# Synthesis of Biocompatible Nanocomposite Hydrogel as a Local Drug Delivery System

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## ABSTRACT

Nanocomposite biocompatible hydrogels (NCHG) were synthesised as model systems for in situ cured potentially local drug delivery devices for curing periodontal infections. The composite consists of the following components: nanoparticles (NPs), matrix gel, and chlorhexidine (CHX) as antibacterial drug. The NPs were obtained by free radical initiated copolymerization of the monomers, 2-hydroxyethyl methacrylate (HEMA) and polyethyleneglycol dimethacrylate (PEGDMA), in aqueous solution. The same monomers were used to prepare crosslinked matrices by photopolymerization. NCHGs were obtained by mixing NPs, monomers, and drug in an aqueous solution then crosslinked by photopolymerization.

Studies of release kinetics revealed that on average 60% of the loaded drug was released. The most rapid release was observed over a 24 hour period for matrix gels with low crosslinking density. For NCHGs the release period exceeded 48 hours.

***Keywords***: nanocomposite, hydrogel, photopolymerization, chlorhexidine diguconate, local drug delivery

## 1 INTRODUCTION

Hydrogels are three dimensional hydrophilic crosslinked polymer networks, which capable of swelling in water. They have soft and elastic nature, which suggests similarities to natural tissues [1]. Their widespread application is well known, for example in the cosmetic industry as moisturising creams and emollients. Hydrogels have important role in ophthalmology as contact lenses [2], or as a local drug delivery system to treat glaucoma [3]. In dermatology it is used for rehydrating necrotical crusts [4]. Hydrogels are also important in dentistry. For example, PerioChip is a hydrogel, used in periodontology as a drug delivery device for the release of CHX [5]. Because of its efficiency, allowing reduction in drug dosage among other advantages, the application of controlled release systems is growing. Among the large number of monomers that are available, HEMA is well known and is commonly used as a crosslinker, providing a very good biocompatible system. The properties of gels based on this monomer were modified by applying other materials for example different crosslinkers, and recently the use of nanoparticles is exponentially increasing [6-8].

In this paper the preparation of nanocomposite hydrogels (NCHGs) is described. The aim of this work is to study the effect on release kinetics of a drug incorporated into such a nanoparticle-gel matrix system. In addition, the effect on release kinetics of nanoparticle-matrix gel porosity, which is a function of cross-linkers density, will also be determined.

## 2 EXPERIMENTAL SECTION

### 2.1 Materials

2-Hydroxyethyl methacrylate (97%, from Sigma-Aldrich, Steinheim, Germany) was purchased as monomer, poly(ethylene glycol) dimethacrylate (Mn:550, from Sigma-Aldrich, St. Louis, MO) as crosslinker and anthraquinone-2-sulfonic sodium salt (~99%, Fluka AG. Buchs SG) as photoinitiator was applied. Chlorhexidine-di-gluconate, dental application grade (20% solution from Spektrum 3D, Hungary), was obtained as active substance. The composed of nanoparticles were done same monomers as the hydrogels, but the initiator was potassium persulphate (Reanal Co., Budapest, Hungary, 98% purity). Sodium-lauryl sulphate was applied as an emulsifier, and n-buthanole as cotenside were purchased from Spektrum 3D, Hungary. All materials were used as received without further purification.

### 2.2 Measurements

*Mechanical assay*: Hydrogels were investigated with INSTRON 4302 Mechanical Analyser with the full scale load range at 0.1 kN, and the crosshead speed at 2 mm/min.

*Dynamic Light Scattering (DLS) measurement*: Hydrodynamic diameter (HD) of NPs was measured with a BI-200SM Brookhaven Research Laser Light Scattering photometer equipped with a NdYAg solid state laser at an operating wavelength of $\lambda o$=532 nm. Measurements of the average size of NPs were performed at 25°C with an angle

detection of 90° in optically homogeneous quartz cylinder cuvettes.

*Scanning electron microscopy (SEM) analysis*: Samples were imaged using scanning electron microscope (Hitachi S4300 CFE, Tokyo, Japan, with W emitter) at 1.5 and 10 kV. hydrogels were dried at 110 °C for 2 hours and sputter-coated with gold twice.

