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Nanotechnology versus other techniques in improving drug dissolution

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Abstract

Many newly discovered drug molecules have low aqueous solubility, which results in low bioavailability. One way to improve their dissolution is to formulate them as nanoparticles, which have high specific surface areas, consequently increasing the dissolution rate and solubility. Nanoparticles can be produced via top-down or bottom-up methods. Top-down techniques such as wet milling and high pressure homogenisation involve reducing large particles to nano-sizes. Some pharmaceutical products made by these processes have been marketed. Bottom-up methods such as precipitation and controlled droplet evaporation form nanoparticles from molecules in solution. To minimise aggregation upon drying and promote redispersion of the nanoparticles upon reconstitution or administration, hydrophilic matrix formers are added to the formulation. However, the nanoparticles will eventually agglomerate together after dispersing in the liquid and hinders dissolution. Currently there is no pharmacopoeial method specified for nanoparticles. Amongst the current dissolution apparatus available for powders, the flow-through cell has been shown to be the most suitable. Regulatory and pharmacopoeial standards should be established in the future to standardise the dissolution testing of nanoparticles. More nanoparticle formulations of new hydrophobic drugs are expected to be developed in the future with the advancement of nanotechnology. However, the agglomeration problem is inherent and difficult to overcome. Thus the benefit of dissolution enhancement often cannot be fully realised. On the other hand, chemical strategies such as modifying the parent drug molecule to form a more soluble salt form, prodrug, or cyclodextrin complexation are well established and have been shown to be effective in enhancing dissolution. Thus the value of nanoformulations needs to be interpreted in the light of their limitations. Chemical approaches should also be considered in new product development.

Introduction

Many new drugs discovered in recent decades are hydrophobic and poorly soluble in water. This poses challenges in their formulation and delivery. Improving the solubility would enhance bioavailability, especially if the drug concerned belongs to Class II (low solubility, high permeability) in the Biopharmaceutics Classification System (BCS) [1] because dissolution is the rate-limiting step. Lipid/organic solutions/emulsions are not always viable because organic solvents are toxic and the liquid volumes required for dosing may be too large to be practical.

Drug dissolution can be improved by increasing the particle specific surface area (surface area-to-mass ratio) because dissolution is a surface phenomenon. Formulating drugs as nanoparticles is such an approach that is gaining global interest due to advancements in nanotechnology. Particles of sizes between a few nanometres to 1000 nm are generally considered as nanoparticles in the pharmaceutical field [2]. Nanoparticles are versatile and can be applied to any route of administration, including intravenous injection, because nanoparticles are sufficiently small for intracapillary passage [3]. The term 'nanoparticle' has many connotations. It has been used to refer to nanometre-sized solids, micelles, liposomes, and dendrimers. This review focuses on the dissolution properties and formulation aspects of nanometre-sized solids. Thus the term 'nanoparticle' is used to refer to such solids in this article.

Dissolution properties of nanoparticles

Dissolution rate of solids in general is described quantitatively by the Nernst-Brunner equation:

$$\frac{dM}{dt} = \frac{DS}{Vh}(C_S - C)$$ (Equation 1) [4]

where *M* is the mass of drug dissolved in time *t*, *dM/dt* the mass dissolution rate, *D* the diffusion coefficient of the solute in solution, *S* the surface area of the solid drug exposed to the solvent, *V* the volume of the dissolution medium, *h* the diffusion layer thickness, C_S the solubility of the drug at the solid surface, and *C* the solute concentration in the bulk solution at time *t*. Nanoparticles increase dissolution rate (*dM/dt*) by increasing two variables in the equation, namely, the surface area (*S*) and solubility (C_S). These are discussed separately below.

Surface area

Nanoparticles have a larger surface area than that of micron-sized particles of the same volume. Consider the following example for the purpose of illustration. A 100 μm cube has a volume of 10^6 μm^3 and a total surface area of 6×10^4 μm^2. If this cube is divided into 100 nm cubes, the total volume remains the same but the total surface area will become 6×10^7 μm^2, which is a thousand-fold increase in surface area. In general, the surface area is increased by the same factor as that for size reduction. By increasing the surface area available to the solvent, the dissolution rate will also be increased (Equation 1). However, this effect is only realised if the nanoparticles are dispersed in, and fully wetted by, the solvent as discrete particles, which is often not the case in reality. Nanoparticles are usually very cohesive due to their high surface energy [5] and large specific surface area available for van der Waals

interaction [6]. Thus they have a high tendency to form aggregates and reduce the effective surface area exposed to the solvent. Nanoparticles have been observed to form random aggregates when exposed to the dissolution medium and displayed dissolution profiles suggestive of those of larger particles [7]. This confirmed that the nanoparticles behaved as aggregates rather than as primary particles during dissolution. Besides the problem of aggregation, the hydrophobicity of the nanoparticles also disfavours wetting. These are the challenges that need to be overcome during formulation and dissolution testing, as discussed in later sections.

