Chapter 11
The Role of Particle Size in Drug Release and Absorption

Giuseppina Sandri, M. Cristina Bonferoni, Franca Ferrari, Silvia Rossi, and Carla M. Caramella

Abstract Solid drug delivery systems are crucial formulations via the oral route. In such drug systems, particle size has a strong impact on drug dissolution and on drug absorption. Its role in dissolution rate is described starting from the Noyes–Whitney equation, the modified form by Nerst–Brunner and the cube root equation. According to these equations diffusion of solute through a boundary layer around the particles is the rate limiting step in both drug dissolution and absorption and, thus, depends upon the specific (external) surface area of the particles, the diffusion coefficient of the solute, the thickness of the boundary layer and the solute solubility. In relation to this, good wetting of the particle surface by the surrounding liquid and adequate particle dispersion play an essential role. Information from dissolution rates suggests that the thickness of the boundary layer is constant for larger particle sizes but dependent upon size for smaller particles. Given the larger surface area of smaller particles, the attention is directed to nanosystems and on their relevance to the bioavailability of poorly soluble drugs. A second advantage of such drug systems is that the solubility increases with decreasing particle size, according to the Freundlich–Ostwald equation. Since dissolution and absorption are closely related, the impact of particle size on drug absorption is described. Moreover, regulatory implications of particle size are reviewed.

11.1 Introduction

It has been recognized that the availability of a drug for gastro-intestinal absorption from solid dosage forms is often reflected by in vitro dissolution rates. It has also been recognized that among the new chemical entities the poorly soluble drugs are more and more common. For these drugs the rate-determining step in the absorption

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of drugs is the dissolution rate of drugs in the gastro-intestinal fluids rather than the rapidity of their diffusion across the intestine wall. The granulometric properties of pharmaceutical powders (both active ingredients and excipients) play an important role on their behavior in technological as well as biopharmaceutically relevant processes. Furthermore they are fundamental in the design and development of drug delivery systems where the drug is loaded as a solid. The solubility and dissolution behavior of drug particles is fundamental to allow drug absorption. Developing a drug delivery system taking into account the granulometric parameters means not only to characterize raw materials (mainly active ingredients and excipients) but also to consider the influence of particle size on technological processes and on biopharmaceutical properties of formulations. In particular as for biopharmaceutical properties dissolution rate has a great impact on drug absorption. Furthermore, the bioavailability of poorly soluble drugs, in particular hydrophobic drugs with extremely low aqueous solubility, is dramatically influenced by drug dissolution rate. The investigation of drug dissolution rate enhancement is a crucial point; in this perspective particle size plays a key role since dissolution rate is mainly dependent on interfacial surface area. Adequate dispersion of powdered solid in a dissolution medium is a prerequisite to start the dissolution process: if particles tend to form clumps in the dissolution medium, then the dissolution surface area available for dissolution is reduced. This effect may be overcome by the addition of a wetting agent (surfactant) to improve the dispersion of clumps into primary powder particles. Therefore, if the particles can be easily wetted by dissolution medium, an increased surface area (a decreased particle size) results and, in turn, an increased dissolution rate. The present chapter is focused on the role of particle size in solubility and dissolution properties. In addition, the effect of nanonization technology on bioavailability of poorly soluble drugs is reviewed.

11.2 Particle Size and Dissolution Properties

The relevance of particle size to dissolution of poorly soluble drugs is well known to scientists involved in oral dosage forms development.

The relationship between particle size and dissolution rate can be derived from the Noyes–Whitney Eq. 11.1 that was introduced in 1897 to explain the dissolution phenomenon [40]. This equation explains the correlation between particle size and dissolution rate and is based on the assumption that in the dissolution process the solubilization is fast, whereas the subsequent diffusion of drug molecules through a diffusion boundary layer surrounding the particle is the rate limiting step.

$$\frac{dm}{dt} = k \cdot (C_s - C_t) \tag{11.1}$$

where:

dm/dt = dissolution rate

C_s = equilibrium solubility of the substance, i.e. the concentration of its saturated solution

C_t = concentration of the substance in the bulk medium at time t

k = constant

t = time.

In 1904 the equation was modified by Nerst and Brunner [6, 36]. They explained the above constant k in terms of surface area, diffusion coefficient and diffusion layer thickness. In this form, it became one of the most used equations to describe drug dissolution:

$$\frac{dm}{dt} = \frac{A \cdot \mathbb{D}}{\delta}(C_s - C_t) \tag{11.2}$$

where:

A = surface area of the undissolved solid drug in contact with the solvent

$\mathbb{D}$ = diffusion coefficient of the solute

δ = thickness of the diffusion boundary layer.

The medium viscosity influences the diffusion coefficient $\mathbb{D}$, which decreases on increasing the viscosity. The thickness of the diffusion layer δ is influenced by both medium viscosity and stirring rate. At a given viscosity δ decreases with increase of stirring rate, while at the same level of stirring rate it increases with increasing viscosity.

When C_t does not exceed 10 % of C_s, the so called sink conditions are satisfied, and C_t can be considered negligible in comparison to C_s. Under these conditions, the dissolution rate can be considered directly proportional to drug solubility and to the interfacial surface area, which is in turn dependent on drug particle size and shape.

