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NANOSUSPENSIONS: A STRATEGY FOR IMPROVED BIOAVAILABILITY

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ABSTRACT

Poor aqueous solubility of lead drug candidates remains an obstacle for drug development in pharmaceutical industries. Drugs with dissolution rate limited drug absorption show low bioavailability due to poor aqueous solubility of the drug. To overcome these problems different formulations of nanosized drugs were developed recently. Pharmaceutical nanosuspensions consist of dispersed solid drug particles in an aqueous vehicle with average particle sizes below 1µm. The present paper is a review of current development in nanosuspension formulation strategies for possible improvement in oral bioavailability.

KEY WORDS

Nanosuspension; solubility; bioavailability; absorption

INTRODUCTION

Formulations of drugs with low solubility in aqueous solvents are problematic with respect to their biopharmaceutic quality, since slow and erratic dissolution is preventing the rapid and complete absorption of these compounds from the gastrointestinal tract. To overcome these problems different formulations of nanosized drugs were developed recently [1]. Pharmaceutical nanosuspensions consist of dispersed solid drug particles in an aqueous vehicle with average particle sizes below 1µm. The major advantages of nanosuspension technology are the increase of saturation solubility and consequently the increase in the dissolution rate of the drug. In 1990 Liversidge et al. developed a product called NanoCrystals® by pearl milling drug powder suspension for hours up to several days [2]. In vivo studies in animals and humans showed improved bioavailability, enhanced absorption rate, improved dose proportionally, reduced fed/fasted variability and reduced inter-subject variability [3,4]. In 1994 Müller et al. further developed drug nanosuspensions (DissoCubes®) by high pressure homogenization in the presence of a suitable surfactant. Those formulations were prepared by passing of a microparticle drug suspension under high pressure through a small homogenization gap. The accruing cavitation forces disintegrate the particles to form drug nanoparticles [5]. High pressure homogenization is also a technique for the preparation of solid lipid nanoparticles (SLN™).

Principle of enhanced oral absorption

The dissolution rate can be enhanced by a reduction in particle size through two mechanisms; an increase in surface area and an increase in solubility due to the increase in the surface curvature [6]. Surface area is inversely proportional to particle size. Thus, if particle size is reduced from 1 µm to 100 nm, the surface area increases 10- fold, which should lead to 10-fold enhancement of the dissolution rate. Assuming that a particle is spherical, dependence of solubility on particle size can be described by the Ostwald–Freudlich equation [7, 8];

$$C(r) = C(\infty) \exp(2\gamma M/r\rho RT)$$

Where C(r) and C (∞) are the solubilities of a particle of radius r and of infinite size. γ, M, and ρ are interfacial tension at the particle surface, the molecular weight of the solute, and the density of the particle, respectively. This equation is analogues to the more general Gibbs–Kelvin equation, which is usually applied to liquid droplets. According to this equation, solubility increases with a decrease in

particle size, i.e., an increase in surface curvature. Given that the particles have a rectangular parallelepiped shape, no solubility advantages are expected because the surfaces are flat. Thus, an increase in surface area can be regarded as a dominant factor for increasing the dissolution rate in nanosizing technology, and the "solubility advantage" is only marginal. An enhanced dissolution rate may not be the only factor for the nanoparticles to achieve better oral absorption. It is well known that Peyer's patches may uptake nanoparticles, and diffusion of nanoparticles in the mucous layer may affect the absorption as well. Diffusion of nanoparticles in the mucous layer is affected by their surface properties as well as by particle size. Lai et al. directly investigated the diffusion of nanoparticles in a mucous layer to find that 500 nm particles diffused very rapidly with a diffusion coefficient only four-fold less than that for the same particles in water, if it is coated with the poly(ethylene glycol) layer, although the mesh size of the mucus had been believed to be 10– 200 nm [9]. In contrast, uncoated 100 nm nanoparticles diffused very slowly, indicating a greater importance of surface property and larger mesh size of the mucous layer than previously thought. These kinds of observation have actively been made for polymeric nanoparticles; however, they should help understanding oral absorption mechanism of simple nanocrystals as well.

