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Overcoming the Challenge of Poor Drug Solubility

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Problem

Recent drug discovery has led to an increasing number of new drugs with low water solubility and hence poor bioavailability, especially via oral administration.[1] The number of such drug candidates has increased enormously and almost 70% of the new drug candidates have shown poor aqueous solubility in the recent years.[2] Since approximately 65% of the human body is made up of water, a drug must have certain water solubility and possess an acceptable bioavailability level. Poorly water soluble drugs tend to be eliminated from the gastrointestinal tract before they get the opportunity to fully dissolve and be absorbed into the blood circulation. This results in low bioavailability and poor dose proportionality, which greatly hinders their clinical translations.[3] In such cases, dose augmentation would be necessary to ensure that the drug attains the therapeutic concentration range in blood. After oral administration, this dose augmentation at times causes topical toxicity in the gastrointestinal tract and such toxicity results in a decline in patient compliance.[4] On the other hand, consuming a large amount of Active Pharmaceutical Ingredient (API) would raise the manufacturing cost of developing and manufacturing the drug product. In short, these poorly water soluble drugs show a number of negative clinical effects including potentially serious issues of inter-patient variability, higher patient costs, inefficient treatment, and more importantly, increased risks of toxicity or even death.

In the drug discovery stage, a number of *in-vitro* assays are conducted to evaluate several biological properties such as efficacy, membrane permeation properties, and genotoxicity. The performance of such poorly water soluble new drug candidates also might be affected in these *in-vitro* cell culture assays because the solubility constraint or precipitation of the drug in the test medium may give inaccurate data regarding the drug properties. In preclinical development, the data quality of the *in-vivo* toxicity assessments also could be degraded since toxicological studies usually require higher exposure than that in pharmacological or pharmacokinetic studies to assure its safety. Overall, the poor bioavailability of a drug substance might result in limited therapeutic potential for clinical use, thereby leading to insufficient clinical outcomes. Therefore, poor water solubility of many drugs is one of the major obstacles in the development of highly potent pharmaceutics.

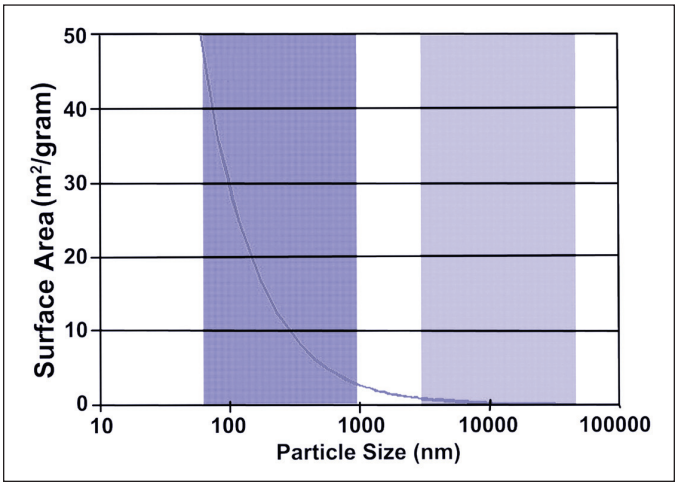

Figure 1. Reducing the particle size leads to an exponential increase in surface area.

Possible Solutions

In contrast to developing completely new drugs, introducing upgraded or advanced formulations greatly reduces the risk, time, and capital invested in drug development. Many approaches have been developed to enhance the dissolution rate as well as bioavailability of poorly water soluble drugs, including both

modifications to the drug substance itself and the creation of specific formulations. Physical modifications often aim to increase the surface area, solubility, and wettability of the drug particles and typically focus on particle size reduction[5,6] or generation of amorphous particle states.[7,8]

