CORE-SHELL COMPOSITE HYDROGELS FOR THE CONTROLLED FORMATION AND RELEASE OF NANOCRYSTALS OF POORLY SOLUBLE ACTIVE PHARMACEUTICAL INGREDIENTS

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Key Words: core-shell hydrogels, nanocrystals, crystallization, formulation, confinement

Although roughly 40% of pharmaceuticals being developed are poorly water-soluble, this major class of drugs still lacks a formulation strategy capable of producing high loads, fast release kinetics, and low energy input. The development of such innovative biocompatible materials has been a major focus of pharmaceutical materials research. In this work, we develop a novel bottom-up approach for producing and formulating nanocrystals of poorly water-soluble active pharmaceutical ingredients (APIs) using core-shell composite hydrogel beads. We show that the API dissolution profile can be modulated by accurately controlling crystal size and loading and shell thickness. Organic phase nanoemulsions stabilized by polyvinyl alcohol (PVA) and containing a model hydrophobic API (fenofibrate) are embedded in the alginate hydrogel matrix and subsequently act as crystallization reactors. Controlled evaporation of this composite material produces core-shell structured alginate-PVA hydrogels with drug nanocrystals ranging from 500 nm to 650 nm embedded within the core. Adjustable loading of API nanocrystals up to 83% by weight is achieved. Our drug nanocrystal-formulated hydrogels exhibit improved solubility and dissolution rates comparable to commercial dissolution. We also demonstrate that the drug release patterns of the fenofibrate nanocrystals contained in the core can be modulated by altering the thickness of PVA shell of the composite hydrogels. The thickness of the polymer shell of the composite hydrogels can be engineered either by varying the volume fraction of organic phase or by changing the overall core-shell particle size. Thus, these composite materials offer a 'designer' drug delivery system by offering a controlled dissolution rate and lag time. Overall, our approach enables a novel means of simultaneous controlled crystallization and formulation of poorly soluble drugs that circumvents energy intensive top-down processes in traditional manufacturing.

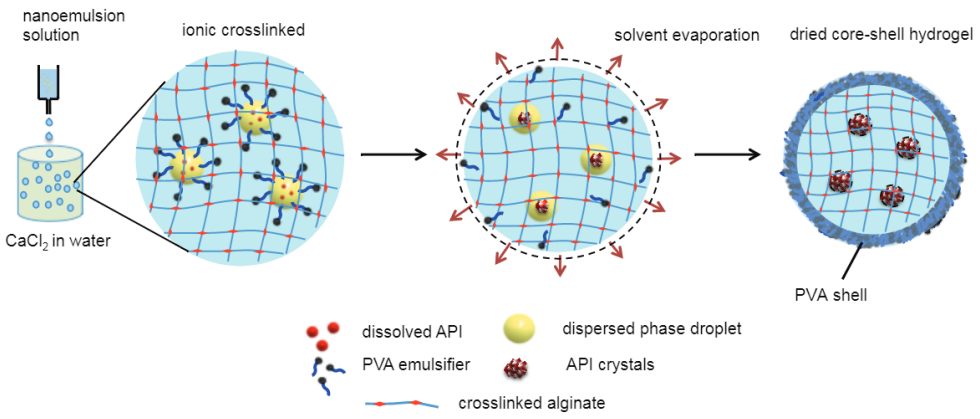

FIGURE 1 –SCHEMATIC ILLUSTRATION OF OUR BOTTOM-UP APPROACH TO CORE-SHELL COMPOSITE HYDROGEL BEAD FORMATION. NANOEMULSION DROPLETS CARRYING HYDROPHOBIC API ARE DISPERSED IN AQUEOUS SOLVENT CONTAINING POLYMER ALGINATE. CROSS-LINKING THE ALGINATE ENTRAPS THE NANOEMULSION DROPLETS IN A POLYMER MATRIX. SUBSEQUENT EVAPORATION FORMS CORE-SHELL HYDROGELS CONTAINING API NANOCRYSTALS EMBEDDED IN THE CORE.