50 double helices link in parallel aggregates, accounting for the large mesh sizes typical of agarose gels.[3] In gels of low agarose concentration (1% w/v), drug diffusivity can be the same as in water.[4]

Agarose beads of sulfamethizole were prepared by Nakano et al.[5-6] for oral sustained release in humans. The drug was added to a hot gel solution before the beads were formed; candidate drugs, hence, must be adequately heat stable. Previous experiments in our laboratories have shown that agarose gel immersed in an aqueous drug solution would load drug to the same concentration as in the surrounding media and that, conversely, on immersing the loaded gel in water, drug release was complete.

The objective of this investigation was to prepare agarose beads loaded with ibuprofen or indomethacin and study the release characteristics and

release mechanism from such beads. Although the original method[7] employed aqueous drug solutions for loading beads, it was limited to water soluble drugs. Water in the beads can be substituted with a water miscible nontoxic organic solvent by soaking in this solvent.[8] Hence the technique could be extended to drugs with low aqueous solubility but with a higher solubility in other suitable solvents. Using ethanolic drug solutions, beads were loaded with indomethacin or ibuprofen. Although ibuprofen has a higher solubility in ethanol, indomethacin was also considered because of its low normal daily dose (150 mg).

The mechanism of release from dried beads into buffered aqueous media was assumed to have three components: *i*) swelling of the gel beads, *ii*) dissolution of drug, and *iii*) diffusion of dissolved drug out of the beads. To investigate the effect of each of these on the release time, three different experiments were done: a) release studies of the model drugs from dried beads, b) release of a fast dissolving drug from dried beads, and c) diffusion of dissolved drug from swollen beads. For the drug used in experiments b and c, the dissolution time should be so short that any difference in release time between swollen and dried beads could be attributed to the swelling of the agarose beads. For experiment c, the drug solubility should be so high that no loaded drug precipitates in the swollen beads. For this purpose we chose chlorpheniramine, a comparable molecular weight drug which is highly water soluble as its maleate salt. The diffusivities in water for the three drugs used in this study are so close that the use of this drug in the diffusion experiment is justified.

MATERIALS

Agarose (type V), chlorpheniramine maleate and indomethacin were purchased from Sigma Chemical Company (St. Louis, MO). Ibuprofen was a gift from Sandoz (Lincoln, NE).

METHODS

Beads were prepared by dropwise addition of a hot agarose (4% w/v, 50 to 60°C) solution from the tip of a needleless syringe into a one liter beaker containing chilled mineral oil and water. (If the hot gel solution was simply dripped into water, the drops spread and coalesced on the surface, and no beads were formed.) When the drops passed the chilled oil phase, the gel had set and the beads were collected from the water phase. Prior to drug loading, the beads were soaked repeatedly in ethanol to substitute ethanol for the water. The beads were loaded by submersing them in an ethanolic drug solution and were dried at room temperature.

The surface morphology of dried beads was studied using electron microscopy. All samples were sputter coated with 20 nm of gold prior to observation. Micrographs were obtained using a JEOL JSM-820 Scanning Electron Microscope equipped with a digital imaging system. Observations were made at 5 kV accelerating voltage and a working distance of 35 to 36 mm. Magnifications and reference bars are shown in the individual micrographs.

The theoretical loading was calculated using equation 1, assuming complete solvent evaporation on drying of the beads.

$$Loading\ (\%) = \frac{Drug\ concentration * 100\ \%}{Drug\ concentration + Gel\ concentration} \qquad (1)$$

The actual loading was determined from the total amount of drug released from weighed beads in 0.2 M phosphate buffer (pH 7.5 and 37°C). The release was monitored using a Hewlett Packard 8451A diode array spectrophotometer (ibuprofen at 264 nm and indomethacin at 284 nm) equipped with a flow-through sample cell.

For the swelling and diffusion experiments, b and c, evenly sized swollen beads from the same batch were chosen under a magnifying glass.