Drug Nanoparticles

A classical formulation approach for such poorly soluble drugs is nanonization that means producing drug nanoparticles with mean particle size below 1 µm.[9] The principle is to increase the dissolution velocity by enlarging the surface area of the drug powder. Consideration of the Noyes-Whitney equation provides the insight as to how the dissolution rate of poorly soluble compounds might improve:[10]

$$\frac{dm}{dt} = \frac{DA}{h}(C_s - C_{bulk})$$

where dm/dt is the dissolution rate of drug, D is the diffusion coefficient of drug, A is the surface area of drug, C_s is the saturation concentration of drug, C_{bulk} is the concentration of drug in the bulk, and h is the thickness of the hydrodynamic boundary layer. As shown in Figure 1, the surface area per gram of the drug increases as the size of the drug particles is decreased from bulk to a micro to a nano scale. The very small particle size results in a large surface area (A) and thus in an increased dissolution rate according to the Noyes Whitney equation. Therefore, drug particles in the nanometer size range will dissolve more rapidly than a conventional formulation and result in increased flux across the gut lumen and to the blood.

Nanoparticles exhibit some interesting surface properties due to their very small size. They are able to deliver Active Pharmaceutical Ingredients (APIs) across a number of biological barriers, i.e., the Blood Brain Barrier (BBB), different types of mucosa and epithelia, and cell membranes for transfection applications. They also show excellent adhesion to biological surfaces, such as the epithelial gut wall[11,12] and this bioadhesion increases with decreasing particle size as shown in Figure 2. The adhesive nature of nanoparticles due to increased van der Waals interactions (due to increased contact areas made available by nanoscale particles' surfaces) with the biological membrane/gut wall[9], not only facilitates permeation, but also assists in reducing food effects hence, leading to enhanced bioavailability.[13] In addition, utilization of the dense, solid state confers an additional advantage of higher mass per volume loading. This is crucial when high dosing is required. Fast dissolution of nanoparticles facilitates its use for API where the absorption window is quite narrow, as the drug will dissolve quickly and in doing so avoid unsuitable environment for API absorption or stability. Other related positive factors include dosing and patient-related factors, namely possible dose reduction or escalation; improved dose proportionality and reproducibility; and enhanced dose tolerance, compliance and reduction in food effects and hence improved efficacy and safety.[13] However, as the van der Waals forces become dominant at nano-scale, they cause the drug nanoparticles to agglomerate.

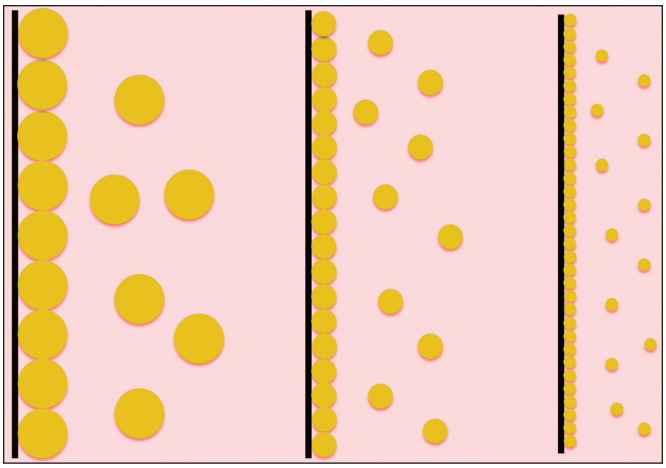

Figure 2. Reducing the particle size leads to greater adhesion to biological surfaces.