The key role played by the initial radius of the particles that undergo dissolution is evident in the Hixson–Crowell equation [16], also known as Cube root equation, derived from the Noyes–Whitney equation:

$$\sqrt[3]{m_t} = \sqrt[3]{m_0} - K\,t \tag{11.3}$$

where:

K = dissolution constant "cube root"

m_t = drug amount undissolved at time t

m_0 = initial drug amount

t = time.

The amount of drug undissolved, m_t, is related to the remaining volume of solid powder and, thus, to the cube of the volume-based mean particle size, $D_{4,3}$. In fact, the Hixson–Crowell equation is rigorously applicable to systems made of spherical particles, but is also quite commonly used to describe the dissolution behavior of populations of non-spherical particles in an approximateve way.

Kaneniwa et al. [22] used the Cube root equation to correlate the dissolution rate to the particle size of sulfamethizole and demonstrated that the increase in dimensions from 60 to 700 μm causes the corresponding decrease in dissolution rate.

As illustrated in Eq. 11.2, the dissolution rate directly relates to the specific surface area of the solid. Dissolution rates are, therefore, measured either by maintaining the surface area constant (in intrinsic dissolution rate measurements), or by taking into account the variation of the particle surface area during dissolution. Nystrom et al. [41] proposed to measure of particle size by means of a Coulter Counter to calculate the surface area of a solid undergoing dissolution. This calculation involved the measurement of the weight of particle population dissolved as a function of time. Under the assumption that the shape of the particles remains constant [8], the authors introduced a new parameter, the surface specific dissolution rate (G):

$$G = \frac{m_0 - m_t}{t((A_0 - A_t)/2)} \tag{11.4}$$

where:

G = surface specific dissolution rate

m_0 = initial weight of solid particles

m_t = weight of solid particles at time t

A_0, A_t = the surface area of solid particles at time zero and time t, respectively

t = time.

The proposed parameter G relates to the loss of weight divided by the loss of surface and, thus, to the inverse of the specific surface area (the surface area per unit weight).

In fact, among the different mean diameters used in particle size characterization, the area-weighted Sauter mean diameter, $D_{3,2}$, gives information that directly relates to specific surface area and, thus, it is profitably used in the pharmaceutical field.

It was however noticed that the increase in dissolution rate by a decrease in particle size can be higher than expected on the basis of the surface area increase. This finding can be explained by taking into account that a decrease in particle size is accompanied by a decreased thickness of the boundary layer δ [5]. This effect is especially pronounced for materials with mean particle size less than 5 μm [3, 5] and was confirmed by Mosharraf and Nystrom [32] in a study involving sparingly soluble materials such as griseofulvin, glibenclamide, barium sulphate and oxazepam.

These topics became of particular interest in pharmaceutical technology after the introduction of biopharmaceutical concerns in the evaluation of the performance of drug delivery systems. One of the paradigms at the basis of biopharmaceutics is that drug absorption requires that the drug is in solution at the absorption site [1, 9]. This focused particular attention on dissolution rate because, as dissolution is the limiting step for absorption, all the factors that affect dissolution are potentially determinant for drug bioavailability.

Among the first results dealing with the use of particle size to explain or predict dissolution rate and therefore absorption, are some findings involving sulfamidics such as sulfadiazine, sulfaisossazole, sulfathiazole and sulfamethizole [22, 23, 48].

The relationship between particle size and dissolution rate appeared evident especially for poorly soluble drugs, while no influence could be found for freely soluble drugs. A quite dramatic influence of particle size on rabbit gastro-intestinal absorption was found for sulfadimetossine: the increase in particle size corresponded to a decrease in maximum plasma concentration, C_{max}, and an increase in the time to reach the maximum concentration, t_{max}, due to slower gastro-intestinal absorption [23].

Similar results were found in man for other drugs, a.o. phenytoin [37]. Neuvonen put clearly in evidence that various biopharmaceutical factors, among which drug particle size, has an important effect on the oral absorption of this drug, and in turn, due to the dose dependent metabolism and narrow therapeutic range, can result in serious clinical consequences [37]. The positive effect of particle size reduction on bioavailability was observed also for digoxin [20, 45] and, although with some discordant results, for griseofulvin [4, 12].

Simoes et al. [47] evaluated the influence of particle size and related properties in particular specific surface area and solubility on the dissolution rate of a sparingly soluble drug indomethacin. As expected a strong influence of the fraction size on the dissolution rate was found. A correlation was established between the mean dissolution time (MDT) and the mean particle size of the various indomethacin fractions. As expected, the dissolution rate increased with a reduction in particle size. The authors confirmed a correlation between the MDT and the mean particle size.

Micronization by means of dry milling (jet milling, ball milling, pin milling) to 2–5 μm sizes was therefore proposed as a useful method to improve bioavailability of this category of drugs. This strategy was proven successful also in more recent studies, such as that performed by Ning et al. [39], where micronization gave results positive to solid dispersion in improving bioavailability, as evidenced by AUC (area under blood plasma concentration-time curve), C_{max} and t_{max} values of glimepiride administered to beagle dogs.

