# EFFECT OF NON-CROSS-LINKED CALCIUM ON CHARACTERISTICS, SWELLING, DRUG RELEASE AND MUCOADHESION PROPERTIES OF CALCIUM ALGINATE BEADS

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**Background**: Alginates are natural, safe, cheap, and biodegradable polymers. They form gel in the presence of divalent cations, such as $Ca^{2+}$, without the need for toxic reactants. Due to these unique properties and the gelation simplicity, calcium alginates beads (CABs) are widely used in many pharmaceutical applications, namely in controlled release delivery systems. The Ca2+ retained by CABs can be either strongly cross-linked with polysaccharide's chains (CL-Ca) or non-crosslinked (NCL-Ca); having a weak interaction with the alginates. NCL-Ca is normally removable by a washing process whereas the CL-Ca is not washable. In this study, ibuprofen-loaded CABs with the same degree of crosslinking and different amounts of NCL-Ca were prepared and the influence of NCL-Ca on beads properties, mucoadhesiveness, swelling and drug release was explored in two different simulated intestinal fluids.

**Methods**: Ibuprofen-loaded CABs were prepared by ionotropic gelation using $CaCl_2$ as a cross-linker. Washing process involved soaking the freshly prepared beads in deionized water. The number, duration, and volume of washes were varied. Beads were then collected and dried at a temperature of 40 °C for 48 h. CABs swelling and drug release studies were performed in phosphate or maleate based simulated intestinal mediums using a USP rotating basket apparatus. The mucoadhesion properties of CABs were evaluated on sheep intestinal mucosa by the in-vitro wash-off method.

**Results**: This study showed that increasing the number or duration of washes resulted in significant decreases in the amount of NCL-Ca. However, the impact washes volume was not significant. Approximately 70% of the initial amount of $Ca^{2+}$ was NCL-Ca which was removable by washing while only 30% was cross-linked (CL-Ca). $Ca^{2+}$ release from the CABs was bimodal where the NCL-Ca was firstly released followed by a slower release of CL-Ca. Washing methods and, thus, the amount of NCL-Ca had significant influences on the CABs characteristics, swelling and mucoadhesiveness, and the drug release profile in SIFs.

**Conclusions**: This study highlights the importance of washing methods and the amount of NCL-Ca to establish CABs properties and understand their behavior in the SIFs. It demonstrates also that the composition of the SIFs is of great significance in order to perform reliable and consistent CABs swelling and release studies.