Pharmaceutica Analytica Acta
ISSN: 2153-2435

Scoutaris and Douroumis, Pharmaceut Anal Acta 2012, 3:8
DOI: 10.4172/2153-2435.1000e131

Editorial Open Access

AFM in Advanced Pharmaceutical Technology

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The necessity for development of new drug delivery systems for poorly soluble drugs and therapeutics which targets directly the pathogenic area requires the design of complex systems in nano-scale. Atomic Force Microscopy (AFM) since its discovery offers a unique tool to develop novel drug delivery systems. Its capability to investigate, characterise surfaces and measure forces with spatial resolution at nano-scale respectively contributes to develop and analyse pharmaceutical systems and biomedical devices with complex structures and chemistries.

Specifically, polymeric nanoparticles and liposomal drug formulation have been studied extensively by using AFM where their size and morphology where revealed [1]. However, apart from topographical information, AFM can provide details on the local compositions of the sample. There are many modes that can be used to achieve this but the most common is to monitor the phase shift of the oscillating cantilever in tapping mode Such 'Phase imaging' can be used to detect nanoscale variation in composition, adhesion, friction, viscoelasticity, and other properties of the materials. Changes in the phase lag often indicate changes in the properties of the sample surface. Phase imaging has proved an extremely useful tool for pharmaceutical characterization. Phase imaging has been used to reveal polymeric forms from single crystal measurements [2] to confirm phase separation of two copolymers for drug delivery [3], to establish the stability of the formulation on different environments [4] and to identify formation of amorphous domains during milling of crystalline salbutamol [5].

Moreover, the ability of AFM to operate on different conditions of temperature humidity and in liquid allows studying the kinetics of range of phenomena. An interesting work was published from Miyazaki et al. where the crystal growth rate of Nifedipine, dispersed in PEG polymer matrix, was quantified [6]. Also, the dissolution process of aspirin on different facets of the crystal was studied by Danesh et al. showing their differences in dissolution rate [7].

The ability of AFM to measure force measurements have been used to investigate interactions among the different compounds in the formulation. To achieve this, the AFM cantilever is modified by attaching a particle directly onto the probe tip and is brought in contact with the substrate of interest, the force required to separate them is the measure of their adhesion. This application of AFM has been used extensively to aerosol drug formulation where the API is associated with a carrier which is released in the site of actions. For instance, AFM has been used to investigate the adhesion force of salbutamol with different excipients [8]. Moreover, localised surface energy and young's modulus of various compounds have been measured. For example, *Young's modulus were derived from both PLA and PLA/everolimus* directly from stent surface on different temperatures. The results showed that everolimus does not affect the mechanical properties of PLA up to 1/1 (w/w) drug loading of the mixture. Also, a significant drop of the Young's modulus in solution was observed at 36°C, suggests that *in vivo* the Tg of the polymer is below body temperature [9]. Furthermore, force measurements have been used to identify the encapsulation the efficiency of liposomes as the rigidity of encapsulating liposomes is higher [10].

An extended application of AFM is the localised thermal analysis. In this case the sample is heated locally with a thermally active probe providing information about the glass transition temperature and the melting point of the sample at this location. LTA has proved useful for thin layers or coatings where bulk methods such as DSC, TMA and DMA cannot be applied. Bulk methods measure the mean thermal properties of a sample, whereas LTA can provide information about the spatial distribution of the thermal properties of a material surface which can be useful to design materials with the desired properties. Two different methods of LTA exists; scanning thermal microscopy (SThM) and nanothermal analysis (NTA) with spatial resolution of 500 nm and 100 nm respectively. LTA has been successfully applied to distinguish can distinguish different components in a drug dosage forms *in situ* with minimal sample preparation and high spatial resolution. Hence, SThM has proved to be a useful tool to discriminate polymorphic forms of drug [11] and the coating of a tablet and its core [12] whereas NTA has been implemented to characterise nano-dispersed pharmaceutical systems to confirm their heterogeneity [13].

The application of AFM in drug developing becomes more and more extended as the barriers need to overcome to bring NCE in the market are getting higher. Also, the continuing development of AFM technology provides scientists with a powerful tool to characterize and developing new medicines. Minimal sample preparation, use in ambient conditions, specimens at nano-scale in makes AFM an extremely versatile and useful weapon in pharmaceutics.

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Received October 22, 2012; **Accepted** October 24, 2012; **Published** October 26, 2012

Citation: Scoutaris N, Douroumis D (2012) AFM in Advanced Pharmaceutical Technology. Pharmaceut Anal Acta 3:e131. doi:10.4172/2153-2435.1000e131

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