The beads were loaded by submersion in a 20 grams/liter aqueous chlorpheniramine maleate solution. The beads for the swelling experiment were dried at room temperature. Chlorpheniramine's diffusion from the swollen beads was measured in duplicate by placing 30 to 50 loaded beads into the phosphate buffer (37°C), and analyzing the release by UV-spectrophotometry at 264 nm. From the release data, diffusion coefficients were calculated for each point in the two intervals that are valid for equations 2a and 2b, describing diffusion from a spherical system.[9-10]

$$\frac{C_t}{C_\infty} = 6\left(\frac{Dt}{\pi r^2}\right)^{\frac{1}{2}} - 3\frac{Dt}{r^2} \qquad for \quad \frac{C_t}{C_\infty} \leq 0.4 \qquad (2a)$$

$$\frac{C_t}{C_\infty} = 1 - \frac{6}{\pi^2}\exp\left(\frac{-\pi^2 Dt}{r^2}\right) \qquad for \quad \frac{C_t}{C_\infty} \geq 0.6 \qquad (2b)$$

where C_t/C_∞ is the drug fraction released, D is the diffusion coefficient and r is the average radius of the beads. Data were analyzed using a customized program written in BASIC for an IBM-compatible personal computer.

RESULTS AND DISCUSSION

Prepared placebo beads were spherical and transparent with an average diameter of 4.5 ($\pm$0.5) mm. When soaked and loaded in ethanol, the beads retained their size but appeared softer. When dried, placebo beads shrank to about a third of their original size, but for drug loaded beads less shrinkage was observed and the bead size increased with higher loading. The actual loading with indomethacin is very near the theoretical value (Table 1). Ibuprofen has a much higher solubility in ethanol than indomethacin, and

TABLE 1

Data for Dried Agarose Beads Loaded from Ethanolic Drug Solutions

Drug	Loading solution (g/100ml)	Average size (mm)	Weight of 100 beads (g)	Loading (%) Theory	Loading (%) Actual	Release time (hrs)
Placebo	-	1.2	0.156	-	-	-
Indomethacin	4	2.0	0.400	50	50	4
	0.4	1.3	0.173	10	9	1
Ibuprofen	30	2.0	0.325	88	47	6
	10	1.8	0.273	71	36	4

higher loading concentrations could be used with this drug. On drying at room temperature, however, much of it migrated to the surface, and deposited as a soft shell that easily came off on handling. This phenomenon accounted for the lower actual loading of ibuprofen. For both drugs, the release time increased with higher drug loading, presumably due to formation of larger drug crystals taking longer to dissolve in the beads (Table 1 and Figures 1 and 2).

Electron micrographs for the five types of beads in Table 1 are presented in Figures 3 - 7. Placebo beads showed a relatively smooth surface, but for loaded beads surface roughness was seen to increase with drug content, possibly resulting from crystallites deposited at or under the surface.

Release profiles for chlorpheniramine from swollen and dried beads are shown in Figure 8 where also the release of indomethacin (9% loading) is given, indicating that there are no obvious burst effects. This indicates that

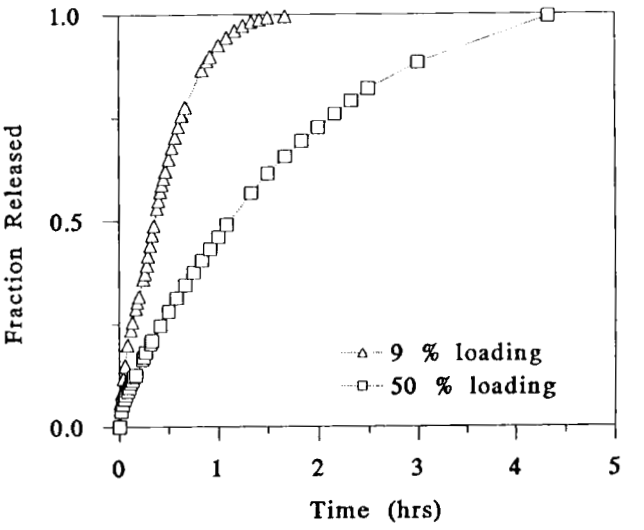


FIGURE 1
Release profiles for indomethacin into pH 7.5 phosphate buffer.

