Controlled Release Roundtable

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Over the past year can you tell us about one significant development regarding controlled release technologies?

Nathan Dormer, Ph.D., Director of Drug Product Development, Adare Pharmaceuticals: I think there are many great technologies in existence that address complex controlled release challenges, but there is a general trend in industry of slowly eliminating barriers to addressing specific patient populations. For instance, consider the pediatric population. Kids think most medicines taste bad, and getting them to take multiple doses a day can be a challenge, to say the least. First, there were pills. However, those could taste bad, so coatings were developed. Even then, pills can be too large to swallow, so liquids entered the scene. Liquids however can have an unpleasant taste, requiring many approaches utilizing large amounts of sweetener and flavorings to mask the taste. Then, you still have the problem of giving these liquids multiple times per day. Enter, extended release-taste-masked liquids and powders, which constitute the latest generation of formats that can serve any patient who is averse to taking medication.

Nélio Drumond, PharmD, Principal Formulation Scientist; Yannick Hildebrandt, Formulation Scientist I; Product Development, Softgel & Oral Technologies, Catalent: The first generation of controlled release technologies started in the 1950s, where the focus was on dissolution-controlled and diffusion-controlled systems.[1] Since then, emerging technologies have shifted towards smart polymers that respond to stimuli such as temperature, pH, electrolyte, or various signaling molecules, as well as enzymes to improve the specificity of drug release at the targeted sites of action. Targeted drug delivery is predicted to be the fastest growing technology segment by 2027 owing to various benefits of the technology, such as increased safety and therapeutic efficacy.[2] This shift of developing improved polymeric biomaterial with new functions is largely driven to overcome both physicochemical and biological barriers, as well as to meet the needs of patients. Some of these smart polymers can also be used to carry macromolecules such as proteins, peptides, genes and cells. Among the different types of stimuli, pH-responsive polymers are probably the most studied material in designing controlled release systems. Some of this class of polymers such as the poly (methyl methacrylate) derivatives, cellulose derivative, chitosan, PEG, polyoxymethylene and polyurethane based polymers have been established and are successful on the market for many years.

Robert Dream, Managing Director, HDR Company LLC: The availability of appropriate materials is the main requisite for the design of controlled-release drug delivery systems (DDS), such as nanoparticles, micelles, microparticles, hydrogels and bioconjugates. These delivery platforms must be biocompatible and present appropriate mechanical, physical, chemical and biological properties, allowing the desired control over drug loading and release and granting the benefits of this therapeutic administration route. Atom transfer radical polymerization (ATRP) is presently one of the most used methods of controlled polymerization, applied to synthesize well-defined functional materials and complex polymeric architectures with programmed molecular weights and low dispersity. There have been recent advances in the synthesis of DDS by ATRP, their preparation methods, characteristics and toxicity challenges due to residual metal catalysts. A brief description of controlled polymer architectures, drug loading and release mechanisms, and ATRP techniques is lately contextualize (2019). It is noted that precise engineering of polymeric materials over molecular architecture, granted by ARTP, is being translated to customized physical properties, allowing fine control over fundamental parameters for the design of DDS.

Jasmine Musakhanian, Scientific & Marketing Director - Pharmaceutical Division, GATTEFOSSE USA: Developments in formulation technologies continue to evolve in many directions. To achieve increased drug solubility, stability, and enhanced/consistent bioavailability, a variety of micro/nano technologies continue to be explored in the realm of vesicles, liposomes, self-nanoemulsifying systems (SMEDDS/SNEDDS), solid-lipid nanoparticles (SLN) and nano lipid carriers (NLC). The utilities of these systems extend from oral to injectable, as well as nasal, sublingual, and transdermal administration routes. Moreover, these nano/micro technologies are considered for delivery of proteins, peptides, and siRNA, in addition to small molecules that may be poorly soluble, poorly absorbed.

Another significant trend to note is the combined use of polymers, lipids, and carbohydrates to achieve new drug delivery systems for new routes of administration. For example, a lipid based nano emulsion technology may be stabilized by a cellulosic or pluronic polymer that will also enhance the mucoadhesive properties of the formulation to develop a nasally administered gel.