Solid Dispersions

Solid dispersions may be defined as the dispersion of one or more active ingredients in molecular and amorphous forms in an inert carrier or matrix in the solid state.[14,15] Dispersing drug nanoparticles in a carrier matrix can prevent aggregation and a fine dispersion will increase the available surface so that wetting and dissolution can occur more rapidly. For formulations targeting dissolution and bioavailability enhancement, solid dispersions often take the form of "solid solutions," where the drug is molecularly dispersed in a hydrophilic polymer. Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size should be reduced to its absolute minimum viz. the molecular dimensions so that the dissolution rate of the drug is determined by the dissolution rate of the carrier. In addition to that, hydrophilic carriers allow a more extensive wetting of the drug particles resulting in the higher solubility and dissolution rate of poorly water soluble drugs. Furthermore, combining the drug with an amorphous carrier can change the degree of crystallinity of the drug. In most cases, the drug is not in the crystalline form, but in the amorphous state and such different solid forms can influence the dissolution, bioavailability, stability, and other drug properties.[16] An amorphous form allows higher solubility and faster dissolution of the drug in comparison to its corresponding crystalline form because of its higher internal energy and greater molecular mobility. Poorly water soluble crystalline drugs, when in the amorphous state, tend to have higher solubility because no energy is required to break up the crystal lattice during the dissolution process. However, as the amorphous phase is metastable compared to the crystalline state, there is some risk that phase transformation (i.e., crystallization) may occur upon storage, limiting their use in pharmaceutical dosage forms. Judicious selection of a carrier to improve the dispersion of drug can lead to stable amorphous formulations.

Present Study

This study focuses on improving the dissolution rate of extremely hydrophobic quercetin (3, 3', 4', 5, 7-pentahydroxyflavone), which is a polyphenolic flavonoid and one of the most prominent dietary antioxidants. Quercetin also has been proven to possess potent chemopreventive and antiproliferative effect and has demonstrated strong inhibition of breast, colon, lung, and ovarian cancer cell growth.[17,18] In spite of this wide spectrum of pharmacological properties, its use in the pharmaceutical field is limited by its low water solubility. Bioavailability of quercetin is shown to be poor and its pharmacological effect is restricted by its poor solubility and fast metabolism. Reducing particle size and creating amorphous states provide a solution to this problem. It is observed from Figure 3a that the original quercetin used in our study exhibited lack of uniformity in size and particles were in the range of 30 to 35 µm. Therefore, efforts have been made to enhance the dissolution rate of quercetin by fabricating its nanoparticles and solid dispersions. There are two main approaches for nanoparticle preparation: top down (break big particles down to nanoscale) and the bottom up (build the nanoparticle from molecular scale building blocks). In the present study, quercetin nanoparticles have been fabricated using the top-down techniques of bead milling and high pressure homogenization; and bottom-up technique of evaporative precipitation of nanosuspension, also has been used to prepare the solid dispersions of quercetin.

Bead Milling

A bead mill consists of a rotating vessel which is partly filled with beads (milling media). The attrition and shear forces generated due to the impaction of the beads with the drug generate sufficiently high energy input to break the drug microparticles into nanoparticles. Aqueous nanosuspensions of quercetin were fabricated by agitating bead mill Bühler PML-2 (Bühler AG, Uzwil, Switzerland) in a continuous mode using yttrium stabilized zirconia milling beads of size 0.4 to 0.6 mm. The smallest average particle size of quercetin nanoparticles obtained after milling the suspension of quercetin containing 5% (w/w) quercetin stabilized with Tween 80 (1% w/w) for 60 minutes was 319 nm[19] as shown in Figure 3b. According to the theory, with a reduction in the size of milling media in a mill, the number of contact points is increased exponentially, resulting in improved grinding and dispersing action and hence, leading to smaller particles. However, in our study, no major difference was observed in the particle size of the quercetin nanosuspensions fabricated using 0.2 mm and 0.4-0.6 mm sized milling beads. Since it is easier to separate the 0.4 to 0.6 mm sized milling beads from the product than the 0.2 mm ones, the 0.4 to 0.6 mm size milling beads were found to be efficient. The market leading technology for the production of drug nanoparticles by wet milling is Elan Corporation's NanoCrystal® technology, which was first developed by Liversidge et al.[20] In 2000, the US FDA approved the first drug Rapamune (sirolimus) that specifically uses nanotechnology to increase solubility.

