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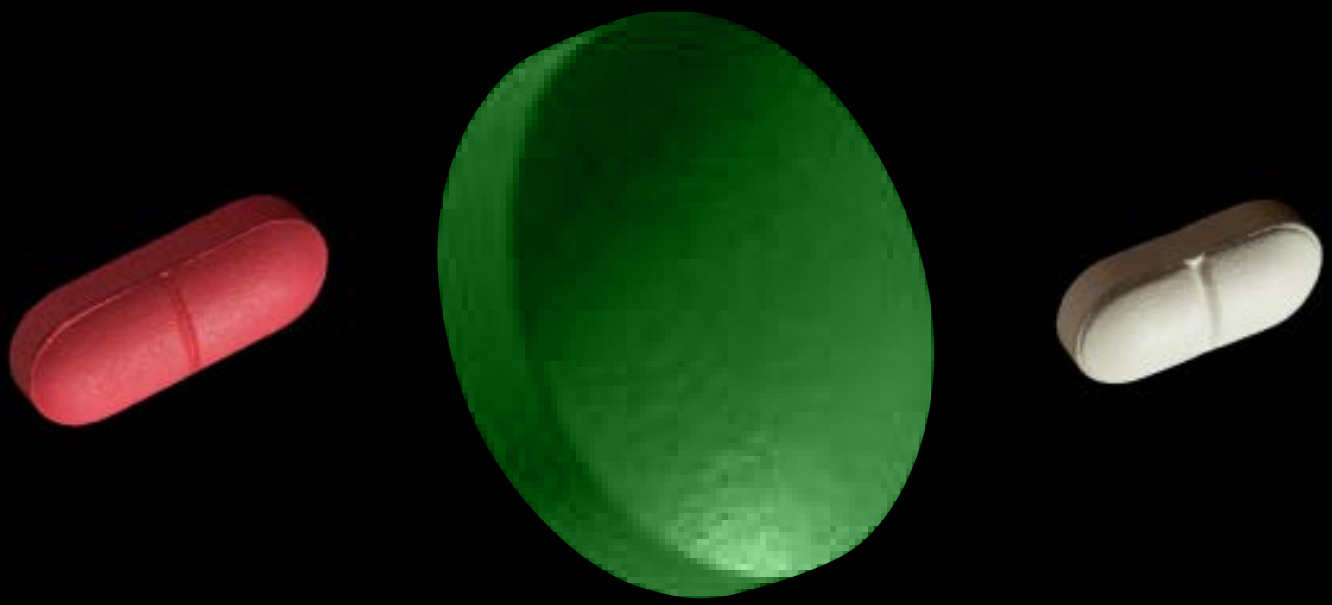

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DIOSNA offers new add-on for pelletizing

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Don’t let the rust set in

How pharma manufacturers can best protect tablet tooling from corrosion

By Liam Preston, Technical Sales Manager, I Holland

Corrosion can severely affect tablet compression tooling if it is not addressed effectively. It can delay production, reduce efficiency and cause contamination problems.

Corrosion can be detected by the appearance of discoloration, etching or common red rust. The main cause of corrosion is acidic substances, which can include ingredients found within the formulation being compressed and even in the surrounding atmosphere. The iron particles in the metal tooling are exposed to oxygen and moisture in the form of humidity or vapor. When the steel is exposed to water, the iron particles are lost to the water’s acidic electrolytes. This means they oxidize the iron particles, which forms corrosion on the punches and dies.

There are several reasons why corrosion can occur, and although challenging, it can be resolved with a combination of the correct steel, coating or treatment selection and proper maintenance procedures.

ATMOSPHERIC MOISTURE

One of the principal causes of corrosion is excessive moisture and humidity. This is because corrosion often forms in areas where liquid is present. Oxygen is found in the air we breathe and humid air carries water. The percentage of water vapor in the air varies based on temperature and can range from as low as 0.2% to up to 4% water vapor.

Excess humidity in the compression room, tool storage area or places where the drug formulation is stored prior to compaction

Optimizing the environment in which tablet compression and storage of tooling takes place can have a significant impact on preventing corrosion.

can have a significant impact on corrosion forming on the tooling. It is therefore extremely important to control the environment in all areas of tablet production.

As we cannot remove oxygen from the air and tooling is made from steel, environmental factors should be in place to regulate the temperature and humidity and minimize moisture to prevent corrosion from forming on the punches and dies.

Corrosion on tablet tooling can delay production, reduce efficiency and cause contamination problems.

FORMULATION CONTENT

All formulations have very different characteristics with varying moisture content, which is often needed to help bind the tablet structure. However, too much water within the tablet can be a cause of corrosion and lead to other problems like sticking.

It is not just moisture content within the formulation that can lead to corrosion. Formulations containing corrosive elements such as chlorine, salts and acids will react with the tooling surfaces and result in oxidation. In addition, wash-in-place systems fitted to some modern tablet presses expose tooling to water and cleaning solutions. Post-compression cleaning procedures can also cause corrosion if not controlled appropriately. It is therefore important that tooling has the appropriate corrosion resistant properties through the correct steel and coating selection.

PROTECTING AGAINST MOISTURE

Optimizing the environment in which tablet compression and storage of tooling takes place can have a significant impact on preventing corrosion, but other solutions,

Adopting a simple structured tooling maintenance process is essential to obtain the maximum life from punches and dies.

including tooling material, coatings and maintenance, should also be considered.

Tool steel selection

Wear and degradation of tooling are inevitable in tablet manufacture. The repetitive cyclic action of compression will take its toll on tooling, particularly if they are not maintained. A substantial influence on tooling deterioration is the formulation being compressed. Some products can cause adverse effects on the punch tips — for example, certain granules are extremely hard and abrasive. These can scratch, wear and impregnate the steel surface. Other granulates can contain corrosive elements which react with the steel. This deterioration can lead to tableting defects like black spots, which are the result of corroded tooling and sticking where the granulation adheres to the punch tip face causing costly wastage, reduced yield and unwanted press downtime.

Although tools are manufactured from hardened and tempered tool steel, the demanding processes involved can lead to deterioration if the tool material is not optimized to suit the formulation being compressed.

High quality tooling should be able to offer a long life, be anti-abrasive and wear-resistant. The appropriate choice of material will help to reduce the risk of damage to the punches and dies from the effects of abrasion, corrosion and impregnation of hard granules.