Solubility

Solubility is also known as the saturation concentration, which is the maximum concentration that a compound can achieve in solution for a particular solvent. For particles of sizes in the micrometre range or larger, the solubility is generally independent of particle size. However, the solubility of nanoparticles increases with decreasing particle size [2]. This can be explained by the Ostwald-Freundlich equation:

$$\ln(\frac{C_{s,r}}{C_{s,\infty}}) = \frac{2\gamma V_m}{rRT}$$ (Equation 2) [8]

where $C_{s,r}$ *and* $C_{s,\infty}$ are the solubilities of a drug particle with radius r and ∞ (i.e. a flat solid drug surface), respectively, γ is the interfacial tension between the liquid medium and the particle, V_m the molar volume of the drug molecule, R the universal gas constant, and T the absolute temperature. From the equation, it is evident that $C_{s,r}$ increases with decreasing particle size. Therefore nanoparticles have a higher saturation concentration than their micron-sized counterparts. Since *dM/dt* is proportional to the concentration gradient $(C_S - C)$ (Equation 1), increasing the solubility will also increase the dissolution rate.

Amorphicity

Depending on the composition and the production method and conditions, the resultant nanoparticles may be crystalline or amorphous (production methods are discussed in a later section). Amorphous solids have higher free energy, enthalpy, and entropy than the corresponding crystalline form [2, 9-11]. That means it is easier for amorphous drugs to go into solution. Consequently, they have higher dissolution rates and solubility than crystals of the same particle size [2, 9-11]. Therefore, from the viewpoint of dissolution enhancement, amorphous nanoparticles would be the ideal formulation [2]. However, this would only be acceptable if the nanoparticles can remain amorphous over the product shelf life because stability is the overriding criterion for any pharmaceutical formulation. There are hitherto no reported studies comparing the dissolution rates between amorphous and crystalline nanoparticles of the same formulation and of the same particle sizes. Particles of different formulations and/or different particle sizes are involved in comparison studies. Perhaps this is due to the difficulty in controlling all the variables except for the solid state. For instance, the dissolution rates of three ziprasidone formulations have been tested: 1) lyophilised ziprasidone mesylate-sulfobutyl ether β-cyclodextrin amorphous complex, 2) wet-milled ziprasidone free base nanocrystal suspension, and 3) jet-milled micron-sized ziprasidone hydrochloride crystals, which differ by salt form, particle size, excipient, and solid state [12].

Nanoparticle production methods

There are two categories of nanoparticle production methods, namely, top-down and bottom-up. Top-down techniques obtain nanoparticles through size reduction of large particles while bottom-up approaches form nanoparticles from assembling molecules in solution. In general,

top-down and bottom-up methods produce crystalline and amorphous nanoparticles, respectively.

Top-down methods

Large drug particles can be broken down to nano-size by wet milling or high pressure homogenisation. In wet milling, the particles are crushed and fragmented by milling beads whilst suspended in a non-solvent, which is usually water for hydrophobic drugs [13-15]. A stabiliser may be added to the suspension if needed to prevent nanoparticle agglomeration [13]. The liquid medium facilitates recrystallisation of amorphous surfaces generated during milling. Industrial scale wet milling (NanoCrystal® Technology, Elan Pharma) has been used for the production of marketed pharmaceutical products, such as Rapamune® (rapamycin/sirolimus; oral tablet), Emend® (aprepitant, oral spray coated capsule), TriCor® (fenofibrate; oral tablet), Megace® ES (megestrol acetate; oral nanosuspension), and INVEGA® SUSTENNA® (paliperidone palmitate; injectable nanosuspension) [13]. These products have better bioavailability than if the drugs were formulated as large particles. More drugs have been successfully wet milled into nano-formulations using a variety of stabilisers. These have been comprehensively reviewed by Merisko-Liversidge and Liversidge [13].

High pressure homogenisation includes microfluidisation and piston-gap homogenisation. In microfluidisation, large particles are milled by the collision of two high pressure fluid jets [16]. On the other hand, piston-gap homogenisation breaks down particles by forcing a liquid suspension of the drug at high pressure through a narrow gap or channel inside a pipe [16, 17]. Bubbles form inside this gap for aqueous liquids. When the bubbles pass out from the narrow gap, they collapse and generate the cavitation energy that break down the particles. The

marked product Triglide® (fenofibrate) is made by high pressure homogenisation by SkyePharma [18].

Bottom-up methods

Nanoparticles can be formed from molecules in solution by precipitation or controlled evaporation of droplets. Since these processes are relatively rapid (in the order of microseconds to a few seconds), there is very little time for the molecules to arrange into regular crystal lattices during particle formation. Thus bottom-up methods often produce amorphous nanoparticles.

Precipitation

Two modes of precipitation are possible: anti-solvent or reactive [19]. In anti-solvent precipitation, a drug solution is mixed with an anti-solvent to induce precipitation of the drug. The solvent and anti-solvent must be miscible. For hydrophobic drugs, the solution is made with an organic solvent (e.g. ethanol, isopropanol, acetone) and the anti-solvent was water. To improve the stability of the nanosuspension, excipients such as surfactants (e.g. sodium glycocholate, sodium dodecyl sulfate, lecithin) [20-22] or polymers (e.g. low molecular weight polyvinylpyrrolidone (PVP), Tween® 80, Poloxamer 188) [21] may be added to the formulation. These stabilisers control particle growth and prevent aggregation after mixing by adsorbing onto nanoparticle surfaces and forming steric or, if they are charged, electrostatic barriers [19]. Reactive precipitation follows a similar procedure to that described above except that precipitation is induced by a chemical reaction instead of an anti-solvent. For instance, an organic solution of salbutamol base is mixed with sulfuric acid to produce salbutamol sulfate nanoparticles [23].

