Improving the Bio-Availability of Drugs Through Their Chemistry

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The development of new drugs is a complex process that requires a multiple of scientific disciplines. As drugs become even more complex, the ability of companies to get products to market has become even more difficult. Today, many potential drugs can fail early during the development process. Inherent in the complexity of the molecules is low solubility and poor bio-availability. While clinically they appear to be good targets, the inability to get them into the body destines them to failure. In addition, with the cost of drug development escalating, companies are often forced to drop products quickly in favor of potentially more active compounds. However, some companies are starting to go back and look at these "failures" and see if they can improve on the solubility and dissolution to improve bio-availability and bring good medicines forward.

There are various ways to improve the overall bio-availability of a drug. One can look at them from either the chemistry side or the formulation side. For this paper, we are going to look at the chemistry side and explore some of the newer methods being developed today.

Scientifically, we can look at several general types of modifications which can eventually bring these products to the market. Modification of either the particle size or the particle shape is a well-documented process that has been used for years. In addition, salt formation can improve solubility. Other modifications of the product can help to improve the ability of the drug to the body.

Particle Modification

The most basic approach would be to look at modifying the particle size to increase solubility. We recognize that as the particle size decreases the surface area increases. As the ratio between volume and surface area increases, the solubility will most often increase as well. Today there are many innovative methods available to create new particles of a wide range of sizes and shapes. Development of amorphous materials versus crystalline materials will also improve solubility. Today, these can be modified and improved during the actual manufacturing of the Active Pharmaceutical Ingredient (API).

Particle Size

We recognize that as the particle size decreases the surface area increases. As the ratio between volume and surface area increases, the solubility will most often increase as well. We also understand that amorphous materials should be more soluble than crystalline products due to the higher Gibbs free energy.[1]

This is one of the oldest methods employed and can be done at either the manufacturing site or the formulation site. Often, formulators will employ some type of milling step to improve the overall mixing and make more even blends of API and excipient. This can also be done at the point of manufacturing but there are some inherent problems with this.

Mechanical milling is well established and there are several types of commercial mills and companies that specialize in particle size reductions. Traditionally, particle size was corrected with the addition of some type of milling step. This allowed us to reduce the particle size and often look at narrower particle size ranges. However, there are several things to consider in milling operations. These include the loss of product and the formation of particles lower than the desired range. One must also be concerned with the loss of product due to the generation of heat in the mills which could result in the particle deteriorating or moving to a different polymorph form. For an expensive product this could add significant cost to the end product. In addition, there is the possibility of metal contamination from the mills themselves.

There are various types of milling operations which include both wet and dry operations but in principle, they all require the use of mechanical force to reduce the size of the particle. Hammer and ball mills have traditionally been used in the pharmaceutical industry. Ball milling has some added advantages since you can develop very good mixes of product and excipients such as PVP polymers. If very small particles are desired, one can move to other techniques such as jet milling. These can be cooled and can give sub 5 micron particles and more narrow ranges.

Milling has several advantages. Milling is one of the oldest techniques used for particle size reduction, is well understood, and easy to implement. There are several significant drawbacks as well. For one, the distribution for traditional equipment can be rather broad and there is the production for fine particles. Jet milling can reduce this. Also, there is heat generated in the operation which could affect fragile materials. The creation of fine particles also results in the loss of product and can also result in waste issues and additional costs.

Continuous Crystallization

The pharmaceutical industry is moving more and more to working in a continuous mode and to develop continuous processes. The overall control, significant CAPEX reduction as well as the ability to handle more difficult and hazardous chemistries has been a few of the reasons for this transition from batch to continuous. To truly develop a continuous process, it would only seem logical that the end stage operations such as crystallization and drying should be continuous as well. With the advent of better methods and our ability to measure the outcomes, continuous crystallization is becoming more popular. This is important since nearly 90% of the products produced today utilize some type of crystallization process at the end.[2]

There is a significant amount of work being done today in both industry and in academia looking at continuous crystallization. There have been multiple papers showing the advantage of continuous processes but how can this help us with the overall particle size of the material being produced. Work at MIT has demonstrated that continuous crystallization can generate narrow particle ranges and directly produce the desired particle size and distribution. This can reduce the potential for the formation of fine particles as well as the need for milling. Overall, this can improve the chemical process while also improving the solubility and therefore the bio-availability of the drugs under development.[3]

Solution crystallization can generally be described in two stages: nucleation and crystal growth.[4] In continuous mode, there are several innovative techniques and new equipment that can operate in a continuous mode. Some of the key operating parameters for crystallization can be improved in continuous flow crystallizers. Work done in oscillatory baffled crystallizers demonstrated that they could induce a much faster rate of cooling. They also found that the aggregates/agglomerates that were formed due to the higher rate of nucleation broke up into smaller rods and rod clusters under agitation. With increased oscillation, they also noted smaller particles sizes. Additional benefits could include reduction of solvent used and one of the most important aspects could be the elimination of the need for milling.