The correct steel is crucial to the successful performance of tablet compression tooling. There are several characteristics that should be addressed when selecting steel:

- Strength: Ability to withstand an applied stress without failure
- Corrosion resistance: Resistance to oxidizing, staining and discoloration
- Toughness: Resistance to chipping, cracking and punch tip breakage
- Abrasive wear resistance: Resistance to abrasive wear of punch tips and die bores
- Adhesive wear resistance: Resistance to adhesive wear, galling and welding
- Hardness: Resistance to impregnation from hard, sharp granules
- Compressive strength: Resistance to die bore ringing and plastic deformation of punch tip edges
- Fatigue resistance: Progressive and localized structural damage that occurs when a material is subject to cyclic loading

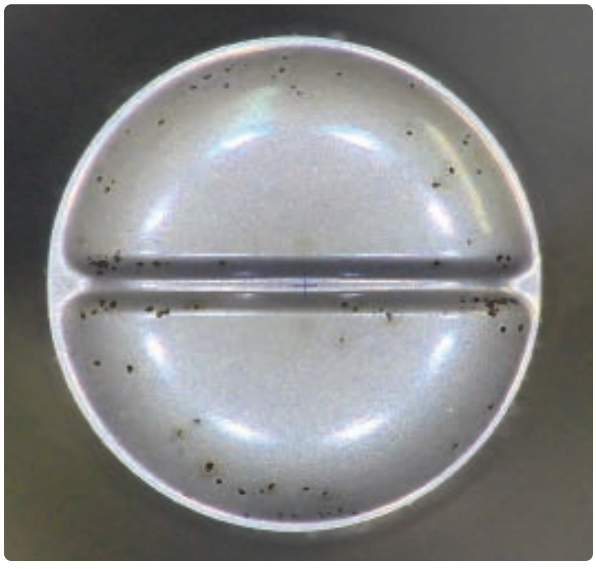
If the tooling being used is prone to corrosion due to environmental effects or because of the characteristics of the formulation, a specially selected tool steel is a good option. Specialized martensitic stainless steels with high chromium content should be used as they have a higher resistance to oxidization, staining and discoloration of the tablet tooling.

Coatings and treatments

The correct tool steel choice is essential in the prevention of corrosion, but so is the tool coating and treatments.

Tool coating selection can have a fundamental impact on production. When used in conjunction with high quality tooling steel, tool coatings are a great method of solving tablet production problems. They allow for better tableting efficiency and output by reducing the requirement for tools to be taken out of production for additional cleaning and maintenance work to remove problematic residue, which, if left untreated, may cause potential production issues, such as corrosion, sticking and picking.

Traditionally, electro-plated hard chromium was the most popular coating used within the tablet tooling industry, but it has many disadvantages. When hard chromium is applied to tooling, a certain amount of hydrogen penetrates the substrate, which can decrease the steel's working load by up to 20%. To counter this effect, the plated tools undergo a baking process known as de-embrittlement that reduces but does not eliminate the unwanted characteristic. It is also subject to micro-cracks which can develop during the plating process when the internal stress exceeds the tensile strength of the chromium. These micro-cracks are problematic because they provide a porous route to the substrate that will allow granule or cleaning solutions to attack the steel beneath.



If tooling is cleaned without corrosion inhibitor or insufficiently dried, corrosion can take place.

Specialized coatings have been developed which are chromium-rich and applied via an advanced Physical Vapor Deposition (PVD) process. The PVD process creates a very smooth dense anti-stick coating. This process incurs none of the drawbacks associated with applying hard chrome.

When it comes to choosing a tool coating, understanding the product being compressed is crucial. For example, if the formulation has a high number of corrosive elements like salts and acids, it will eventually react with the steel and result in oxidation and other forms of decay. In these instances, an appropriate corrosion resistant coating should be selected, for example, those containing chromium or chromium nitride.

Tool maintenance

Incorrect tool maintenance procedures including the handling, cleaning, polishing and storage of punches and dies can have a huge impact on tablet production. All these processes will expose the tooling to materials and environments where there is a risk of oxidization. It is therefore important that tried and tested maintenance practices are in place to prolong tool life.

The purpose of regular tablet tooling maintenance is simple: to minimize compression problems and ensure that it operates at its highest functionality. Ensuring tablet punches and dies are kept in optimum condition to produce high quality tablets is critical for productivity and overall equipment effectiveness (OEE). Frequent audits of procedures should be planned to maintain and protect against corrosion issues. The cost of poor tool care and maintenance not only results in additional unnecessary tool purchases but also in production problems that could have been avoided.

The appropriate cleaning procedures are essential when looking to prevent corrosion. It will remove granule from the punch and help to avoid product contamination and potential production issues such as sticking and picking caused by old product adhering to the surface of the punch tip.

Post-cleaning is also the ideal time to accurately assess the condition of the tooling. If punches are not clean, any visual assessment of the punch tips and die bores can be affected. This would mean that problems like wear, damage or corrosion are missed.

When tooling is removed from the tablet press, it must be thoroughly cleaned to remove any oil or product residue, particularly from difficult to reach areas such as embossing and keyways. One of the most reliable cleaning methods is ultrasonic cleaning. Ultrasonic baths allow for consistent cleaning results, reduced processing and operator time, and reduced risk of tablet contamination. Importantly, ultrasonic cleaning allows for the whole punch to be cleaned including in and around the embossing. It is essential, however, that the process does not cause corrosion of the tooling material, therefore a corrosion inhibitor should be added to the cleaning cycle at a defined concentration. This will form an oxide film on the surface of the

metal, passivating the steel and protecting it from corrosion.

It is also important to remember to thoroughly dry tooling after cleaning to ensure there is no residue of cleaning fluids left on the tooling surface which could cause corrosion.

Appropriate storage is another critical process to consider when preventing corrosion. Tooling can be exposed to moisture if the storage system is not clean and dry. A good storage facility with tooling protected by a layer of non-toxic, FDA compliant oil or grease will help prevent corrosion from forming on the tooling surface. The duration of the tooling storage will determine if oil (short term) or grease (long term) is required.

Handling of the tooling can be another cause for concern. It is always recommended to use gloves when picking up the tooling. This is because acids and moisture are present in human hands and can cause and accelerate corrosion on tooling. It is not unheard of for a rusty fingerprint to be left behind! Ensuring gloves are worn at all times and following proper maintenance procedures and techniques will prevent this from happening.

Adopting a simple structured tooling maintenance process is essential to obtain the maximum life from punches and dies. By applying these recommended best practices problems like corrosion will be prevented and tool life will be extended.

KEEP A CHECK ON CORROSION

The cost of corrosion due to not understanding the characteristics of the formulation and poor tool care and storage not only results in additional unnecessary tool purchases but also in production problems that could have been avoided. It is important to address corrosion at the root cause so tablet production is not affected.

Know the granule being compressed, does it contain hard and abrasive granules or ingredients that contain chlorine, salts and acids? Is there high moisture content in the air where compression and storage take place? If the answer is ‘yes,’ it is important to protect tooling so corrosion does not take hold.

Through the use of the correct tool steel and corrosion-resistant coatings, durability and efficiency of tablet tooling will increase. Add to this effective maintenance and tool care procedures and pharmaceutical manufacturers can obtain the maximum life from tablet punches and dies.