Oh et al. [42] reported that the dose fraction absorbed from suspensions is a function of four dimensionless parameters: absorption number, dissolution number, dose number and initial saturation. The absorption number (*An*) is the ratio of radial absorption rate to axial convection rate; the dissolution number (*Dn*) is the ratio of residence time in intestine to the dissolution time. The dissolution number depends on drug properties such as solubility, diffusivity, density and, in particular, *Dn* is inversely proportional to the square of the initial particle size. Thus, a way to increase *Dn* is to decrease particle size [43]. The dose number (*Do*) is the ratio of dose concentration to solubility. The initial saturation (*Is*) is the ratio of drug luminal concentration at the beginning of the intestine to drug solubility.

After drug suspension administration via oral route, particle size decreases down the tube so that the dissolution rate from particles increases. Drugs with low *Do* and low *Dn* can be completely absorbed by reducing their particle size, while the absorption of drugs with high *Do* and low *Dn* is solubility (*Dn*) limited and requires a higher solubility, in addition to micronization, to enhance the fraction absorbed.

A good knowledge of bioavailability of a drug is also important for regulatory reasons, in view of assuring a constant level of quality and reproducibility and, consequently, adequate predictability of therapeutical effects. This has led during

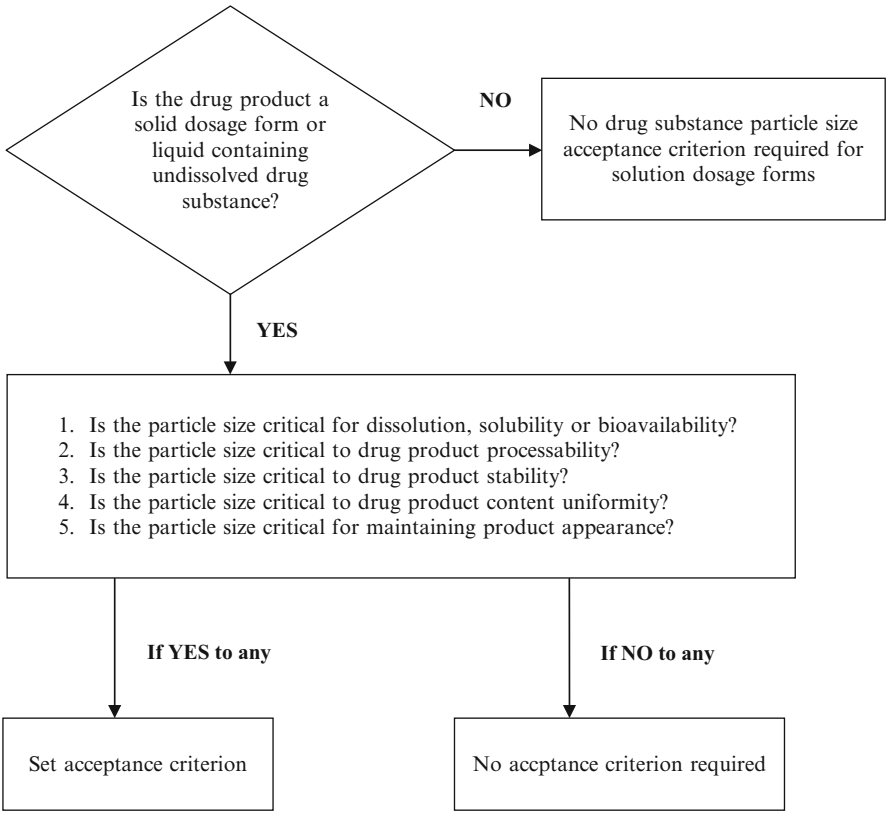

Fig. 11.1 Decision tree on particle size reported in ICH Guideline Q6A [17]; courtesy ICH

the last decennia to the identification of all the possible critical parameters of any formulation. For solid oral dosage forms and liquids containing undissolved drug substances (suspensions), particle size is considered as a parameter to be necessarily taken into account in the definition and control of quality specifications. In fact, the ICH Guideline Q6A [17] on product specifications under the paragraph 3.3.1, New Drug Substances, states that "testing for particle size distribution should be carried out, and acceptance criteria should be decided if particle size affects dissolution rate, bioavailability or stability of a new drug substance in solid or suspension drug product". Indications relevant to the possible role of particle size on drug product properties, in particular on bioavailability, are detailed in decision tree # 3 of the same guideline (Fig. 11.1). In this document the role of particle size in processability, content uniformity and stability of a drug product is clearly recognized. The first question, however, regards the possible effect of particle size on solubility, dissolution and bioavailability, which are strictly related to each other. In case of possible effects of particle size on product performance, definition of specifications will be required (ICH GL).