Bikash Chatterjee, Chief Operating and Scientific Officer, Pharmatech Associates: We are working with a small innovator company, NanoMedical Systems Inc., that has developed a very promising implantable drug delivery solution, leveraging chip manufacturing economies of scale. The novel drug-delivery devices are based on a proprietary nanofluidics platform for sustained release (up to 6 months) of chronic therapies. These devices can be loaded with a variety of drugs, including small molecules, peptides, and proteins, for subcutaneous implantation. The devices (trademarked nStrada™) rely on diffusion (passive or controlled) to achieve steady-state drug concentrations within a few days and then maintain constant release for the duration of the implant. This performance represents a significant improvement over polymer-based implants and depots that suffer from an initial burst release and multiple weeks to achieve steady-state concentrations. A refillable platform delivery system has myriad uses for chronic controlled delivery of drug therapies.

Bhavik Bhatt, Ph.D., Scientist III, Recro Gainesville: The most significant developments have been improvements in applications of existing materials and in processing equipment (automation, etc.). Our understanding of how to formulate or reformulate molecules continues to evolve as does our ability to engineer processes to produce them. Newer equipment is more reliable, easier to operate, easier to clean, and quicker to change over. It also offers better data collection and security, which is key in today's environment prioritizing data integrity.

Dr. Christian Mühlenfeld, EMEA Technical Leader Pharmaceuticals, Ashland: With the improved understanding of biological processes in disease states, parenteral polymer based particulate systems are gaining significant importance for small molecules, peptides and hormones, triggering an increase of research on highly customized controlled-release polymers, such as bioresorbable PLGA, PLGA/PEG and others. Ashland has been working on these kinds of customized polymeric systems that allow scientists to design formulations that result in highly customized release profiles for different kinds of drug molecules, for instance long acting parenteral formulations, potentially resulting in a once monthly or even longer administration of key drugs. This is a great development for chronic diseases where patient compliance is detrimental to treatment outcomes.

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[2]https://www.reportlinker.com/p05879557/Controlled-Release-Drug-Delivery-Market-Size-Share-Trends-Analysis-Report-By-Technology-By-Release-Mechanism-By-Application-By-Region-And-Segment--Forecasts.html?utm_source=GNW

How do issues of bioavailability and solubility affect the development of controlled release products? Are these issues intertwined with each other during product development?

John Tillotson R.Ph., Ph.D., Pharmaceutical Technical Business Director, ABITEC: Bioavailability and solubility of the active ingredient are critical factors during the development of sustained-release products, especially for per-oral formulations. If the API does not become soluble in gastrointestinal fluids, or if it cannot permeate across the gastrointestinal membrane, the therapeutic response is diminished. With an ever-increasing amount of BCS Class II and Class IV actives entering formulation pipelines, solubilization of the active(s) in sustained release products has become an important focus. An effective strategy to provide for increased active solubility and targeted sustained release is the combination of self-emulsifying drug delivery systems (SEDDS) composed of functional lipids, such as Captex®, Capmul®, and Acconon®, with polymeric coatings which provide for sustained and/or modified release. These components can readily be formulated into multi-particulate intermediates, which subsequently can be delivered in capsules, tablets, or sachets. The developed SEDDS system can be layered onto a substrate in a fluid-bed operation, with the sustained-release polymer(s) and any other release modifiers being applied afterwards. Both the SEDDS pre-concentrate and the polymeric systems can be modified, in order to achieve desired emulsion characteristics, varying sustained release profiles, and differing gastrointestinal sites of release. The increased solubility observed while employing a SEDDS system typically leads to enhanced bioavailability.

Dormer: Addressing bioavailability and solubility are paramount in any controlled release application. The hurdles are largest when BCS class IV drugs need rapid dissolution and onset, or when low potency (large dose) BCS class I drugs need extended release. When considering formulation approaches, especially if there are bioavailability or solubility challenges, careful selection of excipients and processes can prevent unwanted non-uniformity in content, performance, or stability. Even with formulations that achieve the desired release rate, bioavailability and solubility challenges often must be addressed with tertiary technologies that modify the API itself or serve as a carrier for the API. Without question, standard formulation approaches often need modification to be compatible with such advanced solutions. The development process is very cyclical and is driven by key BA/BE studies.

Dream: The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Solubility also plays a major role for other dosage forms like parenteral formulations as well. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.