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Pulling antibiotics from the fire

Can policy reform save a market in peril?

By Karen Langhauser, Chief Content Director

Antibiotics — and the companies and people who made them — were once held up as war heroes.

"When the thunderous battles of this war have subsided to pages of silent print in a history book, the greatest news event of WWII may well be the discovery and development — not of some vicious secret weapon that destroys — but of a weapon that saves lives," read the ad for penicillin printed in Life magazine in August 1944.

Now, almost 80 years later, it's antibiotics themselves that may need saving. The pace of innovative drug development has slowed to a crawl, while older antibiotics are rapidly losing ground in the fight against bacteria. And the results could be catastrophic for public health.

Every year, more than 1.2 million people worldwide die from antibiotic-resistant infections, and if no action is taken, it's estimated this number will grow to 10 million per year by 2050.[1,2] The issue is not limited to countries with inadequate health care either — around 2.4 million people could die in high income countries between 2015-2050 if we fail to tackle antimicrobial resistance (AMR).[2]

Public health agencies, scientists and industry groups have been sounding the AMR alarm for years and it hasn't gone unheard. But despite the collective acknowledgement of the dire need to develop and manufacture new, innovative antibiotics to fight off these so-called 'superbugs,' the market dynamics simply aren't cooperating.

> **Despite the desperate need for new antibiotics for public health, nobody can afford to develop and manufacture them if you don't have commercial success.**
>
> — Randy Brenner

Pharma R&D is famously expensive, time-consuming and fraught with risk. However, companies that successfully nab a coveted Food and Drug Administration approval and launch onto the market are handsomely rewarded, at least in theory.

But antibiotics are a special case. While using antibiotics sparingly and in short duration can help preserve their effectiveness, this also makes it extremely challenging for companies to generate a viable return on investment for the innovations they bring to market. And given that the bulk of the players in the antibiotics biz are smaller biotechs, the risk of going belly up, even with a successful product, is very real.

"The antimicrobial ecosystem really is fragile and frankly, failing due to factors that are unique and make the sector completely different than other areas of medicine," says Emily Wheeler, director of Infectious Disease Policy for the Biotechnology Innovation Organization (BIO).

In recognition of how tough the market is, numerous mechanisms have been put in place — mainly in the form of discovery, preclinical and clinical funding — to stimulate the pipeline and give drug developers a running start. The global non-profit partnership, Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), has awarded over $360 million towards early development of innovative antibacterial products.[3] Public-private partnerships through the Biomedical Advanced Research and Development Authority (BARDA), as well as collective industry ventures such as AMR Action Fund have invested billions of dollars towards late-stage development of novel antibiotics. Yet, the market is still steadily burning — and we are running out of time.

"Big Pharma's not interested, investors have gone away — and it has just put the antibiotics industry in a really bad spot," says Randy Brenner, chief development and regulatory officer at Paratek Pharmaceuticals, one of the few companies still active in the antibiotics R&D space.

Fixing the broken market now hinges on policy reform. While the leading bills on Capitol Hill would bring tangible relief in the form of financial incentives, the real

> [PASTEUR] would be an emphatic announcement that the market has changed and investment is welcome in the space.
>
> — Henry Skinner

game-changer lies in the global message the U.S. would send by passing them: The antibiotics market is viable, profitable and no longer ablaze.

THE MARKET'S SLOW BURN

So how did we get here? Discussion of the U.S. antibiotics market often begins with fond memories of the 'golden years' of antibiotic discovery — a time ripe with the approval of novel drug compounds, during which the vast majority of classes of antibiotics used today were discovered.

This charmed antibiotic era, which spanned roughly from the 1950s to the early 70s, also coincided with a revolution in pharmaceutical marketing. Pharma companies began 'detailing' campaigns that aggressively targeted doctors with journal advertising, mailings and, for the first time, the deployment of sales reps. Pfizer's first proprietary drug, a broad-spectrum antibiotic branded as Terramycin, hit the market in 1950 and famously launched the drugmaker's use of a sales force to influence doctors.[4]

This industry-wide combination of antibiotic development and marketing was so successful that the use of antibiotics in the U.S. almost quintupled between 1950 and 1956. While the concept of antibiotic resistance was known, most medical professionals were optimistic that the pharma industry would be capable of staying ahead of antibiotic resistance by keeping up its established pace of innovative drugs.[5]

By the start of the 21st century, AMR was well-documented as a global health concern and 'antimicrobial stewardship' — the coordinated effort to promote responsible antibiotic prescribing — had begun to stem overuse, thus reducing the market demand for antibiotics. In 2005, reports of serious adverse events, including liver failure and death, began surfacing in conjunction with an antibiotic (Sanofi-Aventis' Ketek) that had been approved by the FDA to treat upper respiratory tract infections. Under fire for what many viewed as an approval that should have never been granted, the FDA tightened its rules for clinical trial conduct.[6]

"From around 2005-2012, there was a big lull in antibiotic development primarily due to regulatory uncertainty," explains Brenner. "The FDA was changing guidelines and

The total clinical pipeline for new antibacterial therapeutics consists of 64 unique therapeutics, 48% of which have novel targets.

— The State of Innovation in Antibacterial Therapeutics, BIO Industry Analysis

statistical approaches and making it really difficult for companies to know what the goalposts were to get products approved. The regulatory environment for antibiotics became too risky and too expensive."

Drug development slowed, but the AMR public health crisis kept growing — and policy reform was proposed as a fix. In 2012, the Generating Antibiotic Incentives Now (GAIN) Act was passed into law. The bipartisan legislation granted a five-year extension to the exclusivity period for certain antibiotics — those that had been designated as 'qualified infectious disease products' (QIDP) — with the goal of rewarding innovative companies by giving them more time to recoup development costs.

One of these companies was Lexington, Massachusetts-based specialty antibiotic maker Cubist Pharmaceuticals, which managed to snag QIDP designations for two of its late-stage antibiotic candidates less than six months after GAIN was signed into law.

In what Brenner cites as the "last big M&A in the antibiotics space," Merck snatched up Cubist for $9.5 billion in 2014. Cubist had one blockbuster antibiotic already on the market, and one of its QIDP-designated drugs nearing FDA approval. Merck was looking to strengthen its position in anti-infectives, expecting the acquisition to add more than $1 billion of revenue in 2015.[7]

But after several patents for its newly-acquired blockbuster antibiotic were invalidated, the market didn't deliver for Merck — nor did it deliver for many of the smaller antibiotics companies that had eagerly entered the sector with promising late-stage products post-GAIN Act.

"The challenge that nobody predicted was what would happen when those products got approved. You started to see a lot of unsuccessful commercial scenarios, which really began to drive this whole market dynamic down," says Brenner.