*Release studies*: The matrix hydrogels and NCHGs containing CHX (cylindrical geometry 9 mm x 4 mm) were prepared for release studies. The main purpose of these experiments was to analyse the release rate of the drug from the loaded matrices, from NCHG1 where CHX was only in the matrix, only in the NPs (NCHG2), and finally in both components (NCHG3). The investigated samples were immersed in distilled water (35 ml) and subjected to continuous magnetic stirring. At regular time intervals, an aliquot of 0.5 ml was removed, and the concentration of CHX was measured by HPLC. (Merck-Hitachi LaChrom instrument using C18 column, and UV detection at 257 nm)

## 2.3 Preparation of HEMA-PEGDMA copolymer and nanoparticle

*Preparation of nanoparticle*: HEMA and PEGDMA monomers were dispersed in deionised water containing sodium lauryl sulphate (SLS), an anionic surfactant. The free radical copolymerization was performed with potassium persulphate initiator at 60 °C under nitrogen atmosphere.

*Synthesis of nanocomposites hydrogels (NCHGs)*: The NCHGs were made as in 50/50 HEMA/PEGDMA feed and 15 wt% NPs were dispersed in the clear, yellowish aqueous solution of monomers and photoinitiator. The prepared NPs were loaded with CHX, and allowed to swell for 48 hours. Then these loaded particles were freeze-dried. The solid, loaded particles were then dissolved in the aqueous solution of monomers and initiator in order to form the NCHGs. The initiation of photopolymerization was performed by Kulzer Palatray CU lamp source supplying blue light with 435 nm wavelength for 25 minutes.

# 3 RESULTS AND DISCUSSION

CHX has been used routinely to treat periodontal disease. However, when applied locally it quickly disperses. By incorporating CHX into a polymer matrix, from which it can be slowly released, it can be expected to be more efficacious.

## 3.1 Preparation of nanoparticles

In this report we describe the formation of NPs with a composition of HEMA/PEGDMA=50/50 mol%. The crosslinking density of the NPs is variable, which may effect the rate of release, however this effect will be examined in a further study. Here the vinyl groups of HEMA were crosslinked with the divinyl monomer of PEGDMA by free radical polymerization in micellar polymerization, forming stable NPs.

The particle size of HEMA-PEGDMA NPs was determined by SEM and DLS measurements. SEM micrographs of crosslinked NPs of copolymer were taken from the colloid solution and freeze-dried form, using a concentration of 50 μg/ml. SEM micrographs (Figure 1) confirmed spherical, nanosized copolymer particles. The size of dried particles was in the range of 50-150 nm. The DLS measurements demonstrated that the NPs have a size distribution from 5 nm to 500 nm.

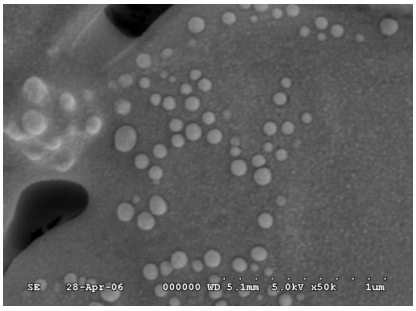


Figure 1: SEM micrograph of 5/5 HEMA/PEGDMA NPs.

## 3.2 Synthesis of hydrogel and nanocomposite (photopolymerization)

The main objective of this work was to design CHX loaded NCHGs, which can release the drug in a slow manner compared to the matrix hydrogels. Because the inner structure, porosity of the gel is the most important parameter for the release properties, present hydrogels were investigated with different composition. The total organic phase was 30 wt% in the aqueous solutions. The ratio of HEMA was changed from 90 mol% to 10 mol% whilst the ratio of PEGDMA crosslinker was varied from 10 mol % to 90 mol%. The polymer solution weighed 2 g and five gels were prepared for parallel release measurements. The produced materials are yellow or white yellow soft and flexible hydrogels with cylindrical shape. The transparency was increased with increasing amount of PEGDMA.