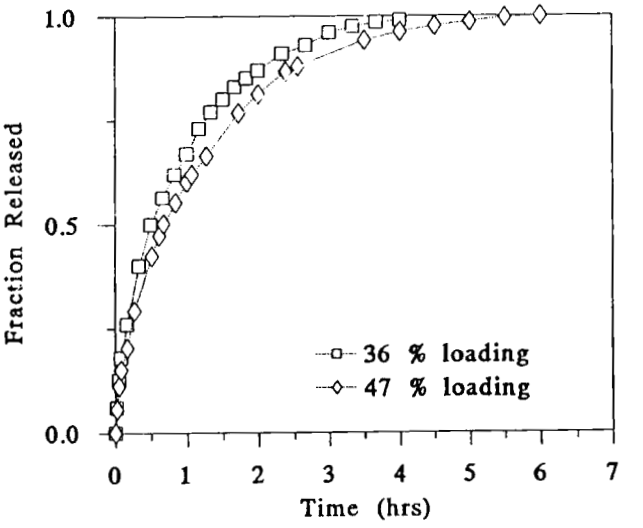


FIGURE 2
Release profiles for ibuprofen into pH 7.5 phosphate buffer.

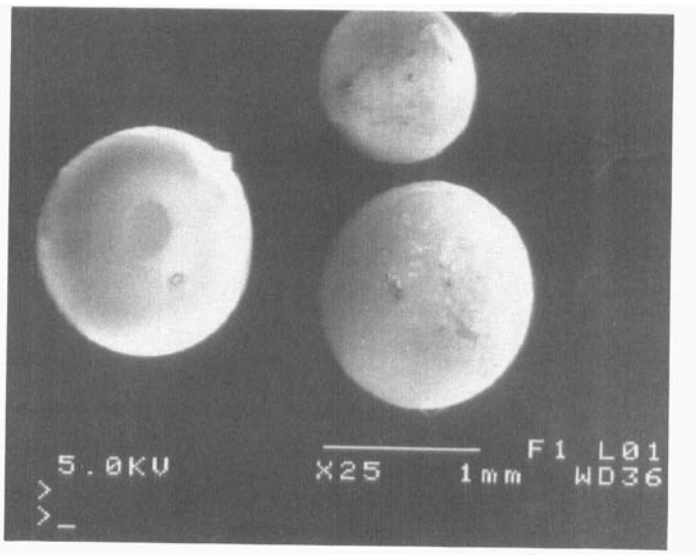


FIGURE 3
Electron micrograph of placebo beads. Diameter calculated from micrograph: 1.0 and 1.4 mm.

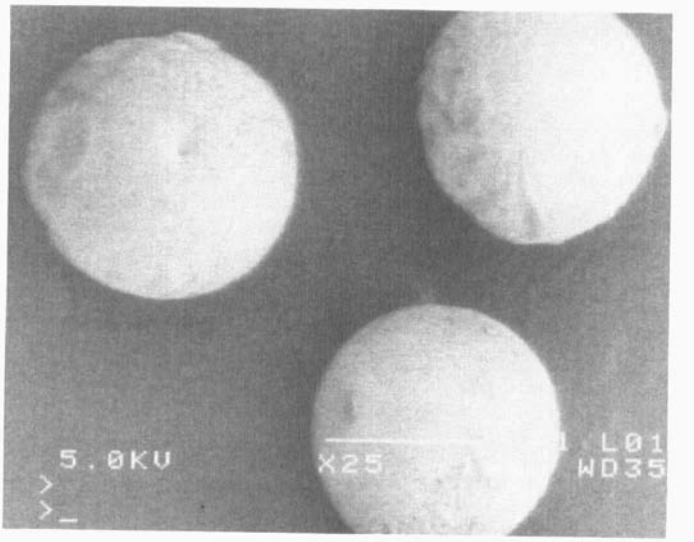


FIGURE 4
Electron micrograph of beads loaded with indomethacin (9 %). Diameter calculated from micrograph: 1.5 mm.

