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Review

Design of experiments for microencapsulation applications: A review

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ABSTRACT

Microencapsulation techniques have been intensively explored by many research sectors such as pharmaceutical and food industries. Microencapsulation allows to protect the active ingredient from the external environment, mask undesired flavours, a possible controlled release of compounds among others. The purpose of this review is to provide a background of design of experiments in microencapsulation research context. Optimization processes are required for an accurate research in these fields and therefore, the right implementation of micro-sized techniques at industrial scale. This article critically reviews the use of the response surface methodologies in pharmaceutical and food microencapsulation research areas. A survey of optimization procedures in the literature, in the last few years is also presented.

Contents

1. Introduction

The increased demand for added-value products has been substantially affecting trends in the global market. Therefore, new and innovative technological techniques as microencapsulation [62,82] and nanoencapsulation [111] have been developed.

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Microencapsulation and nanoencapsulation are generally defined as a set of technologies that allows to entrap active ingredients also known as core materials using a surrounding material namely as encapsulating or shell material [65]. A clear distinction between nanoencapsulation and microencapsulation is not consensual among authors, especially in terms of size: some authors consider that nanoparticles size varies between 1 and 1000 nm, however other researchers claim that nanoparticles size should range between 1 and 100 nm [60,120]. Nevertheless, both technologies aim to create a physical barrier to protect the active ingredient from the external environment, allowing a possible controlled release of it. Usually, micro- and nano-technologies are technically similar: some operational conditions are adapted in order to obtain microparticles or nanoparticles [73].

Nanotechnology is considered a promising technology to effectively entrap compounds [10,68,111] for a wide range of industrial sectors such as electronics, engineering, energy storage and biotechnology [18,33,34,79], nevertheless microencapsulation is the focus of the present review because countless brand-new and reinvented microencapsulated products have been available on the retail market.

2. Microencapsulation

The microencapsulation technology was first presented by Green and Schleicher in 1950s with a patent registration for the preparation of capsules containing dyes, which were developed to be incorporated into paper for copying purposes [44,45]. Nowadays, microencapsulation as it was above described, allows to protect sensitive micro-sized substances from the external environment allowing a controlled release of these micro-sized substances ([11,44,64]. The active ingredient also termed as core material can be temporary or permanently protected within a shell of a second material, designated as encapsulating or wall material [23,24].

The resulting products of microencapsulation techniques are designated microparticles (Fig. 1). Microparticles can be distinguished in microspheres or microcapsules [51] by their internal structure and morphology [62] even though, the terms are often used synonymously. Microspheres and microcapsules are differentiated in reservoir systems and matrix systems, respectively [123].

This technological approach has been explored by pharmaceutical (68%), food (13%), cosmetic (8%), textile (5%), biomedical (3%), agricultural (2%) and electronic (1%) industries [25,44,69,117].

Microencapsulation aims to increase the effectiveness of selected substances in industry [36]. Several authors have been discussing the main advantages of applying microencapsulation techniques in different industry sectors [26,30,31,96,102]. Nevertheless, pharmaceutical and food industries are the main driving forces in microencapsulation advances.

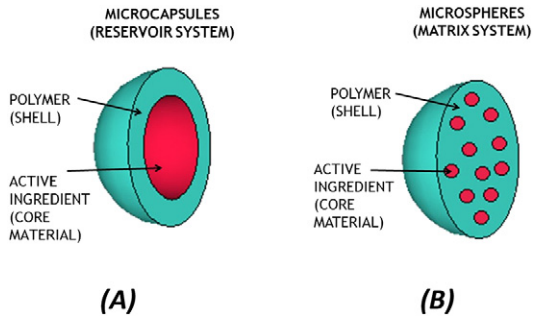

Fig. 1. Differences between microcapsules (A) and microspheres (B) inner morphologies (adapted from [51]).

2.1. Microencapsulation in pharmaceutical industry

Currently, research on microencapsulation for pharmaceutical purposes is focused on finding new drug delivery systems (DDS) to obtain products to reach the market, reducing the adverse reactions and side effects, being suitable for the required administration mode, allowing site-specific delivery, increasing shelf-life, improving patient compliance and allowing a possible controlled and sustained release of compounds [2]. Hence, microencapsulation arises as a potential technological strategy to achieve the above-mentioned goals. Microparticles may be constituted by combinations of the active pharmaceutical ingredients (APIs) and biomaterials. Regarding the microencapsulated APIs, these therapeutic agents can have a short half-life, can be quickly hydrolysed or degraded enzymatically in vivo, which is associated with a more strictly therapeutic regimen (multiple administrations). Therefore, microencapsulation techniques protect the API from degradation, allowing these compounds being appropriately released to obtain the required treatment concentration of API over time [81]. Depending on the biomaterial properties, particularly if they are erodible or non-erodible, they can disappear from where they were administrated or remain there throughout the patient lifetime, respectively. Some examples of microencapsulated APIs are presented in Table 1.

An efficient DDS is the one that allows the API to reach the target site, in the required time and for the desired time. Four major factors are considered to achieve an efficient DDS: administration route, pattern of API release, method of delivery and production process also known as formulation process [108]. Many of the non-microencapsulated API are administered repeatedly which makes the therapeutic regimen more frequent and always under medical supervision and as so, microencapsulation arises as a potential drug delivery strategy to overcome multiple issues associated to multiple administrations. Formulated microparticles must be biocompatible, stable, safe and demonstrate predictable degradation kinetics. However, other factors such as chemical modifications on the particle surface can optimize the system and thus be possible to use microencapsulation for drug delivery systems [51].

Nevertheless, there are few microencapsulated pharmaceutical products available on the market [110]. This can be explained with regards to the size control and size distribution is difficult, resulting in low reproducibility of the production process, especially on a large scale. Thus, DDSs are difficult to be approved. Additionally, it is considered in the case of microencapsulation of APIs is difficult to maintain the bioactivity of the therapeutic agent during all processing steps (preparation, storage and release). The APIs can even lose their therapeutic capacity and even increase the unwanted side effects due to deactivation of the therapeutic agent [118]. Despite the difficulties that have been encountered in the implementation of microencapsulation for DDSs, traditional therapies have been progressively replaced by more advanced technologies such as microencapsulation.

2.2. Microencapsulation in food industry

The food industry is the second main driving force for microencapsulation progress. Increasingly demanding consumers and product requirements are the major motivations for microencapsulation research intended to food industry. In fact, demanding consumers have been required the addition of functional ingredients in the final product. Usually, these ingredients are environmental and/or processing instable and as so, microencapsulation arises as technological approach to overcome the above-mentioned problems and therefore obtain an effective protection of these instable ingredients. Additionally, these compounds may be prone to degradation in gastrointestinal conditions and consequently, an effective protection of these ingredients may be required. Functional ingredients can be used to regulate color, flavour or texture of the final product. Additionally, they can be used as preservatives, being possible to extend their shelf life. As well as