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Building functional materials for health care and pharmacy from microfluidic principles and Flow Focusing ☆

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ABSTRACT

In this review, we aim at establishing a relationship between the fundamentals of the microfluidics technologies used in the Pharmacy field, and the achievements accomplished by those technologies. We describe the main methods for manufacturing micrometer drops, bubbles, and capsules, as well as the corresponding underlying physical mechanisms. In this regard, the review is intended to show non-specialist readers the dynamical processes which determine the success of microfluidics techniques. Flow focusing (FF) is a droplet-based method widely used to produce different types of fluid entities on a continuous basis by applying an extensional coflow. We take this technique as an example to illustrate how microfluidics technologies for drug delivery are progressing from a deep understanding of the physics of fluids involved. Specifically, we describe the limitations of FF, and review novel methods which enhance its stability and robustness. In the last part of this paper, we review some of the accomplishments of microfluidics when it comes to drug manufacturing and delivery. Special attention is paid to the production of the microencapsulated form because this fluidic structure gathers the main functionalities sought for in Pharmacy. We also show how FF has been adapted to satisfy an ample variety of pharmaceutical requirements to date.

Contents

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1. Introduction

1.1. Historical considerations. Tools and functionality

The 20th century has witnessed more than doubling in global life expectancy. In spite of wars and the advent of massive transport systems with a significant global rate of casualties, technological development together with the spread of basic scientific understanding has led to the progressive implantation of common, relatively simple practices and habits in our species (hygiene, food processing, vaccines, orthopedic aids, etc.) that resolve old cumbersome medical and functional problems of our bodies. These practices and habits involve *tools* whose degree of control on the natural processes involved is relatively narrow, but the results and the benefits that the *driven* processes provide are immense. From a historical perspective, natural processes and, in particular, biological processes, inherit an awesome pool of success in terms of individual survival, distilled by natural evolution on time scales as 10^{17} s (or 3000 years). On the other hand, artificial processes, tools and devices, and, in particular, processes aiming to health betterment are characterized by their inherently and extraordinarily short time scale of development compared to the former, i.e. about 10^{10} s or less (300 years or less). This reflects the absolutely unique, explosive power of our species.

Moreover, while the typical length scales associated with the artificial tools mentioned above span from 10^{-3} to 10^{1} m, the real phenomena that they drive or promote are instead processes on the 10^{-9} to 10^{-6} meter scale, either performed by microorganisms or by chemical reactions with a wide range of complexity, whose mechanisms still belong to nature realms. In this sense, the historical evolution of clinical medicine, therapeutics and pharmacy is entirely analogous to that of chemical and process engineering, which ultimately resorts to natural phenomena like turbulence or molecular diffusion driven by intelligent macroscopic design. Indeed, an admirable feature of our species' actions to boost individual and collective survival rate is that relatively small, but progressively larger intelligent intervention (in an *engineering* sense) into natural microscopic processes, from a macroscopic scale, promotes dramatic changes in terms of success. Here, a crucial factor is the intelligent identification of the *functionality* of natural or mass-produced materials that should address bio-availability, therapeutics and excretion aspects.

Naturally, the unstoppable advance of the cycle knowledge–technology–knowledge drives the drift of the artificial, engineering scale down to smaller and smaller figures, reaching molecular scales. Indeed, single atom manipulations can be performed by Atomic Force Microscopy (AFM) [1]. However, that geometrical downscale intervention very often goes in parallel with a downscale of yield, limiting massive productivity. The simple reason for that is the inherent nature of human designs and devices: *functional complexity*. This feature often limits the *number* of devices performing simultaneous or serial tasks, and that limitation is particularly serious when handling fluids (*microfluidics*), in contrast to the handling of charge currents (microelectronics). Many examples of functional complexity of devices performing extensive small-scale intervention in microfluidics can be found in the literature: see the excellent recent review [2] and the references therein. A significant source of impacting references from a single group can be found in [3] as well.

The limitations exerted by functional complexity and robustness impact productivity and, in the long run, massive incorporation of the implied methods or technologies in the global pool of good practicing & good manufacturing. For example, while the complex devices described in [4] yield beautiful micro-structures (multiply and preciously nested droplets in a highly controlled way), their quite limited productivity, robustness and practical functionality in areas like Pharmacy weight against massive implementation of those technologies. Thus, a natural question arises as to what factors limit the trade-off among artificial intervention, mass production and functionality.

1.2. Functional designs, materials and ingredients: mechanics versus Chemistry

Most artificial processes of interest in health care involve the use of substances delivered to an organism as Active Pharmaceutical Ingredients (APIs), Nutraceuticals, etc. An advocacy for the role of engineering design and modeling of drug delivery processes and its historical perspective can be found in the very recent review by Peppas this year [5] and the references therein. In this work we aim to extend such advocacy to a higher degree of detail.

Here, *functionality* involves two fundamental and very often completely separated steps: functional *product manufacturing* and *product* (*drug*) *delivery*. Traditionally, APIs are produced with a fundamental emphasis in chemical nature and limited care about their further handling and delivery; thus, product manufacturing for health care belongs to the fundamental technological realm of Chemistry, in the sense above-described. Chemistry is essentially a macroscopic science or technological field, and its successful and reproducible results have fascinated mankind since ancient times. Here, the accrued scientific knowledge on the structure and dynamics of materials and reactions on the molecular scale allows the mass production of functional materials or ingredients. In these cases, a precise macroscopic control of operational conditions (physical: temperature, pressure, velocity or residence time; chemical: pH, concentrations, etc.) and the use of catalyzers, geometries or surface treatments are enough for a sufficient, massive yield or production. This has several cons, though. First, the inherently stochastic nature of chemical reactions leaves room for the presence of undesired substances (by-products, reactants, etc.) in the final product (e.g., trans fats in artificial fat hydrogenation [6]). Furthermore, the many degrees of freedom appearing in chemical processes provoke the overlapping of operational ranges leading to different products, whose selection or separation is either performed through several secondary steps, or promoted ab initio by the use of specific catalyzers, different forms of the reactants, etc.

On the other hand, mechanical processes imply forces and energies on the molecular scale exceedingly small compared to those necessary to trigger chemical reactions. Chemistry often makes use of mechanical processes and devices to provide limiting frameworks to chemical reactions and minimize the abovementioned handicaps, without changing the chemical nature or reactants. Reducing bulk reactants or ingredients to granular matter is a typical mechanical preparatory step in chemistry; however, granular form can show an immense variety of features. Here, fundamental parameters are the size, shape and homogeneity of grains or particles. First, particle size determines the surface-to-volume ratio of a bulk material when particles are not too different