Like many other antibiotics at the time, Paratek's lead candidate, a tetracycline-class antibiotic now branded as Nuzyra, had been stalled in development until the GAIN Act was passed. Nuzyra is somewhat of an anomaly on the antibiotics market — three years after launch, the drug

is targeting about $100 million in sales this year. Nuzyra, however, has the benefit of being approved as both a once-daily oral and intravenous antibiotic, for community acquired bacterial pneumonia and certain serious skin infections. The company also nabbed a BARDA Project BioShield contract back in 2019 — which now has a total value of $304 million — to develop Nuzyra against pulmonary anthrax.

Even so, says Brenner, "one successful drug doesn't make a successful market. We need other biotech companies to be successful commercially to change the dynamics of the whole space."

STALLING FOR TIME

Those active in the AMR world are now looking towards additional policy reform as the fix.

PASTEUR Act

The Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act establishes a delinked subscription program to encourage innovative antimicrobial drug development targeting the most threatening infections. The bipartisan, bicameral legislation was reintroduced to the House and Senate in June 2021 by U.S. Senators Michael Bennet (D-Colo.) and Todd Young (R-Ind.)

If passed, the law would change the way the U.S. government pays for critically needed antimicrobials, basing it on value to public health, not sales volume.

Contracts would range from $750 million to $3 billion and would be paid out over a period of up to 10 years or through the length of patent exclusivity. In return, patients covered by federal insurance programs would receive these drugs at no cost.

Status in HR:

40 co-sponsors; Last action: Referred to the Subcommittee on Health in Aug. 2021

Status in Senate:

3 co-sponsors; Last action: Referred to the Committee on Health, Education, Labor, and Pensions in June 2021

PASTEUR process starting at IND

STEP 1

Sponsor submits request to HHS secretary (between approval of IND and 5 years post-approval) to have drug designated as a 'critical need antimicrobial.' If approved, designation is good for 10 years.

STEP 2

Sponsor submits a plan for appropriate use of critical need antimicrobial.

STEP 3

Clinical development of critical need antimicrobial.

— Wheeler, Emily. (Dec. 8, 2021). [Presentation]. 2021 ASM/ESCMID Joint Conference.

"From BIO's perspective and throughout the broader AMR stakeholder ecosystem, there is widespread agreement that a combination of policy reforms is critically needed to address the antimicrobial ecosystem and the unique challenges that the marketplace faces," says Wheeler.

But policy enactment doesn't happen overnight and the need for new antibiotics is imminent.

Recognizing this problem, 23 pharma companies — all members of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) — joined forces with the World Health Organization, the Wellcome Trust and the European Investment Bank to launch the AMR Action Fund in 2020, raising nearly $1 billion.

The mission? Sustain the pipeline and bridge the gap by helping to bring 2-4 new antibiotics to market by 2030.

While the independently-run fund, which just announced its first two investments — Maryland-based Adaptive Phage Therapeutics and Pennsylvania-based Venatorx Pharmaceuticals — is often labeled as a 'push' incentive, providing funding to incentivize development, Henry Skinner, AMR Action Fund's chief executive officer, argues it's more.

Companies chosen by AMR Action Fund get more than just a cash infusion. Whether it's helping portfolio companies facilitate collaborations or even work through manufacturing issues, the fund's management team as well as its Scientific Advisory Board boast extensive experience and industry connections in antibiotic development and global health.

"I think of us as a venture capital group uniquely dedicated to AMR. Like a classic VC, we're looking to invest in companies — providing not just capital, but intellectual contributions as well," says Skinner

Venture capital funding — or the lack thereof — has been a major red flag for the U.S. antibiotics market. According to a recent BIO report, venture capital funding for U.S. antibacterial-focused biopharma over the last decade was $1.6 billion — paling in comparison to oncology's $26.5 billion.[8]

In the absence of private investors, public-private partnerships, such as those initiated through BARDA's Broad Spectrum Antimicrobials (BSA) program, have been key in terms of providing support to accelerate late-stage research and development. But at the same time, these partnerships have offered stark evidence as to why push incentives alone simply aren't going to be enough to save the market.

Back in 2010, California-based biotech Achaogen was the first company to win a

contract through BARDA's BSA initiative. The company went on to win additional bids through BARDA, ultimately grabbing $124.4 million to fund the development of its lead drug, plazomicin, for the treatment of serious bacterial infections resistant to multiple antibiotics, as well as for disease caused by certain bacterial biothreat pathogens.[9]

Everyone had high hopes for plazomicin. In 2014, it received a QIDP designation. In 2017, it was the first antibiotic the FDA designated as a breakthrough therapy. Around that time, Achaogen had a market cap of over $1 billion.[10]

Plazomicin was approved by the U.S. FDA as a treatment for drug-resistant urinary tract infections — with a black box warning — under the brand name Zemdri in June 2018. But citing lack of efficacy data, the agency declined to approve the drug as a treatment for bloodstream infections. Falling short of expectations, Zemdri brought in a total of $800,000 from its launch in July to the end of the year, which wasn't enough to offset the company's losses.

Less than a year later after Zemdri hit the market, Achaogen filed for bankruptcy. The company sold Zemdri's worldwide rights (excluding China) to India's Cipla. QiLu Antibiotics Pharma in China picked up the Chinese rights.

DISARM Act

The Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act would allow Medicare to offer an add-on payment to inpatient hospitals that use a qualifying DISARM antibiotic to treat a serious or life-threatening infection. The legislation was reintroduced to the House in June 2021 by U.S. Senator Danny Davis (D-Ill.).

If passed, the law would take away any notion that there's a disincentive for using a newer, more innovative antibiotic.

Will cover FDA-approved QIDP-designated antibiotics, antifungals and biologics

Reimburses DISARM drugs at a set rate (Average Sales Price +2%)

For hospitals to be eligible, they must have a stewardship program in place and participate in the CDC's antibiotics use/resistance tracking program

Status in HR:

3 co-sponsors; Last action: Referred to the Subcommittee on Health in June 2021

"This was a big failure for the space. BARDA can invest in phase 2 and 3, but they can't successfully launch products for us," says Brenner. "Despite the desperate need for new santibiotics for public health, nobody can afford to develop and manufacture them if you don't have commercial success."

FIGHTING FIRE WITH POLICY

PASTEUR

'Pull' mechanisms are designed to complement 'push' mechanisms by incentivizing private sector engagement by creating market demand, sending signals to industry that a viable commercial market exists. To that end, the legislation on everyone's lips right now is the bipartisan, bicameral Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act, which seeks to partially decouple ROI from the volume of sales, and instead base it on the drug's value to public health.

