Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 59 (2007) 1453–1473
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Scanning probe microscopy in the field of drug delivery

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Received 27 July 2007; accepted 10 August 2007
Available online 25 August 2007

Abstract

The scanning probe microscopes (SPMs) are a group of powerful surface sensitive instruments which when used complimentarily with traditional analytical techniques can provide invaluable, definitive information aiding our understanding and development of drug delivery systems. In this review, the main use of the SPMs (particularly the atomic force microscopy (AFM)) and their successes in forwarding drug delivery are highlighted and categorised into two interlinked sections namely, preformulation and formulation. SPM in preformulation concentrates on applications in pharmaceutical processes including, crystal morphology and modification, discriminating polymorphs, drug dissolution and release, solid state stability and interaction. The ability of the AFM to detect forces between different surfaces and at the same time to operate in liquids or controlled humidity and defined temperatures has also been particularly useful in the study of drug delivery. In formulation, the use of SPMs in different drug delivery systems is discussed in light of different host entry routes.

Keywords: Drug delivery; SPM; AFM; Drug formulations; Surface characterisation

Contents

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0169-409X/$ - see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.addr.2007.08.020

1. Introduction

The ability to fully characterise drug systems, to provide drug targeting with high specificity and drug delivery with integrated controlled release are all a major challenge to the pharmaceutical industry [1]. These challenges have, in part, been difficult to meet due to often poor understanding of the physicochemical properties of drug systems. For example in solid dosage forms, surface interactions between particle–particle (for inhalation both drug and excipient combinations) and particle–devices are still not completely understood.

The family of scanning probe microscopes (SPMs) has revolutionised our ability to characterise and understand the interactions between drug systems and their exposed environments. These microscopes have enabled the study of pharmaceutical devices [2–5] and drug particles [6–8] with minimal pre-treatment in both air and liquid at the nanoscale level.

The need to characterise drug systems at the nanoscale plays a major role in all drug delivery issues from the initial characterisation of a new chemical entities (NCE) in preformulation (including, understanding of drug polymorphs, particle size, shape and crystallinity, and dissolution properties) through to drug processing (including, determination of chemical composition and stability studies), formulation (including, determining stability of solid/liquid dosage forms and understanding drug release within target host cells) and manufacture following scale-up.

This review aims to highlight some of the capabilities and successes of the SPMs in unravelling the challenges faced in the development and understanding of drug delivery systems. The future potential of these microscopes as a robust and routine drug formulation screening tool is also discussed. The papers described within this review are not exhaustive of the field but aim to offer a flavour of the broad range of areas in which SPMs have impacted.

2. Techniques

2.1. Concept of scanning probe microscopes

The SPMs are a family of microscopes which stem from the scanning tunneling microscope (STM) that was first developed in 1981 [9]. Since STM typically provides the highest spatial resolutions and access to electronic state information, it has since had a major impact in our understanding of metallic and semiconductor surfaces. However, the STM is less useful than its successors (for example the AFM) in the field of drug delivery because of its requirement of samples to be at least to same extent electrically conductive (or very thin films of non-conductive samples to be on a conductive substrate).

The SPMs are unique compared to other microscopes in that they rely on a fine probe tip to sense a samples surface and in doing so can either obtain topographical (by raster scanning in the x–y direction across the sample surface) [10] or localised force data as in the case of AFMs (by bringing the probe and the sample surface in and out of contact) [11].

Other SPMs, besides AFM, of most relevance to drug delivery include the nearfield scanning optical microscopy (NSOM) (developed in 1998) [12] and scanning thermal microscopy (SThM) [13–15]. These use light and heat respectively as signals which allow the probe to accurately sense and obtain surface profiles of different pharmaceutical samples. The AFM is the most widely used of the SPMs in the field drug delivery.

2.2. Atomic force microscope

2.2.1. Imaging

The AFM was invented and built in 1986 by Binnig, Quate and Gerber [16], based on the success of its predecessor, the STM [9]. The main features of the AFM include its ability to image non-conductive samples (therefore a range of biological and drug particles can be studied) and to measure the surface topography of samples at subnanometer resolution. Most importantly of all for pharmaceuticals the AFM can work under a range of conditions including in air and liquid over a range of temperatures, with minimal sample manipulation and low running costs [17–19].

During AFM imaging a sharp probe tip, usually made of silicon (Si) or silicon nitride (Si_3N_4) located on the underside of a flexible cantilever, raster scans over a sample surface. This motion is achieved using a piezoelectric scanner (Fig. 1). The bend and twist of the cantilever due to the forces of interaction between the tip and sample are monitored via a laser beam that is reflected from the back of the cantilever (often coated with a layer of metal to increase laser reflection) onto a position sensitive, quadrant photodiode detector. A relay to a feedback loop from the photodiode and the piezoelectric position scanner helps to maintain a set deflection, amplitude, frequency or phase of the lever dependent on the imaging mode being used.

There are three principle modes employed in AFM imaging. These are contact mode (CM-AFM), 'tapping' mode (TM-AFM) or intermittent mode and non-contact mode (NCM-