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Review article

Nanoparticle delivery and particle diffusion in confined and complex environments☆

Hisham Al-Obaidi [a], Alexander T. Florence [b, *]

[a] Department of Pharmacy, King's College London, Stamford Street, London SE1 9NH, UK
[b] UCL School of Pharmacy, University College London, Brunswick Square, London WC1N 1AX, UK

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ABSTRACT

Multiple biological, chemical and physical factors influence and dictate the success or otherwise of nanocarrier mediated drug delivery and targeting. One issue is diffusion. This review considers aspects of the movement of nanoparticles in their passage from the selected point of administration to their intended locus of action, with an emphasis on the effects of particle diffusion in the often confined and complex spaces of the body. Diffusion of drugs and carriers rarely takes place in free unbounded spaces *in vivo*, it being more likely to occur, in part at least, in complex, heterogeneous locations, for example between villi and microvilli in the intestine, in the extracellular matrix of tumours and in the crowded environment of cell interiors. Flow in capillaries involves changing pressures, changing capillary radii and asymmetric bifurcations of vessels. Nanocarrier passage through pores and fenestrae in the process of extravasation, which itself is a stochastic process, may be impeded by particle jamming thus hindering procession towards cellular goals. While many of these processes have been difficult to study *in vivo*, there are many basic studies of these phenomena which can be applied to the biological situation. This overview examines diffusion-related phenomena and speculates on their importance in attaining the still elusive goal of achieving a significant proportion of the administered dose of nanoparticles (and hence drug) in target tissues.

At worst, one is in motion; and at best
Reaching no absolute in which to rest,
One is always nearer by not keeping still.

Thom Gunn from a poem in *The Sense of Movement*, Faber, 1957

1. Introduction

Targeting and delivery of drugs in nanoparticulate carriers is obviously dependant for success on both significant accumulation in target structures such as tumours and the release of the active agent at the appropriate site and rate to achieve an optimum concentration profile. To achieve this following intravenous administration, particles must extravasate (a stochastic process), pass into the extracellular matrix and then diffuse towards target cellular structures and perhaps also into cell nuclei. Extracellular matrices are not simple channels [1], and all cells have "crowded" environments [2]. There are of course advantages of drug administration in carrier systems which can result from a change in the biodistribution of active ingredients avoiding non-target organs, but the ultimate goal is normally specific organ targeting. Reduction in the rate of diffusion of particles in many circumstances impedes their ability to navigate readily to these ultimate sites. There are many consequences of diffusional behaviour which are not fully resolved: does reduction in the rate of diffusion of particles in the extracellular space of tumours decrease or enhance the possibility of optimal drug release from perhaps ultimately motionless particles? It is clear that it is dangerous to generalise: what applies to nanoparticles with one specific drug does not necessarily apply to systems of different construction, size, shape, flexibility and surface characteristics. Demetzos and Pippa [3] have recently provided one means of addressing the "nanosimilarity" or otherwise of constructs. And if tumours are targets they are in a sense moving targets often changing physically and biologically with time as they grow.

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* Corresponding author.
E-mail address: ataylorflorence@aol.com (A.T. Florence).

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Diffusion of both drug molecules and particles may occur under a range of conditions, in static systems such as in unstirred media, in flowing or turbulent media, in systems which have obstacles to their movement, or close to the walls of vessels and cells where there might be interactions between particles and walls. So-called anomalous diffusion is a feature of fractal systems [4] where particles are trapped in various bottlenecks and structural dead-ends.

We became interested in the topic of diffusion in complex or confined spaces when studying the dynamics of microparticles "corralled" inside isolated lipid vesicles [5] (a simple but instructive model system) and by an earlier encounter with the obstruction effect [6]. This short overview in considering diffusion and related issues elaborates on concerns expressed by many on the separation of expectations of nanoparticle targeting and the physical and biological realities in present approaches [7]. The challenges of the body's intricacies must be better understood. It is unlikely that an all-encompassing theoretical treatment will for some time predict particle flow and diffusion from administration via complex pathways to geometrically complex target elements. Here we can only address some of the issues in discussing particle diffusion in static and flowing media, in confined elements of the body such as capillaries, fenestrae, extracellular matrices, the intestinal epithelia, villi and microvilli, cells and nuclear pores.