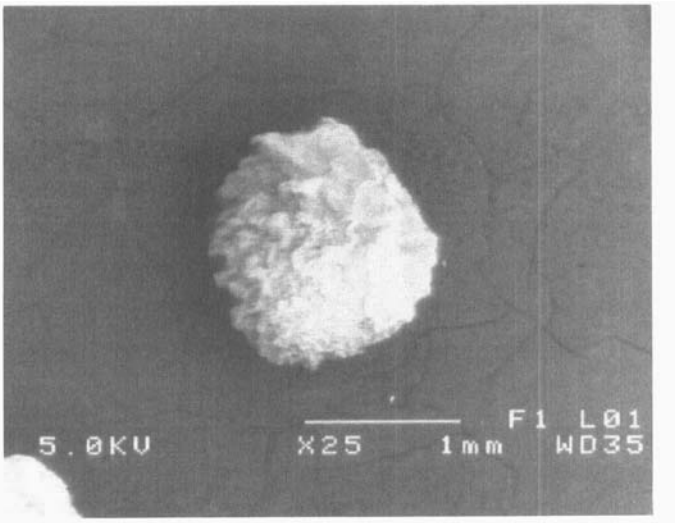


FIGURE 5
Electron micrograph of bead loaded with indomethacin (50 %). Diameter calculated from micrograph: 2.0 mm.

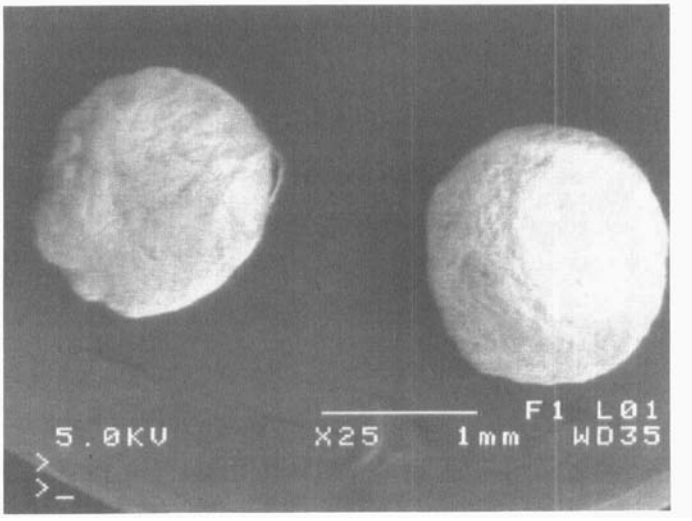


FIGURE 6
Electron micrograph of beads loaded with ibuprofen (36 %). Diameter calculated from micrograph: 1.6 mm.

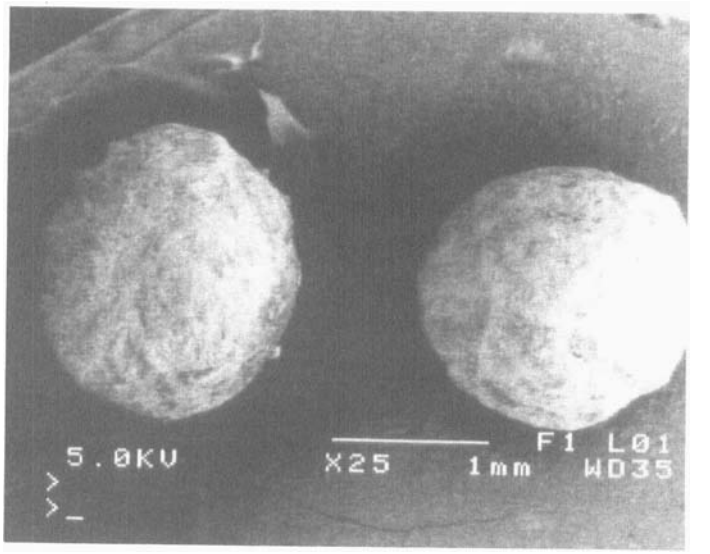
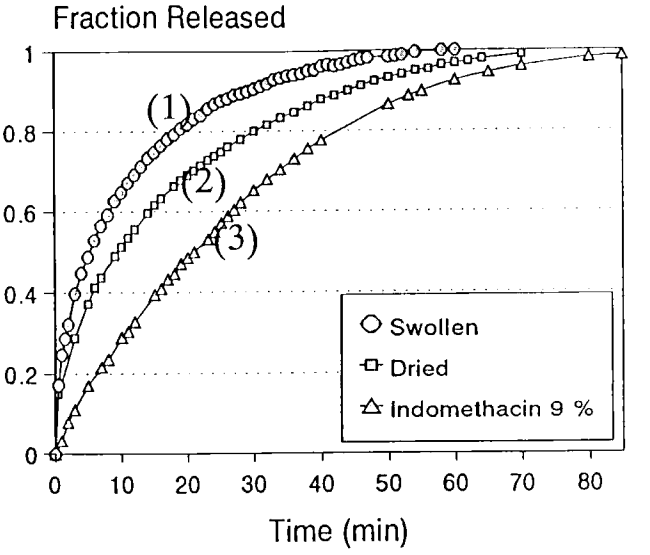
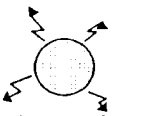