High Pressure Homogenization

Nanosuspensions of quercetin (5% w/w) in Milli-Q water with Tween 80 as a stabilizer (1% w/w) were produced by LAB 40 (APV Deutschland GmbH, Unna, Germany) using a high pressure piston gap homogenizer. Prior to high pressure homogenization at 1500 bar (20 cycles), the coarse quercetin suspension was pre-milled at increasing pressures (2 cycles at 300 bar, 2 cycles at 500 bar, 1 cycle at 1000 bar) to diminute very large particles in order to prevent blocking of the homogenization gap. In APV LAB 40, the drug suspension, contained in a cylinder of diameter about 3 cm, passes through a very small homogenization gap in the homogenizer having a width of 25 µm under a high pressure (100-2000 bar), which leads to a high streaming velocity. According to the Bernoulli's law, in a closed system, the flow volume of liquid per cross-section is constant, which implies that the reduction in the diameter leads to a tremendous increase in the dynamic pressure (i.e., also streaming velocity), and simultaneously a decrease in the static pressure when the suspension is in the homogenizer gap. When the static pressure falls below the vapor pressure of the water, it starts to boil at room temperature and gas bubbles form, which implode when the suspension leaves the gap and comes under the normal pressure conditions again (cavitation). The formation of gas bubbles and their implosion causes shock waves, whose enormous power along with the turbulent flow and shear forces leads to the diminution of particles of the suspension.[9] The quercetin particle size decreases with increasing number of homogenization cycles. The number of homogenization cycles required is mainly influenced by the hardness of the drug, the finesse of the starting material and the requirements of the application route or the final dosage form.[9] In the case of quercetin nanoparticles, 20 cycles were found to be optimum and the smallest average size obtained for quercetin was 338 nm[19] as seen from Figure 3c. The technology based on high pressure piston gap homogenization of particles in pure water was developed by Müller et al.[21] and later acquired by SkyePharma and has the trade name of DissoCubes™. However, there are no marketed products based on this technology at present.

Evaporative Precipitation of Nanosuspension (EPN)

Quercetin was dissolved in a solvent (ethanol) and then a nanosuspension was formed by quickly adding an antisolvent (hexane). Drug nanoparticles in the nanosuspension were obtained by quick evaporation of the solvent and antisolvent using a rotary evaporator, followed by vacuum drying. The type of antisolvent, drug concentration, and solvent to antisolvent ratio were optimized in order to yield the smallest particles. The morphology and size of the particles changed with the type of antisolvent used. With water as an antisolvent, the particles were big, irregular, and flake type.[22] However, with hexane, the particle morphology was more needle-like with smaller particle size. It was observed that increasing the solvent to antisolvent ratio and decreasing the drug concentration in solvent resulted in lower particle sizes. Drug concentration of 5 mg/ml and the solvent to antisolvent ratio of 1:25 (v/v)

resulted in the smallest particles of size 739 nm[22] as shown in Figure 3d. It should be noted that the amount of the residual solvents (ethanol and hexane) in the samples prepared by EPN was below the acceptable level for residual solvents in pharmaceuticals as determined by FDA for the safety of the patient. Hexane is a Class 2 solvent, whose amount should be limited (290 ppm) and ethanol is a Class 3 solvent, with low toxic potential and minimum amount of 5,000 ppm.[18] For the EPN prepared samples, the amount of hexane was below 125 ppm and ethanol was below 20 ppm as determined by gas chromatography, hence satisfying the FDA criteria. Precipitation techniques are not being used at present to fabricate drug nanoparticles at industrial scale. However, evaporative precipitation of nanosuspension is a simple and cost effective method and can be developed further for large scale production.