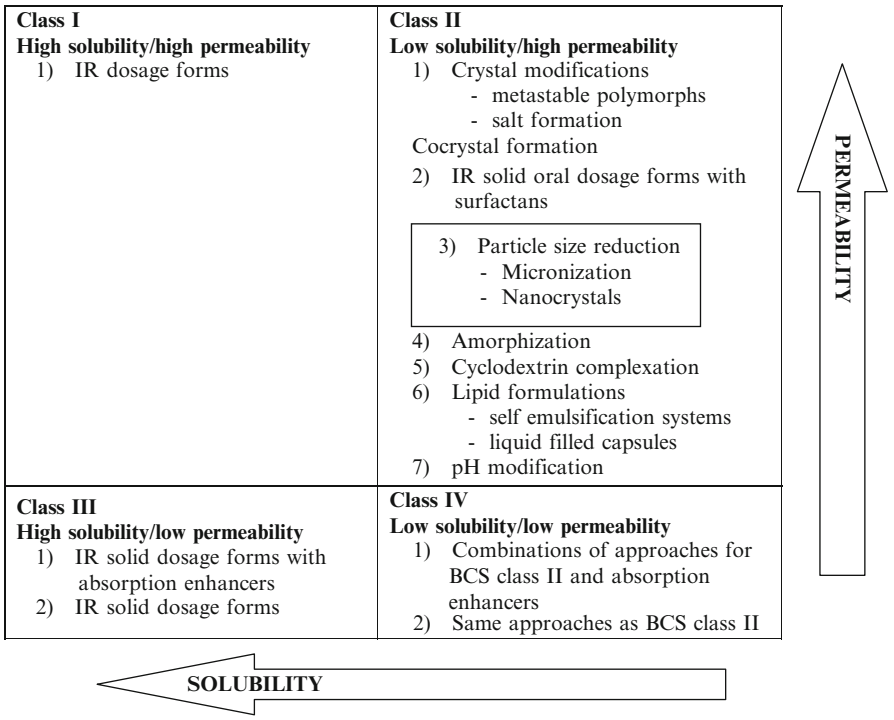

Fig. 11.2 Formulation design for poorly water soluble drugs based on BCS: basic approaches and practical applications [24] (Copyright Elsevier Ltd; reproduced with permission)

The observations reported in early studies [7] on the relevance of particle size on dissolution rate, that is particularly evident when poorly soluble drugs are concerned, have been more recently revised and reconsidered, in a regulatory perspective, in the frame of the Biopharmaceutical Classification System (BCS) [2].

BCS was developed to avoid in vivo bioequivalence studies for drug products characterized by rapid dissolution in vitro, being based on drugs that are very soluble and have good permeability (class I). In these cases, in vivo studies can be substituted by in vitro studies based on dissolution tests. BCS based bio-waiver approach can be extended also to class III drugs (with good solubility and poor permeability). Drugs with low solubility and good permeation (class II) and with low solubility and poor permeation (class IV) pose much more concerns from a regulatory point of view, since small changes in physical-chemical properties can significantly affect dissolution and absorption and require more extensive in vivo characterization. The increasing attention for this topic depends on the fact that it is estimated that about 40 % and 60 % of the new drug entities exhibit poor solubility, with related uncertainty on bioavailability and clinical use [28].

BCS represents therefore a reference also for the formulative approach, since poorly soluble drugs are a major challenge for formulation process. As evidenced

by Kawabata et al. [24], the physical-chemical properties of a drug, and particle size among them, are key factors for reproducibility, bioavailability and therapeutic effect of a given formulation (Fig. 11.2). Particle size reduction was therefore suggested as technological strategy for class II and IV drug formulation, both as micronization and as reduction to nano-crystals.

The regulatory concerns and the recognition of the particle size relevance for bioavailability led in more recent years to the development of an intensive research about possible prediction of bioavailability in physiologically based models simulating gastrointestinal transit and absorption. In some studies, samples containing drugs of different formulas, characterized by different dissolution profiles according to Noyes–Whitney equation, have been evaluated through this modeling approach. Among the commercial software available for pharmacokinetic simulation are GastroPlus™, PK-Sim® and Stella®.

11.3 Nanonization

Although micronization represents a simple and attractive technology to enhance dissolution rate by increasing surface area, it has often experienced limited success. In particular, poorly soluble drugs even though micronized, tend to be eliminated from the gastro-intestinal tract before there are fully absorbed due to an insufficient solubility in the gastro-intestinal fluids. Although the micronization improves the dissolution rate in comparison to conventional milling, this is, sometimes, not enough to significantly and effectively increase drug solubility/dissolution. This results in highly intra – and inter- individual variability of plasma profiles and lack the of dose response, especially for substances belonging to BCS class II.

The nanonization of a drug substance is the logical subsequent step to micronization for surface area increase and dissolution rate enhancement. Nanonization refers to the reduction of drug particle size to the sub-micrometer range. There are two main approaches for nanonization: “top down” and “bottom up” technologies. The “top down” approach is by far the more popular and it basically relies on mechanical attrition to render large crystalline particles into nanoparticles [25]. Examples of the “top down” approach include Elan’s NanoCrystal® wet-milling technology [31] and SkyePharma’s Dissocubes® high-pressure homogenization technology [25, 34]. The “bottom up” approach is based on controlled precipitation/crystallization [44]. This process involves dissolving the drug in a solvent and precipitating it in a controlled manner to nanoparticles through addition of an anti-solvent (usually water). This technology is available from DowPharma (Midland, MI, USA) and BASF Pharma Solutions (Florham Park, NJ, USA). A hybrid approach is also feasible. Baxter’s NANOEDGE® technology employs both “bottom up” and “top down” approaches through microprecipitation and homogenization [25].

