Injectable alginate based hydrogels with adjustable resorbtion rate

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Statement of Purpose: Alginates are biocompatible polymers with the unique property to form gel structures under physiologic relevant conditions. The successful use of alginates as biostructures may in several cases, however, rely on the ability to control *in vivo* administration and resorbtion of the polymer network. We have previously developed an internal alginate gelling system (self-gel) with the ability to be moulded *in vitro* or injected before gelling. This is obtained by mixing a sodium alginate solution with calcium alginate particles and gel formation occurs as a result of exchange of calcium ions between the insoluble and soluble alginate fraction. The gelling process initiation and gelling rate has also been demonstrated to be strongly dependent upon the presence of non-gelling ions like Na^+ (Fig.1). As a result of this, injectable gel formulations highly responsive to physiologic sodium levels may be made. In order to control *in vivo* resorbtion time formulation factors like MW distribution, polymer sequence distribution (mannuronic and guluronic acid content) and degree of calcium cross-linking may be adjusted. However, changing such factors to promote *in vivo* resorbtion may also be a compromise with respect to other properties like initial gel strength and elasticity. In the present study we have further explored the alginate based gel system by combining alginate with hyaluronic acid as a factor to control gel properties.

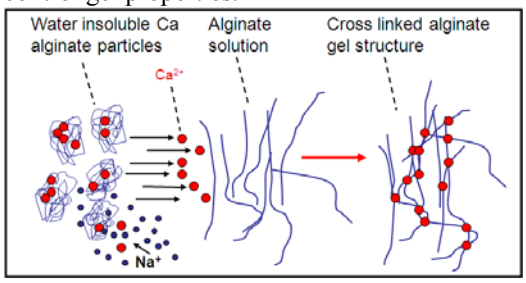

Figure 1. Alginate gelling principle

Methods: Selected calcium alginate particles and PRONOVA sodium alginate grades were used, and the two compounds were mixed immediately before testing. For selected samples sodium hyaluronic acid (HA 150) was added together with the two alginate components. Furthermore, in order to test the effect of sodium as a gelling initiator, NaCl was added to one of the syringes. Gel structure build up was followed by using Bohlin rheometry. In order to test gel resorbtion rate, different formulations were prepared and compared in an accelerated dissolution study *in vitro* (lowered calcium levels). For this, gel formulations were moulded and stored in a 0.9 % NaCl and 0.3 mM $CaCl_2$ solution at 37ºC and gel weight was recorded with time (physiologic calcium level is about 1.3 mM).

Results: By mixing the two components gelling was initiated and the buildup could easily be followed on the rheometer (Fig.2). In the absence of sodium and hyaluronic acid no significant gelling seemed to occur within at least two hours, while sodium strongly promoted gel formation. By including hyaluronic acid, gel formation was fully initiated after about ten minutes and the addition of sodium ions to this formulation also further promoted gel formation strongly.

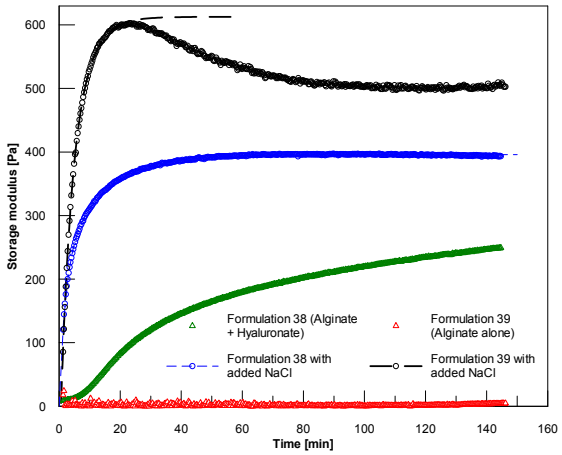

Figure 2: Storage modulus as a function of time for alginate formulations in the absence and presence of sodium chloride and hyaluronic acid.

The stability testing of the two formulations in an accelerated dissolution study at 0.3 mM $CaCl_2$ clearly demonstrated a higher resorbtion rate in the presence of hyaluronic acid (Fig.3). This effect probably relates to an increased exchange of calcium ions within the polymer network in the presence of the negatively charged non-gelling polymer and sodium counterions.

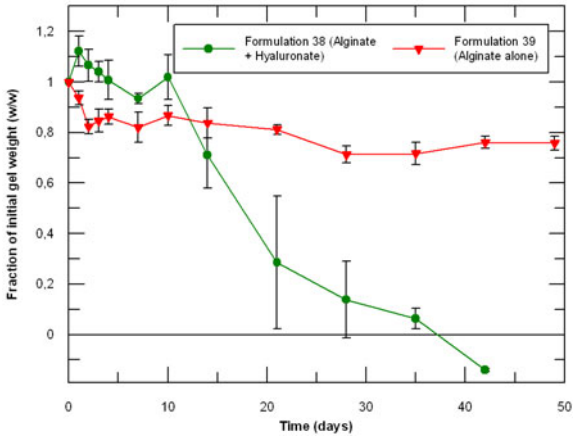

Figure 3. Accelerated resorbtion study of alginate gels at sub-physiologic calcium levels (0.3 mM) in the absence or presence of hyaluronic acid.

Conclusions: The data supports that alginate self-gel formulations with a range of profiles may be successfully designed as injectable matrices for cells or other. Through formulation modifications, among other by combination with hyaluronic acid, the gel formation kinetics and resorbtion profile may be optimized.