Center for Pharmaceutical Development (CPD)

Georgia Tech, Andreas (Andy) Bommarius, 404.385.1334, andreas.bommarius@chbe.gatech.edu
University of Kentucky, Eric Munson, 859.323.3107, eric.munson@uky.edu

Magnesium Stearate: Relating Physicochemical Properties to Functional Properties Such as Dissolution

Researchers at the Center for Pharmaceutical Development (CPD) have been performing research to enable the pharmaceutical manufacturers make more effective tablets.

One of the most common ingredients in a tablet is magnesium stearate. Magnesium stearate is structurally similar to sodium stearate, which is better known as soap. This is used as a lubricant for the tablet press to ensure that the tablet releases properly after it is compressed. Its lubrication properties come from its fatty acid composition of stearates, palmitates, and other fatty acids.

Magnesium stearate is extremely difficult to study because it is both a complex mixture of chemical species and it can exist in multiple forms each of which have different properties. Compounding the situation is the fact that it is present in very low quantities in most tablets; making it even more difficult to study. CPD researchers have synthesized their own magnesium stearate so that they can both better understand how magnesium stearate's composition affects the tablet properties and also study how it changes form once it is compressed into tablets.

By understanding how magnesium stearate affects the tablet making process, companies can better predict how to add it into the mix, at what ratios, and what grades to get the optimal tablet without loss of product from malformed tablets and to make safer and better tablets that will help patients.

Magnesium stearate is an extremely problematic additive to study because of its complex nature and low concentration in a tablet. With the CPD approach of making our own magnesium stearate enables us to study it using advanced analytical techniques that have not been used to study it previously. Most importantly, we can now study what happens to the magnesium stearate when it is compressed into tablet form. When this is done it impacts both magnesium stearate's performance as a lubricant and the potential negative effects upon how a tablet dissolves.

The major beneficiaries of our research are the pharmaceutical industry. The ability to predict the properties of how magnesium stearate will perform in a formulation is crucial to making tablets reproducibly and avoiding potential product recalls. It will also speed up the development process by informing companies when their magnesium stearate supply changes, which can result in product delays.

> **Economic impact:** Every pharmaceutical company seems to have a story where magnesium stearate caused a problem due to inconsistencies with suppliers or form changes that resulted in product failure. This breakthrough CPD research could have dramatic impacts on improving product quality through improved quantitative understandings of magnesium stearate's functional properties and, more importantly, how variations impact product performance.

For more information, contact Eric Munson at the University of Kentucky, eric.munson@uky.edu, Bio http://pharmacy.mc.uky.edu/faculty/EricMunson.php, 859.323.3107.

Development of a Valuable New Enzyme, Amine Dehydrogenase

First and foremost, pharmaceuticals have to be efficacious, or in other words, they need to work to cure a disease or at least stop its progression. Next, however, pharmaceuticals have to be safe, and last, but not always least, they have to be affordable. Safe pharmaceuticals contain the active ingredient but no impurities. Affordable pharmaceuticals often are those that can be produced with a selective and inexpensive process.

Georgia Tech researchers at the Center for Pharmaceutical Development (CPD) have developed such a process for those pharmaceuticals than contain chiral amines, i.e., nitrogen groups. The FDA requirements around chiral active pharmaceutical ingredients (APIs) have become more stringent in recent years. Chiral molecules are non-superimposable mirror images, like handedness. Of these chiral compounds, chiral amines have had a particularly large and growing demand due to their high biological activity.

The Bommarius Research Team at Georgia Tech has met this demand with the noteworthy development of an amine dehydrogenase to an outstanding level. Not only has the group been successful in modifying an enzyme to produce this activity, but it has gone beyond an "academic" demonstration of this concept to provide an industrial-feasible and suitably applicable level of activity (rate of conversion) with this new enzyme's capacity.

Multiple versions of this enzyme have been produced, thus creating a new class of enzymes that stand to enable a less expensive process to drug production, and a process with fewer impurities.

Previous methods of producing chiral amines chemically have relied on heavy metals, high-pressure hydrogenation, or crystallization. These operations are costly, hazardous, and not environmentally-friendly.

This breakthrough amine dehydrogenase route is capable of aminating numerous ketones with near perfect selectivity (handedness), making for a more efficient and greener route to produce these compounds. This work presents a viable alternative to the growing class of transaminases. Despite high levels of recognition, including the Presidential Green Chemistry Award, this class of enzymes has substantial disadvantages, such as the cost for the amine and incomplete conversion owing to an unfavorable equilibrium. While these challenges have been met with some level of success, there is a need to produce these chiral amines more efficiently by selective amination of ketones using free ammonia, which has been recognized as one of the most aspired enzymatic reactions previously unavailable by the ACS Pharmaceutical Roundtable. This route allows for increased efficiency and less waste.

This breakthrough has the potential to impact specialty chemicals with a particular emphasis on pharmaceuticals. It will allow for less expensive and more environmentally-friendly routes to chiral amines over the chemical synthesis.

> **Economic impact:** The economic impacts of this breakthrough work will be both in cost-savings of production and in decreased use of organic solvents. It will simplify syntheses and creation of higher-quality product compounds. The potential impact is further exemplified by the tremendous interest in this project by center members. The vast majority of CPD member companies have prioritized this project as one of their top interests.

For more information, contact Andreas (Andy) Bommarius at Georgia Tech, andreas.bommarius@chbe.gatech.edu, Bio www.chbe.gatech.edu/faculty/bommarius, 404.385.1334.