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Nanosuspensions by precipitation are quite easy to produce. They can be made with standard laboratory glassware and magnetic stirring, if the materials and conditions are optimal [19]. However, to have better control on the precipitation kinetics and particle size distribution, more sophisticated techniques and apparatus are needed to achieve rapid micro-mixing [19], which is mixing on the molecular scale dominated by diffusion [24]. Such methods include high-gravity controlled precipitation (HGCP) [25-27], flash precipitation using confined liquid impinging jets (CLIJ) [20, 28, 29] or multi-inlet vortex mixers (MIVM) [22, 30-33], supercritical fluid technology [34-36], and sonoprecipitation [37]. Of these, HGCP can produce both amorphous [38, 39] and crystalline [23, 39-41] nanoparticles and has been applied in industrial scale production.

Controlled droplet evaporation

Solutes in droplets will form particles after the solvent has evaporated. If the initial droplet size is sufficiently small or if the solute concentration is dilute, then nanoparticles will result after drying. This can be achieved with a Nano Spray Dryer [42, 43], an aerosol flow reactor [44-48], or an electrospray [49, 50], all of which involve atomising the drug solution into an aerosol followed by solvent evaporation and particle collection. The drying parameters may affect the characteristics of the nanoparticles. There was a systematic study that investigated the various factors that influenced the production of spray dried bovine serum albumin nanoparticles [43]. The morphology and particle size were affected by the concentration of surfactant (Tween 80) and nozzle mesh size, respectively [43]. The inclusion of the surfactant produced smooth spherical particles. On the other hand, wrinkled, donut-shaped, and irregular particles were produced without the surfactant. This was attributed to a change in

the balance between surface and viscous forces of the protein solution by the surfactant [43]. The aerosol flow reactor offers control on the temperature history and droplet residence time during drying. Spherical beclomethasone dipropionate nanoparticles with a geometric mean diameter of 80 nm at 40°C have been produced using this method [19]. When the drying temperature was adjusted to 160°C, the particle size increased to 125 nm and cavities formed inside the particles. The faster evaporation rate at the higher temperature led to the formation of a solid crust at the particle surface that prevented the diffusion of solute to the interior [19]. The drying temperature may also influence the solid state of the resultant nanoparticles. Therefore, the aerosol flow reactor may be used to control the particle polymorphic form and morphology.

Stability issues of nanoparticles

Stability issues can be chemical or physical in nature. Nanoparticles are either dried or suspended in a liquid with low solubility for the drug. Therefore they are quite stable chemically in general. The major issue for nanoparticles is physical instability, which include agglomeration, Ostwald ripening, and solid state changes.

Due to their large specific surface area and high surface energy, nanoparticles in liquid media tend to aggregate to lower the energy state of the system. This may lead to sedimentation, uneven dosing, and dissolution rate reduction because the exposed surface area is decreased [51]. Stabilisers such as surfactants (e.g. sodium dodecyl sulphate, Tween 80) and polymers (e.g. polyvinylpyrrolidone, Pluronics®) may be added to the formulation to improve the stability of nanosuspensions. A comprehensive list of stabilisers is available in the literature [51, 52]. The stabilisers adsorb onto the surface of the nanoparticles and provide steric and/or

electrostatic barriers to keep the nanoparticles apart, hence stabilising the nanosuspension. Ions in the liquid medium form an electric double layer on the surface of the nanoparticles in suspension because particle surfaces are charged [51]. The electric potential at the outer layer is called the zeta potential and is an important indicator of the physical stability of the nanosuspension. The zeta potential should be about ±30 mV minimum if the nanosuspension is to be stabilised by electrostatic repulsion only [53]. If the stabilisation is to be maintained by both steric and electrostatic means then ±20 mV is adequate [53].

Ostwald ripening occurs due to the differential solubility between particles of different sizes. The smaller the particle, the higher is its solubility (Equation 2). If the drug is sufficiently soluble in the liquid, it can gradually dissolve from the smaller particles and come out of solution on the larger particles. Consequently there would be a net increase in particle sizes. A narrow size distribution will minimise Ostwald ripening [54]. If the drug is hydrophobic and the nanosuspension was produced by anti-solvent precipitation, the residual solvent content can be removed to lower the solubilising capacity of the liquid. Hence Ostwald ripening can be minimised [54]. Stabilisers adsorbed on the surface of the nanoparticles also decreases mass transfer that leads to particle growth [55].

As mentioned above, top-down techniques may introduce amorphous regions on the milled particles. On the other hand, amorphous particles are often produced from bottom-up processes. Amorphous materials have a higher energy state than their crystalline counterparts. Thus they would change into the crystalline form under favourable conditions, such as temperature, humidity, and other ingredients in the formulation. The presence of crystalline particles can also induce the crystallisation of amorphous material [56]. However, amorphous hydrocortisone and all-trans retinoic acid nanosuspensions made by precipitation have been

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found to be stable after storage at room temperature for 3 months and refrigerated for 6 months, respectively [57, 58]. Besides the crystallisation of amorphous solids, crystalline nanoparticles may undergo polymorphic changes. Nanosuspensions were made from two crystal forms of diclofenac (DCF1 and DCF2) by high pressure homogenisation [59]. It was found that this top-down technique transformed DCF2 to DCF1 in the resultant nanosuspensions, while the original DCF1 remained the same form as nanoparticles.