Drumond and Hildebrandt: The solubility of the drug substance in gastric and intestinal media impacts the bioavailability, as the drug molecule can only be absorbed into the systemic circulation in a solubilized state. Both, solubility and the overall bioavailability will have an extensive impact on the drug release profile and are key aspects in finding the most suitable controlled release technology for a specific drug substance and targeted release profile. Ideally prolonged release drug products should provide constant drug release during the transit of the drug product from gastric to intestine. This can be challenging because gastric and intestinal bioavailability of drug substances can vary significantly which could result in sudden rise or fall of the drug release. Poor bioavailability is often an issue in immediate release dosage form development but for sustained release formulations, high drug bioavailability in individual patients can cause increased plasma concentrations up to a toxic level. Understanding the pharmacokinetic processes around the drug molecule supports the successful development of controlled release drug products.

Musakhanian: Bioavailability being the rate and extent to which a drug reaches the systemic circulation, is an encompassing term and covers all modes of delivery whether immediate, sustained, or controlled. Formulation development can only begin with understanding of the drug solubility, permeability, absorption, and half-life, and that only in the context of the drug delivery system being considered. Changing the formulation type, combination of excipient(s), and or route of administration can significantly impact the bioavailability of a compound with outcomes ranging from insufficient dose below the therapeutic concentration range or to highly toxic dose(s) accumulating over time. Such undesirable outcomes may be associated also with the lack of consistency or variability of the drug solubilization, permeation, and absorption. Briefly, controlled release technologies aim to optimize drug bioavailability.

Adam Lambert, Vice President of Product and Process Development, Pharmatech Associates: Both bioavailability and solubility have a major impact and are primary drivers of controlled release dosage forms development. Drugs with different bioavailability and solubility characteristics will have significantly different development pathways. For a BCA class 1 drug, the primary issue for formulating a controlled release product is controlling the rate at which the drug solubilizes and diffuses from the matrix in order to obtain the desired release/adsorption profile.

For a BCS Class 4 compound there are many considerations. Improvement of the drug solubility/bioavailability are of primary concern. Different technologies will need to be evaluated to improve overall solubility and uptake of the drug. Once this is done, developing a dosage form that will deliver the drug over the desired time can then be initiated.

In general, a good understanding the physicochemical characteristics of the drug of interest are of primary importance in the development of a controlled release dosage form.

Bhatt: Bioavailability and solubility certainly affect the development of controlled release products, and they are, of course, intertwined with each other. If an API doesn't have suitable solubility, then there will most likely be problems with bioavailability. One needs to have knowledge of the API's physicochemical properties, including pH solubility, solubility in solvents, crystallinity, particle size, solid and solution state stability profiles, PK data, GI profile, and bioavailability when considering formulation approaches in development. Answering questions like, "What is the target PK profile and why?" and "What tools and technologies are available to strategically design the formulation that will achieve this PK profile?" are needed before plunging ahead.

Mühlenfeld: Low water solubility or limited permeability of poorly bioavailable small molecules, peptides or proteins - which have practically no permeability at all in the GI tract – represent major challenges also to formulators of controlled release products. Therefore, polymeric excipients are the key components in the design and development of a controlled release dosage form intertwined with issues in bioavailability. The combination of different polymers with unique characteristics aid in the design of a formulation for effective delivery of a poorly bioavailable substance.

Currently, what specific indications benefit most from controlled release products? Are there additional indications that could benefit from integrating a controlled release application?

Dormer: From my perspective, placing the patient's best interest first, any modality in which we can lessen the burden, the better. Whether that means taking a drug less frequently, making it easier to take, less painful to administer, faster to administer, more forgiving with respect to when it's taken; all of these are opportunities to consider controlled release. I would urge commercial teams and development programs to look closely at their pipelines, in conjunction with market surveillance and incoming opportunities, to find ways to "supercharge" ease-of-use for existing approved products. There are many patient populations that are silently suffering with their dosage form type, administration regimen, or overall API/product fit. We can do more for these people. Overall, there is need for more patient centric solutions.

Dream: Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% of NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

Drumond and Hildebrandt: Controlled release products are mostly beneficial for indications involving complex dosing/administration regimens. Treatments which require repetitive daily administration can become difficult to manage, especially considering cases of polypharmacy or patients suffering from several chronic diseases and comorbidities. As an example, an immediate release tablet which needs to be administered three times a day in order to provide therapeutic effect, could be theoretically formulated into a controlled release tablet which would only require a single daily dose administration, reducing the pill burden and increasing patient compliance. Controlled-release formulations are also safer, thanks to a decrease of side effects related to dangerous spikes in drug concentrations which could potentially happen with immediate release tablets. All of these demonstrate that a controlled-release drug reformulation can be a superior product when compared to the original drug. Nevertheless, the formulation of controlled release products is highly dependent on the pharmacokinetic properties of the active ingredients as not all drug substances can be formulated into a controlled release delivery system.