The sub-micrometer particles are stabilized with surfactants or polymers in nanosuspensions to avoid agglomeration. These nanosuspensions increase dissolution rates of drug compounds and complement other technologies developed to

enhance bioavailability of insoluble drugs (BCS Class II and IV) such as the use of solubility enhancers (i.e. surfactants), liquid-filled capsules or solid dispersions of drugs in their amorphous state. The success of the nanonization approach has been confirmed by several commercial available products containing nanosized drugs (Table 11.1).

The underlying basis for dissolution-limited bioavailability and its improvement by nanonization is illustrated in Fig. 11.3 (modified from Gao et al. [11]).

According to the Nernst–Brunner equation, the dissolution of particles is not only dependent on particle surface area, but also on the thickness of the diffusion boundary layer δ [21]. There are different theories on the relation between δ and particle size. In particular, Hixson assumes δ to be constant and consequently the increase in surface area is the unique driving force for dissolution rate enhancement. However, other models do not assume that the thickness of the boundary layer remains constant on changing particle size.

For instance, Higuchi et al. (1963) assume that the diffusion boundary layer thickness decreases proportionally with the particle size. According to this assumption a 12.5 fold increase in surface area would cause a theoretical increase in dissolution rate by 156.25 factor compared with the initial dissolution rate of micronized material [14].

Other relationships between the thickness of the diffusion boundary layer, δ, and particle size have also been considered. For instance, Niebergall et al. [38] proposed that δ correlates with the square root of the particle radius; Hintz and Johnson proposed the concept of a transitional particle size of 30 μm, implying that δ is constantly 30 μm for particles larger than 30 μm, whereas the diffusion layer is equal to particle radius for particles smaller than 30 μm [15]. Sheng et al. [46] found a dependency of δ on medium agitation. From these results it can be concluded that calculations of the dissolution rate are strongly dependent on the choice of the theoretical model.

Most modern software packages for plasma level simulation (e.g. GastroPlus®) use a constant δ value for simulating the dissolution of a drug. This causes only an approximate predictability of the mathematical models and suggests that the dissolution rate should be experimentally determined to obtain reliable results.

Besides the dissolution rate, nanonization increases saturation solubility, according to the Freundlich–Ostwald equation:

$$C_S = C_\infty \exp\left(\frac{2\lambda M}{r\rho RT}\right) \tag{11.5}$$

where:

C_s = saturation solubility of the nanonized drug
C_∞ = saturation solubility of an infinitely large drug crystal
λ = the crystal/medium interfacial tension
M = molecular weight of drug
r = particle radius

Table 11.1 Marketed products containing drug nanocrystals [11] (Copyright Elsevier Ltd.; reproduced with permission)

Trade name	INN name	FDA approval	Company	Adminstration route	Indications	Therapeutic benefit
Casamet®	Nabilone	2005	Lilly	Oral	Antiemetic	High bioavailability
Rapamune®	Sirolimus	2000	Pfizer (Wyeth)	Oral	Innumosuppresant	High patient compliance, tablet formulation instead of solution
Emend®	Aprepitant	2003	Merck	Oral	Antiemetic	High bioavailability, no food effects
Tricor® Lyphantyl®	Fenofibrate	2004	Fournier Pharma, Abbott Laboratories	Oral	Hypocolesterolemic	No food effects
Triglide®	Fenofibrate	2005	Sciele, Shionogi Pharma Inc.	Oral	Hypocolesterolemic	No food effects
Megace® ES	Megestrole acetate	2005	PAR Pharmaceuticals	Oral	Appetite stimulant	No food effects, high patient compliance
Invega® Sustenna® Xeplion®	Paliperidone palmitate	2009	Janssen	Parenteral, Intramuscular	Antidepressant	High bioavailability

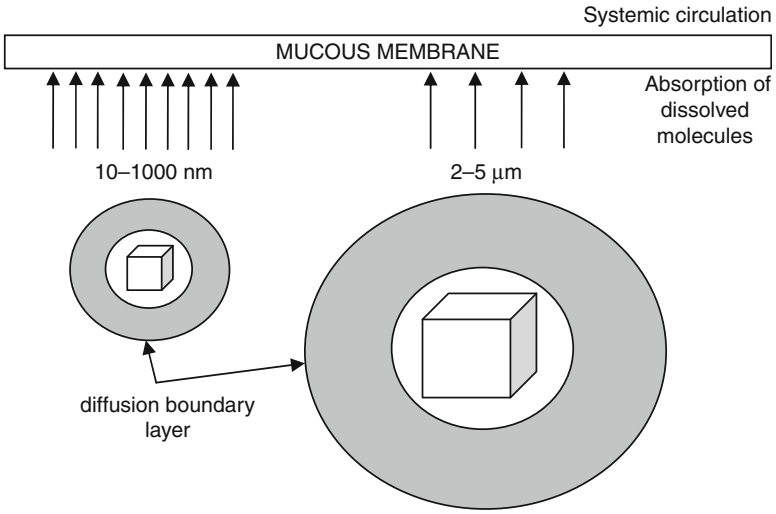

Fig. 11.3 Thickness of boundary layers of nanocrystals (10–1000 nm) and micronized particles (2–5 µm) (Modified from [11]; copyright Elsevier Ltd.; reproduced with permission)

ρ = particle density
R = gas constant
T = temperature.