Formulation strategies for enhancing nanoparticle dissolution

Although a couple of nanoparticle formulations are marketed as suspensions (Megace ES and INVEGA SUSTENA), all the others are oral tablets (Rapamune and TriCor) or capsules (Emend). For patient compliance and ease of storage and handling, solid dosage forms are desired whenever possible. It may also be preferable to formulate some parenteral products as dry powders for reconstitution because stability is generally better in the solid state. After the nanoparticles are produced by a wet method (e.g. wet milling or precipitation), the nanosuspension would need to be dried before processing into usable solid dosage forms. Possible drying methods include spray drying [22, 60, 61], freeze drying [62, 63], spray freeze drying [64-66], and fluid bed granulation [67]. The nanoparticles would very likely be agglomerated after drying. That is very difficult to avoid. The important requirement is that the dried nanoparticles can redisperse readily and fully when they come into contact with water [7, 68, 69]. If they remain aggregated in liquid then the maximal surface area is not regained. This obviously defies the original aim of formulating them as nanoparticles for dissolution enhancement.

Redispersion of hydrophobic nanoparticles in water is particularly difficult due to their nonpolar nature [61]. Thus hydrophilic excipients are often added to nanosuspensions to minimise agglomeration of the nanoparticles upon drying and aid their future redispersion [13, 19, 21, 69]. These excipients form a matrix in which the nanoparticles are embedded after drying, hence they are called 'matrix formers'. Examples of conventional matrix formers include sugars (e.g. lactose, sucrose), polyols (e.g. mannitol, sorbitol), and hydrophilic polymers (e.g. high molecular weight polyethylene glycol (PEG), polyvinyl alcohol (PVA), PVP) [54, 69, 70]. Some excipients that are normally used in tablet and capsule formulations have been tested as non-traditional matrix formers (e.g. anhydrous dicalcium phosphate, microcrystalline cellulose, colloidal silicon dioxide, Inutec®SP1 (a polymeric surfactant modified from inulin) [18, 69]. The hydrophilic matrix enhances the wetting, redispersion, and dissolution of the nanoparticles by drawing water into the aggregates. Surfactants added for stabilising the nanosuspension would also facilitate wetting [13]. It has been shown that the dissolution of cyclosporine A nanoparticles was enhanced by co-spray drying with increasing amounts of mannitol as the matrix former [22]. Although the various types of matrix formers share the same mechanism of action, their actual performance may depend on other formulation factor [69]. Sucrose was found to improve the dissolution of loviride nanocrystals after freeze drying but it did the opposite with itraconazole [18, 71]. It was also observed that if too much sucrose was added, agglomeration became more prominent in the final phase of freeze drying [18]. On the contrary, higher amounts of microcrystalline cellulose increased dissolution of lyophilised itraconazole nanocrytals [18]. Of these non-traditional matrix formers listed above, microcrystalline cellulose and Inutec SP1 showed the best redispersion effects with itraconazole [18, 69]. The effects of mannitol and PVA on the redispersion of spray freeze dried polycaprolactone (PCL) nanoparticles have been investigated [64]. After spray freeze drying, the PCL nanoparticles were distributed

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throughout the porous mannitol matrix. On the other hand, although PVA coated the surface of the compact nanoparticle agglomerates but achieved better redispersion in water than mannitol [64]. The aforementioned examples illustrate that the type and amount of matrix former used should be considered on a case-by-case basis. A list of various drug-matrix former combinations reported in the literature is available in a review by Van Eerdenbrugh et al [52]. It is possible to produce a solid dosage form from dried nanoparticles that has the same bioavailability as the corresponding nanosuspension by optimising the type and proportion of excipients [13].

Dissolution improvement of herbal medicines using nanoparticles

Besides enhancing the dissolution of synthetic drugs, nanotechnology has also been applied to hydrophobic therapeutic compounds derived from medicinal herbs, such as curcumin, artemisinin, camptothecin, and berberine. Thus formulating them as nanoparticles may improve their solubility and bioavailability.

Curcumin is a polyphenol from turmeric rhizomes (*Curcuma longa*) and has anti-inflammatory, antioxidant, and anticancer properties. Curcumin-loaded poly(lactic-coglycolic acid) (PLGA) nanoparticles had been produced by first adding raw curcumin to a PLGA/chloroform solution under ultrasonication [72]. Then this mixture was added to a 2% PVA aqueous solution/ethanol mixture, also under ultrasonication, to produce the nanosuspension. This suspension was centrifuged to remove the solvents and replaced with deionised water, followed by lyophilisation. The mean diameter of the spherical curcumin particles was 45 nm, with an encapsulation efficiency of approximately 91% [72]. They were found to reduce the viability of several prostate cancer cell lines more significantly than the

raw drug [72]. Another curcumin nanoparticle formulation was prepared by anti-solvent precipitation, followed by organic solvent removal by rotary evaporation [73]. The mean diameter of the resultant amorphous particles was approximately 143 nm. The dissolution profile of these nanoparticles in aqueous medium was significantly better than that of the raw micron-sized drug, with > 99% and < 1% curcumin released after 60 minutes, respectively [73].

Artemisinin is an anti-malarial isolated from the Chinese herb, *Artemisia annua* (qing hao), and has also been identified to possess anticancer properties [74]. Nanoparticles with mean diameters of about 800 nm of this compound had been produced by spray drying an ethanol solution. These particles showed fast dissolution, with > 90% artemisinin released in 2.5 minutes [74]. The dissolution rate could be controlled for sustained release by coating the nanoparticles with various layers of oppositely charged polymers such as alginate, chitosan, and gelatin [74].