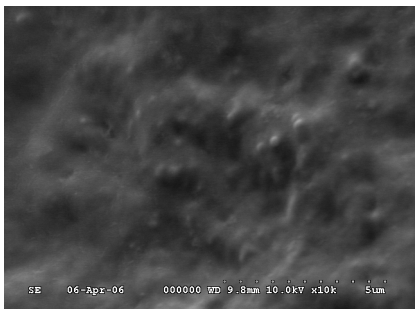


Figure 2: SEM micrograph of broken NCHG of 66% HEMA/PEGDMA=5/5 and 33% NPs.

In the NCHG the amount of monomers in the hydrogel was constant. The ratio of NPs was 15 wt% vs. the total mass of the hydrogel, and 50 wt% vs. amount of monomers. The composite gels were more consistent than matrix gels and were more rigid and more transparent.

The SEM micrograph of broken sample is in the Figure 2, this picture shows large number of NPs in the matrix. This image shows particles with a size of about 200 nm ball-shaped nanoparticles inside the matrix.

## 3.3 Mechanical assay

The assay of mechanical properties was repeated ten times to ensure reliable results. The matrix hydrogels were investigated in five different mol ratios (Table 1). When the amount of crosslinker was increased, the compression strength also increased and, depending on the cross-linker density, by as much as in excess of 400% comparing sample 1 to sample 5. In the case of matrix gels the compressive strength of sample 1 (HEMA/PEGDMA 9/1) changed from 0.18 MPa to 0.59 MPa for sample 3 (HEMA/PEGDMA 5/5) and than to 0.79 MPa for sample 5 (HEMA/PEGDMA 9/1). The compression strength values are very similar for the NCHG was 0.56 MPa compared to the 0.59 MPa value of the 50/50 matrix gel (sample 3). Nevertheless the strain was altered accordingly, because when the ratio of PEGDMA was only 10% and 25% the samples were very soft, but when it was augmented (50, 75 or 90%) the specimens were brittle. The gels were harder and more rigid when the amount of crosslinker was increased. For the NCHG it was observed that the compression strength value does not change related to the matrix, however the flexibility decreases. The shape of compressive strengths values is shown the Figure 3.

| (a) | 1 | 2 | 3 | 4 | 5 | NCHG |
|---|---|---|---|---|---|---|
| (b) | 90-10 | 75-25 | 50-50 | 25-75 | 10-90 | 50-50+NPs |
| (c) | 56,5 | 53,13 | 46,41 | 38,46 | 31,98 | 25,29 |
| (d) | 0,176 | 0,339 | 0,593 | 0,614 | 0,789 | 0,5596 |

Table 1: The summary of results of mechanical assays of matrix hydrogel samples (1-5) and NCHG (a) line. The (b) line is the ratios of HEMA-PEGDMA, (c) line is the rates of percent strains (%), (d) line is the Stress at maximum (MPa).

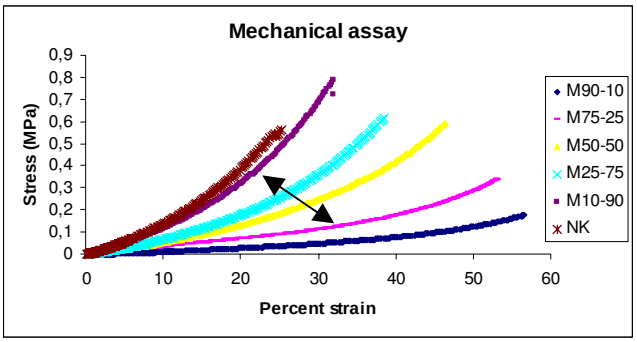


Figure 3: The effect of the ratio of crosslinker in the matrix and that of the NPs for the compression properties of the hydrogels. Black arrow indicates two samples (M50-50 matrix and NCHG nanocomposite hydrogel) with the same composition of matrix gel (HEMA/PEGDMA=5/5) however, the NCHG sample consists of 30% of NPs.)