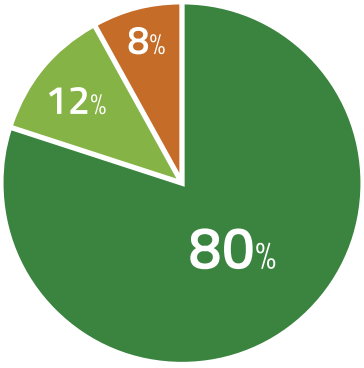
Under PASTEUR, developers would appeal to a Department of Health and Human Services (HHS) committee to have their drugs designated as 'critical need antimicrobials' — a criteria that would be defined within the bill and updated to reflect changing resistant threats.

Developers who qualify would be eligible for contracts ranging from $750 million to $3 billion, over 5-10 years, with the first payment granted upon the drug's FDA approval.

While proposed policies tend to come and go, with most not managing to survive Congressional committee, PASTEUR, which was reintroduced last summer, has built up momentum.

Antibacterial therapeutics being tested in the clinic

- Discovered by small companies
- Discovered by large companies
- Discovered by non-profit institutes/ universities



The State of Innovation in Antibacterial Therapeutics, BIO Industry Analysis

"We continue to really see a steady increase of support on the PASTEUR bill, specifically on the House side. The House PASTEUR bill currently has 40 co-sponsors — and half of these co-sponsors were added since the beginning of 2022," says Wheeler.

Growing recognition of the AMR crisis in Washington has given the proposed legislation legs.

In fact, when President Biden announced his $5.8 trillion Fiscal Year 2023 Budget proposal this past March, the HHS Budget in Brief section specifically made reference to a delinked proposal designed to combat AMR, using wording that was reminiscent of PASTEUR.

"We were encouraged to see that because the budget often provides an indicator of priorities for the administration, in terms of both legislation and regulatory policies. To see AMR prioritized in any capacity, we chalk it up as a really positive step — and to build on that, the few details that were included had common elements to the PASTEUR proposal," says Wheeler.

DISARM

While not as well-known as PASTEUR, the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act was reintroduced to Congress in June 2021.

The reimbursement reform legislation would allow Medicare to offer an add-on payment to hospitals that use a qualifying DISARM antibiotic to treat a serious infection.

This is an important piece of policy for antibiotics makers because the Medicare Severity Diagnosis Related Groups payment system (commonly known as the 'DRG') incentivizes hospitals to prescribe less expensive, generic antimicrobial drugs rather than novel antimicrobials — even if those new drugs have superior data.

Given that approximately 40% of all U.S. Medicare spending is on hospital services, Medicare reimbursement is a significant consideration for pharma companies looking for market success with new antibiotics.[11]

"Even for a product like Nuzyra, which has both an oral and an IV formulation, to be successful, you still need to start in the hospitals. But because hospitals receive bundled payments covering both services and antibiotics, they are disincentivized to use novel antibiotics until patients fail treatment with cheaper generics first," says Brenner.

Essentially, DISARM would help ensure that novel antibiotics can compete on a level playing field with generics.

Policies like DISARM are especially important to smaller companies with innovative antibiotics already on the market, such as Paratek.

"Now being on the market and seeing the challenges that are out there, a law like PASTEUR will give a couple of years to companies, but it's not going to be sustainable long term," says Brenner. "But policies like DISARM Act are really what we think will be the game-changer for getting this entire sector up and going again, because ultimately what the world needs to see are successful launches to change the commercial dynamics of these products."

CASCADING EFFECT OF NEW POLICY

One pivotal outcome of passing both PASTEUR and DISARM would be a jump start to commercial success. According to Brenner, market wins will trigger widescale change.

Venture capital funding for U.S. antibacterial-focused biopharma over the last decade was $1.6 billion — paling in comparison to oncology's $26.5 billion.

— The State of Innovation in Antibacterial Therapeutics, BIO industry analysis

"With commercial success, you'll see Big Pharma wanting to get back into the antibiotic space. Once we can incentivize the companies with deep pockets, that just opens the whole market up again for much bigger investments in R&D, manufacturing and commercialization," says Brenner.

In terms of bringing investment back into the antibiotics sector on a global scale, Skinner looks to policy reform like PASTEUR as the industry's "greatest hope."

"If the U.S. passes PASTEUR or something like it, I think that leadership will help spur policymakers across other countries to pursue similar solutions. It would be a sign of good things to come around the world, and I think it would help attract other investors back in the space," says Skinner.

While the U.K. piloted the world's first 'subscription' incentive scheme for antibiotics, announcing last month that England's National Institute for Clinical Excellence will offer Pfizer and Japan's Shionogi flat rate contracts to make new antibiotics available to the National Health Service, the U.S. is still the world's largest pharma market, generating almost half of total revenues worldwide. This means that the U.S. pharma industry, and the policies that benefit it, have considerable influence around the world.

Policy reform would also be good news for global organizations like the AMR Action Fund.

According to Skinner, with pull incentives and reimbursement reform in place, there would be an increase of capital flowing into the field, which would enable AMR Action Fund to invest in more companies and bring more products to market. This would start a chain reaction that would ultimately be "transformational" to the field.

Overall, pro-antibiotics U.S. policy says to the world that antibiotics are back from the brink of destruction.

"It would be an emphatic announcement that the market has changed and investment is welcome in the space. That will then invigorate the field and create robust pipelines — and we'll have the antibiotics we need going forward," says Skinner.

BUILDING A FIRE-RESISTANT HOUSE

While policy reform promises to bring much-needed rescue to a market currently engulfed in flames, the uncertainty that comes with pending legislation can be especially taxing for a pharma industry constantly tasked with optimizing pipelines.

Part of the onus falls on lawmakers and governments around the world in terms of providing both clarity and allineation on policies.

"AMR is a global problem, and we need to really align incentives and our thinking globally. If the U.S. has one set of expectations about what they're going to reward, and the U.K. has another and Germany, a third and Japan, a fourth…that's going to fragment this and make it extremely difficult to bring about the investment and change we need," says Skinner.

But even as policy continues to unfold, drug developers can set themselves up for success by staying informed on the specific designations outlined in each piece of legislation — for example, which antibiotics would be designated as 'critical need antimicrobials' under PASTEUR.

"As the PASTEUR Act continues to move forward in Congress, there will be opportunities for it to modify slightly from its current form. But, staying up to date on the progress of the policy and the potential implementation process will be important for drug developers in terms of knowing what targets to shoot towards in order to have an opportunity to utilize these novel mechanisms," says Wheeler.

If passed in its current form, PASTEUR will create a committee on critical need antimicrobials that will solicit input from a government advisory group comprised of external experts, including representatives from patient advocacy organizations and the pharma industry.

According to Wheeler, there are parameters included in the draft legislation right now that provide some guideposts; for example, looking to the Centers for Disease Control and Prevention's Antibiotic Resistance Threats Report or the World Health Organization's Global Priority Pathogens List to keep up on antibiotic-resistant pathogens.