Equation 11.5 shows that solubility of a given substance at given conditions depends upon particle size and also upon drug molecular weight. During dissolution, Ostwald ripening may occur: large particles can grow at the expense of dissolving small particles.

According to Eq. 11.5, 10–15 % increase in solubility could be expected for a drug having M = 500, ρ =1 g/ml, particle size of 100 nm and crystal-intestinal fluid interfacial tension λ = 15–20 mN m^{-1} [26]. However, a more pronounced increase in solubility was experimentally determined; for instance, Muller and Peters [35] reported a 50 % increase in solubility of an insoluble antimicrobial compound when the particle size was reduced from 2.4 µm to 800 or 300 nm. Such an increase in solubility causes an increase in dissolution rate proportional to solubility and, thus, a significantly higher bioavailability. The presence of surfactants as stabilizers of nanosuspensions, further enhanced dissolution rate of the insoluble antimicrobial compound in comparison with micronized suspensions due to increases in surface wetting.

Drug nanocrystals are generally reported as safe and well tolerated systems for many administration routes when compared with conventional products. In particular, nanocrystals can be profitably administered via conventional routes, suitable as oral and parenteral, as well as employed for ophthalmic and pulmonary administration [11]. A fine particle size helps in improving safety of oral administered poorly soluble drugs, by increasing the distribution uniformity in the gastrointestinal fluid and avoiding a high and prolonged local concentration [29]. Nanosized particles are also beneficial for a better tolerability in mucosal administration.

Table 11.2 Changes of pharmacokinetic properties of oral drug nanocrystal formulations compared with the conventional formulations

	Dosage form		Ref
Fenofibrate	Aqueous nanosuspension (194–356 nm)	1.8–12.5 fold increase in Cmax; 1.7–17 fold increase in bioavailability; 1.3–2.3 fold reduction in tmax	[27]
Fenofibrate	Aqueous nanosuspension (340 nm)	1.67 fold increase in Cmax; 1.3 fold increase in bioavailability; 4.9 fold reduction in tmax	[13]
Aprepitant	Aqueous nanosuspension (120 nm)	No food effect at a dose of 2, 80, 125 mg/kg	[50]
Itraconazole	Aqueous nanosuspension (267 nm)	1.2–1.8 fold increase in Cmax; 1.2–1.8 fold increase in bioavailability; fsted/fed ratio of AUC markedly reduced	[33]

Many reports show that drug nanocrystals possess many positive effects on oral drug delivery of poorly soluble drugs. In particular, changes of pharmacokinetic parameters occurr after nanocrystals administration: these generally include increased maximum plasma concentration (C_{max}), reduced time to maximum plasma concentration (T_{max}), enhanced area under blood concentration–time curve (AUC) and reduced fasted/fed variability in comparison with conventional formulations as reported in Table 11.2. In particular, when drugs are administered as nanocrystals, a high drug concentration gradient takes place between GIT and blood vessel which will markedly improve absorption and result in a high bioavailability. This behavior is conceivably determined by the increased saturation solubility and dissolution rate of drug nanocrystals in digestive juice. One classic example is danazol, a poorly soluble gonadotropin inhibitor. The absolute bioavailability of marketed danazol conventional microsuspensions (200 mg, 10 μm) was only 5.2 % in beagle dogs. When administered as an aqueous nanosuspension (200 mg, 169 nm), an absolute bioavailability of 82.3 % could be achieved, with a 15 fold *Tmax* reduction and *Cmax* increase [30].

Jinno et al. [18] measured the cilostazol plasma kinetics after oral administration to beagle dogs, under fasted and fed conditions, of suspensions containing three different particle size distributions. The in vitro dissolution profiles in both water and biorelevant dissolution media showed an influence of particle size but the results could neither quantitatively predict the increase in bioavailability on decreasing particle size nor the food effect observed in vivo. Starting from these results, Willmann et al. [49] combined a physiologically based pharmacokinetic (PBPK) model for gastro-intestinal transit and absorption with a mechanistic dissolution model, previously developed by Johnson [19], to predict the influence of particle size on the plasma pharmacokinetics of cilostazol in beagle dogs.