Quercetin Solid Dispersions

Solid dispersion of quercetin in polyvinylpyrrolidone (PVP) and Pluronic F127 (F127) also were prepared by evaporative precipitation of nanosuspension. Both quercetin and the carriers were dissolved in ethanol and later the common antisolvent (hexane) was added, followed by quick evaporation and vacuum drying. Quercetin to carrier ratio used was 1:1 (w/w). The 5 mg/ml quercetin concentration in ethanol an ethanol to hexane ratio of 1:25 were used.[22] X-ray diffraction (XRD) was used to study the nature of drug in solid dispersions. The complete absence of any diffraction peak corresponding to the crystalline drug indicates that the drug is no longer present in the crystalline form, but exists in the amorphous state. As seen from Figure 4, the original quercetin have several diffraction peaks suggesting its crystalline nature. PVP is amorphous as indicated by its diffraction spectrum without any prominent peak. On the other hand, F127 is semi-crystalline and exhibits two sharp diffraction peaks at 2θ =19.12° and 23.27° as seen from Figure 4. It can be clearly observed that the quercetin peaks were absent in its dispersion in PVP and F127.[22] In addition to the fact that the drug is present in an amorphous form, the results also suggest that the drug is dispersed at molecular level in the polymer matrix. The presence of a

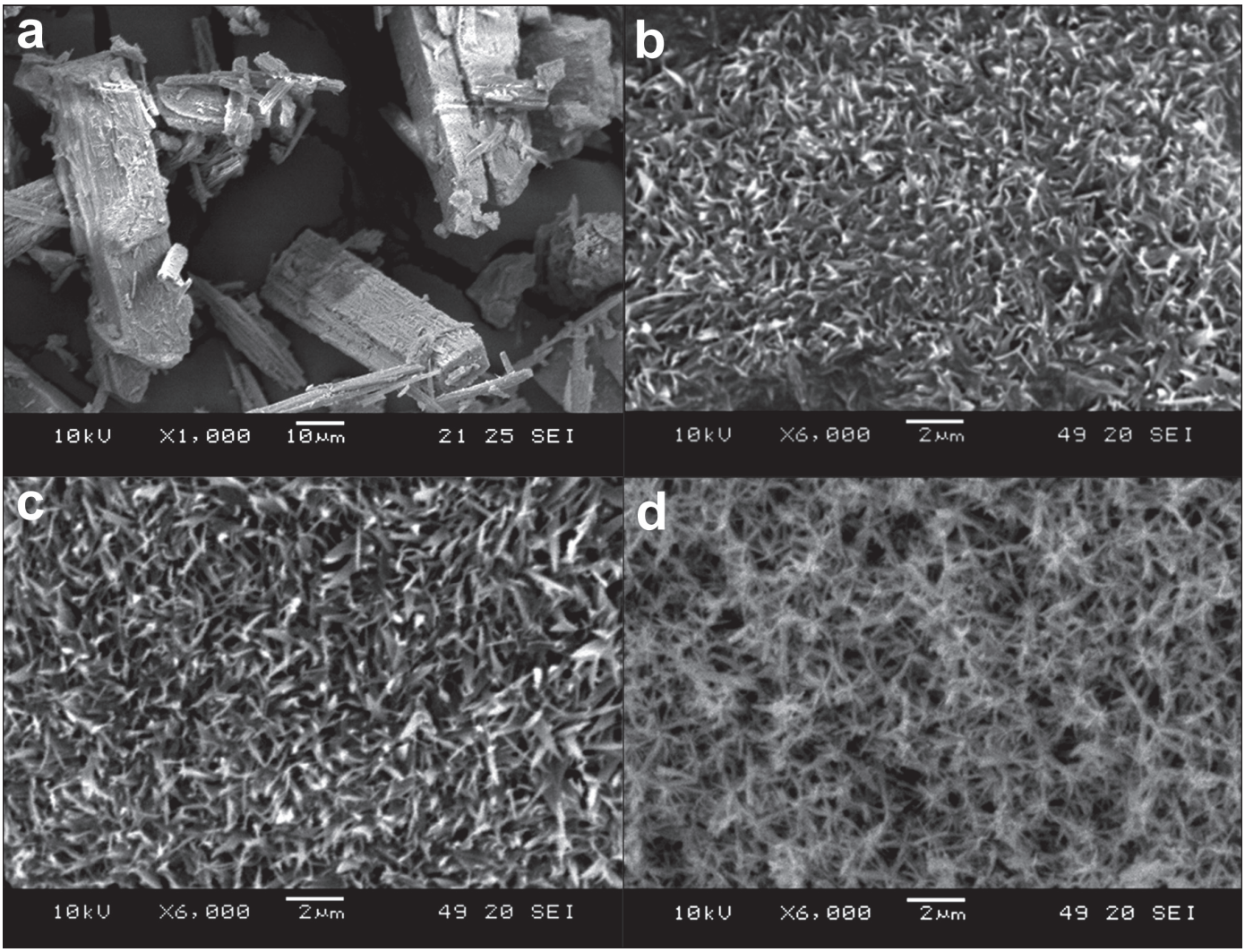

Figure 3. Scanning electron microscopic photographs indicating clear reduction in particle size of quercetin by many folds, (a) original quercetin; and quercetin nanoparticles produced by (b) bead milling, (c) high pressure homogenization and (d) evaporative precipitation of nanosuspension.

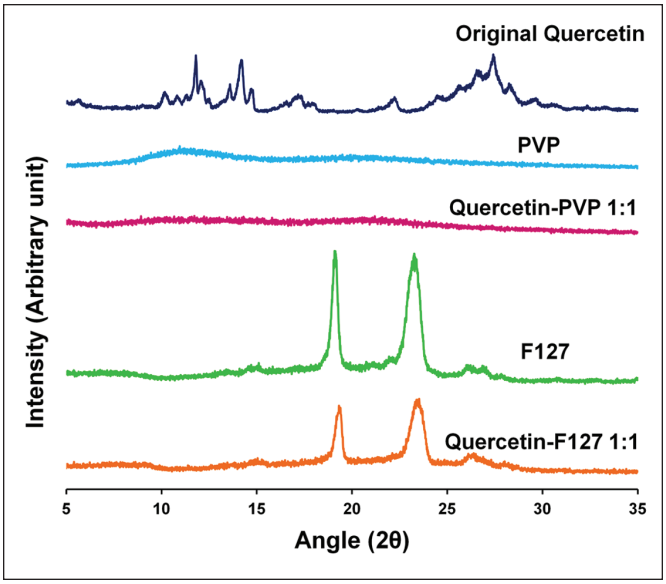

Figure 4. X-ray diffractograms for original quercetin, PVP, F127, quercetin-PVP and quercetin-F127 dispersion at 1:1 ratio.

polymer or polymeric additive has been shown to possess an inhibitory effect on the precipitation and hence, the reduced crystallinity of the resulting drug.

Research on new solid dispersions and the related fabrication processes have been widely reported in the literature during the past several decades. Today a number of solid dispersion products are marketed including: Kaletra® and Norvir® (Abbott), Nimotop® (Bayer), Gris-PEG® (Pedinol), Cesamet® (Meda Pharms), Intelence® (Tibotec), Certican® or Zortress® (Novartis), Isoptin SR-E® (Abbott), Crestor® (Astrazeneca), Nivadil® and Prograf® (Astellas Pharma, Inc.), Rezulin® (Pfizer), Sporanox® (Janssen Pharmaceutic), and Toramat®, Vociflon®, Montelukast®, Palibone®, Iasibon®, Razilan® and Ostiral® all from Pharmathen S.A.