David Elder, Principal Consultant, David P Elder Consultancy: Adherence or compliance has long been a significant issue in many disease states, e.g. psychosis, HIV/AIDs. Long term adherence is estimated to be only half, i.e. 50%, reducing the effectiveness on many key treatments. The health care cost implications are also significant. In the US alone, the cost is estimated at over $100 billion/year.[1] Therefore, long acting therapies; particularly once weekly oral[2] or once monthly (or longer)[3] injectable dosing regimens would significantly enhance treatment outcomes.

Musakhanian: Classic examples are antidepressants, analgesics, and sleep disorder medicines. Mid-stream formulations include treatments for addiction rehabilitation; degenerative ocular diseases and improvement of attention deficit (ADHD) syndrome in children. A high priority for the regulatory bodies has been tamper proofing of drugs like opioids.

Aside from optimization of the drug plasma levels, the benefits of controlled release products include reduced frequent dosing especially if the treatment involves injections, mitigation of side effects associated with systemic delivery by local administration, and improved patient compliance. Moreover, accessibility of a treatment without the need for medical supervision and subsequent reduction in drug costs are of high value.

Lambert: There are many therapeutic areas that can and do benefit from controlled release dosage forms.

Pain Management and Drug Abuse – Many pain medications are controlled substances that benefit from controlled release dosage forms. Continuous delivery of pain medication reduces the overall dose required for maintenance of pain reduction. Additionally, since

many of the drugs used in pain management are prone to abuse, controlled release formulations can also be designed to prevent the extraction and abuse of the drug.

Drugs for Geriatric Patients – Many elderly patients take many medications on a daily basis. Reducing the number of times patients have to take medications and limiting the total number of doses patients need to take will improve compliance and, ultimately, the efficacy of therapeutics.

Pediatric – Similar to controlled release drugs intended for geriatric populations, controlled release pediatric formulations can improve compliance and reduce the number of doses.

In general, indications where patients are taking a large number of medications, or where compliance is a concern will benefit from the broader availability of controlled release dosage forms.

Bhatt: With advances in polymeric materials and processing technology, a wide array of molecules across the solubility and bioavailability spectrum can be formulated in controlled release systems that can lead to improved patient compliance treatment outcomes. Rather than specific indications, the therapeutic effectiveness of the drug versus its clearance rate from the body seems to be affecting the development of controlled release products. For instance, drug molecules that require lower dosing amounts and rates, as well as molecules that demonstrate lower clearance rates, are better suited for incorporation into a controlled release system, especially when considering the oral administration route. Additionally, controlled release formulations may allow for fewer side effects due to reduced peaks and troughs in blood levels. This is a huge therapeutic advantage for patients if the debilitating effects of a disease appear quickly once the drug concentration falls out of the therapeutic window.

Mühlenfeld: Today the primary use of controlled release technologies is seen in CNS, Gastrointestinal diseases, cardiovascular, pain and endocrine therapies. Any therapeutic indication that requires long-term patient compliance such as chronic diseases, may benefit from controlled release technologies.

In addition to oral solid dosage products, what other types of drug delivery methods can benefit from a controlled release formulation?

Heath Bowers, Ph.D., Pharmaceutical Technical Business Director, ABITEC: Beyond solid oral, parenteral dosage forms benefit the most from controlled release formulations. The ability to reduce injection frequency improves the quality of the therapy, patient compliance, and in some cases efficacy. Several marketed parenteral therapeutics exist today and utilize a wide variety of formulation strategies to achieve controlled release. BYDUREON® BCISE™ utilizes poly (D,L lactide-co-glycolic) microspheres in a medium chain triglyceride vehicle such as CAPTEX® 355 EP/NF to achieve sustained release of the GLP-1 agonist exenatide. This controlled release formulation reduces the injection schedule to once every seven days. Exparel® utilizes multivesicular liposomes made with lipids like CAPTEX 8000 NF to achieve a controlled release of bupivacaine. Bupivacaine is administered multiple times during an epidural. Exparel however provides a steady amount of bupivacaine in the blood stream reducing the need for multiple injections.