The dissolution model was based on the Noyes–Whitney equation for spherical particles with a predefined particle size distribution, assuming the events illustrated

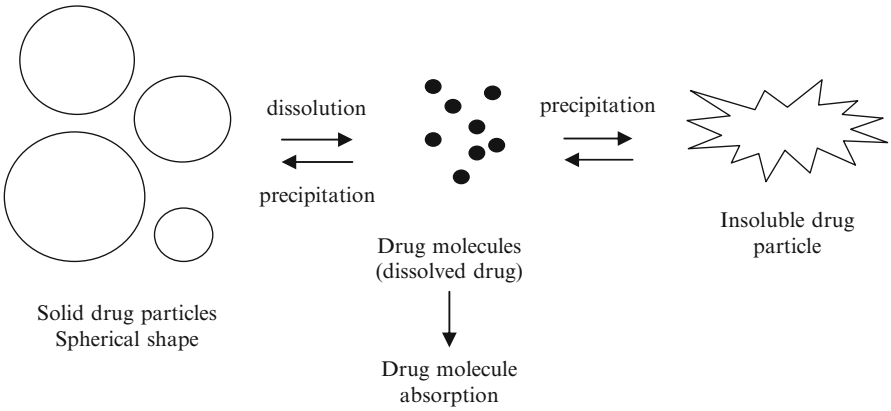

Fig. 11.4 Structure of the dissolution model: solid spherical particles of different diameter dissolved in gastrointestinal fluids (Modified from [19]). Precipitation can occur leading to particles similar to the original ones or to insoluble particles. Drug molecules can be absorbed

in Fig. 11.4. Three different cilostazol suspensions with different particle size distributions, previously described in the study of Jinno et al. [18], were used:

(a) Hammer-milled crystal sample with a median particle size of 13 μm,
(b) Jet-milled sample with a median particle size of 2.4 μm,
(c) Spray-dried powder with a median particle size of 0.22 μm.

The comparison between simulated curves and experimental data demonstrated that the dynamic dissolution model enabled an almost exact prediction of the decrease in rate and extent of absorption on increasing particle size, both in fasted and in fed conditions. In fact the bioavailability of cilostazol was increased by the reduction of particle size and consequently by the increase of dissolution rate. The model was also able to put in evidence that the rate-limiting step for absorption was dissolution in the case of the two micronized suspensions (obtained by hammer-milling and jet-milling), and it was the permeation across the intestinal epithelium for the nanocrystals. The use of the simulation approach in formulation development should aid the selection of the appropriate drug particle size for solid oral dosage forms, and could potentially support specification selection. In Fig. 11.5 the dissolution profiles of cilostazol from the suspensions in water at 37 °C are reported [18]. Dissolution study was performed at 50 rpm following USP Apparatus 2. About 5 mg of cilostazol was applied in 900 ml water. Results are expressed as the mean with the bar showing standard deviation values of six experiments and simulated curves (solid lines). The reduction of particle size dramatically increase cilostazol bioavailability (Fig. 11.5): in particular the highest enhancement with a minimum food effect was observed for the NanoCrystal cilostazol suspension, while the jet-milled suspension determined a moderate improvement of bioavailability in comparison with conventional hammer-milled crystals and showed a significant food effect. This means that food intake did not increase the

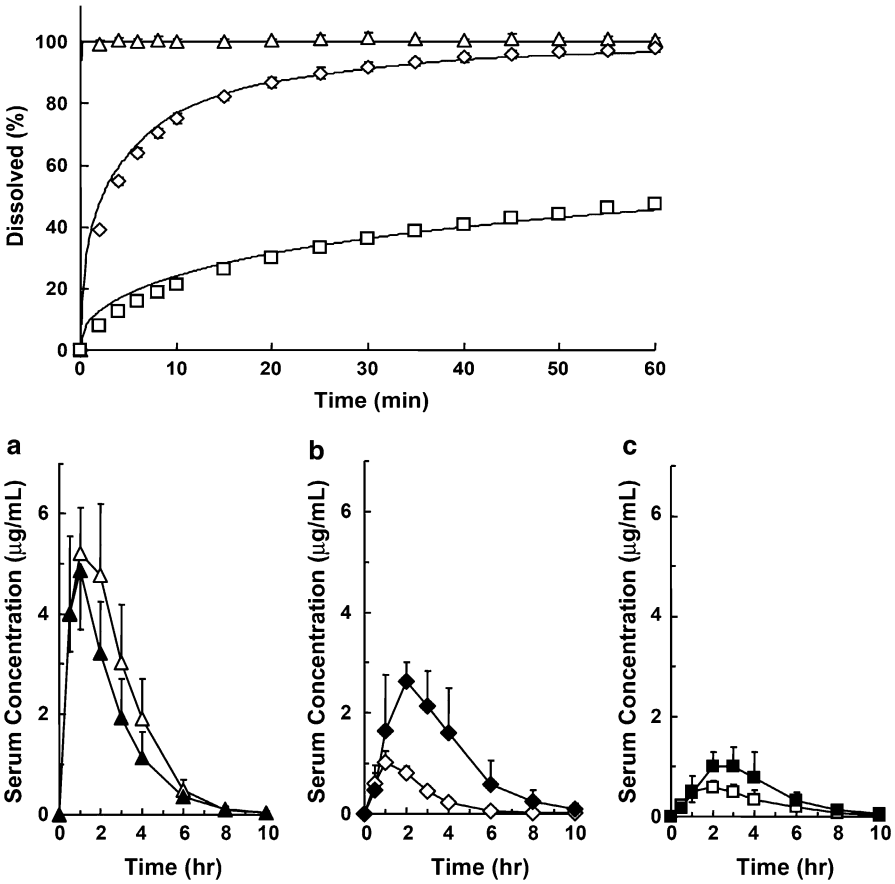

Fig. 11.5 Dissolution –time profiles for NanoCrystal® spray-dried cilostazol powder (median particle size 13 μm) (Δ) (**a**); jet-milled crystal (median particle size 2.4 μm) (◊) (**b**); hammer-milled crystal (median particle size 0.22 μm) (□) (**c**), reported in the upper part. In the lower part, plasmatic curves corresponding to the administration of each particle suspensions at a dose of 100 mg/body in beagle dogs are reported: the open symbols correspond to fed state, the closed ones to fasted state [18] (Copyright Elsevier Ltd.; reproduced with permission)

