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# A Versatile Technique to Produce Porous Polymeric Scaffolds: The Thermally Induced Phase Separation (TIPS) Method

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## Abstract

Among the various scaffold fabrication techniques, thermally induced phase separation (TIPS) is one of the most versatile methods to produce porous polymeric scaffold and it has been largely used for its capability to produce highly porous and interconnected scaffolds. The scaffold architecture can be closely controlled by varying the process parameters, including polymer type and concentration, solvent/non-solvent ratio and thermal history. TIPS technique has been widely employed, also, to produce scaffolds with a hierarchical pore structure and composite polymeric matrix/inorganic filler foams.

**Keywords** Porous scaffolds; Thermally induced phase separation; Gradient

## Introduction

The so-called scaffold is one of the building blocks of the tissue engineering approach; the design of a scaffold includes the selection of its constitutive material, its design architecture and often the surface and/or bulk treatment(s) [1]. The scaffold is a three-dimensional support suitable for the growth of a tissue or an organ, aiming to temporarily replace the functions of the extracellular matrix and to guide the proliferation and growth of cells [2]. Several studies showed that, without a proper template, the cells tend to arrange in a two-dimensional (2D) layer forming a flat structure with poor mechanical properties [3]. In particular, by using scaffolds, transplanted cells can be delivered to a specific site place in a tissue hence driving the growth of cells inside towards a desired target. Thus, scaffolds represent the free space available for the tissue to develop and a physical support for cell growth. To achieve these objectives, the scaffold must possess some basic requirements: biocompatibility, biodegradability, topological features, mechanical properties, sterilizability, etc. [4]. Several biomaterials (natural [5,6] or synthetic [7,8]) have been exploited to mimic as good as possible the tissue to regenerate. The choice of the biomaterial is also related to its production

technique, in order to attain the optimum porosity, pore interconnectivity and mechanical properties. Among the possible techniques the most widely adopted are solvent-casting and particulate leaching [9], phase separation methodologies [10], gas-foaming [11], CAD/CAM based methods [12] and electrospinning [13].

## Thermally Induced Phase Separation (TIPS) Technique

Thermally Induced Phase Separation (TIPS) is a widely adopted procedure for scaffold preparation, suitable for obtaining a well-interconnected porous structure.

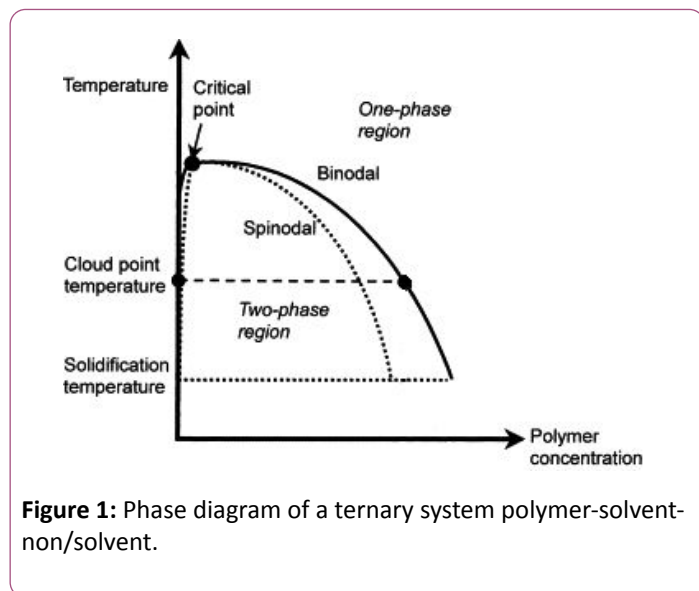
This technique is based on the change in temperature to induce the de-mixing of a homogeneous polymer solution, thus creating a multi-phase system. When the de-mixing of the solution occurs, the homogeneous solution separates into a polymer-rich and a polymer-less phase. The de-mixing can be solid-liquid (usually for binary polymer-solvent mixtures), or liquid-liquid (usually for ternary polymer/solvent/non-solvent mixtures).

One of the most relevant advantages of this technique is the possibility to obtain a well-interconnected polymer network with an easy-to-tune, fast and adaptable process. As a function of the separations conditions, it is possible to obtain a wide range of different morphologies with various characteristics, such as: open or close pores, fibrous structure, membrane/like architecture, etc. [14-17].

Lots of polymers have been used, among which it is worth to mention polylactic acid[18], polyurethane[19], polycaprolacton [20], etc.