Process improvements are not limited to just osculating crystallizers but there are some general trends seen in continuous crystallization. In particular to cost reduction, the overall consistency of the product quality and particle size distribution can significantly improve the product. The elimination of fines can potentially reduce some of the toxic effects and rapid absorption. The LD 50 of some compounds can easily be affected by the particle size of the API. The smaller and narrower range of the particles can improve overall product solubility and dissolution.

Another potential improvement seen in continuous crystallization could be the formation or lack of formation of particular polymorphs using continuous crystallization. Experiments conducted at MIT and published demonstrated that one could get 100% formation (no other polymorph detected) of a particular crystal form. In addition, even with seeding with the unwanted crystal, the same results were noted over time. Considering the different polymorphs could have different solubility and bio-availabilities, the ability to lock in the correct form could be instrumental in the success of the drug.[5]

Nanoparticles

Professor Taniguchi defined nanoparticles in 1974. Today, the most common definition of nanotechnology is the manipulation,

observation and measurement at a scale of less than 100 nanometers.[6] The absorption, distribution, biotransformation and excretion of a drug involve its transport across cell membranes. API's in the nanometer particle size can offer unique advantages over conventional particle sizes. This could lead to enhanced performance and have higher saturation solubility and rapid dissolution. The reduction of toxicity can also be a major consequence of the nanoparticle formulations.[7]

Consider that to achieve therapeutic levels over time; the initial concentrations must be very high. Over a fixed period of time these levels will be reduced. These high initial levels could be toxic and has been seen in chemotherapy agents. Today, we are developing a greater number of drugs with increased potency and the nanoparticulate drug delivery systems are going to be even more important

Today the formation of nanoparticles is possible and a commercial option for the development of an API. The formation of nanoparticles is described as either a "top down" or "bottom up" process. These processes have been used to manufacture commercial products.

The bottom up approach requires the formation of particles using various methods including the use of supercritical solutions to create the fine particles. Today this is the most popular method for developing nanoparticles using the bottom up approach. Additional methods have been referenced in many articles. The basic idea is to dissolve the API in some type of solvent and precipitate/crystallize it from solution using an anti-solvent, usually water.[7]

The Rapid Expansion of Supercritical Solutions (RESS) approach requires the saturation of a super critical fluid with a solid substrate followed by rapid depressurization of the solution through a heated nozzle into a low pressure chamber. This produces a rapid nucleation of the substrate in the form of very small particles that are collected in the gaseous stream. The RESOLV process is an adaptation of the RESS process that consists of spraying the supercritical solution into a liquid. This approach has been used in the formation of nanoparticles of various products including Ibuprofen and Naproxen.[8]

The top down approach requires the use of mechanical processes. High pressure homogenization and milling can be used to create very small particles. High pressure homogenization will result in the particles disintegrating and forming very small particles. High pressure homogenization has been used in the food industry for many years. Homogenization is a fluid mechanical process that involves the subdivision of particles or droplets into micron sizes to create a stable dispersion or emulsion for further processing.

The basic principle for high pressure homogenization is that fluid passes through a minute gap in the homogenizing valve. This creates conditions of high turbulence and shear, combined with compression, acceleration, pressure drop, and impact. This causes the disintegration of particles and dispersion throughout the product. After homogenization, the particles are of a uniform size, typically from 0.2 to 2 micron, depending on the operating pressure. The homogenizer is the most efficient device for particle and droplet size reduction. The actual properties of the product vary with pressure and product type in a complex relationship. In general, higher processing pressure produces smaller particles, down to a certain limit of micronization.[9]

The use of nanoparticles is not a new method. Rapamycin Sirolimus which was launched by Wyeth in 1999 was the first FDA approved product manufactured using nanoparticles. Since then, several products have been approved by the FDA. In addition, products like Fenofibrate have been reformulated using nanoparticles and the result was an improved product.[9]

The smaller particle size in general can increase bioavailability and improved penetration through membranes. This could result in lower dosages and lower toxicity. Also, this could result in more targeted bio-distribution and the reduction of the influence on variability. One of the most important points is that it can decrease the formulation development time and thus reduce the time to get to market.

