CHAPTER I
INTRODUCTION

Wound healing is a specific biological process involving the general phenomenon of tissue regeneration (Boateng, *et al.*, 2008). The entire process of wound healing is a complex and ordered cascade of events, which can be divided into four distinct, but overlapping, phases of hemostasis, inflammation, proliferation and maturation (MacKay and Miller, 2003; Enoch and Leaper, 2005; Deng, *et al.*, 2007; Stojadinovic, *et al.*, 2008). Additionally, wound healing involves a complex series of interactions among different cell types, cytokine mediators and the extracellular matrix (ECM) components (MacKay and Miller, 2003; Enoch and Leaper, 2005; Stojadinovic, *et al.*, 2008).

Although wound healing is the natural process of regenerating damaged and/or lost tissues, an appropriate wound dressing should be able to enhance the healing process considerably, by mediating at the right stage of or providing excellent conditions for wound healing (Kokabi, *et al.*, 2007). Generally, an effectual wound dressing should maintain a moist environment upon absorption of the wound exudates, protect the wound from secondary infection, reduce necrosis of the wound bed, provide adequate gaseous exchange, regulate and/or mediate the release of certain growth factors and cytokines, and also be elastic, biocompatible with tissues and blood, non-toxic and non-antigenic (Purna and Babu, 2000; Lin, *et al.*, 2001; Kokabi, *et al.*, 2007; Boateng, *et al.*, 2008; Singh and Pal, 2008). Moreover, an effectual wound dressing should promote a rapid healing of the wound and, once healed, the detachment of the dressing should not cause secondary trauma to the neo-tissues (MacKay and Miller, 2003; Boateng, *et al.*, 2008).

Based on these requirements, biocompatible polymeric hydrogels are promising materials for uses as wound dressings, since they can be tailor-made with specific needs (Kokabi, *et al.*, 2007; Boateng, *et al.*, 2008; Singh and Pal, 2008). Such needs, in addition to the general requirements for an effectual wound dressing, include non-irritating and non-adhering properties, immediate pain relief, ease of handling and replacing without compromising patients' comfort, transparency to allow easy monitoring of the wound bed, and facilitation of the migration and mitosis

of epithelial cells (Kokabi, *et al.*, 2007; Boateng, *et al.*, 2008; Singh and Pal, 2008). By definition, hydrogels are three-dimensional, hydrophilic, water-insoluble polymeric networks (Peppas, *et al.*, 2000; Hoffman, 2002; Liu, *et al.*, 2005; Sokolsky-Papkov, *et al.*, 2007; Hamidi, *et al.*, 2008; Singh and Pal, 2008). The internal networks may result from physical and/or chemical domains that retain their integrity, either in whole or in part, when being surrounded by a large amount of water molecules. The functions of hydrogels in biomedical applications, including wound dressings, result from their ability to absorb a large quantity of water (Liu, *et al.*, 2005; Singh and Pal, 2008).

Among numerous polymers capable of forming into hydrogels, alginate and gelatin, an abundant natural bio-copolymer obtained from the cell wall of brown algae (Augst, *et al.*, 2006) and prepared by partial hydrolysis of collagens, respectively, are ideal materials to fabricate into wound dressings. Because of intrinsic properties of alginate and gelatin, such as natural abundance, relatively low material and production costs, high water absorbance, ion-exchange capability, biocompatibility and non-immunogenicity (Groves and Lawrence, 1986; Sartori, *et al.*, 1997; Augst, *et al.*, 2006; Dong, *et al.*, 2006; Coviello, *et al.*, 2007; Pongjanyakul and Puttipipatkhachorn, 2007; Hong, *et al.*, 2008; Pielesz and Bak, 2008), alginate- and gelatin-based hydrogels have been widely used in pharmaceutical and medical applications, particularly as wound dressing materials (Groves and Lawrence, 1986; Almeida and Almeida, 2004; Augst, *et al.*, 2006; Dong, *et al.*, 2006; Coviello, *et al.*, 2007; George and Abraham, 2007; Pongjanyakul and Puttipipatkhachorn, 2007).

Nowadays, the development of wound dressings has changed from the traditional passive to the more functionally active types, with an aim of imparting specific functions (Purna and Babu, 2000; Kokabi, *et al.*, 2007). Therefore, in this study the concept of interactive biomaterial-based hydrogels was used to achieve the most desirable properties for wound dressings. The purpose of the present contribution is to develop wound dressings with enhanced wound healing property, through the use of pharmacological agents or with antimicrobial activity through the use of nAg. Among various phyto-chemicals, extracts from *Centella asiatica* Linn. Urban or Buabok (in Thai) have traditionally been used to heal wounds, burns and ulcerous abnormalities of the skin (Kartnig, 1988; Cheng and Koo, 2000). The

influence of the plant extracts on wound repair has been attributed to the presence of four major trisaccharide triterpenoid components in the extracts (i.e., asiatic acid, asiaticoside, madecassic acid and madecassoside) (Inamdar, *et al.*, 1996). Among these components, asiaticoside is the most active component associated with the healing of wounds (Maquart, *et al.*, 1990).

In this way, the scope of this research work is to develop the gelatin- based (in the form of either nanofibers or hydrogel pad) and alginate-based (in the form of hydrogel film) wound dressings containing active substances. These substances are herbal extract or the most active ingredient from *Centella asiatica*, asiaticoside and the effectual antimicrobial agent; nAg. In addition, the potential use of the prepared gelatin- and alginate-based hydrogels as wound dressings was evaluated. Various properties (i.e., morphology, mechanical integrity, physical properties, antibacterial activity and indirect cytotoxicity) of both of the neat and the active substance-loaded gelatin- and alginate-based wound dressings, as well as the release characteristic of active substances from gelatin- and alginate-based wound dressings, were investigated.