2009b). Limited number of studies also showed use of glycerol formal and triacetin in SPI systems, these solvents has earlier history of using in veterinary formulations (Bleiberg et al. 1993).

The search for novel solvents for use in SPI systems is an on-going process with a number of factors such as polymer solubility, toxicity, system stability, biocompatibility and the potential for a single unit formulation posing barriers to this development. Although the regulatory authorities approve the 'gold-standard' solvents such as NMP and DMSO, evidence relating to toxicity and suitability is conflicting and sometimes contradictory therefore there is a need for further research and improvement. Movement towards the use of solvent mixtures can be observed through literature in order to obtain the most suitable 'solvent strength' to enable predictable and modifiable controlled release. For example, Zingermann and Chern patented a combination of glycerol formal (hydrophilic) and triacetin (hydrophobic) solvent that showed the blood levels of fipronil (flea adulticide) for 12 mon after subcutaneous injection (Chern and Zingerman 2004).

2.3 Method of SPI hydrogel implant formation

Two different forms of phase inversion have been identified and recorded in previous literature, according to their rate of phase inversion as detailed below. For example, rapid injection of the SPI hydrogel formulations results in rod-like implants whereas slower injection yields more spherical implants (Schoenhammer et al. 2009a).

2.3.1 Fast Phase Inversion (fPI)

These systems undergo phase inversion at a rapid rate (from seconds to minutes) resulting in formation of a thin membrane with a porous implant structure (Graham et al. 1999; Packhaeuser et al. 2004) (Fig. 1). This change is a result of solvents that are 'strong' and 'hydrophilic' in nature (McHugh 2005). As the affinity of the solvent for the non-solvent increases, the rate of sol-to-gel phase inversion also increases. fPI systems are of a lower viscosity and, therefore, require lower force of injection. fPI have improved biocompatibility hydrophilic nature of the solvent (Raman and McHugh 2005). Mashak et al. 2011 investigated the addition of aliphatic esters, namely ethyl heptanoate, methyl heptanoate and ethyl nonanoate, to a PLGA in NMP solution. Here rapid NMP removal resulted in implant formation, which is due to increased interaction between PLGA and the esters and also by a reduction of the affinity between PLGA/ester and NMP. Additives resulted in highly porous matrix compared control PLGA/NMP system. Most rapid phase inversion was seen in the systems containing ethyl heptanoate.