"It's already a difficult financing space, as we've seen from the multiple bankruptcies. If pull incentives are the solution to that, developers have to match their product to where those incentives are demanding the products be. If you fall short, you'll fall into a black hole where you're not going to get rewarded for innovation," warns Skinner.

But ultimately, drug developers can cover most of their bases by setting a high bar for innovation right from the start, focusing

on robust drugs that address critical unmet needs.

"When these rules get promulgated and the details emerge, if your drug is too incremental, it's not going to make the mark," says Skinner. "This is a field where you want to swing for the fences and make a big difference."

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Smarter dosage security

How on-dose authentication can help protect patients and brands from the rise in counterfeit drugs

By Gary Pond, Global Program Manager – Authentication, Colorcon

COVID-19 has changed our lives in many ways and exposed us to risks unconnected with the virus. One impact of the pandemic is a dramatic increase in the level of online drug sales, making products more vulnerable to counterfeiting and diversion.

One in four American consumers now buy their medicines online, and in 2018 the U.S. Food and Drug Administration estimated that only 3% of online pharmacies complied with U.S. pharmacy laws and practice standards.[1] Writing in the American Journal of Tropical Medicine and Hygiene in 2019, doctors from the U.S. government, universities, hospitals and the pharma company Pfizer warned that the rise in "falsified and substandard medicines" has become a "public health emergency" and that poor quality drugs exact an annual economic toll of up to $200 billion.[2] On top of the direct harm they cause, counterfeit drugs are a major driver of antimicrobial resistance.

For criminals, counterfeiting is low risk/high reward, with relatively lenient sentences and the potential to make millions of dollars in successful operations. The International Federation of Pharmaceutical Manufacturers and Associations reports that every medicine is vulnerable to counterfeiting, including life-saving medicines. The widespread use of pill presses means that we are now dealing with counterfeiters who can change production and ingredients rapidly to satisfy market demand. And while counterfeiters often target lifestyle drugs, life-saving medicines are the fastest-growing category.

The FDA has estimated that only 3% of online pharmacies comply with U.S. pharmacy laws and practice standards.

There are many examples of what the rise in fake drugs means in human terms. Counterfeit fentanyl pills made to look like Xanax were discovered in every U.S. state in 2020 and linked to a sharp rise in fentanyl-related deaths. In the same year, Italian police seized 84 million Captagon pills that were produced by ISIS in Syria, containing amphetamines worth over $1 billion. The Drug Enforcement Administration's National Drug Threat Assessment Report 2019 showed that although the supply of Chinese manufactured fentanyl had been restricted over the past decade, overall supplies were increasing from newly formed Mexican and Indian cartels.

Pharmaceutical companies are accountable for ensuring that their medicine is safe when it comes into the hands of patients, and many countries have introduced serialization legislation which requires product identifiers to be affixed to each package to provide traceability throughout the distribution supply chain. Yet, despite the widespread introduction of serialization, the supply of counterfeit drugs is continuing to rise, and brand owners must develop robust strategies to safeguard consumers and protect their supply chain from external threats.

HOW THE INDUSTRY CAN FIGHT BACK

There is growing recognition that serialization alone will not solve the problem of counterfeit medicines. As serialization matures it will be valuable for track and trace, but for high value or high-risk products where supply chain security is imperative, more advanced measures are needed. Security technologies may be classified as overt or covert:

- Overt technologies are features that are visible to consumers and are incorporated on a product or its packaging. Holograms on the packaging and pearlescent pigments incorporated into tablet coatings are examples of overt technologies that are difficult to mimic, but such devices may give patients a false sense of security and provide little protection as counterfeiters become more sophisticated and are able to replicate these features.
- Covert technologies are designed to be difficult to identify and require testing to authenticate the product. If the security features are not easily seen or detected, then it will be very difficult for a counterfeiting organization to find and defeat these measures.

For the highest risk products, in addition to the use of security tags on packaging, on-dose microtaggants offer a much higher level of security, and allow each individual tablet or capsule to be authenticated.

A MOVE TOWARDS ON-DOSE AUTHENTICATION

Traceability and security measures focused on the packaging level may not be enough to protect patients. Even if a package is authentic, it may be impossible to determine whether the medicine inside is real or fake and whether it has been diverted.

To combat this, there is now a move towards "on-dose authentication." This is achieved by incorporating microtaggants into coatings or inks used on pharmaceutical and nutraceutical products — and there are many exciting new options and applications on the horizon.

Microtaggants are uniquely encoded materials that are virtually impossible to replicate or reverse engineer. They can be incorporated into tablet coatings or into the inks used on tablets or capsules, and may then be detected using either field or lab-based equipment. This reduces the risk of counterfeiting and product diversion, and facilitates quality control and returns monitoring. Crucially the technology requires no additional manufacturing equipment or processes, which makes it economical and easy to implement. The FDA has stated that when microtaggants are pharmaceutically inactive and incorporated into new or existing drugs, they can be treated as excipients without the need for further clinical trials, allowing them to be incorporated into drugs already on the market, as well as into new drug products.

Two different types of microtaggants are available — one produced from non-biologic DNA and the other from silica. These taggants are not visible to the naked eye and are used in very small quantities but can easily be detected using field instruments.

DNA microtaggants

DNA is robust and easy to detect and, because it is possible to produce different versions of the same DNA molecule, it can be made regional, product or company specific. The microtaggants are simply added to the standard tablet film coating or capsule printing process and can then be detected using appropriate reagents (like lock and key). The microtaggants are not damaged by exposure to heat and pressure during manufacturing, and the integrity of the DNA remains consistent throughout the shelf life of the product.

Silica microtaggants

Spectrally-encoded silica microtaggants can be detected by the way in which they reflect light, and can be customized with unique information for product verification and traceability. Like DNA, the

The cost per tablet of incorporating microtaggants is a fraction of a cent.

microtaggants are incorporated into the film coating or printing ink and applied during the manufacturing process. Silica is already present in virtually all tablet and capsule formulations, making it an easy material to include.

Recent work has focused on developing convenient and reliable smartphone readers, and proofs of concept demonstrate that these could allow drugs with silica microtaggants to be tested directly in the field, allowing instant verification by law enforcement and border agencies.

The possibility of authentication apps would also allow patients to play larger roles in verifying their medication. Apps can also be leveraged to bring more value through patient engagement and brand loyalty. It also raises the possibility of incorporating microtaggants into drugs for clinical trials to ensure that the right product gets to the right patient at the right time, thus improving visibility and compliance and providing real-time patient support.

CHOOSING THE BEST SOLUTION

It is important to understand how effective and reliable an authentication process will be, and the benefits that will be gained as a trade-off for the time and resources required to implement advanced technology. This should take account of costs, security and capacity, including the ability to scale authentication points at required locations.