Camptothecin is an alkaloid from *Camptotheca acuminate*, is another anticancer compound. It had been formulated with a modified glycol chitosan–5β-cholanic acid conjugate, which acted as the carrier [75]. Camptothecin was mixed the carrier polymer in dimethyl sulfoxide (DMSO), followed by dialysis, centrifugation, and lyophilisation to obtain the nanoparticles. The drug encapsulation efficiency was > 80%, with mean particle diameters of about 280 nm [75]. The anticancer activity of the nanoparticles was compared to that of raw camptothecin dissolved in 10% DMSO/phosphate buffered saline on tumour-bearing mice by intravenous injection. The nano-formulation reduced the tumour volume more significantly than the raw drug solution when both were administered at 30 mg camptothecin/kg [75].

Berberine is an alkaloid found in a variety of plants, mainly from the *Berberis* species but also from the Chinese herbs *Phellodendron amurense* (huang bo) and *Coptis chinensis* (huang lian) [76]. This compound has been shown to have many therapeutic properties, including antimicrobial, antihypertensive, antidiabetic, anti-hypercholesterolaemia, antidepressant, and anticancer, amongst others [76]. Berberine-chitosan nanoparticles had been prepared by anti-solvent precipitation [77]. The particles were spheroidal, with a mean diameter of 268 nm and an encapsulation ratio of about 65%. The *in vitro* berberine release rate in saline in 6 and 24 hours was 56.8% and 65.6%, respectively [77]. The release rate was higher in artificial gastric juice, which was acidic, at 85.1% in 24 hours [77].

Dissolution testing of nanoparticles

During product development, it is imperative to measure the dissolution of a formulation to assess its performance. To serve this purpose, the testing method must be able to determine dissolution behaviour accurately. It has been shown for micon-sized hydrophobic particles that wetting worsens with decreasing particle size [78]. This problem is even more significant for nanoparticles, especially if they are in powder form, so it is important to employ a suitable method for their dissolution measurement.

Current dissolution equipments for pharmaceutical powders include the paddle, basket, flow-through cell, and dialysis bag [68]. Except for the dialysis bag, the other three are official apparatus of the British and United States Pharmacopoeias (BP and USP) but they are not specified for nanoparticles [79, 80]. Until recently, the methods have been used on nanoparticle formulations by researchers with varying success due to a lack of comprehensive assessment on their suitability for nanoparticles [68]. Using nanoparticles of cefuroxime

axetil, a BCS Class II compound, as a model drug, Heng et al [68] compared the effectiveness of the four dissolution apparatus. Only the flow-through cell could determine the dissolution profile of the nanoparticles properly and reproducibly [68]. This was corroborated by the fact that the flow-through cell is recommended in the current edition of the BP for lipophilic solid dosage forms [79] and its effectiveness for these formulations had been demonstrated in previous studies [81, 82]. In this setup the powder is held on a plane inside the cell and is exposed to a constant flux of dissolution medium [68]. This minimises potential problems due to poor wetting and powder floatation. The discriminating power of the apparatus is higher at low flow rates [83]. The dissolution profile could not be accurately measured by the other three apparatus [68]. The paddle method showed poor wetting and high variability because the powder floated on the surface of the dissolution medium [68]. In the basket method, although the powder was initially forced to submerge into the dissolution medium, the powder floated and aggregated together afterwards inside the basket [68]. This also resulted in high variability in the data. The paddle and basket methods had been shown to generate non-uniform convections in the dissolution medium and introduce errors in the measurements [84, 85]. The dialysis bag acted as a barrier to dissolution, even though the molecular cutoff size was 12–14 kDa [68]. The low drug level detected in the bulk dissolution medium indicated that drug diffusion from the dialysis membrane was the rate-limiting step and caused an artefact in the measurement.

After the suitability of the flow-through cell was established for nanoparticles, the apparatus has been successfully employed to differentiate the dissolution profiles of cyclosporine A nano-matrix formulations containing various amounts of mannitol as the hydrophilic matrix former [22]. However, even when the flow-through cell is used, a small amount of surfactant (e.g. 0.1% w/v sodium dodecyl sulfate[68], 0.25% w/v Myrj [22]) may be required in the

dissolution medium to facilitate wetting. The surfactant concentration cannot be too high because it will introduce artefacts by enhancing dissolution, especially if it is higher than the critical micelle concentration [86].

Theoretical versus actual dissolution behaviour

The primary aim of formulating hydrophobic drugs into nanoparticles is to increase their dissolution and ultimately, their bioavailability. The advantage of nanoparticles can only be fully utilised if they are completely dispersed so that all of the available surface area is exposed. Since the surface area is increased by the same factor as that for size reduction (see above) and the dissolution rate is directly proportional to the surface area (Equation 1), therefore the dissolution rate is increased by the same factor as that for size reduction. Indeed, this has been demonstrated in the dissolution of nanoparticles in suspension that had not undergone drying [55]. The dissolution rate of megestrol acetate and griseofulvin nanosuspensions produced by supercritical fluid extraction of emulsions was found to be five- to ten-fold higher than their jet-milled, micron-sized counterparts [55]. The volume-weighted diameters of megesterol acetate and griseofulvin nano- and micro-particles being compared were 254 vs 2900 nm and 760 and 5900 nm, respectively. The factor of size reduction for both drugs falls within the range of increase in the dissolution rate (Figure 1). Through mathematical modelling, the main determinants of the dissolution of these nanoparticles were identified to be the specific surface area and surface dissolution kinetics [55].