Formulation strategy

Solid nanoparticles can be produced via either a top-down or bottom-up procedure. The industrial top-down procedure includes media-milling and high-pressure homogenizer technologies [10, 11], which have produced the nanoparticulate solid formulations currently on the market. Nanoparticles can also be produced by dry-milling using the appropriate type and amount of excipients [12, 13]. The bottom-up procedure requires control of the crystallization process, which may be followed by a homogenizing process similar to the top-down production. Nanoparticles can be prepared by spray-drying or supercritical fluid technology as well [14, 15]. "Nanosizing" usually refers to size reduction down to 100– 300 nm in the pharmaceutical field. Sometimes the definition includes particles up to 1000 nm. Although nanosizing itself is not difficult by using commercial equipments, physical stability during storage may become a problem. Since the nanosized particles have very high surface energy, aggregation tends to occur easily. Media should be removed for manufacturing tablets. However, the resultant formulation may not disintegrate into nanoparticles after oral administration. Thus, polymers or surfactants are usually added before size reduction to enhance stability. Unfortunately, it is difficult to predict long-term physical stability for nanosuspensions. This is totally the same problem with that of solid dispersions.

Improvement of oral absorption

The biopharmaceutical advantages of oral nanoparticles include increased bioavailability and diminished food effect. Jinno et al. compared oral absorption of cilostazol using 220 nm, 2.4 µm, and 13 µm particles [16] to find that the AUC in beagle dogs increased with decreasing particle size, and that the effect was more pronounced in the fasted state. As a result, the food effect was diminished by using 220 nm nanoparticles. Wu et al. investigated the effect of nanosizing for MK-0869, which is currently on the market as Emend® [17]. Again, oral absorption of the drug increased with decreasing particle size. The AUC ratio from 5.5 µm and 120 nm particles was 4.3. The food effect was 3.2-fold for the 5.5 µm particles, however, it decreased to 0.96-fold by reducing the particle size down to 120 nm. Since Emend® is used to treat chemotherapy induced nausea and vomiting, patients cannot have meals before taking the drug. Thus, improvement in oral absorption in the fasted state is very meaningful for this drug.

Advantages and disadvantages

The advantages and disadvantages of nanosuspensions are very similar to those of solid dispersions. Nanosuspensions can be transformed into solid dosage forms after drying, thus the user friendly formulation can be expected. However, experience with formulation design and industrial production is still required. Although some polymers and surfactants are known to have a stabilization effect, the types and amounts must be determined through screening. Since no protocols have been established for predicting long-term physical stability during storage, a relatively long developmental period is required. As same as the case of the solid dispersions, nanosuspension technology can be used

for replacing inconvenient self-emulsifying formulations. Rapamune® is an immunosuppressive drug, which was originally marketed as a self-emulsifying oral solution. The formulation required refrigeration, and needed dilution with water before taking. Restrictions were placed on the dilution procedure, such as no use of grapefruit juice or paper cups. This formulation was replaced with tablets manufactured by nanosuspension technology, which can be stored at room temperature.

Selection of dosage form

If the oral absorption can be improved by simple additives, no further efforts may be required in the formulation study. Unless the simple additives work, liquid formulation should be considered next, since they can be developed relatively quickly. However, high solubility and stability in the oil vehicle is required for the liquid formulations. If the dose/solubility ratio exceeds 10 mL, the capsule number is expected to be more than 10. Whether or not this capsule number is acceptable totally depends on the developmental strategy, however, it is not recommended as the author's view. Amorphous solid dispersions and nanosuspensions have great advantages over the liquid forms as discussed previously. However, it may be difficult to complete formulation development in the normal developmental timelines for these formulations mainly due to the physical stability issues, although they may be applicable as final formulations. Also should be mentioned is that platform formulation and technology must be designed in advance for utilizing any supersaturatable dosage forms.

CONCLUSIONS

There is a plethora of technology available to enhance the solubility and solubility related bioavailability of drugs [18]. Solubility of API may be improved by employing metastable crystalline forms, salt forms, or cocrystals. However, use of metastable forms is not a common strategy, because the increase in solubility is usually not great and this strategy involves risk of physical instability. The salt form is a good option for improving solubility (dissolution rate), and thus extensive screening is usually employed in pharmaceutical companies. Cocrystals may or may not improve solubility, and investigation of the characteristics of cocrystals and screening methodology are actively continuing. Promising supersaturatable dosage forms from a practical viewpoint include liquid-filled capsules, self-emulsifying formulations, solid dispersions, and nanosuspensions. Liquid-filled capsules are now regarded as a common formulation technology, and their development is relatively easy. This is also true for self-emulsifying formulations. However, the liquid formulations may be inconvenient due to the large formulation volume and strict storage conditions. Solid dispersions and nanosuspensions can overcome such inconveniences, although progress in formulation technology including establishment of a protocol to predict physical stability is still required.

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