2. Brownian motion and diffusion

The diffusion of small molecules, macromolecules and particles is evident in all biological systems and is the main mechanism by which biochemical messages are transferred [8,9]. The 19th century Scottish botanist Robert Brown [10] first described the motion of pollen particles in a static liquid suspension; the relationship between this Brownian motion caused by thermal motions in the liquid and the coefficient of diffusion of the particles (D), their radius (r) and the viscosity (η) of the continuous phase at a temperature (T) was solved by Einstein [11] and is embodied in the Stokes–Einstein equation (Equation (1)) for a single spherical particle of radius, r, where k is the Boltzmann constant. As $D = kT/f$ where f is the particle's frictional coefficient, ($f = 6\pi\eta r$) in a medium of viscosity η such that:

$$D = kT/6\pi\eta r \quad (1)$$

Equation (1) provides the stationary (self) diffusion coefficient in the absence of a concentration gradient (as in Brownian motion) and also in some of the situations discussed in the review.

The flux (J) of material, where dc/dx is the concentration gradient is given by

$$J = -D(dc/dx) \quad (2)$$

These equations have assisted in explaining many biological and physical processes such as the movement of DNA and proteins [12,13] and the absorption of drugs across epithelia [14]. R.K. Jain and colleagues [see for example: [15] have done much to illuminate the physicochemical and biological issues of tumour targeting.

The Stokes–Einstein equation is used widely to determine the radius of particles through techniques such as dynamic light scattering [16]. There are limits to its use, a lower size limit [17] (of around 2 nm) and an upper limit perhaps where sedimentation of larger particles is more dominant. Tuteja et al. [18] discuss the diffusion of particles in polymer liquids finding this to be faster than predicted by the Stokes–Einstein equation due to the fact – they surmise – that the particles have a smaller size than the polymer mesh.

The Brownian movement of asymmetric particles is clearly of interest with the advent of carbon nanotubes and other constructs as potential drug carriers. There are both the rotational and translational aspects of the behaviour of non-spherical carriers to be considered (see, for example references [19,20]). Brownian motion of ellipsoids has been addressed [21] considering the diffusion coefficient related to two frictional coefficients, γ_a and γ_b, respectively for parallel and perpendicular diffusion, hence $D_o = KT/\gamma_o$. As $\gamma_a < \gamma_b \dot{c} D_a > D_b$ when free rotation is impeded as it might be in restricted spaces. If the particles can rotate, rotational diffusion "washes out directional memory" in the words of Han et al. [21].

Fig. 1 represents the areas considered in this review in relation to three possible routes of particle administration, namely the intravenous, and oral routes and direct administration into the brain, the last to avoid a discussion here of the penetration of particles across the blood–brain barrier, a topic in itself.

The cytoplasm of individual cells is very heterogeneous in nature with organelles such as the Golgi complex in the micrometre size range to others with a size range of around 100 nm such as the endoplasmic reticulum (ER). The presence and size of cell organelles implies that hindrance to diffusion of nanoparticles is likely and considerable [22,23], and this at the end of the tortuous journey from site of administration. As suggested by Fig. 1, the procession to the site of action is challenging. Sinek and colleagues [24] summarise the general situation so well writing "the performance of micro-and nanodevices must be considered in the context of a dynamic, biological environment, spanning several scales and modes, including the intravascular, the intratumoral and even the intracellular … it is not only what such devices do in isolation that requires investigation, but also what they do in the body, and what the body does, or attempts to do, to them".

Orally administered nanosystems are a case in point. They will be present in the heterogeneous contents of the gastrointestinal tract. Some will escape and interact with the gut associated lymphoid tissue and Peyer's patches where a degree of uptake can occur [25] and they are then transported via the lymphatic system towards the blood circulation; others are absorbed by enterocytes. The presence of villi and microvilli which facilitate the absorption of drug molecules may have an influence on the uptake of nanoparticles, but the question is in which way? Uptake of nanoparticles may result from the entrapment of the nanoparticles within the confines of the villi despite the movement of the intestinal contents towards the colon. Does hindered diffusion result in enhanced absorption of particles entrapped close to the villous surfaces? It is perhaps a balance between the convective flow of the fluid versus entrapment. Outcomes will depend on the properties of the nanoparticles such as their shape and surface charge or decoration. Hydrophilic poloxymer coatings deter nanoparticle uptake by the gut-associated lymphoid tissue (GALT) [26] perhaps by making close contact with absorbing surfaces difficult.

Even in tissue culture – on which much exploratory work depends – particles *"diffuse, settle and agglomerate"* cellular dose is therefore a function of these factors as pointed out by Teeguarden et al. [27]. The same group [28] have developed a computational model to encompass these phenomena to better estimate in vitro dosimetry of nanoparticles.

3. Particulate diffusion

Normal patterns of unfettered particulate diffusion as a function of time are shown in Fig. 2. As time progresses particles move out from the point of origin but not in an equal manner. Thus in this situation few particles would have reached the extremities. This model does not encompass convection, flow and the other factors which can propel particles *in vivo*.

Particle size is of key importance as the Stokes–Einstein Equation (1) for a single particle dictates. Particle concentration matters