It must be noted that in the above study the nanoparticles remained in suspension after production and did not undergo drying. The nanoparticles were stabilised with lecithin,

Pluronics, PVA, Span 80, or Tween 80 [55]. Known volumes of the suspensions were introduced directly into dissolution bath with constant stirring. The nanoparticles could remain well-suspended under these favourable circumstances thus their dissolution conformed to theory. However, ideal dissolution behaviour of nano-formulations is rarely encountered because nanoparticles agglomerate easily, especially if they have been dried [7, 87, 88]. Sager et al [87] reported the difficulty and variability in dispersing carbon black and titanium dioxide nanoparticles in biological fluids such as phosphate buffered saline and murine bronchoalveolar lavage fluid. Micron-sized agglomerates were observed by optical and electron microscopy. Consequently the effective surface area exposed to the liquid media was reduced.

Agglomeration and even fusion of pure drug nanoparticles often occur upon the drying of nanosuspensions. Interparticulate fusion was observed in the scanning electron micrographs of lyophilised diclofenac nanoparticles produced by high pressure homogenisation [59] and the vacuum-dried cefuroxime axetil nanoparticles made by anti-solvent precipitation [7]. The 300 nm cefuroxime axetil nanoparticles were 'interconnected by many bridges', akin to the shape of peanuts [7]. The dissolution behaviour of the dried powder was found to consist of two stages. The bridges between the primary nanoparticles dissolved first and released the individual particles [7]. Then the nanoparticles formed random agglomerates in the liquid and continued the dissolution in this configuration. This was supported by the observation that the dissolution rate could be increased by dispersing the agglomerates using ultrasonication [7]. Although the tabletting of nanoparticle powders may worsen the dispersion due to the extra interparticulate bonding former under high pressure, loading the powder into a capsule only slightly improved the dissolution rate over tabletting [88]. This indicates that the aggregation of the nanoparticles in the liquid is the rate-limiting factor. Increasing the amount of

surfactant in the formulation can partially increase drug release [88] but it will not eliminate the problem altogether. Due to the potential toxicity and adverse effects on the physicochemical properties of the formulation, there are limits to the amount of surfactant that can be incorporated. Therefore, despite the significant effort that has been devoted to developing nano-formulations, it may not be suitable for all hydrophobic drugs, especially if aggregation is a major problem. The solubility issue in these cases may be better solved by using other strategies.

Other dissolution enhancement techniques

Increasing the surface area of drug particles by size reduction is a physical approach to improve dissolution. On the other hand, chemical techniques involving molecular transformation or interactions may also be used for that purpose. Examples of these include the applications of soluble salt forms, prodrugs, and cyclodextrin complexes. Micelles and liposomes have also been used to enhance dissolution. However, they are only limited in wet formulations (i.e. emulsions). It is very challenging to dry micelles and liposomes without damaging them. On the other hand, the other three modalities enumerated above can be easily produced as solids, which is precisely the state that requires dissolution enhancement the most. Therefore they are examined in turn below.

More soluble salt forms of an otherwise poorly soluble drug have long been employed in pharmaceutical formulations. Since the solubility of a compound depends largely on its chemical structure, the salt forms are the best candidates for achieving better dissolution. The improvement in the solubility of an organic molecule may be enhanced more significantly by an ionised functional group than by any other single method [89]. For instance, the aqueous

solubility of naproxen base, naproxen sodium, and naproxen choline at 25°C is 0.07, 266, and 472 mg/mL, respectively [89]. This improvement in solubility of four orders of magnitude is very difficult to achieve by simply formulating the drug as nanoparticles. In general, the pharmacology of the various salt forms of a given drug should not differ [89]. However, the physicochemical properties of the salt forms are expected to be different. This results in differences not only in their solubility, but also their dissolution rate [89]. Thus their pharmacokinetics and pharmacodynamics would also differ. Besides their influence on clinical effects, differences in physicochemical properties (e.g. density, melting point, hygroscopicity, stability, polymorphism, compactability etc) would also affect formulation and manufacturing [89-91]. Selection methods of the optimal salt form for drugs have been reported in the literature [90, 91].

Prodrugs have also been used in the pharmaceutical industry for many years. These are modified compounds that have an inert promoiety covalently bonded to the drug molecule to render preferred physicochemical properties. The promoiety is subsequently removed by enzymatic and chemical processes inside the body to regenerate the parent drug to exert therapeutic actions. The promoiety is typically joined to the parent molecule via a phosphate, ester, or peptide bond because they can be cleaved by the phosphatases, esterases, and peptidases in the body, respectively. The prodrug approach can increase dissolution if an ionisable or polar promoiety is added to a poorly soluble molecule. Many examples of prodrugs used for enhancing dissolution and bioavailability (e.g. fosphenytoin, sulindac sulfoxide, amiodarone disodium phosphate etc) are available in a comprehensive review by Stella and Nti-Addae [92]. Even covalently bonded lipid promoieties has been shown to increase water solubility of the poorly soluble phenytoin from 0.03 mg/mL of the parent molecule up to 2.38 mg/mL of the conjugates [93]. Obviously, the prodrug has different

physicochemical properties to those of the original compound. However, unlike a salt form, the prodrug is supposed to be inactive until after bioconversion. Thus the timing of the removal of the promoiety with respect to dose administration is very important as it can affect the pharmacokinetics and pharmacodynamics [94]. The location and kinetics of the bioconversion process will affect the therapeutic outcome. Any unwanted adverse effects of the supposedly inert prodrug should be considered too. Nevertheless, the prodrug approach is worthwhile for improving solubility because small chemical modifications can yield marked changes in the physicochemical properties [93].