Dormer: Really, any product can be formulated for controlled release, but the reasons for pursuing these formulations depend on addressing an unmet clinical need and if the application is practical from scientific and clinical perspectives. On the other side of the controlled release coin are injectable or "parenteral" applications. Most people do not like getting shots. The needles, the pain, the side effects; it is just not an experience that patients cherish. When you introduce a controlled release solution to these applications, there is a large positive impact on patient acceptability and compliance. Instead of daily self-administered injections, these products can be once weekly, once, monthly, or even once yearly. There are formulation challenges with finding the right amount of dose, or "stuff" to inject that will still be acceptable in terms of patient comfort, efficacy, and safety, but more often than not, there are opportunities to decrease the amount of time a patient spends around needles and injections in their day-to-day lives, which is always a plus.

Dream: Injectable drug products as well as combinatory drug-medical device products could benefit from long- and short-term release technologies.

Drumond and Hildebrandt: In addition to the oral delivery route, the injectable, ocular, and topical routes can highly benefit from controlled release formulations. The PEGylation of proteins for parenteral delivery (e.g., for oncology) was a huge technological advancement which allowed the reduction of dosing frequency and the incidence of side effects for high potent drugs administered in anti-cancer treatments. The development of transdermal patches (via matrix or reservoir delivery) and subcutaneous inserts for hormonal therapy, which can be applied into the skin and replaced only after weeks or months, are also another example of controlled-release formulations to benefit patient compliance. Lastly, patients with ocular conditions can also benefit from controlled release products. Examples include iontophoresis patches and ocular inserts. The iontophoresis mechanism allows higher amounts of drug to be delivered directly into the eye, therefore reducing repetitive administrations, while ocular inserts provide a constant release mechanism of drug inside the eye for several months.

Elder: The recent announcement by ViiV Healthcare of the approval of Cabaneva, by Health Canada, was a significant step forward in the treatment of HIV.[3] Cabaneva is a long acting, intramuscular implant of two important anti-HIV drugs; cabotegravir, an intergrase strand transfer inhibitor (INSTI) and rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI)). 85% of study participants indicated a preference for the once monthly injectable compared to their standard once daily, oral treatment. Merck is also developing a long acting, implant of islatravir, a nucleoside reverse transcriptase translocation inhibitor (NRTTI).[4]

Musakhanian: Injectables, ocular treatment, patches … see answers to question 3.

Whether administered orally as a tablet or delivered by a patch on the skin, the goal of a CR formulation is to offer a predictable, constant

plasma concentration of the drug, over a fixed period of time. Controlling the drug release rate is beneficial for improving the drug efficacy, safety, and simultaneously reducing its undesirable side effects. Moreover, it is desirable for improving acceptance and patient compliance.

Lambert: The development of controlled release technologies and formulations spans the entire gamut of dosage forms available. Parenteral, suspension, suppository, and transdermal dosage forms all have examples of controlled release delivery technology applications, with opportunities to make improvements and advancements. Will one delivery method benefit more than others, it depends on the therapeutics and indications of the drugs.

Bhatt: Drug products with other routes of administration can benefit from controlled release formulations, including transdermal, parenteral (IM, IV, SC, IP, IT, etc.), nasal, rectal, vaginal, and drug eluting stents. And certainly, drug molecules that require frequent administration can benefit from being incorporated into controlled release formulations. For example, recent studies on nanoparticle injectable formulations that utilize PLGA polymers tend to benefit from lower dosing rates. Developing intravenous depot vehicles that sustain/control the release of the enclosed molecule will significantly improve patient compliance and outcomes. This will be extremely helpful for drug products that require frequent administration under medical supervision/guidance in a hospital setting.

Mühlenfeld: Parenteral formulations can certainly benefit from a controlled release formulation. Think about long acting parenteral formulations that can be administered once monthly or even longer. This offers great promise for chronic diseases where patient compliance is detrimental to treatment outcomes, such as contraception and schizophrenia.

Looking ahead, what are some technical limitations that must be overcome to expand the use of controlled release technologies?

Dormer: Like I mentioned before, any time you want to enact a controlled release solution, you will inherently have to administer more drug, and we have to find ways to do that. For instance, say that there is a 100 mg pill you take every three hours. You would love to take that pill only once per day when you wake up. Your body still needs the 100 mg dose four times though or 400 mg. Therefore, while we can make a dosage form that slowly releases 400 mg throughout the day, replacing taking it every three hours, the pill you have to take in the morning is going to be larger. This is fine for patients who can swallow pills, but it becomes exceedingly challenging when your patient is a child or someone with swallowing disorders. This is why extended release liquids are gaining traction. Same principles apply to injections; we can make the injection once monthly instead of weekly, but the injection volume will likely be much higher. However, with advances in solubility and bioavailability, that large injection becomes much more feasible, and you have a product that is extended release and has the same or less discomfort than the old weekly injection. It is all related.