**Figure 1** reports the phase diagram of a typical ternary solution. The thermodynamic equilibrium boundaries are represented by the binodal and the spinodal curve. At high temperatures (above the binodal curve) the polymer solution is in the one-phase region and the solution is homogeneous. Upon decreasing the temperature, the solution reaches the binodal curve and de-mixing into a polymer-rich and a polymer-lean phase occurs. The area between binodal and spinodal curve is

the metastable region, where a (quite slow) mechanism of nucleation and growth takes place, leading to (relatively) large pores. On the opposite, the separation mechanism taking place in the spinodal region, called spinodal decomposition, is very fast and usually leads to the formation of a network of small interconnected pores.

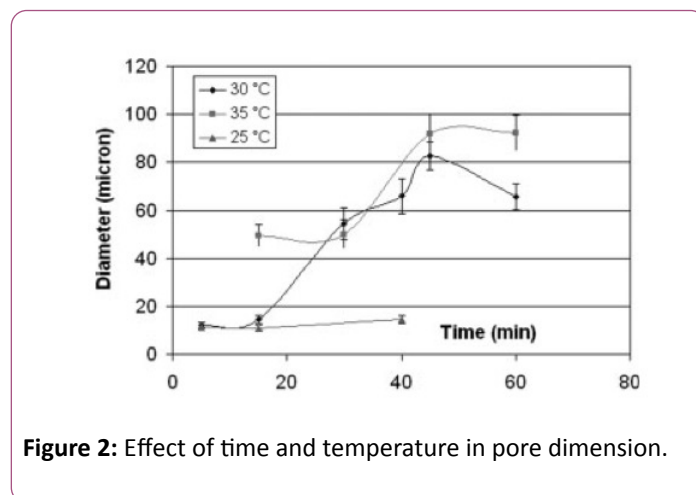


## Operating Parameters

Distribution, shape and size of the pores are the result of a delicate balance between different parameters among which the most important are polymer type and concentration, polymer molecular weight, solvent/non-solvent ratio and cooling path.

- **Polymer concentration:** as the concentration increases, keeping constant the cooling path, pore dimension and porosity decrease accordingly.
- **Polymer molecular weight:** an increase of the molecular weight implies an increase of the viscosity of the solution that plays a crucial role during the formation of the two phases. The foams at higher molecular weight result more homogeneous compared to the others ones.
- **Solvent/non-solvent ratio:** the first attempts to produce scaffold via TIPS were carried out starting from a binary solution polymer/solvent. In this case, the scaffolds present a ladder-like structure due to the solidification of the solvent, and the final scaffold structure is mainly dominated by the progress of the crystallization of the solvent. Inducing a liquid-liquid phase separation by adding a non-solvent allowed a significant improvement in the scaffold architecture together with an increase in the sensitivity of the solution to the tuneable parameters, above all the thermal history
- **Cooling path:** one of the principal advantages of the TIPS technique is the possibility to tune the structure by playing with the temperature vs. time pathway. As a matter of fact, starting from the same solution, the final morphology of the scaffold can exhibit very different features (in terms of pore dimension, distribution, interconnectivity, etc) by simply tuning the cooling path. The graph in **Figure 2** [21] reports

the trend of pore dimension as a function of the temperature and time. It is evident that at 25°C pore size is basically independent of the demixing time. For the examined solution at 25°C the predominant process is spinodal decomposition, not related to time. For the remaining two temperatures, 30°C and 35°C, when increasing the demixing time from 15 to 45 minutes the pore dimensions are more than quintupled, and the sigmoidal shape typically exhibited by saturation or “space-filling” processes (like nucleation and growth) is visible.



These criteria have a significant influence not only on the onset of the phase separation, in which the domains of the nucleating phase start to grow, but also in the next steps. Indeed, the coalescence of the separate phase, continues minimising the free energy due to the presence of the interfacial surfaces. This process, called coarsening, causes the increase of the pore dimension [22].

By taking advantage of the TIPS process, since the pore dimension is mainly dependent on the residence time in the metastable region [23], Mannella et al. [24] proposed an experimental apparatus able to impose a different T vs. time pathway on two sides of a sample. In this way a gradient of pore dimension was obtained along the scaffold thickness in a single step, without requiring the junction of the multiple layers.

TIPS technique was adopted, too, to produce also composite scaffold by adding ceramic fillers: hydroxyapatite, bioglass, keratin [25], etc. starting from binary [26,27] or ternary solution [28].

## Conclusion

TIPS technique allows the formation of an interconnected porous structure through an easy-to-tune fabrication process. The technique has demonstrated a remarkable potential to obtain scaffolds with a wide range of pore sizes. The process can be tuned by manipulating the processing parameters, e.g. thermal history, to fabricate scaffolds with the desired architectures and pore morphologies. By taking advantage of the relative ease in tuning the final topology of the scaffold, foams with hierarchical structures have been obtained by creating thermal or concentration gradient. Furthermore, inorganic filler

can be suitably incorporated into the scaffold matrix in a one-step process to enhance the bioactivity and the mechanical properties of the scaffold.

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