Poorly soluble drugs have been formulated with cyclodextrins (CDs) to form aqueous soluble complexes. The pharmaceutically relevant cyclodextrins are α-, β-, and γ-CDs, which are naturally occurring cyclic oligosaccharides consisting of six, seven, and eight glucose units, respectively. The CD molecules are ring-shaped, with a hydrophilic outer surface and a hydrophobic cavity. Thus lipophilic drug molecules can interact with the cavity and form a complex with the CDs. These CDs have long been used in medications and foods [95]. However, of these three CDs, β-CD has the lowest water solubility (18.5 mg/mL) and parenteral toxicity so it has only been used in a limited number of oral and topical products [96]. Thus other CD derivatives with covalently bonded substituted groups have been devised to modify the physicochemical properties and molecular structure of the CDs [95-97]. A list of these derivatives and marketed products that contain them are available in the reviews by Stella and He [95] and Loftsson et al [96], respectively. The kinetics of complexation has been covered in these reviews so it will not be discussed here. Despite the usefulness of CDs, there are some disadvantages with the technique [97]. The drug molecule must be of a certain size and geometry able to interact with the confined hydrophobic cavity of the CD. There may also be potential issues with toxicity, regulation, and quality control of the CDs,

especially the synthetic ones with substituted groups. However, since several substituted CDs have been approved for some marketed products [96] and the formulation technique is well established, CD complexation is a viable method for dissolution enhancement.

The major difference between the chemical approaches (salt forms, prodrugs, and CD complexes) and physical approach (nanoparticles) in improving dissolution is that the former manipulates the physicochemical properties of the drug molecule, which are the major determinants of solubility, rather than simply increasing the particle surface area. Besides, nanoparticles always will have the problem of aggregation in liquid, which is difficult to overcome even though initially the nanoparticles may be dispersed as individual particles. More importantly, the chemical approaches have had a much longer history of applications than the relatively new field of nanotechnology. The knowledge and experience in the use of salt forms, prodrugs, and CD complexes gained over the past decades are transferrable to new drugs with low solubility. Therefore, the value of nanoparticles in dissolution enhancement may have been overestimated. Undoubtedly, nanoparticles can facilitate dissolution but the actual improvement is often lower than that expected in theory. More importantly, the chemical approaches can potentially excel the nanoparticles in that regard. It is thus advisable to have a realistic view of the value of nanoparticles and keep a broad perspective on the usefulness of other strategies in enhancing drug dissolution.

Conclusion

Nanoparticles have been advocated in recent years for their effectiveness in enhancing dissolution, bioavailability, and convenience in administration. With an increasing number of hydrophobic drugs discovered and advancement in nanotechnology, much effort and

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resources have been spent on developing nanoformulations. Although wet milling appears to be the main method of commercial nanoparticle production (owing to the number of approved products already and more still in the pipeline), there are other directions that are worth exploring.

Firstly, with the growing prominence and number of nanoparticle formulations, official pharmacopoeial and regulatory guidelines should be devised for the dissolution testing of nanoparticles. Although the effectiveness of the various dissolution apparatus has been compared in a recent research article [68], there is still no definitive standard for the procedure. Formulators are still free to select and adapt a setup to suit their own purpose. Since each method has its own problems, data generated from different apparatus may not be comparable. Even the flow-through cell cannot entirely eliminate aggregation during dissolution testing [7]. Thus there is a need to reach a consensus on one or a set of apparatus and methods that can accurately measure the dissolution of nanoparticles. If the existing official pharmacopoeial apparatus do not satisfy this end, then they may require modification or an entirely new device may need to be developed. That was how the Next Generation Impactor (BP Apparatus E and USP Apparatus 5 for aerosol testing) [79, 80] came to be specifically designed to fulfil the requirements that were not met by older generation pharmacopoeial impactors [98]. The establishment of standards for dissolution testing of nanoparticles will definitely have a vast positive impact on the research and development of nano-formulations.

Secondly, despite the high interest in nanotechnology nowadays, researchers should be conscious of the inherent shortcomings of nanoformulations. The agglomeration of nanoparticles limits the exposed surface area, and hence the effectiveness of dissolution

enhancement by size reduction. Moreover, small chemical modifications to the parent molecule (e.g. transformation to a more soluble salt form, prodrug, or CD complex) can increase solubility more significantly than by nano-sizing. Therefore, although nanoformulations do possess some benefits in enhancing drug dissolution, their value and cost effectiveness should be viewed in the light of their limitations. The more established chemical approaches may also be considered in the formulation of future products. A summary of the points examined in this review is summarised in Table 1.

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Table 1. Summary of aspects of nano-formulations and other techniques for dissolution enhancement.