Dream: Naturally occurring enzymes are remarkable biocatalysts with numerous potential applications in industry and medicine. However, many of their catalyst properties often need to be further tailored to meet the specific requirements of a given application. Within this context, directed evolution has emerged over the past decade as a powerful tool for engineering enzymes with new or improved functions. The recent advances in applying directed evolution approaches to alter various enzyme properties such as activity, selectivity (enantio- and regio-), substrate specificity, stability, and solubility. Special need to be paid to the creation of novel enzyme activities and products by directed evolution.

Drumond and Hildebrandt: An increased emergence of poorly water-soluble drug substances has been observed in the last years. Overcoming solubility limits of the drug molecule will probably play a key role in the development of controlled release drug products for upcoming drug substances. With respect to drug product safety, dose dumping in sustained release drug product is an important issue to address. The potential increase of plasma concentration up to a toxic level caused by individual patient related factors must be prevented. Therefore, the development of sustained drug release technologies that mitigate the risk of dose dumping would allow the expanded application of controlled release technologies. In organic solvent-based functional coating of controlled release systems, the technicalities of solvent recovery must be taken into consideration. The elimination of organic solvents out of coating processes would result in a decrease of required safety precaution (explosion risk) with minimal environmental impact and lower manufacturing costs. As the application of organic coating are often required for technical reasons, improved polymers and coating technologies need to be developed to overcome the need of organic solvents to simplify the manufacturability of controlled release dosage forms.

Elder: In the field of long acting injectables (LAIs) there are still many significant issues. There needs to be a better understanding of the impact of physicochemical properties of polymers, e.g. polylactide-co-glycolide (PLGA) and product performance; including developing methods to fully characterize the structures of branched PLGA polymers.[5] In addition, the intrinsic variability of these polymers as it impacts on inter-batch and inter-supplier variability needs further research.[6] Finally, better understanding of the impact of radiation on polymer performance is required, as many PAIs are sterilized using gamma irradiation.[7]

Lambert: There are several areas where technical limitations are rate limiting for making controlled release technologies available.

In general scalability of developed technologies is a rate limiting step between the bench and the pharmacy. There are many examples in literature where the enabling controlled release technology is not feasible due to the equipment and technology required to manufacture the product at commercial scale does not exist.

Additionally, industry and regulatory authorities need to work together to determine more streamlined ways of approving novel excipients and technologies. Many controlled release technologies consist of complex chemistries and under the current regulatory framework, gaining approval for human use is complex. This complexity adds costs and time to the approval process, and in many cases precludes

the pursuit of technology advancement. It is critical that industry and regulatory authorities work together to develop strategies for approval that reduce the burden for industry without compromising the safety for patients if many of these technologies are to become available.

Bhatt: For oral-controlled drug delivery applications, the greatest limitation to expanding the use of controlled release technologies is the need for development of unique formulations for every potential drug candidate. This is a major financial and technical burden for R&D centers that develop controlled release products.

Availability of preconstructed controlled drug delivery platforms/formulations, or the ability of forming in situ controlled release systems that demonstrate controlled release characteristics independent of the drug molecule incorporated would not only lead to faster product development times associated with clinical trials, process development, scale-up, technical transfers, etc., but also cut down on financial burdens associated with mass producing multiple controlled release drug products in manufacturing centers. As industry and regulatory agencies drive for risk-based scale-up, a preconstructed controlled drug delivery platform may also reduce some of the possible blind spots observed in confounding variables that interplay between raw material characteristics and processing parameters in QbD-based approaches, which may be overlooked when developing drug-molecule-specific systems.

Mühlenfeld: Controlled-release dosage forms for oral delivery are relatively mature with matrix, osmotic pumps and multi-particulate systems being the primary technologies. Meanwhile with the increased interests in continuous manufacturing, matrix formers that can be easily handled will be in higher demand. In addition, more polymer type and molecular weight grade choices will be beneficial to achieve target release profiles in a more precise way. Lastly, AI based systems would be helpful to reduce the time for formulation development.

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