14.1. INTRODUCTION
Secondary metabolites are compounds produced mainly by actinomycetes and fungi, usually late in the growth cycle (idiophase). Although antibiotics are the best known secondary metabolites, there are others with an enormous range of other biological activities. Moreover, the last two decades have been a phase of rapid discovery of new activities and development of major compounds of use in different industrial fields, mainly: pharmaceutical and cosmetics, food, agriculture and farming. Some examples are: anti-inflammatory, hypotensive, antitumor, anticholesterolemic, but also insecticides, plant growth regulators and environmental friendly herbicides and pesticides. These compounds are usually produced by liquid submerged fermentation, but many of these metabolites could be advantageously produced by solid-state fermentation.

Although solid-state fermentation (SSF) systems have been used in several oriental countries since antiquity, SSF has been transformed, in the last 25 years, for new purposes using new approaches of microbiology, biochemistry and biochemical engineering. This higher degree of control has allowed the use of SSF to produce sophisticated and valuable molecules like secondary metabolites (SMs).

Ten or even five years ago reviews on this field pointed out that SSF was an emerging technology with great potential for the production of SMs at industrial scale. The authors commented that mycelial morphology associated with the microorganisms used for secondary metabolite production is well suited for growth on a solid support. Also that SSF presents advantages like: higher product yield, often in shorter times, higher product stability, lower energy requirements; while some disadvantages, like more complicated scale-ups as well as difficulties in monitoring and controlling process parameters, were also mentioned (Barrios-González & Mejía 1996; Balakrishnan & Pandey 1996; Robinson et al., 2001).
Today, industrial SMs production by SSF is a reality. Some years ago an Indian company started industrial scale production of some secondary metabolites. It has since become a successful enterprise and the Food and Drug Administration (FDA) of the USA has approved the technology (SSF) developed by Biocon India for the production of fungal metabolites for human application (Suryanarayan 2003). In the near future the competition, between conventional SmF and SSF processes, promises to be tougher and more interesting. In the last 10 years the study of secondary metabolite (SM) production by SSF has been characterized not only by an increase in the number of publications, but also by the increase in the proportion of SMs with biological activities different from antibiotics. Another interesting feature of this stage is the surprisingly high productivity of SMs obtained in the processes designed in these studies. Ten years ago, a similar review described only one process with a production level above 7 mg/g (Barrios-González & Mejía 1996), while higher yields are quite common in recent work (see Table 2).

As was 10 years ago, SM production in solid culture was most often studied in SSF on natural substrates. This trend is represented by a considerable amount of pragmatic work directed to design high producing processes for particular SMs, most of them using agricultural products or wastes (SSF on natural substrates). Authors have looked for more efficient solid substrates for the production of particular SM. Generally, the same work is followed by the search of nutritional supplements and/or process conditions, often by sophisticated statistical methods. As a result, this new stage is characterized by a surprisingly high production yield of different SMs.

SSF has also been studied using inert solid support materials, which greatly facilitates basic studies. However, production yields as high as the ones obtained in SSF on solid substrates are also reported in these systems. Basic studies have also been performed on simplified model SSF systems, like membrane cultures (on agar media in Petri dishes). However, Rahardjo et al., (2004) have warned for a careful use of this model system since it could be artificial and not describing the actual SSF. The authors showed that this kind of culture presents a different metabolism and kinetics, in relation with SSF.

Many advantages of SSF are a consequence of the different physiology shown by fungi and other microorganisms on a solid substrate, in relation to the one presented in SmF. The molecular and physiological reasons underlying the different behavior of microorganisms in SSF are presently not well characterized, but a deeper understanding of this physiology is required to explore the possibilities for controlling or directing product formation in SSF. This information would also be of key importance to design efficient methods for strain improvement for these processes.