bioavailability of the NanoCrystal® cilostazol suspension. This occurs because dissolution rate of NanoCrystal® cilostazol is fast enough even under the fasted condition, where the absorption might be permeability-limited. Therefore, the further increase in the dissolution rate would not contribute to the improvement of the absorption.

Other papers that compare micronized particles and nanocrystals have been recently published: in particular they deal with the relationship between particle

size and bioavailability of poorly soluble drug substances. Eg., Fu et al. [10] studied the relationship between dissolution and bioavailability of nimodipine microcrystals and nanocrystals aqueous dispersions, obtained by microprecipitation, with the aim of determining the critical size responsible for the improvement of oral bioavailability. Three size levels were considered in this study: 16.3, 4.1 and 0.83 μm, and the average volume-weighted particle sizes were determined by a laser diffraction method.

All three samples showed comparable aqueous equilibrium solubility, determined by shaking flasks, and the dissolution curves in purified water and 0.05 % SDS were also similar. However the pharmacokinetics data obtained in beagle dogs showed that AUC values were 1.69 and 2.59-fold higher for dispersions of 4.1 and 0.83 μm sizes than was for the 16.3 μm dispersion.

These results suggest that the aqueous solubility and the supersaturation dissolution were not effective indexes in evaluating the bioavailability of colloidal dispersions, and moreover they could not discriminate the in vivo performance. Fu et al. [10] evidenced that there is a critical particle size to improve the bioavailability of nimodipine and it ranges between 0.83 and 4.1 μm.

In another study, aprepitant (an antiemetic antagonist of NK1 receptor) release from micro-sized and nano-sized powders and its pharmacokinetics in fasted and fed humans is described (Shono et al. 2010) by means of Noyes–Withney equation coupled with STELLA® 9.0 software (Cognitus Ltd., North Yorkshire, UK). The change in particle size modifies the dissolution rates, and consequently the rate of drug appearance in plasma. The model was able to correctly simulate the experimental behavior, both in vitro and in vivo.

11.4 Final Remarks

The interest on particle size characterization and on its influence on bioavailability is renewed by regulatory requirements and by the introduction of the new nanonization technology. In particular several kinds of nanosized active ingredients are nowadays commercially available, and others are undergoing development studies. Nanonization to obtain a nanocrystal formulation is an approach well-adaptable to drugs having different chemical-physical properties. Moreover, the employment of excipients to stabilize nanocrystals, and in particular the use of surfactants for nanocrystal surface modification should further enhance drug bioavailability and could achieve prolonged release and targeted (site-specific) drug delivery.

In addition, nanotoxicological investigations of drug nanocrystals should be extensively carried out to better understand the fate of nanocrystals at a cellular level and to find new potential for nanocrystal applications for innovative treatment approaches.

11.5 Definitions, Abbreviations and Symbols

Absorption number	Ratio of the mean residence time to the absorption time.
Dissolution number	Ratio of mean residence time to mean dissolution time.
Dose number	Ratio of the total amount of drug added to the amount soluble in 250 ml water (being the standard volume of liquid available for dissolution in our gastro-intestinal system)
Fasted condition	Without eating food
Fed condition	After eating food
Food effect	Effect of the presence of food on drug fate in gastrointestinal tract
Initial saturation	Ratio of drug luminal concentration at the beginning of the intestine to drug solubility
Intrinsic dissolution	Dissolution rate of pure substances under the condition of constant surface area
Sink conditions	Conditions where C_t is negligible in comparison to C_s
AUC	Area under the blood plasma concentration-time curve
BCS	Biopharmaceutical Classification System
GIT	Gastro-intestinal tract
GL	Guideline
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals for human use
IR	Immediate release
NK1	Neurokinin 1
SDS	Sodium dodecylsulfate
A	Surface area
An	Absorption number
C_{max}	Maximum plasma concentration
C_s	Solubility of the substance
C_t	Concentration at time t
C_∞	Saturation solubility of an infinitely large drug crystal
D	Particle size (diameter of an equivalent sphere)
$D_{3,2}$	Area-weighted Sauter mean diameter
$D_{4,3}$	Volume-weighted mean size
Do	Dose number
Dn	Dissolution number
$\mathbb{D}$	Diffusion coefficient of a solute
dm/dt	Dissolution rate
G	Surface specific dissolution rate
Is	Initial saturation
M	Drug molecular weight,
m	Drug amount
R	Gas constant,
r	Particle radius
T	Temperature

(continued)

t	Time
t_{max}	Time to reach maximum plasma concentration
δ	Thickness of the diffusion boundary layer around a particle
λ	Crystal/medium interfacial tension
ρ	Particle density

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