FIGURE 7
Electron micrograph of beads loaded with ibuprofen (47 %). Diameter calculated from micrograph: 1.8 mm.

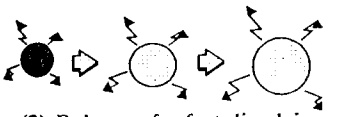
the drug crystallites seen in the micrographs are deposited under the bead surface. In Figure 9, diffusion coefficients calculated using equations 2a and 2b are presented. An average value of 648 ($\pm$14) x 10^{-12} m^2/s was estimated for the diffusivity of chlorpheniramine in a 4% (w/v) agarose gel. The consistency of the diffusion coefficient over the release time indicates an even distribution of drug in the beads.

On swelling, the beads returned to the size of fresh placebo beads. The difference in release of a fast dissolving drug from swollen and dried beads is illustrated in Figure 8. The release from the dried beads was slightly slower, and, since the drug itself dissolves very fast, the delay ($\leq$ 10 minutes) was attributed to the time required for the agarose bead to swell. For ibuprofen and indomethacin, however, the observed release times are substantially longer than justified by bead swelling and diffusion. This was

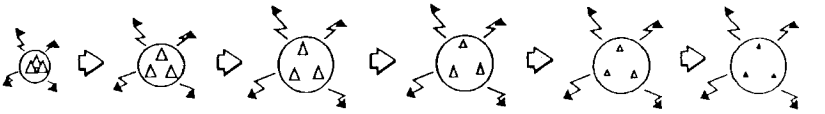




(1) Diffusion of dissolved drug (chlorpheniramine maleate) from swollen beads.



(2) Release of a fast dissolving drug (chlorpheniramine maleate) from dried beads.



(3) Release of a low solubility drug (indomethacin, 9 %) from dried beads.

FIGURE 8

Release profiles for chlorpheniramine from swollen and dried agarose beads and release of indomethacin (9 % loading) into pH 7.5 phosphate buffer.

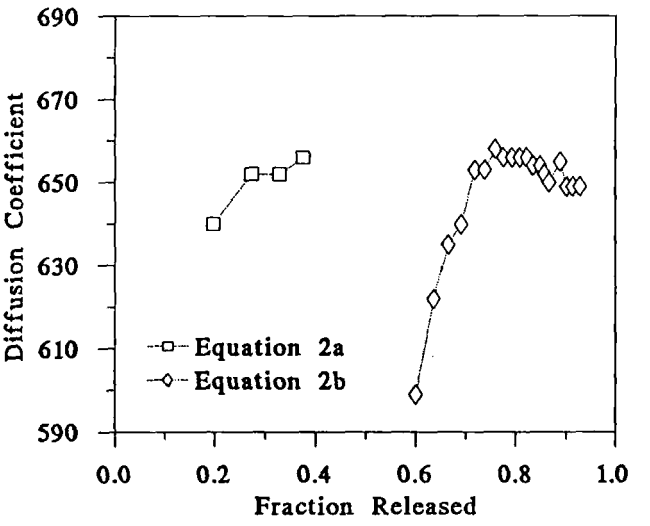


FIGURE 9

Diffusion coefficients, $D/(10^{-12}\ m^2/s)$, for chlorpheniramine in swollen 4% (w/v) agarose beads.

attributed to slow dissolution of crystalline drug in the beads. The swelling rate of loaded agarose beads, however, may also be affected by the aqueous solubility of the drug.

The crystals of the non-steroidal anti-inflammatory drugs, presumed to cause stomach irritation, are contained inside the beads until they are dissolved, and stomach protection could be obtained. The method presented allows relatively high loadings with a slow and complete release and is beneficial for heat sensitive drugs.

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