Nanoparticle production methods	Top-down	● Wet milling; Approved products: Triglide (fenofibrate)[17] ● High pressure homogenization; Approved products: Rapamune (rapamycin/sirolimus), Emend (aprepitant), TriCor (fenofibrate), Megace ES (megestrol acetate), INVEGA SUSTENNA (paliperidone palmitate)[12]
	Bottom-up	● Precipitation: Standard laboratory apparatus, HGCP, CLIJ, MIVM, supercritical fluid, sonoprecipitation[19, 21, 24-40] ● Controlled droplet evaporation: Nano Spray Dryer, aerosol flow reactor, electrospray[41-49]
Formulation strategies for nanoparticle dissolution enhancement	Drying of nanosuspensions	● Spray drying, freeze drying, spray freeze drying, fluid bed granulation[21, 59-66]
	Incorporation of hydrophilic matrix formers	● Conventional: sugars (lactose, sucrose), polyols (mannitol, sorbitol), polymers (high molecular weight PEG, PVA, PVP)[53, 68, 69] ● Non-traditional: anhydrous dicalcium phosphate, microcrystalline cellulose, colloidal silicon dioxide, Inutec®SP1[17, 68]
Dissolution testing of nanoparticles		● Pharmacopoeial (BP and USP): Paddle, basket, flow-through cell[67] ● Dialysis bag[67] Note: No official dissolution method is specified for nanoparticles hitherto. The flow-through cell has been shown to be the most suitable[67]
Theoretical versus actual dissolution behaviour		● Ideal case: The factor of increase in the dissolution rate of megesterol acetate and griseofulvin nano- and micro-suspensions (254 vs 2900 nm and 760 and 5900 nm, respectively) was comparable to that of size reduction[54] ● Usual case: Nanoparticles agglomerate easily, especially after drying[7, 80, 81], sometimes even interparticulate fusion occurs[7, 58] ● Two stages of nanoparticle dissolution: 1) Interparticulate bridges dissolve and primary nanoparticles are released; and 2) Nanoparticles form aggregates and continue the dissolution in this manner[7]

|		
Other dissolution enhancement techniques	Chemical approaches	• Soluble salt forms: E.g. solubility of naproxen base (0.07 mg/mL) could be increased to 266 and 472 mg/mL by using naproxen sodium and naproxen choline, respectively[82] • Prodrugs: E.g. solubility of phenytoin (0.03 mg/mL) could be increased up to 2.38 mg/mL by adding a covalently-bonded promoiety to the parent molecule[86] • Cyclodextrin complexes: many marketed products using α-, β-, and γ-cyclodextrin and their substituted counterparts[88,89]
Future directions		• Establishment of regulatory and pharmacopoeial standards for dissolution testing of nanoparticles • Besides nano-sizing, chemical approaches for dissolution enhancement should also be considered in product development
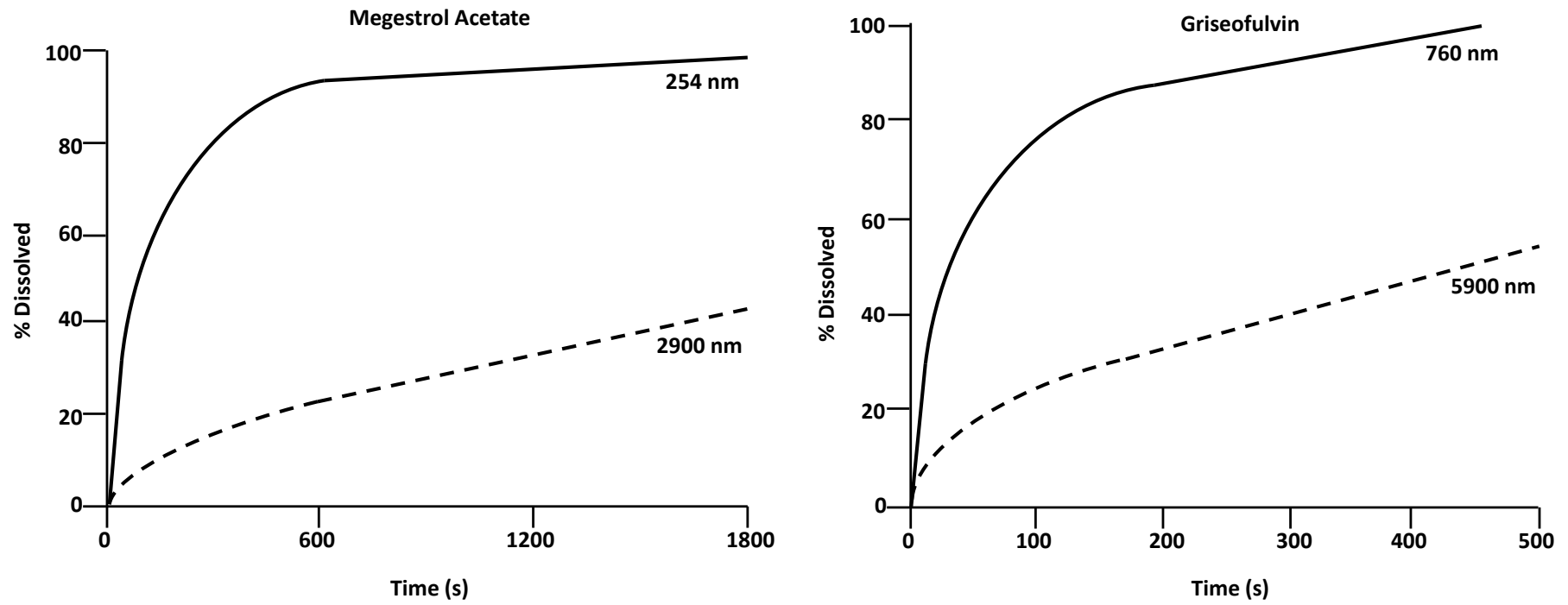
Figure 1. Dissolution profiles of megesterol acetate and griseofulvin nano- and micro-particles. Data adapted from Reference [55].