The cost per tablet of incorporating microtaggants is a fraction of a cent, and relative to other manufacturing costs the overall cost to the producer of the finished dosage form is negligible. If an authentication solution is machine-readable, it will be faster and more reliable than manual inspections, and suitable for high-volume applications. Quality teams which manage patient interactions will be able to use on-dose authentication to determine if a product is real or fake in their local offices, providing shorter turnaround times and more cost-effective processes by reducing the need for referrals to forensic labs, which are often overburdened.

Because the quantities of microtaggants that are added to the film coatings or inks are so small, the use of microtaggants does

not affect how coatings are applied, and will not affect a product's stability, disintegration or dissolution. It is worth noting that even though the use of microtaggants is not a safety issue, manufacturers must notify the regulator that the microtaggant is included as part of their annual report.

No one solution is perfect, and a multi-layered approach can incorporate the strengths of a range of security measures. It's up to brand owners, product security and risk officers to determine the most appropriate solution for their product — and at least now we can say that "we have the technology" to beat the scammers and take control through digital authentication.

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The right granulation method

Making granulation decisions is key to successful tableting

By Devang Patel, Kerry Cruz, Robert Sedlock, & Rahul Haware

The tableting of the blended powder formulation with or without granulation is an important cog of a tablet manufacturing chain. This decision dictates a transformation of the blended powder formulation into a robust tablet. The granulation step imparts the suitable powder bulkiness, flowability and strength required for: an easy handling, a uniform dispensing from the hopper, and to confer the desired strength of the final tablet.

Two granulating methods such as dry granulation (roller compaction) and wet granulation are used in the pharmaceutical tableting process. Tableting without granulation is called direct compression (DC). A dry granulation roller compaction is used for the moisture and thermo-sensitive bulkier and poorly flowing materials.[1]

A downside of dusty dry granulation is its inability to handle poorly compressible materials and impaired material re-workability. The wet granulation is executed for low and high dose formulations. The active pharmaceutical ingredient (API) binding with the excipients during wet granulation reduces the potential segregation of the low dose formulation. It can relegate elasticity concerns associated with the poorly compressible high dose formulations.

The main snare of such multi-step, and labor-intensive granulation process is its unsuitability for the moisture- and thermo-sensitive APIs.[2] Non-granulating, cost-effective, DC methodology is a 'process of choice' in today's high-paced modernized tablet manufacturing arena. The U.S. FDA has provided the

The tableting of the blended powder formulation with or without granulation is an important cog of a tablet manufacturing chain.

recommendations about continuous pharmaceutical processing under the ICHQ8 guideline. A pharmaceutical continuous manufacturing is achieved with a real-time process monitoring using Process Analytical Technology (PAT) tools.[3] These PAT tools include various advanced spectroscopic near infra-red and Raman spectroscopy sensors. PAT sensors are placed inside the instruments for providing a real process monitoring to avoid any process deviations from the set standards or specifications. A DC process has fewer steps than other granulating process. This feature provides its relatively easy adoption for a possible continues manufacturing using PAT sensors.

Certainly, tableting with and without granulation have their unique advantages and limitations. The final formulation features are the main player, which prescribe the choice of a granulating and non-granulating methodology regardless of their advantages and inadequacies.

The main aim of the present study is to understand how the granulating and non-granulating methodology choices are transformed in the tableting performance depending on the API amount. More specifically, this study examines whether granulating and non-granulating choices are the functions of poorly compressible API amount in the final formulation. A model acetaminophen formulation was used to test this hypothesis.

EXPERIMENTAL DESIGN

A poorly compressible acetaminophen formulation was selected in the fractions of 20% w/w, 40% w/w, and 60% w/w. Silicified microcrystalline cellulose was used as a binder. Its amount in the final formulation was varied depending on the amount of acetaminophen. Magnesium stearate (0.5% w/w) was employed as a lubricant and glidant. A total of three acetaminophen formulations were generated. Acetaminophen formulations were dry granulated and wet-granulated with a roller compactor and laboratory mixer-granulator, respectively. The generated dry and wet acetaminophen granules, as well as acetaminophen formulations prepared using non-granulating direct compression method, were compacted using a rotary tablet press at 50, 100, 150, 200, 250, 300 MPa compression pressures and 25 RPM

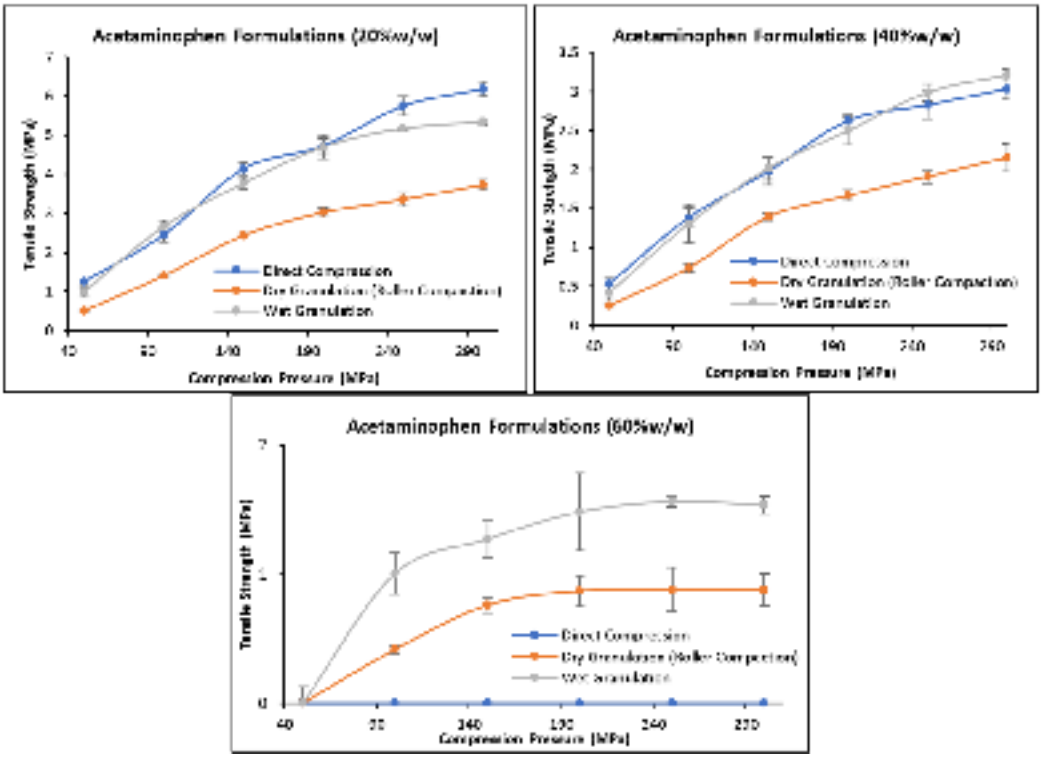
turret speed. An important component of USP<1062> such as tabletability profile (tensile strength vs. compression pressure) was used to compare the impact of granulation and non-granulation method on the tablet robustness of the model acetaminophen formulations. Strain rate sensitivity study was also performed at 150 MPa compression pressure and 20, 40, 60, 80, 100 RPM turret speed to study the impact of granulating (wet and dry) and non-granulating methods on the formulation sensitivity to the applied compression speed.