Dissolution Study

The dissolution test was performed using a USP II rotating paddle apparatus with a Pharmatest PTW SIII (Pharma Test, Germany) at 37°C and a rotating speed of 100 rpm in 900 ml of DI water. Quercetin samples containing an equivalent of 5 mg of quercetin were dispersed in the dissolution medium. At certain time points, samples were withdrawn from the dissolution chamber and then filtered and analyzed using high performance liquid chromatography. The dissolution test for each sample was performed in triplicate and the dissolution data was averaged. As seen from the dissolution profile in Figure 5, only about 8% of the original quercetin dissolved within 60 minutes, showing a very poor dissolution rate. On the other hand, all the formulations prepared showed the drastic increase in the dissolution rate. The greatest increase in the dissolution rate is exhibited by the solid dispersion systems. The possible explanation is the reduction in the particle size to molecular level or the generation of an amorphous state (as shown earlier by XRD study). The quercetin nanoparticles presented increasing the order of dissolution rate with decreasing particle size as: evaporative precipitation of nanosuspension < high pressure homogenization ≤ bead milling although there was no significant difference in the dissolution profile of quercetin nanoparticles prepared by high pressure homogenization and bead milling. To sum up, nanosizing and amorphization of quercetin tremendously enhanced its dissolution rate. As a result, the quercetin nanoparticles and solid dispersions prepared are expected to demonstrate a better bioavailability than the original drug powder.

Conclusion

Looking at the average particle size, bead milling produced the smallest particle size, followed by high pressure homogenization, and then evaporative precipitation of nanosuspension. Comparison of the three methods of fabrication showed that each technique had its own advantages and disadvantages. Bead milling has the disadvantage of increased time and costs associated with the separation procedure of the milling material from the drug nanosuspension and the potential erosion from the milling material leading to product contamination. High pressure homogenization is an energy intensive process and the application of such high pressures can affect the large-scale pharmaceutical production. Moreover, when a suspension is produced from these methods an additional drying process is required to obtain the powder form for oral administration. But they have the advantage that the drugs that are poorly water soluble in both aqueous as well as organic media can be easily formulated into nanoparticulate suspensions. On the other hand, evaporative precipitation of nanosuspension is comparatively a cost effective, low energy, and simple process, and no post processing is required, but the drug compound should be soluble in an organic solvent, which should be miscible with an antisolvent. Solid dispersions of quercetin in PVP and F127 also were produced by evaporative precipitation of nanosuspension. Solid dispersions are an excellent alternative and have shown the positive results,

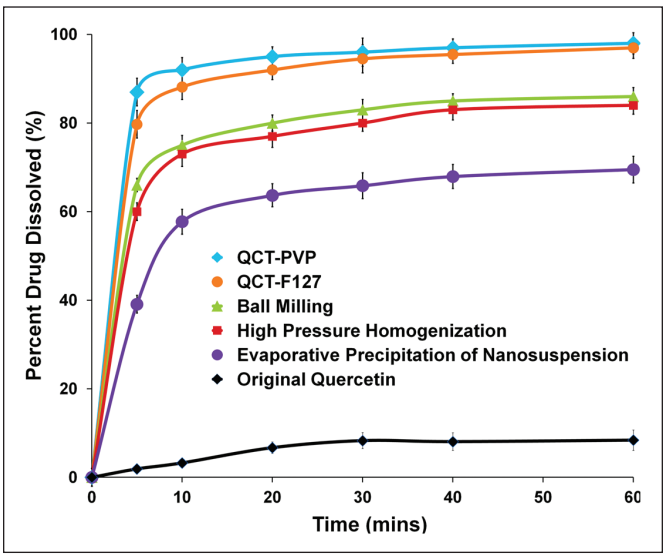

Figure 5. Dissolution profile of original quercetin; quercetin nanoparticles prepared by bead milling, high pressure homogenization and evaporative precipitation of nanosuspension; and quercetin-PVP and quercetin-F127 dispersion at 1:1 ratio.

but there are issues related with the long term stability of the formulations.

In the future there is a lot of potential for the development of the bottom up precipitation techniques for large scale production of drug nanoparticles and further improvement of the milling and homogenization techniques. Solid dispersion is a promising approach, which is already very prevalent. Surfactants can be added to a carrier matrix, thus, forming a ternary dispersion, for superior stability of the formulations and better dispersion of drug in the carrier.

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