## 3.4 Release properties

The release curves of CHX from basic hydrogel (50% HEMA and 50% PEGDMA) and from the NCHG are shown in Figure 4. The release profiles were investigated in the case of matrix and for the NCHG with variation of the reservoir. Samples were loaded as follows: only the matrix was (NCHG1), only into the NPs (NCHG2), and when both of these components contained drug (NCHG3). The amount of NPs was 15 wt% in all samples and the loaded drug was 45 mg in the NPs, and 15 mg in the matrix. The measurements were performed for three parallel experiments to ensure reliable results. In the first four hours the difference was not too considerable, but after the seventh hour remarkable difference was observed. The release from the matrix gel was the fastest than the NCHG where only the matrix was loaded (Figure 4a). Accordingly, the effect of NP could be followed in the initial period. This controlled release was continued to forty-eight hours after the degree of delivered drug closes to consistent (Figure 4b, and extended part in Figure 4c). The maximum ratio of the released drug in each case reached up to 60% of loaded drug, the main difference is altogether the time, which it is eventuating. For the NCHG1 sample with loaded matrix and empty NPs shows an unexpected profile. In the first period CHX is released, but then its concentration declines. The NPs entrapped a part of the drug. The reason of this phenomenon has not been understood yet.

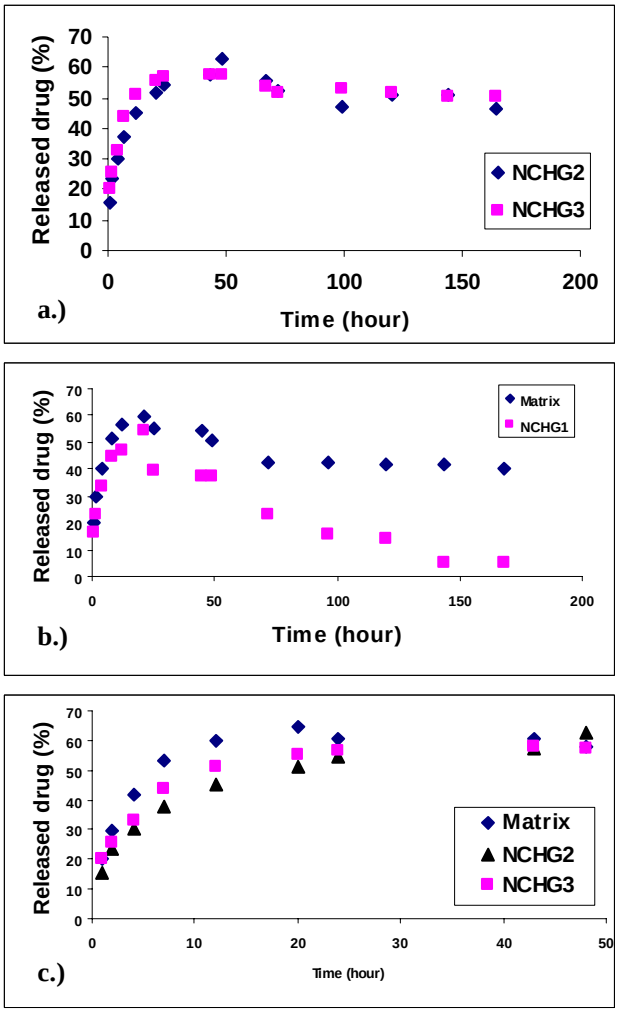


Figure 4: Release profiles of matrix gel (50/50 HEMA/PEGDMA), and the NCHG (66% of 50/50 HEMA/PEGDMA hydrogel and 33% of 50/50 HEMA/PEGDMA NPs).

## 4 CONCLUSION

Nanocomposite hydrogels were successfully prepared by incorporation of nanoparticles into the gel matrix. The integrated gel system showed distinct advantages compared to simple hydrogels as drug delivery systems. The swelling ratio of NCHG is up to 200% related to the solid content and results in a flexible, soft gel for implantation into the periodontal pockets or for application as a surface film on infected gums. The compression strength increased with higher content of the cross linker, PEGDMA. Adding NPs to the matrix this value remains constant. The release slope of CHX declined for NCHG, indicating a slower release of the drug from the composite hydrogels. When CHX was excluded from NPs incorporated in the gel, an unexpected apparent decline in the released drug was observed. These results will be further investigated. In situ polymerization of hydrogels offers flexibility for local placement of drugs in the treatment of periodontal disease.

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