KEY FINDING OF THE STUDY

The acetaminophen formulations tabletability profiles are shown in Figure 1. Tablets of directly compressed and wet granulated formulations containing 20% w/w and 40% w/w acetaminophen exhibited similar tabletability profiles. These profiles are different from the dry granulated acetaminophen formulations. The dry granulated tablets of 20% and 40% w/w acetaminophen showed lower tensile strength at a given compression pressure when compared to the directly compressed and the wet granulated acetaminophen

FIGURE 1

Tabletability profiles

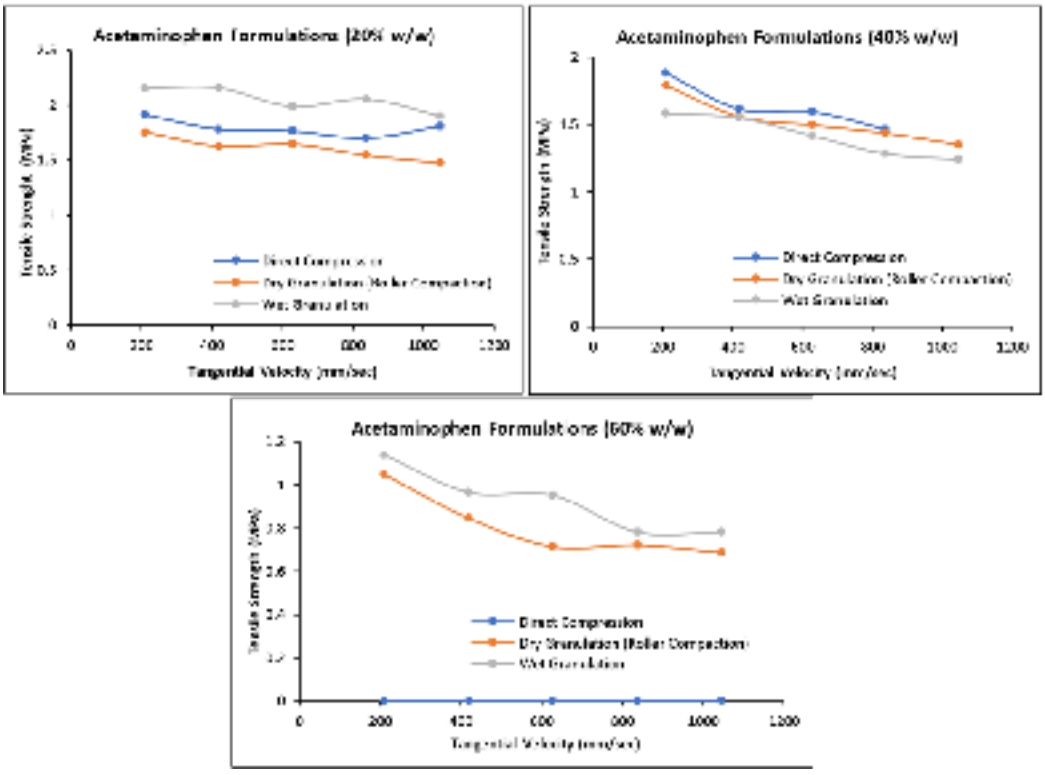


formulations. A weaker tableting of the dry granulated acetaminophen formulation could be attributed to the impaired material reworkability during the dry granulation.[4] The compact sheets formed in the roller compaction step of dry granulation utilizes the material's deformation potential. These sheets further experience milling stress in their transformation into dry granules of the desired size. Such multi-step dry granulation could consume a substantial amount of the material deformation potential. Consequently, engineered dry granules display a significant reduction in the material deformation during the actual compression cycle phase of the tableting. It leads to the formation of weaker tablets, which is called as 'reworkability issue' of dry granules.[4] The tabletability profile trend was changed by increasing the acetaminophen amount in the formulation (> 40% w/w). The wet granulated formulation containing 60% w/w acetaminophen formed the stronger tablets as compared to the dry granulated formulation.

Acetaminophen is known as a poorly deforming elastic material.[5] These findings indicate the wet granulation is a 'right choice' of handling elasticity issue of such

FIGURE 2

Strain rate study (tensile strength vs. tangential velocity)



poorly compressible high-load formulation, regardless of its above-mentioned limitations. The inability of direct compression methodology to form tablets with 60% w/w acetaminophen formulation appears to confirm the study's hypothesis.

In the second stage, the compression speed sensitivity of the acetaminophen formulations was analyzed by plotting the tablet tensile strength as a function of the tangential velocity (Figure 2). The turret speed of 20, 40, 60, 80, 100 RPM represents the tangential velocity of 209.3, 418.7, 628.0, 837.3, 1,046.7 mm/s respectively, based on 200 mm Pitch Circle Diameter (PCD) of the tablet press. The maximum commercial rotary tablet speed is 90 RPM for an 840 mm diameter turret. It translates into approximately 3,958 mm/s tangential velocity. The applied tangential velocity in the present study was 200 mm/s to 1,100 mm/s.

A material deformation is a time dependent phenomenon. A slow compression speed provides a sufficient time for the translation of an applied compression stress on the material during the compression cycle.[6] It led to a better material deformation necessary for a particle bonding during the compact formation. The compression speed is an important issue specifically with the deforming materials as compared to the fragmenting materials. Deforming materials produce weaker tablets at high compression speed due to an impaired deformation. The wet granulated formulations containing 20% and 60% w/w acetaminophen exhibited high tablet tensile strength at applied compression speed as compared to the dry granulated and directly compressed formulations. The similar pattern was not found with 40% w/w acetaminophen formulation. Acetaminophen is elastically deforming material.[5] Overall, the wet granulated poorly compressible acetaminophen formulation exhibited less sensitivity to the compression speed as compared to the dry granulated and the direct compressed acetaminophen formulations.

TAKE HOME MESSAGE

The wet granulated acetaminophen formulation produced stronger tablets. These formulations exhibited less sensitivity to the applied compression stress. Thus, the wet granulation performed using the laboratory mixer-granulator was a 'better choice' when compared to the direct compression or the dry granulation for acetaminophen formulation. This is specifically important when the amount of poorly compressible elastic acetaminophen was exceeded above 40% w/w in the final formulation.

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