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Heterocyclic methacrylate-based drug release polymer system

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A heterocyclic methacrylate polymer system, developed originally as a low shrinkage polymer system, has been investigated as a drug release polymer and as a biomaterial for encouraging bone or cartilage regeneration. The system is based on poly(ethyl methacrylate) polymer powder mixed with tetrahydrofurfuryl methacrylate monomer and polymerized at room temperature (PEM/THFM). Promising results have been obtained with this biomaterial, and hence its water uptake properties were investigated in detail, in order to throw some light on the release processes that are involved *in vivo* and *in vitro*. Water soluble large molecule analogues were incorporated into the system; these additives increased the water uptake of the system. Isobornyl methacrylate was used as a diluent for the monomer to further reduce the water uptake of the system. In all cases the uptake kinetics did not obey simple diffusion theory, the process being very prolonged and complex.

1. Introduction

A heterocyclic methacrylate polymer system (PEM/THFM), had originally been developed for use as hearing aid and temporary crown and bridge materials in dentistry. This system, compared to existing PMMA based materials, exhibited:

(i) a much lower shrinkage [1];
(ii) a low reaction exotherm;
(iii) excellent biological properties [2];
(iv) reasonable mechanical properties [3].

However the system had a high water uptake (up to 34% in two years) [4], which at first sight was thought to be a disadvantage (e.g. water absorption reduces the strength of polymers). In fact the high water uptake of the system transpired to be the key to its success as a drug release polymer, and as a material for encouraging cartilage repair, a use not anticipated.

The release of gentamicin is greatest with the PEM/THFM system compared to the London Hospital Medical College and PMMA bone cements. This led to further investigations of the system as [5, 6]:

(i) A drug delivery polymer for therapeutic agents. These included growth hormone, growth factors, proteins, antibiotics and possibly anti-inflammatory drugs.
(ii) A material for encouraging cartilage repair. The polymer system was implanted into 4.5 mm osteochondral defects in the pattellar groove of the distal femur in rabbits.

The water absorption properties of the system are principally related to the release processes that are involved *in vivo* and *in vitro*. Therefore the water uptake/desorption properties of the material were investigated in detail.

2. Experimental procedures

Samples were prepared as explained in an earlier paper [1] by mixing poly(ethyl methacrylate) (10 g) with tetrahydrofurfuryl methacrylate monomer (6 ml). The (PEM/THFM) system was used as a control. Bovine albumin (protein), acridine orange (dye) and genotropin (growth hormone) were incorporated in the system as water soluble large molecule analogues. A set dose of each additive was mixed with the polymer powder component (10 g) prior to adding the monomer. Isobornyl methacrylate was used as a diluent for the monomer to reduce the water uptake. Water absorption measurements were carried out as explained previously [4]. Subsequently some samples were desorbed after 11 months.

3. Results and discussion

The histology of the reparative tissue in the distal femur of rabbits demonstrates the presence of numerous chondrocyte clones and abundant supportive subchondral bone on top of the polymer (Fig. 1). It is evident from *in vivo* studies that the polymer swells slightly *in situ* in the tissue, thus forming a good bond with the subchondral bone. Also, the biomaterial is well tolerated *in vivo*. Furthermore, the high water uptake property of the system leads to absorption of the surrounding tissue fluid and also permits drugs

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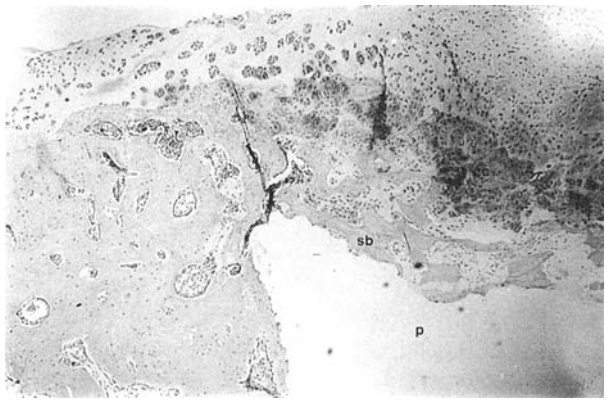

Figure 1 PEM/THFM polymer system for repair of osteochondral defects; p = polymer, cc = chondrocyte clones and sb = subchondral bone.

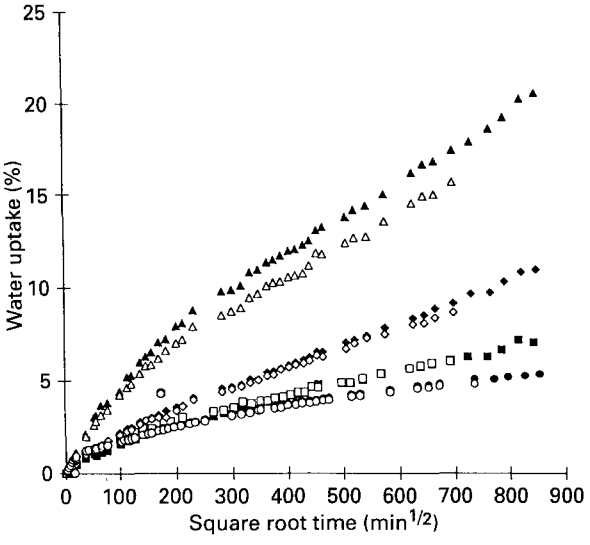

Figure 2 Water absorption data for the PEM/THFM system (control) and with additives (■ control (1); □ control (2); ◆ acridine ○ (1); ◇ acridine ○ (2); ▲ albumin (1); △ albumin (2); ● ISO-B (1); ○ ISO-B (2).

etc. to diffuse out of the material. This latter process encourages the regeneration of bone and cartilage. Inclusion of growth hormone or antibiotics in the system may improve the tissue repair associated with the material and prevent infection, respectively.

The system is a good delivery vehicle for therapeutic agents. The polymer exhibited a dose-dependent release of growth hormone, antibiotic and protein into phosphate buffered saline at 37 °C, when tested using *in vitro* elution studies.

The water uptake results confirm that, with the incorporation of water soluble large molecule analogues, the water uptake of the PEM/THFM system is increased. Isobornyl methacrylate decreases the absorption of water (Fig. 2). In all cases the uptake kinetics did not obey simple diffusion theory. These systems are still taking up water after 20 months, and have not yet equilibrated. The data for the growth hormone incorporated system shows that the material has taken up about 34% water in 22 days, the sample being less than 1 mm thick.

In all the above cases, the reason for the enhanced uptake is not altogether clear. Absorption of water by the water soluble polymers should result in their swelling; but the matrix is a glassy polymer with a modulus of $\sim$ 1.3 GPa. A possible mechanism is the formation of crazes at the sites of the additive particles. It is observed that the specimens become opaque on water uptake, and the opacity remains after desorption; this is consistent with craze formation.

Subsequent desorption of some of the samples showed this process to be very much more rapid than the corresponding sorption process. Also, the plots are linear in the initial region showing the desorption process to be diffusion controlled.

4. Conclusions

The mechanism of uptake is clearly complex, and is under further investigation. However, it has been demonstrated that additives increase the water absorption of the heterocyclic polymer system described. The system has been effective as a drug release polymer as well as a biomaterial for encouraging bone and cartilage repair. The polymer is biocompatible in bone and cartilage but not biodegradable. Further work is aimed to establish whether hydrophilicity is important in the design of polymers for tissue repair.

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