The process is not without drawbacks however. Surfactants are needed to assure that the materials do not re-agglomerate on standing. The same effect can happen once the product is in a biological system due to the very larger surface area. Also, the biological half-life could be shorter due to the fast uptake in the reticulo-endothelial system. Nanoparticles can also result in high immunogenicity and acute and chronic toxicity. One most also be aware of potential unforeseeable safety problems.[10]

Crystal Engineering

This is a new and emerging method of controlled crystallization. Crystal engineering technologies can be applied to pharmaceutical substances to improve drug solubility. This can employ a number of different methods including the formation of salts, co-crystals, metastable polymorphs, and high energy amorphous forms.

Salt Formation

The formation of salts is one of the most common strategies used in the pharmaceutical industry today. Based on the number of products on the market today, over 50% of the approved drugs are some type of salt. Salts are formed by the interaction of two compounds that are ionized in solution having opposite charges. These products can be crystallized as a salt form. Intermolecular coulombic forces of attraction result in the interaction of the counterions. All acid and base compounds can form salts and the success and stability of the compounds depends on the acid or base or the acidity and basicity constants of the species involved.[11]

The formation of salts can bring added advantages to the formation of the API. For one, the formation of the salts are well understood and basic counterions are common and in principle safe and effective. They can alter the solubility and the dissolution of the API. In addition while it may not directly improve the dissolution or solubility in some cases it often increases the melting point which can make the milling operation more acceptable.

There are disadvantages to this method as well that must be considered. The percentage of actual drug in the formulation can be decreased which could result in larger amounts of drug being

required. The HCl salt can reduce the dissolution for products in the gastric fluids. They also add an additional chemical step and the corrosiveness of the salts can result in tableting problems. Also the selection of the salt can be limited to the intended pharmaceutical profile.[11]

Co Crystals

Co-crystals can be an alternative to salt formations in the case of neutral compounds and weakly ionized products. The definition of co-crystals is still open to general debate. However, there is agreement that by definition a co-crystal is a crystalline material of at least two different components.

There are critical questions regarding the formation and use of co-crystals in the formulation of an API that must be addressed. In particular consider the following:

- Can the chemical and physical stability of the product be improved?
- Can the solubility of the API be altered by modifying it into a co-crystal?
- Can the dissolution rate improve by co-crystalline compounds relative to the individual API's?
- Can the bio-availability of the API be improved using co-crystals?

There have been a number of studies done in the past which have demonstrated that the various parameters listed above can be affected by the formation of co-crystals.[12] While melting point is important, the focus of this has been on improving dissolution and bio-availability. Improvements in dissolution have been noted in many examples. Care needs to be taken here since the dissolution can be affected by the coformer used and it is often hard to determine if in fact one actually gets a co-crystal. There is limited data on the improvement of bio-availability.

Summary

New drug candidates with poor solubility, low dissolution rates and limited bio-availability can be dramatically improved in the early stages of the development of the API. Conventional methods such as milling and salt formation while still exceptable and widely used cannot work for everything and as drugs become more potent, the need for better methods that can be introduced into a manufacturing setting are critical.

Newer techniques in particle design can often overcome the limitations of conventional methods and are often more efficient. These new methods still rely heavily on the principles of previous methods and build on these technologies. It is important to note that many of these methods are now commercially available and advances in equipment manufacturing and analytical methods have greatly improved over the last few years.

While this paper concentrated on a few of the new methods being developed or already commercialized, there are still others out there that can turn failure into success. We have already seen that the use of cyclodextrins, polymers and liposomes have demonstrated improvements in solubility as well as stability of drugs.

The question is when and where to start the development and implementation of these methods. We find today that companies have been built just on the premise of solid state research looking at various salt formations. Others specialize on particle size reductions. The point is that looking at the overall physical characteristics and form of your API early can have a very positive effect on the outcome.

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Author Biography

James R. Bruno *is the owner of Chemical and Pharmaceutical Solutions. He has thirty years of experience in the pharmaceutical and fine chemical market place During his career he has worked on a global basis to develop commercial processes for the manufacturing of intermediates and API's. Bruno is a Past Chairman of the Rider University Scientific Advisory Board and Past President of Drug Chemical and Associated Technologies.*