the oven at a temperature of 90°C for 2 h. This system displayed a slow swelling rate and low extent of swelling overall, reaching a maximum of approximately a 50% mass increase, beyond the 24 h period, suggesting that this type of material would be more suitable for the production of drug delivery systems for prolonged release.

Besides polyanhydride and acrylate type polymers, only mixtures of polysaccharides (dextran, gelatin) and poly(vinyl alcohol) (PVA) have been reported to be used successfully to produce hydrogel-forming microneedle arrays for drug delivery (Hong et al. 2014). Yang et al. (2012) used PVA, dextran, and carboxymethylcellulose (CMC) to prepare what they have termed 'phase-transition microneedles', using a similar casting method to that described previously, albeit with some key differences. A ceramic material, known as purple clay, was used to form the female microneedle mould and upon addition of the polymer solution, a vacuum was applied to the opposite side of the mould in order to force the formulation into the tips of the microcavities. The filled mould was then frozen at −20°C for 2 hours and thawed at 4°C for 1 hour, with this freeze-thaw cycle repeated twice more, with the aim of forming microcrystalline junctions within the structure, to cross-link and solidify the polymer. Following this process, the arrays possessed sufficient strength to be detached from the mould and dried, before sterilization by steaming in an oxirane vapour. Similarly, Demir et al. (2013) prepared swelling microneedle arrays by crosslinking 20% w/v PVA and 10% w/v gelatin. The formulation was cast into polydimethylsiloxane micromoulds and then frozen at –20°C for 12 h, followed by thawing at 25°C for 12 h, with this cycle repeated three times, creating a physically cross-linked system by cryogelation.

Safety and biocompatibility

In general, hydrogels are highly biocompatible, as reflected in their successful use in the peritoneum (Sutton 2005) and other sites *in vivo*. This is due in part to the high water content and, also, the physiochemical similarity of hydrogels to the native extracellular matrix. With respect to microneedles, the biocompatibility of the materials used for manufacture is considered important, as when applied to the skin, the needles are introduced into the body intradermally. All polymers in the formulations discussed, have been widely used in other pharmaceutical applications, prior to microneedle manufacture. PVA is known to be biocompatible and has been commonly employed as a biomedical excipient, as it is non-toxic and non-carcinogenic, with both swelling properties and bioadhesive characteristics (Baker et al. 2012). Likewise, PMVE/MA and its acid form (Gantrez® type co-polymers) have been extensively used for over 40 years as thickening and suspending agents in topical salves and ointments, as well as in denture adhesives (Mrak et al. 1988).

The biocompatibility of PEG-cross-linked PMVE/MA-based hydrogel microneedle materials was evaluated by Donnelly et al. (2012) using three different cell-lines; fibroblasts (Balb/3T3), keratinocytes (NRERT-1) and a 3D keratinocyte organotypic raft culture. No significant reduction in cell viability was observed in any test, indicating that this type of hydrogel-based microneedle material was likely to be biocompatible. *In vitro* skin irritancy studies showed that the microneedle formulation was likely to also be non-irritant, resulting in significantly less interleukin-1 alpha